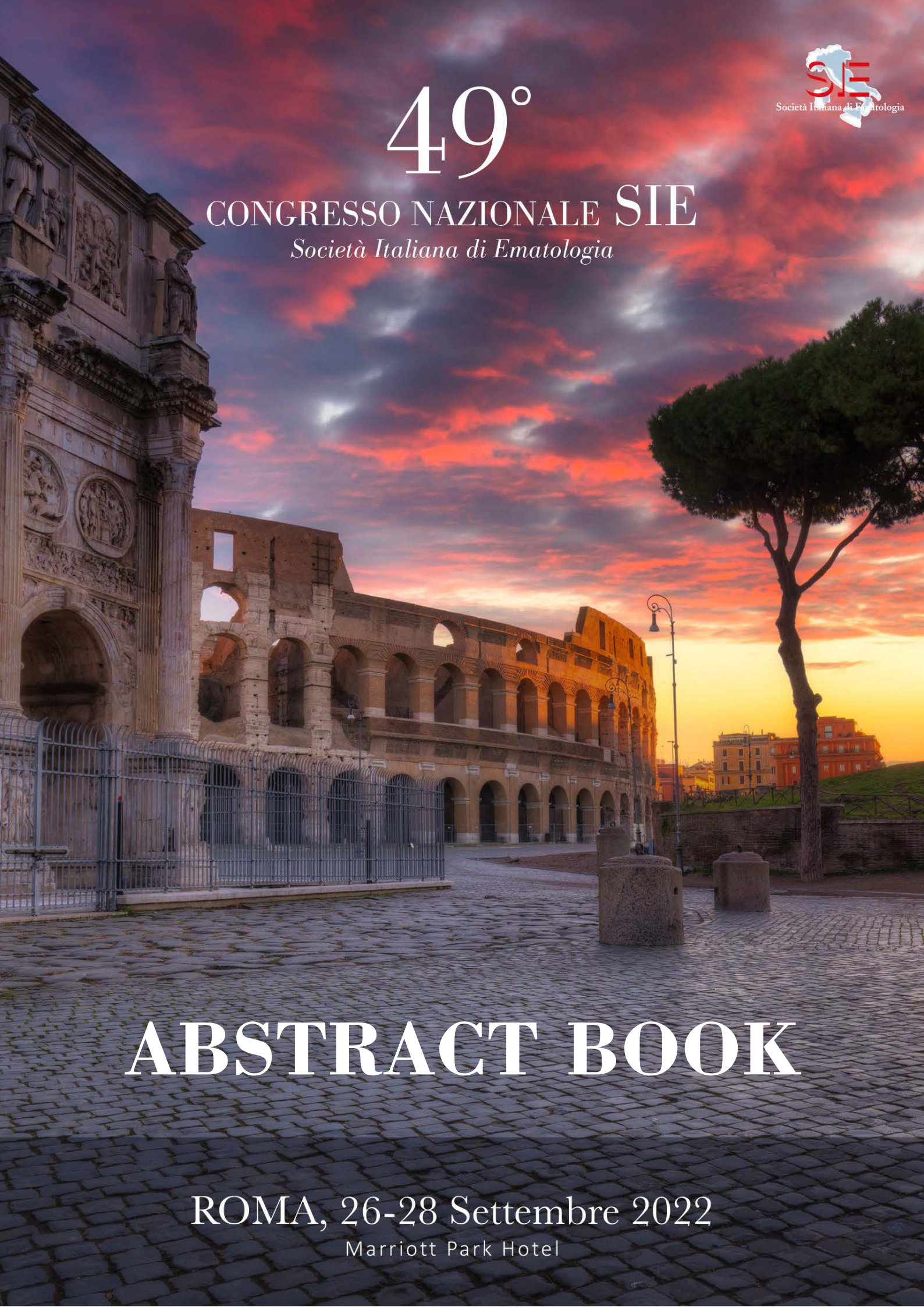


49°

CONGRESSO NAZIONALE SIE

Società Italiana di Ematologia

ABSTRACT BOOK

ROMA, 26-28 Settembre 2022

Marriott Park Hotel

49°

CONGRESSO NAZIONALE SIE

Società Italiana di Ematologia

ROMA, 26-28 Settembre 2022

Marriott Park Hotel

CONSIGLIO DIRETTIVO SIE

Paolo Corradini, *Presidente*
Emanuele Angelucci, *Vice Presidente*
Sergio Siragusa, *Vice Presidente*
Francesco Buccisano
Roberto Cairoli
Michele Cavo
Nicola Di Renzo
Marco Ladetto
Mario Luppi
Francesca Patriarca, *Tesoriere*
Martina Pennisi, *Segretario*
Maria Teresa Petrucci

COMITATO SCIENTIFICO SIE

Pier Luigi Zinzani, *Presidente*
Daniela Cilloni
Anna Falanga
Gian Luca Forni
Ferdinando Frigeri
Massimo Offidani
Valeria Santini

SEGRETERIA PERMANENTE SIE

Via De' Poeti, 1/7 - 40124 Bologna
Tel. +39 051 6390906 - Fax +39 051 4210174
E-mail: segreteriasie@ercongressi.it
www.siematologia.it

SEGRETERIA ORGANIZZATIVA

Studio E.R. Congressi
Via De' Poeti, 1/7 - 40124 Bologna
Tel. +39 051 4210559 - Fax +39 051 4210174
E-mail: ercongressi@ercongressi.it
www.ercongressi.it

49°

CONGRESSO NAZIONALE SIE

Società Italiana di Ematologia

ROMA, 26-28 Settembre 2022

Marriott Park Hotel

49° CONGRESSO NAZIONALE SIE

Società Italiana di Ematologia

ROMA, 26-28 Settembre 2022

BEST ABSTRACTS

B01

AGILE: A GLOBAL, RANDOMIZED, DOUBLE-BLIND, PHASE 3 STUDY OF IVOSIDENIB + AZACITIDINE VERSUS PLACEBO + AZACITIDINE IN PATIENTS WITH NEWLY DIAGNOSED ACUTE MYELOID LEUKEMIA WITH AN IDH1 MUTATION

M. Riva[1], L. Giaccone[2], M. Bernardi[3], C. Cerchione[4], F. Passamonti[5], P. Zappasodi[6], R. Cairoli[1], P. Montesinos[7], C. Recher[8], S. Vives[9], E. Zarzycka[10], J. Wang[11], G. Bertani[1], M. Heuser[12], R.T. Calado[13], A.C. Schuh[14], S.P. Yeh[15], S.R. Daigle[16], J. Hui[16], S.S. Pandya[16], D.A. Gianolio[16], S. de Botton[17], H. Döhner[18]

[1]Department of Hematology, Oncology and Molecular Medicine, Niguarda Cancer Center; [2]SSD Trapianto allogenico di cellule staminali ematopoietiche Oncology Department, AOU Città della Salute e della Scienza; [3]Hematology and Bone Marrow Transplantation Unit, San Raffaele Scientific Institute; [4]Hematology Unit, Istituto Romagnolo per lo Studio dei Tumori "Dino Amadori" - IRST IRCCS; [5]Hematology, ASST Settelaghi - Ospedale di Circolo; [6]Hematology Clinic, Fondazione IRCCS Policlinico San Matteo; [7]Hospital Universitari i Politècnic La Fe; [8]Institut Universitaire du Cancer de Toulouse Oncopole, CHU de Toulouse; [9]Hospital Universitario Germans Trias i Pujol-ICO Badalona, Josep Carreras Research Institute, Universitat Autònoma de Barcelona; [10]Department of Hematology and Transplantology, Medical University of Gdansk; [11]Institute of Hematology & Hospital of Blood Disease – Peking Union Medical College; [12]Hannover Medical School; [13]Ribeirão Preto School of Medicine, University of São Paulo; [14]Princess Margaret Cancer Centre; [15]China Medical University; [16]Servier Pharmaceuticals; [17]Institut Gustave Roussy; [18]Ulm University Hospital

Background: Mutations in isocitrate dehydrogenase 1 (IDH1) are known oncogenic drivers in acute myeloid leukemia (AML), with 6–10% of AML patients harboring a mutant IDH1 gene. Ivosidenib (IVO) is a small molecule designed to inhibit mIDH1, and silence the oncogenic pathways that are activated by this mutation. This randomized, placebo (PBO)-controlled, global phase 3 study evaluated the efficacy and safety of IVO+azacitidine (AZA) as a frontline therapy for AML patients not eligible for intensive chemotherapy (IC).

Methods: Patients with untreated AML, centrally confirmed mIDH1 status, not eligible for IC, were randomized to receive either IVO 500 mg once daily or PBO. Both groups also received AZA 75 mg/m^2 for 7 days in 28-day cycles. Event-free survival (EFS), overall survival (OS), response rates, blood counts, transfusion dependence, health-related quality of life (HRQoL) and adverse events were assessed.

Results: Totally, 146 patients were randomized to IVO+AZA (n=72) and PBO+AZA (n=74). The median age of patients in the treatment groups were 76 and 75.5 years, respectively. EFS was significant in favor of IVO+AZA (HR=0.33; P=0.0011). Median OS was 24.0 *vs* 7.9 months for IVO+AZA *vs* PBO+AZA, respectively (HR=0.44; P=0.0005) and the CR rates were 47.2% and 14.9% in the IVO+AZA and PBO+AZA, respectively (P<0.0001). Mean neutrophil count increased from baseline (0.99 x 10^9/L) to week 2 (2.05 x 10^9/L) and week 5 (4.07 x 10^9/L), and then stabilized in a normal range in the IVO+AZA group, whereas the mean neutrophil count initially declined before recovering to near-normal levels after week 36 of treatment in the PBO+AZA group. Significantly more patients in the IVO+AZA group became RBC/platelet transfusion independent (P=0.0032). IVO+AZA was associated with preserved or improved HRQoL from treatment cycles 5 to 19, whereas there were few clinically meaningful improvements in the PBO+AZA group. Common grade ≥3 AEs occurring in >20% of patients in both groups included febrile neutropenia, anemia, thrombocytopenia and pneumonia.

Conclusions: In patients with IC-ineligible, newly diagnosed mIDH1 AML, IVO+AZA significantly improved EFS, OS, and clinical response when compared with PBO+AZA. Blood counts rapidly recovered in patients given IVO+AZA and they were less dependent on RBC/platelet transfusion than those given PBO+AZA. There were improvements in HRQoL in the IVO+AZA group. The safety profile of IVO+AZA was favorable and consistent with previous studies.

B02

ASCIMINIB ITALIAN MANAGED ACCESS PROGRAM: EFFICACY PROFILE IN HEAVILY PRE-TREATED CML PATIENTS

M. Breccia[1], A. Russo Rossi[2], B. Martino[3], E. Abruzzese[4], M. Annunziata[5], G. Binotto[6], A. Ermacora[7], C. Fava[8], L. Giaccone[9], V. Giai[10], A.P. Nardozza[11], P. Coco[11], A. Gozzini[12], L. Levato[13], A. Lucchesi[14], L. Luciano[15], M.C. Miggiano[16], G. Rege-Cambrin[17], M. Santoro[18], B. Scappini[19], A.R. Scortechini[20], P. Sportoletti[21], E. Trabacchi[22], F. Castagnetti[23]

[1]Department of Translational and precision medicine-Az, Policlinico Umberto I-Sapienza University, Roma; [2]Hematology and Transplantation Unit, University of Bari, Bari; [3]Azienda Ospedaliera "Bianchi Melacrino Morelli", Reggio Calabria; [4]Hematology, Sant Eugenio Hospital, Roma; [5]Division of Hematology, AORN Cardarelli, Napoli; [6]Hematology Unit, University of Padova, Padova; [7]Department of Internal Medicine, Pordenone General Hospital, Pordenone; [8]Clinical and Biological Sciences, University of Turin, Torino; [9]Department of Molecular Biotechnology and Health Sciences, University of Turin, Struttura Semplice Dipartimentale Allogeneic Stem Cell Transplant, Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino, Torino; [10]Division of Haematology, Città della Salute e della Scienza, Torino; [11]Novartis Oncology, Medical Department, Novartis Farma SpA, Orig-

gio; [12]Department of Cellular Therapies and Transfusion Medicine, AOU Careggi, Firenze; [13]Department Hematology-Oncology, Azienda Ospedaliera Pugliese-Ciaccio, Catanzaro; [14]Hematology Unit, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Meldola; [15]Hematology Unit, AUOP Federico II, Napoli; [16]Hematology Department, San Bortolo Hospital,Vicenza; [17]Medicina Interna e Ematologia, Ospedale San Luigi, Università di Torino, Torino; [18]Hematology, University Hospital Paolo Giaccone, Palermo; [19]Hematology Unit, Azienda Ospedaliero-Universitaria Careggi, Firenze; [20]Division of Hematology, Azienda Ospedaliero Universitaria Ospedali Riuniti Ancona, Ancona; [21]Institute of Hematology, Centro Ricerche Emato-Oncologiche, Ospedale S. Maria della Misericordia, University of Perugia, Perugia; [22]Hematology Unit and BMT Center, Ospedale G. Saliceto, Piacenza; [23]Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Ialy

Later lines patient with chronic myeloid leukemia (CML) have limited therapeutic possibilities, highlighting the need of novel treatment options for this subset of patients. Asciminib (ASC), with its new mechanism of action, is an allosteric BRC-ABL inhibitor that has shown efficacy in patients treated with two or more Tyrosine Kinase Inhibitors (TKIs).

We share our experience on ASC use in CML patients outside of clinical trials.

Fig.1 Baseline characteristics (n=34)

Age at baseline (median, range)	63 (21-85)
Gender (n, %)	
Male	18 (52.9)
Female	16 (47.1)
Sokal risk at diagnosis (n, %)	
Low	7 (20.6)
Intermediate	9 (26.5)
High	10 (29.4)
Unknown	8 (23.5)
BCR::ABL1 mutation (n)	
Wild type	24 (70.6)
Mutated	10 (29.4)
T315I	5 (14.7)
Mutated but other than T315I	5 (14.7)
n of pts having T315I and other mutation(s)	3 (8,8)
Best response before asciminib (n, %)	
Less than MR2	6 (17.6)
MR2	8 (23.5)
MR3	4 (11.8)
MR4 or better	15 (44.1)
Unknown	1 (2.9)
N. of TKI before asciminib (n, %)	
2	9 (26.5)
3	8 (23.5)
≥4	17 (50)
Time (years) from diagnosis to asciminib (median, range)	10 (1-34)
Prior use of ponatinib (n, %)	20 (58.8)
Reason for last TKI discontinuation	
Resistance	21 (61.8)
Intolerance	10 (29.4)
Not available	3 (8.8)
Time on Asciminib months (median,range)	8.7 (3.3-31.9)
Comorbidities (n, %)	
0	7 (20.6)
1	5 (14.7)
2	5 (14.7)
≥3	17 (50)
Pts who started asciminib at suggested full dose (n/N)	
T315I	4/5 (80)
Other than T315I	28/29 (96.6)
Pts who had dose modification (n, %)*	
increased	2 (6.9)
decreased	7 (20.6)
not changed	25 (73.5)

*respect to their respectively starting dose

Figure 1.

We describe retrospective data from 34 chronic phase CML patients in their 3rd or later line, treated with ASC between April 2019 and October 2021 in 22 Italian institutions. The drug was granted by Novartis under a Managed Access Program (MAP). Efficacy was analyzed by comparing the response registered at the latest time point (last FU, 34 pts evaluable) or at 3 months (3M, 27 pts evaluable) *vs* the response at baseline. Patient recruitment, dosing regimen and safety were recorded according to the MAP recommendations.

Patients' characteristics are shown in Figure 1. Median time on ASC was 8.3 months for the whole cohort. Twenty-five patients (73.5%) were pretreated with at least 3 or more TKIs and 50% have reported to have ≥3 comorbidities. Approximately 59% of patients received prior ponatinib. All the T315I patients (14.7%) had a previous ponatinib exposure.

Approximately 70%, 40% and 22% achieved or maintained respectively Molecular Response of 2 log reduction (MR2), Major Molecular Response (MMR), Deep Molecular Response (DMR) at 3M and last FU time point. Eighteen out of 27 (66.7%) and 20/34 (58.8%) of patients, at 3M and last FU respectively, showed a response improvement respect the baseline. Approximately 37% and 35%, without MMR response at baseline, reached at least an MMR at 3M and last FU, respectively. We observed that ponatinib treated patients showed a reduced probability of reaching MR2, MMR and DMR responses compared to ponatinib naive patients at both 3M and last FU time points. Seventy-five percent of patients with a T315I mutation showed a response improvement, respect to baseline, already after 3 months on ASC. No new safety findings were observed.

ASC has shown a promising efficacy profile and tolerability in a setting of CML patients resistant and/or intolerant to 2 or more TKIs and with a high comorbidity burden. Our results confirmed what observed in sponsored trial and in the other world-wide programs, strongly suggesting a possible role for this new agent in the future therapeutic scenario.

B003

ABSTRACT NOT PUBLISHABLE

B04

PIRTOBRUTINIB, A HIGHLY SELECTIVE, NON-COVALENT (REVERSIBLE) BTK INHIBITOR IN PREVIOUSLY TREATED MANTLE CELL LYMPHOMA: UPDATED RESULTS FROM THE PHASE 1/2 BRUIN STUDY

P.L. Zinzani[1], M. Wang[2], N. Shah[3], A. Alencar[4], J. Gerson[5], M. Patel[6], B. Fakhri[7], W. Jurczak[8], X. Tan[9], K. Lewis[9], T. Fenske[3], C. Coombs[10], I. Flinn[11], D. Lewis[12], S. Le Gouill[13], M.L. Palomba[14], J. Woyach[15], J. Pagel[16], N. Lamanna[17], J. Cohen[18], M. Barve[19], P. Ghia[20], T. Eyre[21], C. Ujjani[22], Y. Koh[23], K. Izutsu[24], E. Lech-Maranda[25], C. Tam[26], S. Sundaram[27], M. Yin[28], B. Nair[28], D. Tsai[28], M. Balbas[28], A. Mato[14], C. Cheah[9]

[1]Institute of Hematology "Seràgnoli" University of Bologna; [2]MD Anderson Cancer Center; [3]Medical College of Wisconsin; [4]Sylvester Comprehensive Cancer Center; [5]University of Pennsylvania; [6]Florida Cancer Specialists/Sarah Cannon Research Institute; [7]University of California San Francisco; [8]Maria Sklodowska-Curie National Research Institute of Oncology; [9]Linear Clinical Research and Sir Charles Gairdner Hospital; [10]University of North Carolina at Chapel Hill; [11]Sarah Cannon Research Institute; [12]University Hospitals Plymouth NHS; [13]Service d'hématologie clinique du CHU de Nantes, INSERM CRCINA Nantes-Angers, NeXT Université de Nantes; [14]Memorial Sloan Kettering Cancer Center; [15]The Ohio State University Comprehensive Cancer Center; [16]Swedish Cancer Institute; [17]Herbert Irving Comprehensive Cancer Center, Columbia University; [18]Winship Cancer Institute, Emory University; [19]Mary Crowley Cancer Research; [20]Università Vita-Salute San Raffaele and IRCCS Ospedale San Raffaele; [21]Oxford University Hospitals NHS Foundation Trust, Churchill Cancer Center; [22]Fred Hutchinson Cancer Research Center; [23]Department of Internal Medicine, Seoul

National University Hospital; [24]National Cancer Center Hospital; [25]Institute of Hematology and Transfusion Medicine; [26]Peter MacCallum Cancer Center, Royal Melbourne Hospital, and University of Melbourne; [27]Department of Hematology and Medical Oncology, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai; [28]Loxo Oncology at Lilly

Background: Covalent BTK inhibitors (BTKi) have transformed the management of mantle cell lymphoma (MCL), but the majority of patients (pts) will require additional treatment. Pirtobrutinib is a highly selective, non-covalent (reversible) BTKi that inhibits both wild type and C481-mutated BTK with equal low nM potency.

Methods: BRUIN is a multicenter phase 1/2 study (NCT03740529) of oral pirtobrutinib monotherapy in pts with advanced B-cell malignancies who have received >2 prior therapies. The primary objective for phase 1 was to determine the recommended phase 2 dose (RP2D). The primary objective of phase 2 was ORR. Secondary objectives included DoR, PFS, OS, safety and tolerability, and pharmacokinetics. Response was assessed every 8 weeks from cycle 3, and every 12 weeks from cycle 13, measured according to Lugano Classification. Safety was assessed in all pts.

Results: As of 27 Sept 2020, 323 pts (170 CLL/SLL, 61 MCL, 26 WM, 26 DLBCL, 13 MZL, 12 FL, 9 RT and 6 other NHL) were treated on 7 dose levels (25-300mg QD). Median age was 69 (50-87) years for MCL pts. Among the 61 MCL pt, median number of prior lines of therapy was 3 (1-8) and a majority of them had received a prior BTKi (93%), an anti-CD20 antibody (98%) or chemotherapy (92%). No DLTs were reported and MTD was not reached (n=323). 200mg QD was selected as the RP2D. Fatigue (20%), diarrhea (17%) and contusion (13%) were the most frequent TEAEs regardless of attribution or grade seen in >10% pts. The most common AE of grade ≥3 was neutropenia (10%). Treatment-related hemorrhage/hypertension occurred in 5 (2%)/4 (1%) pts. 5 (1%) pts discontinued due to TEAEs. 52 prior BTKi treated MCL pts were efficacy evaluable with an ORR of 52% (95%CI 38-66; 13 CR (25%), 14 PR (27%), 9 SD (17%), 11 PD (21%) and 5 (10%) discontinued prior to first response assessment). Median follow up was 6 months (0.7-18.3+). Responses were observed in 9/14 pts (64%) with prior autologous or allogeneic stem cell transplant, and 2 of 2 with prior CAR-T cell therapy.

Conclusion: Pirtobrutinib demonstrated promising efficacy in heavily pretreated, poor-prognosis MCL following multiple prior lines of therapy, including a covalent BTKi. Pirtobrutinib was well tolerated and exhibited a wide therapeutic index. Updated data, including approximately 60 new pts with MCL and an additional 10 months since the prior data cut will be presented.

B05

ORAL COMPLEMENT FACTOR B INHIBITOR IPTACOPAN IN PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH) PATIENTS (PTS) WITH ACTIVE HEMOLYSIS DESPITE ANTI-C5 THERAPY: LONG-TERM EFFICACY AND SAFETY FOLLOWING ECULIZUMAB (ECU) WITHDRAWAL

A.M. Risitano,[1,2] A. Röth,[3] J. Soret,[4] C. Frieri,[2,5] F. Sicre de Fontbrune,[5] L. Marano,[1,2], F. Alashkar,[3] L. Benajiba,[4] S. Marotta,[2,6] K. Kulmatycki,[7] P.K. Nidamarthy,[8] N. Fagan,[9] G. Junge,[10] R. Peffault de Latour[4,5]

[1]Hematology and Bone Marrow Transplant Unit, AORN Moscati; [2]Department of Clinical Medicine and Surgery, University of Naples Federico II; [3]West German Cancer Center, Department of Hematology and Stem Cell Transplantation, University Hospital Essen; [4]Clinical Investigations Center, Hôpital Saint-Louis; [5]French Référence Center for Aplastic Anemia and Paroxysmal Nocturnal Hemoglobinuria; [6]Hematology and Bone Marrow Transplant Unit, AORN Cardarelli; [7,10]Novartis Institutes for Biomedical Research; [8]Novartis Healthcare Private Limited; [9]Novartis Ireland Limited

Background: Despite standard of care (SoC) anti-C5 therapy, intravascular hemolysis (IVH) and/or extravascular hemolysis (EVH) is common in PNH pts. In Cohort (Ct) 1 of the multicenter, open-label, Phase II X2201 trial (NCT03439839), the oral factor B inhibitor iptacopan significantly reduced lactate dehydrogenase (LDH) levels at week (wk) 13 when used as add-on therapy in PNH pts with active hemolysis despite receiving ECU (Risitano *et al*. 2021). We report long-term efficacy and safety after all pts had received iptacopan for ≥52 wks.

Methods: Adult PNH pts with LDH ≥1.5 × upper limit of normal (ULN) despite ECU treatment received iptacopan 200 mg twice daily (bid; Ct 1; n=10), or if LDH ≥1.25 × ULN and hemoglobin (Hb) <105 g/L, iptacopan 50 mg bid (Ct 2; n=6), as add-on therapy. After ≥26 wks of iptacopan add-on therapy, ECU could be withdrawn and pts could receive iptacopan monotherapy.

Results: As of 17 February 2021, 9/10 Ct 1 pts and 6/6 Ct 2 pts had received iptacopan monotherapy. Per protocol, 5/6 Ct 2 patients with LDH levels above ULN had their iptacopan dose raised to 200 mg bid. Pts who discontinued ECU generally maintained the increased Hb levels achieved with iptacopan add-on therapy; most had Hb >120 g/L at their latest visit (Figure 1). Improvements in LDH and other hemolytic biomarkers were mostly sustained after ECU withdrawal. Fewer pts had red blood cell transfusions during the study versus the year before the study (3/10 *vs* 10/10 in Ct 1; 1/6 *vs* 4/6 in Ct 2). No breakthrough hemolysis was reported. The most common adverse events (AEs) were headache (5/16 pts), asthenia, hypertriglyceridemia and pyrexia (4/16 pts each). Five pts had serious AEs, including two fatal events. One developed lymphoproliferative disorder; this was suspected to be iptacopan related, but there were pre-existing risk factors including profound lymphopenia. This pt had fatal septic shock (considered unrelated to iptacopan) after salvage chemotherapy (47 wks after iptacopan discontinuation). Another pt had fatal squamous cell carcinoma of the oral cavity; this evolved from a pre-existing precancerous lesion so was considered unrelated to iptacopan.

Conclusions: In PNH pts, iptacopan led to long-term hematological benefit and control of IVH and EVH that was maintained after SoC withdrawal. Iptacopan was well tolerated with no new safety concerns. Phase III trials will study iptacopan monotherapy in anti-C5-treated (NCT04558918) and anti-C5-naïve (NCT04820530) PNH pts.

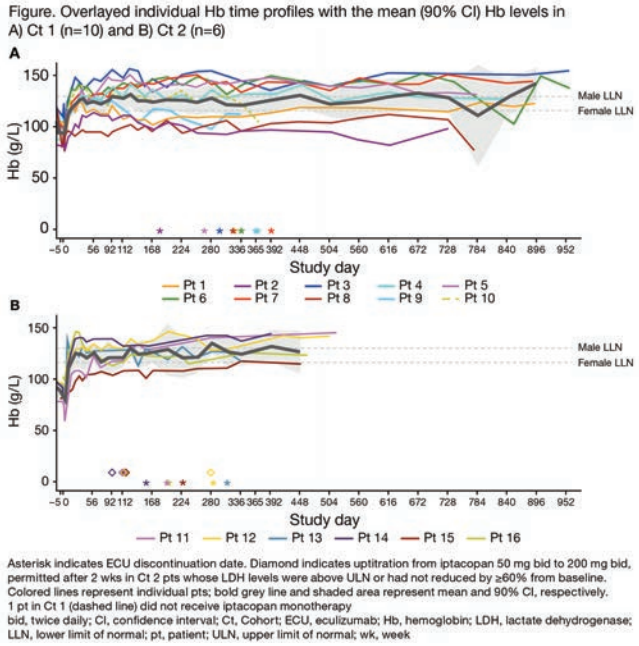


Figure 1.

B06

IMMUNOGENICITY AND CLINICAL EFFICACY OF ANTI-SARS-COV-2 VACCINATION IN PATIENTS WITH HEMATOLOGICAL MALIGNANCIES: RESULTS OF A PROSPECTIVE COHORT STUDY OF 365 PATIENTS

M. Salvini[1], C. Damonte[2], L. Mortara[2], F. Maggi[1,2], A. Bruno[2,3], G. Pellegrini[1,4], B. Mora [1,2], M. Brociner[1], A. Ingrassia[1], R. Mattarucchi[1], B. Bianchi[1], D. Sirocchi[1], S. Agnoli[1], E. Rumi[5,6], M. Merli[1], O. Borsani[6], M. Franchi[4], P.A. Grossi[1,2], F. Passamonti[1,2]

[1]ASST Sette Laghi; [2]University of Insubria; [3]IRCCS MultiMedica; [4]University of Milano-Bicocca; [5]Fondazione IRCCS Policlinico San Matteo; [6]University of Pavia, Italy

Anti-SARS-CoV-2 vaccination represents the most effective strategy to reduce the severity of Covid-19. Objectives of this prospective study (NCT04878822) were to assess immunogenicity and clinical efficacy of mRNA anti-SARS-CoV-2 vaccines in adult patients with hematological malignancies (HMs). Humoral immunity was assessed with DiaSorin's Liaison SARS-CoV-2 TrimericS IgG assay; T-cell-mediated immunity was tested by quantifying spike-specific IFNγ-producing T-cells by enzyme-linked immunosorbent spot (ELISpot) assay and by characterizing different subpopulations of T-cells through fluorescence activated cell sorting (FACS).

Overall, the seroconversion rate after full vaccination was 82% (298 out of 365), while the seroconversion rate in 57 seronegative patients who underwent booster vaccination was 37% (21 out of 57). In the multivariate analysis, the variables significantly associated with negative serology testing were diagnosis of lymphoma (RR 3.01, 95% CI 1.53-5.93; P=0.0014), immunotherapy (RR 9.42, 95% CI 2.66-33.33; P=0.0005), treatment with biologics (RR 4.05, 95% CI 1.29-12.71; P=0.0166), and being on active treatment (RR 8.09, 95% CI 2.93-22.31; P<0.0001). The latter also negatively affected the magnitude of antibody titer (P<0.001). The evaluation of cell-mediated immunity showed positive responses across both seropositive and seronegative patients, although generally lower in the latter. T-cell subset analysis by FACS showed that anti-SARS-CoV-2 vaccination stimulates the development of spike-specific memory T-cells.

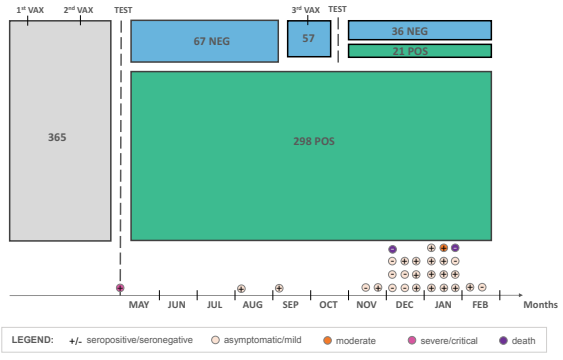


Figure 1.

During a median follow-up of 269 days (min-max, 13-356), we registered 29 cases of SARS-CoV-2 breakthrough infection, with an overall incidence of 2.98 per 10,000 person-days (see figure). We reported a significant rise in infections after the spread of the Omicron variant (from 1.17 to 9.82 per 10,000 person-days; P<0.0001). Overall, the risk of breakthrough infection in seropositive patients was significantly lower as compared to seronegative patients (HR 0.11, 95% CI 0.03-0.43; P=0.0017). By comparing our results with those collected in a group of patients with HMs who had developed Covid-19 in the pre-vaccination period of the pandemic, we found that the rate of severe or critical disease (10% *vs* 33%; P=0.0242), the rate of hospitalization (17% *vs* 50%; P=0.0024), and the median duration of disease (16 days *vs* 22 days; P=0.0094) were all significantly lower in vaccinated patients as compared to non-vaccinated patients.

B07

RUXOLITINIB IN PATIENTS WITH POLYCYTHEMIA VERA RESISTANT AND/OR INTOLERANT TO HYDROXYUREA: RESULTS FROM A EUROPEAN MULTICENTER OBSERVATIONAL STUDY IN ITALIAN SUBGROUP

V. De Stefano[1], S. Siragusa[2], G.A. Palumbo[3], M. Breccia[4], F. Pane[5], D. Luzi[6], A. Tafuri[7], C. Selleri[8], E.M. Elli[9], A. Volpe[10], G. Carli[11], G. Benevolo[12], S. Galimberti[13], E. Lucia[14], P. Sportoletti[15], M. Bruno Ventre[16], M. Musso[17], F. Mannelli[18], G. Caocci[19], A. Malato[20], F. Lanza[21], A. Ricco[22], N. Di Renzo[23], M. Bonifacio[24], L. Maurillo[25], S. Cabibbo[26], F. Lunghi[27], M.L. Randi[28], F. Cavazzini[29], B. Martino[30], M. Tiribelli[31], D. Cilloni[32], S. Rupoli[33], G. Binotto[34], G. Auteri[35], D. Cattaneo[36], B. Mora[37], F. Passamonti[38], A. Ibatici[39], E. Rumi[40], M. Caramella[41], G. Visani[42], E. Abruzzese[43], F. Palandri[44], P. Guglielmelli[45], P. Stefanelli[46], A. Iurlo[47]

[1]Full Professor of Hematology, Catholic University, Fondazione Policlinico Gemelli IRCCS; [2]Full Professor of Hematology, PROMISE Department, University of Palermo; [3]Department of Medical Surgical Sciences and Advanced Technologies "G.FIngrassia", University of Catania; [4]Hematology, Department of Translational and Precision Medicine, Az. Policlinico Umberto I-Sapienza University; [5]Full Professor of Hematology Director of the Department of Clinical Medicine and Surgery Director of the U.O.C. Hematology and bone marrow transplants Federico II University Hospital of Naples University of Naples Federico II Via S; [6]Medical Director, S.C. Oncohematology, Oncology Department, Santa Maria Terni Hospital; [7]Full Professor of Hematology, Department of Clinical and Molecular Medicine, Director of Hematology, University Hospital "Sant'Andrea"; Department of Clinical and Molecular Medicine, "Sapienza" University of Rome; [8]Hematology and Bone Marrow Transplant, University Hospital of Salerno, University of Salerno; [9]Hematology Division and Bone Marrow Unit, San Gerardo Hospital; [10]Hematology, San Giuseppe Moscati Hospital; [11]U.O.C. Hematology, ULSS8 Berica, San Bortolo Hospital; [12]SSD Myeloma Unit and Clinical Trial and S.C. Hematology, Department of Hematology and Oncology A.O. City of Health and Science of Turin; [13]Department of Clinical and Experimental Medicine, University of Pisa; [14]UOC Hematology, Hospital of Cosenza; [15]Department of Medicine and Surgery, Institute of Hematology and Center for Hemato-Oncological Research, University of Perugia; [16]ASST Fatebenefratelli, Sacco Milano, UOS Hematology; [17]UOC of oncohematology and tmo, Oncology Department La Maddalena Palermo; [18]CRIMM, AOU Careggi; [19]Hematology Hospital Businco, ARNAS Brotzu; [20]UOC di Oncoematologia Ospedali Riuniti Villa Sofia-Cervello Palermo; [21]Head, Section of Hematology & Romagna Metropolitan Transplant Network University Hospital; [22]Hematology with Transplantation Unit, AOU Policlinico; [23]UOC of Hematology and Stem Cell Transplantation; Immunotransfusional, Hematological and Oncological Department; "Vito Fazzi" Hospital; [24]Associate Professor of Hematology, Department of Medicine, University of Verona Policlinico G.B.Rossi; [25]UOC Hematology, Tor Vergata Polyclinic Foundation; [26]Director of UOSD HEMATOLOGY ASP RG, Giovanni Paolo II Hospital; [27]Haematology and Bone Marrow Transplant Unit, IRCCS San Raffaele Hospital; [28]First Medical Clinica, Department of Medicine- DIMED, University of Padova; [29] Arcispedale SAnna, U.O. Hematology; [30]MD, Head Unit of Hematology, Department of Hemato-Oncology and Radiotherapy, Grande Ospedale Metropolitano "Bianchi-Melacrino-Morelli"; [31]Assistant Professor of Hematology, Division of Hematology and BMT, Department of Medical Area, Uni-

versity of Udine – Azienda Sanitaria Universitaria Friuli Centrale; [32]Full Professor of Hematology, University of Turin; [33]Simple Hospital Structure (SOS) in Hemostasis and Thrombosis; [34]Padua School of Medicine, Department of Medicine, Hematology and Clinical Immunology Unit; [35]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli"; Department of Specialized, Diagnostic and Experimental Medicine, University of Bologna; [36]Department of Oncology and Hemato-Oncology, University of Milan, Hematology Division, Foundation IRCCS Ca 'Granda Maggiore Policlinico Hospital; [37]Hematology, University of Insubria, Circolo Hospital - ASST Sette Laghi, Viale Borri; [38]Full Professor of Hematology, University of Insubria, Director, Hematology, Circolo Hospital - ASST Sette Laghi, Viale Borri; [39]UO Hematology and Cellular Therapies, IRCCS San Martino Polyclinic Hospital. Largo RBenzi; [40]Department of Molecular Medicine, University of Pavia; Division of Hematology, Institute of Hospitalization and Scientific Care (IRCCS) Policlinico San Matteo; [41]S.C Hematology, Niguarda Cancer Center; ASST Niguarda, Piazza Ospedale Maggiore; [42]Hematology-AORMN Pesaro; [43]Hematology, S. Eugenio Hospital, Tor Vergata University, ASL ROMA2; [44]IRCCS University Hospital of Bologna, Seràgnoli Institute of Hematology; [45]Associate Professor of Hematology, Director of the Center of Research and Innovation of Myeloproliferative Neoplasms, AOU Careggi, University of Florence; [46]Novartis Oncology, Novartis Farma SpA, Origgio; [47]Hematology Division, Foundation IRCCS Ca 'Granda Ospedale Maggiore Policlinico

Hydroxyurea (HU) is a commonly used first-line treatment in patients with polycythemia vera (PV). However, intolerance and resistance to HU has been reported in PV patients. This phase IV, European, observational study assessed the efficacy and safety of ruxolitinib (RUX) in adult patients with PV who were resistant and/or intolerant (R/I) to HU in the real-world setting with a 24-month follow-up. Results from the Italian subgroup are presented here. Primary objective was to describe profile and disease burden of PV patients who were R/I to HU and treated with RUX. Secondary objectives included evaluation of effectiveness and safety of RUX, clinical routine management of patients, impact of RUX from a pharmacoeconomic perspective, and evaluation of cardiovascular risk in PV patients who were R/I to HU. Of the 350 patients enrolled and treated with RUX in the study, the Italian subgroup comprised of 182 patients. Total 114 patients (62.6%) completed 24 months of study; 40 patients (21.0%) discontinued the study with no reason given and 28 patients (15.4%) discontinued with the main reasons (≥2%) being lost to follow-up (4.9%) and progressive disease (2.7%). Disease history at baseline is presented in Table 1.

65.4% patients were resistant to HU and 56.0% were intolerant to HU. Median (min-max) hematocrit (HCT) value at baseline was 45.34% (31.7-61.0) and 55.7% of patients had HCT >45%. HCT levels dropped rapidly in the first 12 weeks and then were sustained throughout the 24-month period. Proportion of patients not requiring any phlebotomy were 86.8% from week 4 to month 24. Mean (SD) HCT was 45.34% (4.14) for 160 patients at baseline and 39.49% (4.54) for 84 patients at month 24. Mean (SD) hemoglobin was 140.72 (15.34) g/L for 160 patients at baseline and 128.28 (15.48) g/L for 85 patients at month 24. Total 14 patients (7.7%) had thrombotic event, 5 patients (2.7%) died, and adverse events that led to death were pneumonia, leukocytosis, myeloid leukemia, prostate cancer, and cardiac arrest (n=1 each).

Present data provide insights into the profile and the disease burden of Italian patients with PV who are R/I to HU and treated with RUX. The data demonstrated that RUX treatment achieved HCT control in the majority of patients with a decrease in phlebotomies. Overall results from the Italian subgroup analysis were consistent with the total study group and demonstrate the effectiveness and safety of RUX treatment in the real-world setting.

Table 1. Disease history in the Italian subgroup at baseline.

Disease history	N=182
Time since diagnosis of PV, months, median	85.92
Resistance and/or intolerance to HU,[a] n (%)	182 (100)
HU intolerant	102 (56.0)
HU resistant	119 (65.4)
Hematocrit, %, mean ± SD	45.34 ± 4.149
Hematocrit category, n (%)	
<40%	15 (9.4)
≥40%-≤45%	56 (35.0)
>45%-<48%	46 (28.8)
≥48%	43 (26.9)
WBC, x10^9/L, mean ± SD	13.3 ± 8.23
WBC count category, x10^9/L, n (%)	
≤10	69 (43.7)
>10-≤15	36 (22.8)
>15	53 (33.5)
Platelet count, x10^9/L, mean ± SD	453.8 ± 257.83
Platelet count category, x10^9/L, n (%)	
<100	2 (1.3)
≥100-<400	79 (50.6)
≥400-<600	40 (25.6)
≥600	35 (22.4)
RBC count, x10^{12}/L, mean ± SD	5.5 ± 1.37
Hemoglobin, g/L, mean ± SD	140.72 ± 15.348
Phlebotomies 12 months prior to first dose of ruxolitinib,[b] n (%)	
0	75 (42.4)
>0-≤2	50 (28.2)
>2-≤4	25 (14.1)
>4-≤6	14 (7.9)
>6-≤8	6 (3.4)
>8	7 (4.0)
Spleen enlargement as measured by palpation, cm, n (mean ± SD)	103 (3.2 ± 4.87)
Spleen length as measured by ultrasound, mm, n (mean ± SD)	47 (145.9 ± 33.24)
Splenomegaly as measured by palpation, n (%)	
No enlargement (0 cm)	45 (43.7)
Mild (<4 cm)	28 (27.2)
Moderate (4-8 cm)	17 (16.5)
Massive (>8 cm)	13 (12.6)
ECOG performance status, n (%)	
Grade 0	60 (73.2)
Grade 1	22 (26.8)

Grade 2	0
Grade 3	0
Grade 4	0
Summary of PV history,[c] n (%)	
Bone marrow biopsy	140 (76.9)
Reticulin fibrosis	
Grade 0	57 (31.3)
Grade 1	72 (39.6)
Grade 2	4 (2.2)
Grade 3	1 (0.5)
Hypercellular bone marrow	109 (59.9)
Genetic analysis	168 (92.3)
JAK2V617F mutation	173 (95.1)
Exon 12 mutation	9 (4.9)
JAK2V617F allelic burden, n (mean ± SD)	46 (55.3 ± 26.74)

ECOG, Eastern Cooperative Oncology Group; HU, hydroxyurea; PV, polycythemia vera; RBC, red blood cell; SD, standard deviation; WBC, white blood cell.

The denominator used for percentages is the number of non-missing data.

N denotes the number of patients in the enrolled set for the Italian subgroup.

[a]Resistance and/or intolerance to HU is reported from the "Assessment of Resistance/Intolerance to HU" case report form. Patients can be counted as both resistant/intolerant to HU, and other cytoreductive therapy other than HU.

[b]For the frequency of phlebotomies, the counts for missing can increase from 3 months, to 6 months, and 12 months. This is due to an unknown number of phlebotomies at 6 or 12 months.

[c]Percentage is based on N (enrolled set).

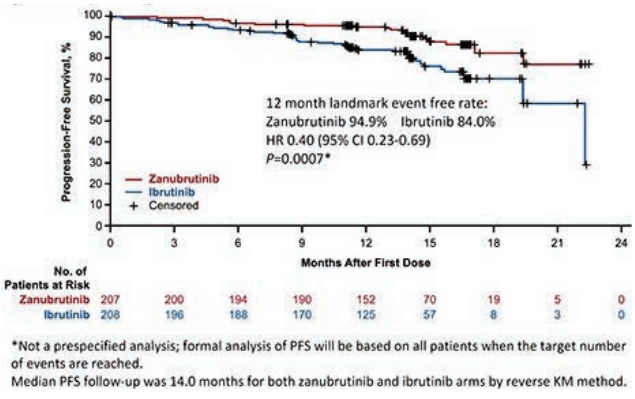
B08

FIRST INTERIM ANALYSIS OF ALPINE STUDY: RESULTS OF A PHASE 3 RANDOMIZED STUDY OF ZANUBRUTINIB *VS* IBRUTINIB IN PATIENTS WITH RELAPSED/REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA

M. Coscia[1,2], P. Hillmen[3], B. Eichhorst[4], J. Brown[5], N. Lamanna[6], S. O'Brien[7], C. Tam[8,9,10,11], L. Qiu[12], M. Kazmierczak[13], K. Zhou[14], M. Šimkovič[15,16], J. Mayer[17], A. Gillespie-Twardy[18], M. Shadman[19,20], A. Ferrajoli[21], P. Ganly[22,23], R. Weinkove[24,25], T. Salmi[26], K. Wu[26], W. Novotny[26], W. Jurczak[27]

[1]Department of Molecular Biotechnology and Health Sciences, University of Torino; [2]Division of Hematology, A.O.U. Città della Salute e della Scienza di Torino; [3]St James's University Hospital; [4]Department of Internal Medicine, University of Cologne; [5]Dana-Farber Cancer Institute; [6]Herbert Irving Comprehensive Cancer Center, Columbia University; [7]Chao Family Comprehensive Cancer Center, University of California; [8]Peter MacCallum Cancer Centre; [9]University of Melbourne; [10]St Vincent's Hospital; [11]Royal Melbourne Hospital; [12]Chinese Academy of Medical Sciences, Peking Union Medical College; [13]Department of Hematology and Bone Marrow Transplantation, Poznan University of Medical Sciences; [14]Affiliated Cancer Hospital of Zhengzhou University, Henan Cancer Hospital; [15]4} Department of Internal Medicine - Hematology, University Hospital; [16]Faculty of Medicine, Charles University; [17]Department of Internal Medicine-Hematology and Oncology, Masaryk University and University Hospital; [18]Blue Ridge Cancer Care; [19]Fred Hutchinson Cancer Research Center; [20]Department of Medicine, University of Washington; [21]Department of Leukemia, The University of Texas MD Anderson Cancer Center; [22]Department of Haematology, Christchurch Hospital; [23]Department of Pathology and Biomedical Science, University of Otago; [24]Wellington Blood and Cancer Centre, Capital and Coast District Health Board; [25]Malaghan Institute of Medical Research; [26]BeiGene (Beijing) Co., Ltd., BeiGene USA, Inc; [27]Maria Sklodowska-Curie National Institute of Oncology

Treatment of CLL/SLL has been transformed with Bruton tyrosine kinase inhibitors (BTKi) such as ibru. Zanu is a next-generation BTKi designed to maximize BTK occupancy and minimize off-target kinase inhibition, which may improve efficacy and safety outcomes. ALPINE (BGB-3111-305; NCT03734016) is a global, randomized, phase 3 study of zanu *vs* ibru in patients (pts) with R/R CLL/SLL. Presented here are results of a preplanned interim analysis that occurred ~12 mo after enrollment of the first 415 pts (of 652 total pts). Pts with R/R CLL/SLL were randomized 1:1 to receive zanu 160 mg twice daily or ibru 420 mg once daily until disease progression. Randomization was stratified by age (<65 y *vs* ≥65 y), geographic region, refractory status, and del(17p)/TP53 mutation status. The primary endpoint was overall response rate (ORR) by investigator assessment per 2008 IWCLL guidelines or Lugano criteria (SLL), to evaluate noninferiority of zanu to ibru response ratio at a noninferiority margin of 0.8558. If noninferiority was demonstrated, a hierarchical testing approach was used to test superiority of zanu *vs* ibru in ORR. From 5Nov2018 and 20Dec2019, 415 pts were randomized. Treatment groups were balanced for baseline characteristics (zanu *vs* ibru): age ≥65 y 62.3% *vs* 61.5%; male 68.6% *vs* 75%; >3 prior therapy lines 7.2% *vs* 10.1%; del(17p) 11.6% *vs* 12.5%; TP53 mutated without del(17p) 8.2% *vs* 5.8%. At a median follow-up of 15 mo, ORR was significantly higher with zanu *vs* ibru (78.3% *vs* 62.5%, 2-sided P=0.0006 compared with prespecified α=0.0099 for interim analysis). ORR was higher in pts with del(11q) (83.6% *vs* 69.1%) and del(17p) (83.3% *vs* 53.8%) with zanu, as were overall 12-mo progression-free survival (PFS; 94.9% *vs* 84.0%; Figure 1) and overall survival (97.0% *vs* 92.7%). The rate of atrial fibrillation/flutter (AF) was significantly lower with zanu *vs* ibru (2.5% *vs* 10.1%, 2-sided P=0.0014, compared with prespecified α=0.0099 for interim analysis). Rates of major bleeding (2.9% *vs* 3.9%), and adverse events leading to discontinuation (7.8% *vs* 13.0%) or death (3.9% *vs* 5.8%) were also lower with zanu. The rate of neutropenia was higher with zanu (28.4% *vs* 21.7%), while grade ≥3 infections were lower with zanu (12.7% *vs* 17.9%). In this interim analysis, zanu had a superior response rate, improved PFS, and a lower rate of AF compared with ibru. These data suggest that more selective BTK inhibition, with more complete, sustained BTK occupancy, improved efficacy and safety outcomes.



*Not a prespecified analysis; formal analysis of PFS will be based on all patients when the target number of events are reached.

Median PFS follow-up was 14.0 months for both zanubrutinib and ibrutinib arms by reverse KM method.

Figure 1.

B09

ON-DEMAND PLERIXAFOR WITH CYCLOPHOSPHAMIDE AND G-CSF FOR HEMATOPOIETIC STEM-CELL MOBILIZATION IN MULTIPLE MYELOMA PATIENTS: FINAL RESULTS OF THE MOZOBL06877 STUDY

R. Mina, F. Bonello, F. Fazio, V. Bongarzoni, R. Saccardi, F. Marchesi, G. Bertuglia, P. Curci, R.M. Lemoli, S. Ballanti, T. Dentamaro, G. Benevolo, A. Capra, R. Floris, P. Tosi, A. Olivieri, D. Rota-Scalabrini, C. Cangialosi, M. Cavo, P. Corradini, G. Milone, M. Boccadoro, A. Larocca

European Myeloma Network Italy

Background: Around 5-15% transplant-eligible newly diagnosed multiple myeloma (NDMM) patients (pts) fail hematopoietic stem-cell (HSC) collection (<2×10^6/kg $CD34^+$ cells [$CD34^+$]/kg). Plerixafor (PLX) increases HSC yield and lowers the mobilization failure rates. We present the results of the prospective, observational MOZOBL06877 study (partially supported by Sanofi investigation funds) to evaluate the role of PLX in HSC mobilization in NDMM pts treated with novel agents.

Methods: NDMM pts undergoing HSC mobilization with cyclophosphamide (2-4 g/m²) + granulocyte colony stimulating factor (G-CSF, 5-10 mcg/kg/day) were enrolled. "On-demand" PLX was administered in pts with <20 $CD34^+$/uL after ≥4 days of G-CSF or if <1×10^6 $CD34^+$/kg were collected on the first apheresis day. The primary endpoint was the rate of poor mobilizers (PMs), defined as pts failing HSC mobilization (<2×10^6 $CD34^+$/kg) or requiring PLX. Secondary endpoints were the identification of predictive factors of being PMs and safety.

Results: 301 NDMM pts were analyzed; 72% received VTd induction, 9% a lenalidomide (Len)-based and 3% a daratumumab (Dara)-based regimen. 48 pts (16%) were PMs: 14 (5%) failed HSC mobilization (4 despite the use of PLX), while 34 (11%) required PLX rescue to achieve adequate HSC yield. Reasons for PLX administration were: <20×10^6 $CD34^+$/L after ≥4 days of G-CSF in 25 pts (66%) and HSC cell yield <1×10^6/kg after the first apheresis day in 13 pts (34%). Overall, 287 (95%) pts collected ≥2×10^6/kg $CD34^+$. In pts mobilized with PLX, the median number of $CD34^+\times10^6$/L increased from 17.5 (IQR 10.8-25.6) before PLX to 58.3 (IQR 34.2-100.2) after PLX. The median number of collected $CD34^+$/Kg was 10.2×10^6 (IQR 8.3-13.2) and 6.5×10^6 $CD34^+$/kg (IQR 4.6-9.6) in pts who did not require and required PLX, respectively; apheresis was completed in a median of 1 (IQR 1-2) and 2 (IQR 1-2) days, respectively. In a multivariate analysis (Figure 1), predictive factors of being PMs were bone marrow (BM) plasma cells >60% (OR 4.35, P<0.001), use of Len (OR 3.11, P=0.02) or Dara (OR 4.56, P=0.07), pre-mobilization ANC <2500/uL (OR 2.24, P=0.02) and Hb <12 g/dL (OR 2.27, P=0.02). Grade 3 infections occurred in 3 pts (1%), with no grade 4-5 reported.

Conclusion: "On-demand" PLX was an effective rescue strategy, reducing mobilization failure from 16% to 5%. High BM plasmacytosis, low ANC and Hb before mobilization and Len/Dara use were associated to an increased risk of mobilization failure or PLX need.

Figure. Multivariate analysis of factors associated with an increased risk of being poor mobilizers (i.e., failing HSC mobilization or requiring plerixafor)

Parameters	OR (95% CI)	p-value
Bone marrow PCs at diagnosis > 60%	4.35 (2.12-8.93)	< 0.001
Lenalidomide during induction	3.11 (1.18-8.25)	0.02
Daratumumab during induction	4.56 (0.9-23.05)	0.07
ANC pre-mobilization < 2500/mmc	2.24 (1.18-4.76)	0.02
Hb pre-mobilization < 12 g/dL	2.27 (1.12-5.55)	0.02

Abbreviations. HSC, hematopoietic stem-cell; OR, odds ratio; CI, confidence interval; PCs, plasma cells; ANC, absolute neutrophil count, Hb, hemoglobin.

Figure 1.

B10

LONG TERM FOLLOW-UP INTERIM ANALYSIS OF THE EQOL-MDS TRIAL FOR THE EVALUATION OF ELTROMBOPAG FOR THE TREATMENT OF THROMBOCYTOPENIA OF MDS

E.N. Oliva[1], M. Riva[2], I. Carmosino[3], G. Zini[4], P. Niscola[5], V. Santini[6], A. Poloni[7], V. Gaidano[8], A. Patriarca[9], I. Capodanno[10], P. Salutari[11], G. Sanpaolo[12], G. Reda[13], D. Ferrero[14], A. Guarini[15], G. Beltrami[16], M. Bocchia[17], A. Castelli[18], U. Germing[19], S. Impera[20], G.A. Palumbo[21], A. Molteni[22], A. Liberati[23], A. Ricco[24], A. Stamatoullas[25], A. Candoni[26], F. Rivellini[27], N. Di Renzo[28], F. Buccisano[29], G. Avvisati[30], C. Frairia[31], E. Messa[32], D. Mannina[33], A. Romano[34], G. Caocci[35], C. Selleri[36], S. Mancini[37], L. Fianchi[38], F. Rodeghiero[39], E. Vigna[40], P. Fenaux[41], S. Greve[1], P. Cufari[1], C. Mammì[42], M.C. Cannatà[42], M.G. D'Errigo[42], I. Bova[42], R. Latagliata[43]

[1]U.O.C. Ematologia Grande Ospedale Metropolitano Bianchi Melacrino Morelli; [2]Dipartimento di Ematologia, ASST Grande Ospedale Metropolitano Niguarda; [3]Dipartimento di Ematologia, Policlinico Umberto I; [4]Fondazione Policlinico Universitario A. Gemelli IRCCS, Roma. Università Cattolica del Sacro Cuore; [5]U.O. di Ematologia, Ospedale Sant'Eugenio; [6]U.O. di Ematologia, A.O.U. Careggi, Università di Firenze; [7]Clinica di Ematologia, AOU Ospedali Riuniti di Ancona; [8]S.C. a Direzione Universitaria di Ematologia, Azienda Ospedaliera SS. Antonio, Biagio e Cesare Arrigo; [9]Divisione di Ematologia, AOU Maggiore della Carità; [10]U.O. di Ematologia A.U.S.L.-IRCCS di Reggio Emilia; [11]Dipartimento Oncologico-Ematologico P.O. Spirito Santo; [12]U.O. Ematologia Casa Sollievo della Sofferenza IRCCS; [13]UOC Ematologia, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico; [14]Dipartimento di Ematologia, Università di Torino; [15]UO Ematologia, IRCCS Istituto Tumori "Giovanni Paolo II"; [16]U.O Ematologia e terapie cellulari, Ospedale Policlinico San Martino; [17]UOC di Ematologia, Policlinico Santa Maria alle Scotte; [18]SSD Ematologia - Ospedale degli Infermi; [19]Dept. of Hematology, Oncology, and Clinical Immunology, Heinrich-Heine-University; [20]U.O. C. Ematologia, A. O. ad Alta Specializzazione Ospedale Garibaldi Nesima; [21]UO di Ematologia con TMO, AOU "Policlinico-V.Emanuele"; [22]Divisione di Ematologia ASST di Cremona; [23]S.C. Oncoematologia, Università degli Studi di Perugia, A.O. Santa Maria, Terni; [24]U.O.Ematologia con Trapianto, Azienda Ospedale Policlinico di Bari; [25]Centre Henri Becquerel, Rue d'Amiens; [26]Divisione Ematologia, P.O. Santa Maria della Misericordia, A.S.U.F.C di Udine; [27]Divisione Ematologia P.O. A. Tortora di Pagani-ASL Salerno; [28]U.O. di Ematologia, Ospedale Vito Fazzi; [29]Divisione di Biopatologia e Diagnostica per Immagini, Policlinico Universitario Tor Vergata; [30]UOC Ematologia, Medicina Trasfusionale e Terapia Cellulare, Università Campus Biomedico; [31]Dipartimento di Oncologia ed Ematologia, S.C. Ematologia 2°, A.O. Citta' della Salute e della Scienza di Torino; [32]Divisione Ematologia, ASL Torino 4; [33]DIvisione Ematologia, Ospedale Papardo; [34]Divisione di Ematologia, IRCCS Istituto Regina Elena (IFO); [35]U.O. Ematologia, Ospedale "Roberto Binaghi"; [36]U.O.C. Ematologia e Trapianti di Cellule Staminali Emopoietiche,A.O.U. San Giovanni di Dio e Ruggì D'Aragona; [37]Divisione di Ematologia e Trapianto, A.O. San Camillo-Forlanini; [38]U.O.C. Ematologia, Policlinico Gemelli; [39]U.O. Ematologia, Ospedale San Bortolo; [40]Divisione Onco Ematologia, Ospedale L'Annunziata; [41]Groupe Francais des myélodysplasies (GFM); [42]U.O.S. di Genetica Medica Grande Ospedale Metropolitano Bianchi Melacrino Morelli; [43]Divisione di Ematologia, Ospedale Belcolle, Italy

There are scarce therapeutic options for severe thrombocytopenia of myelodysplastic syndromes (MDS). We have previously reported on the short-term safety and efficacy of eltrombopag for the treatment of severe thrombocytopenia of International Prognostic Scoring System low and intermediate-1 risk MDS in a single-blind, randomised, placebo-controlled, phase 2 trial (EQoL-MDS trial, Oliva et al., Lancet Hematol 2017). We report the interim analysis of the long-term follow-up on

safety and efficacy. One hundred and sixty-nine subjects with platelet count ≤30 Gi/L were randomized (2:1) to receive eltrombopag or placebo until progression. The median follow-up time was 25 weeks (interquartile range 14-68 weeks). Platelet responses, defined according to International Working Group criteria, occurred in 47 (42%) eltrombopag versus 6 (11%) placebo subjects (odds ratio 5.9 [95% confidence interval 2.3–14.9], p<0.0001). In the eltrombopag arm, median time to response was 2 [interquartile range (IQR): 1-7] weeks at a median dose of 50 mg (IQR 50-150) with a median duration of response of 38 (IQR: 16– 182) weeks. Grade 3-4 bleeding events occurred in more placebo subjects (40%) than eltrombopag (21%; p=0.005). Grade 3–4 adverse events occurred in 45% of subjects on eltrombopag versus 19% on placebo (χ^2=9·4, p=0·002 with stopping rule for safety not reached). Acute myeloid leukemia or MDS progression was observed in 19 (17%) on eltrombopag versus 9 (16%) on placebo (χ^2=0.05, p=0.94). Overall and progression-free survival were similar between arms. Next generation sequencing of bone marrow samples did not demonstrate prevalence of clonal progression in the eltrombopag arm (and some subjects losing mutations early during treatment) with respect to placebo. QOL-E MDS-specific, total, and treatment outcome index scores significantly improved with increasing platelet counts and this was also true for EORTC QLQ-C30 role function, cognitive function, and social function scores. In conclusion, this is the first randomized, placebo-controlled clinical trial that evaluates the efficacy and safety of eltrombopag in lower risk MDS. Eltrombopag is not associated with a risk of progression, is clinically safe and effective in raising platelet counts, reducing bleeding events and in sustaining quality of life and symptoms in lower-risk MDS.

B11

HEALTH-RELATED QUALITY OF LIFE IN TRANSPLANT-INELIGIBLE REAL-LIFE MULTIPLE MYELOMA PATIENTS TREATED WITH BORTEZOMIB-MELPHALAN-PREDNISONE (VMP) *vs* LENALIDOMIDE-DEXAMETHASONE (RD)

M. D'Agostino[1], S. Bringhen[1], P. Curci[1], M. Marcatti[1], A.P. Falcone[1], M. Michieli[1], M. Grasso[1], F. Pane[1], E. Rivolti[1], F. Cattel[2], M. Mirabile[1], F. Fioritoni[1], M.T. Petrucci[1], V. Cotugno[2], A. Capra[1], S. Pezzatti[1], M.L. Mosca Siez[1], M. Cantonetti[1], G. Margiotta Casaluci[1], A.M. Cafro[1], R. Floris[1], M. Offidani[1], G. Pietrantuono[1], A. Evangelista[3], M. Boccadoro[1], A. Larocca[1]

[1]European Myeloma Network Italy; [2]S.C. Farmacia Ospedaliera, A.O.U. Città della Salute e della Scienza di Torino; [3]Unit of Clinical Epidemiology, A.O.U. Città della Salute e della Scienza di Torino and CPO Piemonte, Italy

Background: Multiple Myeloma (MM) is a chronic disease, and patients (pts) receive long-lasting treatment. Thus, the impact on health-related quality of life (HRQoL) may be burdensome, especially in elderly pts. Bortezomib-melphalan-prednisone (VMP) and lenalidomide-dexamethasone (Rd) represented standard-of-care treatments for transplant-ineligible (NTE) newly diagnosed (ND)MM pts before the introduction of daratumumab upfront. No prospective data are available comparing HRQoL in pts receiving VMP *vs* Rd in a randomized fashion.

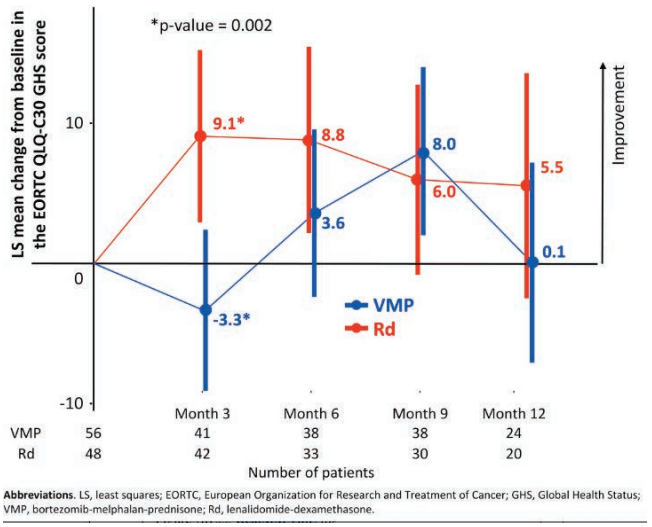
Aims. We conducted an analysis of Patient Reported Outcomes (PROs) in the context of a randomized multicenter phase IV trial (Real MM Trial, NCT03829371; funded by the Italian Medicines Agency AIFA - Independent Research).

Methods: NTE NDMM pts were randomized to receive 9 VMP cycles *vs* continuous Rd. PROs were collected and analyzed using the validated EORTC QLQ-C30 scales and the EQ-5D-5L visual analog scale (VAS) instruments. The PROs analyses included pts from the interim analysis (median follow-up: 14.0 months).

Results: At the data cut-off (17-12-2021), 104 pts (56 in the VMP arm and 48 in the Rd arm) had available PROs and were eligible for the analysis. Overall, 46% of pts had >75 years and 40% were frail. No differences in terms of baseline characteristics and response rates were found in the VMP *vs* Rd arms. Mean baseline values were similar in the two arms. After the start of treatment, Global Health Status (GHS) was significantly worse with VMP *vs* Rd at 3 months (-3.3 *vs* +9.0; *P*=0.002), while from the 6-month time point onwards no differences can be found due to an improvement in GHS in the VMP arm (Figure 1). The physical functioning scale was worse in the VMP *vs* Rd arm at 3 (-7.8 *vs* +0.04; *P*=0.070) and 6 months (-8.2 *vs* +3.2; *P*=0.013), with no differences in later time points. The role functioning scale behaved similarly (-5.9 *vs* +5.2 at 3 months with VMP *vs* Rd; *P*=0.038). VMP also increased fatigue (+9.4 *vs* -2.7; *P*=0.015), nausea (+8.6 *vs* +2.8; *P*=0.04), and appetite loss (+12.0 *vs* -3.0; *P*=0.007) at 3 months, with an improvement in the symptoms thereafter. In both arms, pain decreased after treatment. The EQ-5D-5L VAS scale showed a significantly worse score in the VMP *vs* Rd arm at 3 months (-7.9 *vs* +1.7; *P*=0.005).

Conclusion: A comparison of PROs in real-life NTE NDMM pts treated with VMP *vs* Rd showed a worse HRQoL in the VMP arm early in the treatment course that improved thereafter.

Figure. Change in Global Health Status from baseline according to treatment arm



Abbreviations. LS, least squares; EORTC, European Organization for Research and Treatment of Cancer; GHS, Global Health Status; VMP, bortezomib-melphalan-prednisone; Rd, lenalidomide-dexamethasone.

Figure 1.

B12

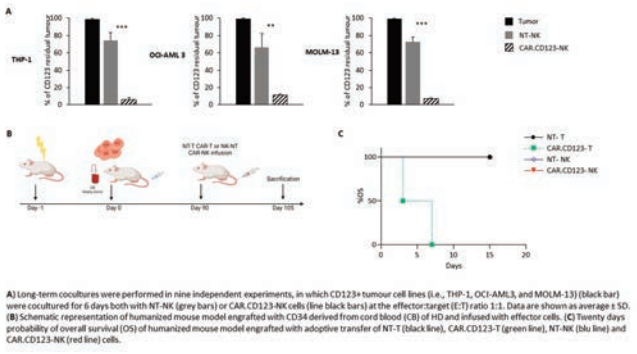
CAR.CD123-NK "OFF-THE-SHELF" CELL THERAPY AS INNOVATIVE TREATMENT FOR ACUTE MYELOID LEUKAEMIA WITH HIGH EFFICACY AND NEGLIGIBLE TOXICITY

S. Caruso[1], R. Ciccone[1], S. Manni[1], M. Guercio[1], M. Pezzella[1], S. Di Cecca[1], M. Sinibaldi[1], L. Iaffaldano[1], A. Pitisci[1], G. Buonsante[1], A. Sarcinelli[1], A. Silvestris[1], F. Del Bufalo[1], M. Algeri[1], P. Merli[1], E. Velardi[1], G. Volpe[1], B. De Angelis[1], C. Quintarelli[1,2] F. Locatelli[1 3]

[1]Department Onco-Haematology, and Cell and Gene Therapy, Bambino Gesù Children Hospital, IRCCS, Rome, Italy; [2]Department of Clinical Medicine and Surgery, University of Naples Federico II, Naples, Italy; [3]Dipartimento Materno-Infantile e Scienze Urologiche, Sapienza University of Rome, Rome, Italy

We documented that Acute Myeloid Leukaemia (AML) cells show a high expression levels of the CD123 antigen, this finding providing the biological basis to develop an antigen-specific Chimeric Antigen Receptor (CAR) cell therapy to treat this heterogeneous clonal disorder. CAR T-cells could represent an innovative approach for AML, but its applicability needs to take in account toxicity related to Cytokine Release Syndrome (CRS), especially in patients with high leukaemia burden, and the "vein to vein" time is often unfeasible in patients with relapsed/resistant AML. In this scenario, an allogeneic cell approach with Natural Killer (NK) cells could provide advantages to immediately treat AML patients without graft-versus-host reactivity. We thus engineered NK cells to express a 2nd-generation CAR directed against CD123 (CAR.CD123 NK) designed to enhance NK-cell cytotoxicity against CD123+ AML cells. Compared to un-modified NK cells (NT-NK), CAR.CD123 NK cells showed a significantly greater anti-leukaemia activity not only towards CD123+ tumour cell lines (6,5%±10%, 5,1%±5% and 7,7%±9% of residual THP1, MOLM-13 and OCI-AML3 cells; $p<0.01$ *vs* NT-NK) but also against CD123+ primary AML patient's blasts (p=0,0005). Moreover, CAR.CD123 NK cells resulted into improved the Overall Survival (OS) of human CD123+ THP-1 leukaemia-bearing immune-deficient mice, with 81% alive mice at the end of experiment (Day +60). Importantly, low level of CD123 is also reported on bone marrow (BM) cells from healthy donors, representing one of major issue for the clinical translation of adoptive therapy targeting this antigen. To evaluate the comparative on-target off-tumour effect of CAR.CD123 T and NK cells, we developed a humanized mouse model engrafted with cord blood-derived CD34+ cells. All mice infused with CAR.CD123 T cells died by day 5, developing toxicity against primary human BM cells with a decrease number of total hCD45 cells, and in particular, of hCD34+CD38- hematopoietic stem cells. By contrast, the treatment with CAR.CD123 NK cells was not associated to toxicity, with all the mice surviving at the end of the experiment, and no reduction of circulating CD123+ cells in peripheral blood or in BM.

Our *in vitro* and *in vivo* data prove the feasibility of this innovative ''off-the-shelf'' therapeutic strategy based on CAR NK cells targeting CD123+ leukemic cells in AML, in the absence of toxicity against normal haematopoietic precursors.



A) Long-term cocultures were performed in nine independent experiments, in which CD123+ tumour cell lines (i.e., THP-1, OCI-AML3, and MOLM-13) (black bar) were cocultured for 6 days both with NT-NK (grey bars) or CAR.CD123-NK cells (line black bars) at the effector:target (E:T) ratio 1:1. Data are shown as average ± SD. **(B)** Schematic representation of humanized mouse model engrafted with CD34 derived from cord blood (CB) of HD and infused with effector cells. **(C)** Twenty days probability of overall survival (OS) of humanized mouse model engrafted with adoptive transfer of NT-T (black line), CAR.CD123-T (green line), NT-NK (blu line) and CAR.CD123-NK (red line) cells.

Figure 1.

ORAL COMMUNICATIONS

Myeloproliferative neoplasms I

C001

PELABRESIB (CPI-0610) MONOTHERAPY IN PATIENTS WITH MYELOFIBROSIS (MF) — UPDATE OF CLINICAL AND TRANSLATIONAL DATA FROM THE ONGOING MANIFEST TRIAL

F. Passamonti[1], M. Kremyanskaya[2], J. Mascarenhas[2], F. Palandri[3], A.M. Vannucchi[4], S. Verstovsek[5], C. Harrison[6], P. Bose[5], G.J. Schiller[7], R.K. Rampal[8], M.W. Drummond[9], V. Gupta[10], A. Patriarca[11], N. Granacher[12], J. Scandura[13], W. Prejzner[14], L. Teichmann[15], N. Curto-García[6], R. Hoffman[2], G. Colak[16], J. Cui[16], M. Talpaz[17]

[1]Università degli Studi dell'Insubria; [2]Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai; [3]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli"; [4]Azienda Ospedaliero Universitaria Careggi; [5]MD Anderson Cancer Center; [6]Guy's and St Thomas' Hospital; [7]David Geffen School of Medicine at UCLA; [8]Memorial Sloan Kettering Cancer Center; [9]Beatson West of Scotland Cancer Centre; [10]Princess Margaret Cancer Centre, University of Toronto; [11]Azienda Ospedaliero Universitaria Maggiore della Carità di Novara SCDU Ematologia; [12]ZNA Stuyvenberg Antwerpen; [13]Weill Cornell Medicine; [14]Medical University of Gdańsk; [15]Universitätsklinikum Bonn; [16]Constellation Pharmaceuticals a MorphoSys Company; [17]Rogel Cancer Center, The University of Michigan

Pelabresib (CPI-0610) is an investigational, selective, oral small-molecule BET inhibitor that can modify the expression of genes involved in NF-κB signaling in MF. We present updated results from Arm 1 of MANIFEST (NCT02158858), an ongoing Phase 2 study investigating pelabresib monotherapy in pts with advanced MF who are refractory/resistant, ineligible or intolerant to Janus kinase inhibitor (JAKi) treatment and typically have a very poor prognosis.

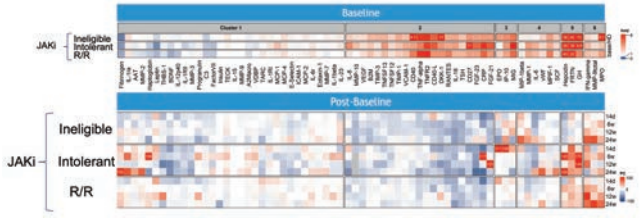


Figure 1. ELISA analysis of a panel of 68 plasma cytokines at baseline compared with HD, and response of cytokines to treatment longitudinally after 14 days and 6, 12 and 24 weeks of treatment. Cytokines were clustered in six groups based on their overexpression pattern at baseline compared with HD and downregulation by pelabresib. D, day; ELISA, enzyme-linked immunosorbent assay; HD, healthy donor; JAKi, Janus kinase inhibitor; PC, percentage change; R/R, refractory/resistant; w, week.

Eligibility criteria are MF pts with DIPSS risk category of ≥Int-2, platelets ≥75 × 10^9/L and ≥2 symptoms measurable (score ≥1) per MFSAF v4.0. Additional criteria include RBC transfusion dependence (TD) per Gale criteria in the TD cohort or spleen volume of ≥450 cc by CT/MRI in the non-TD cohort. Pts were enrolled as TD (defined as ≥2 U RBCs/month over 12 wks) and non-TD if TD criteria were not met. The primary endpoint in TD cohort is RBC transfusion independence (TI; defined as no transfusion for ≥12 wks) and ≥35% spleen volume reduction (SVR35) at Wk 24 in the non-TD cohort. Secondary endpoints include number of pts with ≥50% total symptom score reduction (TSS50) per MFSAF v4.0 at Wk 24 and safety. Changes in plasma levels of proinflammatory cytokines and bone marrow morphology/fibrosis were assessed as exploratory endpoints. As of 10 Sep 2021, 86 pts were treated for a median treatment follow-up of 22 months (reverse Kaplan–Meier estimate, 95% confidence interval [CI] 10–25). In the TD cohort, 16% (4/25) pts achieved TI. In the non-TD cohort, 18% (7/38) pts achieved SVR35 at Wk 24. At Wk 24, 11% (7/64) of all evaluable pts achieved SVR35 (median change: –24%), and 28% (18/64) pts achieved TSS50 (median change: –40%). 86 pts were evaluable for safety. The most common (≥20%) TEAEs of any grade were thrombocytopenia (38%), diarrhea (34%), nausea and asthenic conditions (33% each), anemia (24%), dysgeusia and respiratory tract infections (23% each), pruritus (22%) and constipation (21%). For the exploratory endpoint, 68 cytokines evaluated in plasma samples were clustered in six groups based on their overexpression pattern at baseline compared with healthy donors and downregulation by pelabresib. 21 cytokines associated with MF pathogenesis were the most strongly downregulated by Day 14 and sustained through 24 wks (Figure 1).

Data suggest pelabresib monotherapy was generally well tolerated and demonstrate signals of clinical activity in MF pts refractory/resistant, ineligible or intolerant to JAKi treatment.

C002

AN OBSERVATIONAL, MULTICENTER, RETROSPECTIVE ANALYSIS OF PATIENTS WITH BLASTIC PLASMACYTOID DENDRITIC CELL NEOPLASM TREATED WITH TAGRAXOFUSP IN THE EUROPEAN EXPANDED ACCESS PROGRAM

E. Angelucci[1], E. Deconinck[2], M. Anant[3], D. Manteigas[4], M. Riggi[3], M. Herling[5]

[1]IRCCS Ospedale Policlinico San Martino; [2]Regional University Hospital of Besançon; [3]. Stemline Therapeutics Switzerland GmbH; [4]Cmed (Clinical Research Services); [5]University Hospital Leipzig

Introduction: Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare aggressive hematologic malignancy, with poor prognosis. It is characterized by clonal expansion of plasmacytoid dendritic cells which overexpress CD123, the interleukin-3 receptor alpha. Primary sites are skin and bone marrow, followed by peripheral blood, lymph nodes, viscera, and central nervous system. Tagraxofusp (TAG), a CD123-targeted therapy, was approved by the European Medicines Agency in 2021. In 2019, a Global Expanded Access Program (EAP) was implemented to provide access to patients (pts) prior to regulatory authorization of TAG in realworld practice.

Aims: We conducted a European multicenter non-interventional, retrospective analysis of BPDCN pts treated with TAG. Main objectives were rates of complete response, and incidence and severity of capillary leak syndrome (CLS). Secondary outcomes included rate of pts bridged to stem cell transplantation, progression-free survival, overall survival, safety (incidence and severity of adverse events [AEs]), and number of TAG doses administered in each cycle.

Methods: The main inclusion criterion was diagnosis of BPDCN, confirmed by hematopathology with established marker panels (including CD123). Training of physicians, nurses, and pharmacists was mandatory before delivering the treatment. Analysis included all pts enrolled in the European EAP from August 2019 to December 2021. Pts received TAG intravenous infusions at 12 mcg/kg/day on days 1–5 of a 21-day cycle. Hospitalization was required only for the first cycle.

Results: Overall, 76 adult (median age 64 years, range 21–85) and 4 pediatric pts (1, 4, 14, and 16 years) were included across 57 European centers in Germany, France, Italy, Switzerland, UK, Spain, and Austria. Most pts were male (78%), representing real-world distribution. Sixty-three pts received TAG as first-line and 17 pts as second-line or beyond. The median number of cycles was 2.5 (range 1–8) in first-line and 2.6 (range 1–13) in second-line or beyond. No deaths due to CLS were re-

ported. Analysis is ongoing and data on safety, efficacy, number of pts transplanted, and time-related parameters will be reported at the meeting.

Conclusion: This is the largest retrospective analysis of real-world clinical practice outside of a clinical trial in BPDCN pts treated with TAG. Preliminary results confirm the feasibility and safety of TAG, allowing for administration also in elderly pts, with manageable safety.

C003

MYELOID NEOPLASMS-ASSOCIATED GENE MUTATIONS IN 639 PATIENTS WITH POST-POLYCYTHEMIA VERA AND POST-ESSENTIAL THROMBOCYTHEMIA MYELOFIBROSIS: A STUDY OF THE MYSEC COHORT

B. Mora[1,2], P. Guglielmelli[3], A. Kuykendall[4], M. Maffioli[1], G. Rotunno[3], R.S. Komrokji[4], F. Palandri[5], J.-J. Kiladjian[6], A. Iurlo[7], G. Auteri[5], D. Cattaneo[7], V. De Stefano[8], S. Salmoiraghi[9,10], T. Devos[11], F. Cervantes[12], M. Merli[1], A. Campagna[13], G. Benevolo[14], M. Brociner[1], F. Albano[15], J. Gotlib[16], M. Caramella[17], M. Ruggeri[18], D.M. Ross[19], F. Orsini[20], C. Pessina[20], I. Colugnat[20], F. Pallotti[2,20], T. Barbui[10], L. Bertù[2], M.G. Della Porta[13], A.M. Vannucchi[3], F. Passamonti[1,2]

[1]Hematology, Ospedale di Circolo, ASST Sette Laghi; [2]Department of Medicine and Surgery, University of Insubria; [3]Center for Research and Innovation of Myeloproliferative Neoplasms, University of Florence; [4]. Malignant Hematology Department, Blood and Marrow Transplantation, HLee Moffitt Cancer Center and Research Institute; [5]Institute of Hematology, Azienda Ospedaliero-Universitaria S.Orsola-Malpighi di Bologna; [6]Centre d'Investigations Cliniques, Hôpital Saint-Louis et Université Paris Diderot; [7]UOC Hematology, Foundation IRCCS Ca'-Granda Ospedale Maggiore Policlinico; [8]Hematology, Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore; [9]Hematology and Bone Marrow Transplant Unit, ASST Papa Giovanni XXIII; [10]FROM Research Foundation, ASST Papa Giovanni XXIII; [11]Department of Hematology, University Hospitals Leuven and Department of Microbiology and Immunology, Laboratory of Molecular Immunology (Rega Institute), Ku Leuven; [12]Hematology Department, Hospital Clinic, IDIBAPS, University of Barcelona; [13]Cancer Center, IRCCS Humanitas Clinical and Research Center; [14]Hematology, Azienda Universitario-Ospedaliera Città della Salute e della Scienza di Torino; [15]Hematology - Dept. of Emergency and Organ Transplantation, University of Bari; [16]Division of Hematology, Stanford Cancer Institute, Stanford University School of Medicine; [17]Hematology, ASST Grande Ospedale Metropolitano Niguarda; [18]Hematology Department, San Bortolo Hospital; [19]Haematology Directorate, SA Pathology, Royal Adelaide Hospital and Flinders Medical Centre; [20]Laboratory of Cytogenetics and Molecular Biology, Ospedale di Circolo, ASST Sette Laghi.

Background: Polycythemia vera (PV) and essential thrombocythemia (ET) could evolve to post-PV (PPV-) and post-ET (PET-) myelofibrosis (MF), called secondary MF (SMF). In primary MF, non-driver myeloid neoplasms-associated gene variants (M-GVs) influence clinical decisions. In SMF, information on M-GVs is scant.

Aims and methods: To assess the pattern of distribution of M-GVs, their correlations with SMF subtype and driver mutations in SMF patients of the MYSEC (*Myelofibrosis Secondary to PV and ET*) project, studied by NGS (Next Generation Sequencing). Associations were investigated by Chi-square or Fisher exact test.

Results: 639 NGS-annotated SMF patients entered the analysis. Clinical and molecular differences at diagnosis between PPV- (n=290) and PET-MF (n=349) cases confirmed previous findings of the MYSEC project (PMID: 27885272). A total of 441 (69%) patients showed M-GVs: 223 (51%) had one, 137 (31%) two, 52 (12%) three, 23 (5%) four and 6 (1%) five or more. PPV-MF subjects reported more frequently one M-GV, while those with PET-MF at least three ($p=0.02$). Mean number of M-GVs was 1.4 per patient (range, 0-7). In detail, it was 1.2 (range, 0-4) and 1.5 (range, 0-7) per patient in PPV- and in PET-MF, respectively ($p=0.01$). The most frequent (≥5% of dataset) M-GVs involved: *ASXL1* (n=181, 41%), *TET2* (n=145, 33%), *DNMT3A*(n=49, 11%), *TP53* (n=43, 10%), *EZH2* (n=39, 9%), *SF3B1* (n=31, 7%), *U2AF1* (n=29, ~7%), *ZRSR2* (n=27, 6%), *CBL* and *RUNX1* (n=21 each, 5%). In PET-MF there was a significantly higher frequency of M-GVs in *ASXL1* (47% *vs* 34%, $p=0.01$), *SRSF2* (5% *vs* 1%, $p=0.01$), *U2AF1* (9% *vs* 4%, $p=0.04$) and *CBL* (7% *vs* 2%, $p=0.01$) compared to PPV-MF. The latter was significantly associated with *ETV6* alterations (5% *vs* 1% in PET-MF, $p=0.04$). As regards driver mutations, we found an association between "triple negative" status (TN) and M-GVs in *SETBP1* (38%, $p=0.002$), *IDH2* (25%, $p=0.02$), *EZH2* (25%, $p=0.05$) and *SRSF2* (25%, $p=0.01$). Figure 1 shows the frequency of M-GVs in the MYSEC cohort, distinguished by SMF subtype (a) and driver mutations (b).

Conclusion: 69% of 639 SMF patients presented at least one M-GV. The most frequent (≥10%) M-GVs were in *ASXL1*, *TET2*, *DNMT3A* and *TP53*. Different pathways of progression among PPV- and PET-MF have been disclosed. TN cases clustered with potentially targetable M-GVs. This is the first study exploring the mutational landscape of a wide cohort of SMF patients, paving the way for further investigations on the topic.

Figure 1. Pattern of distribution of myeloid neoplasms-associated gene variants in 441 patients with post-polycythemia vera and post-essential thrombocythemia myelofibrosis, distinguished by diagnosis (a) and driver mutation status (b).

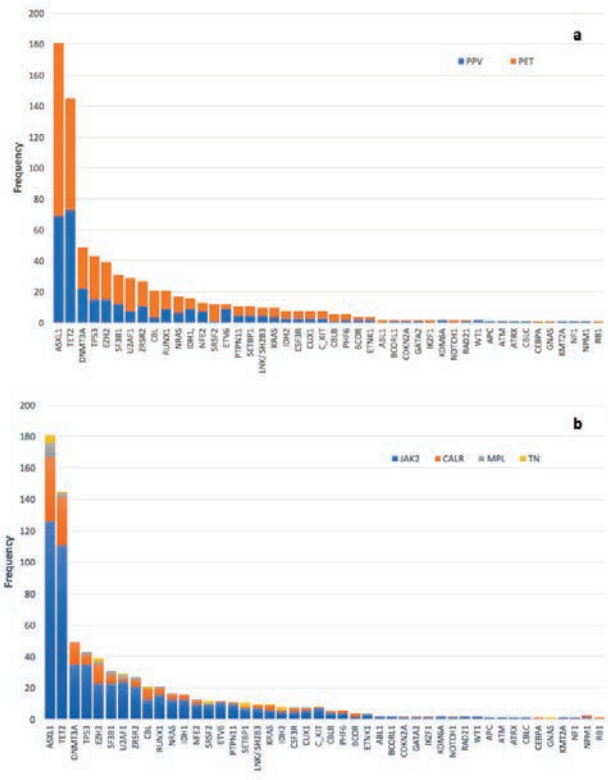


Figure 1.

C004

NAVITOCLAX PLUS RUXOLITINIB IN JAK-INHIBITOR-NAIVE PATIENTS WITH MYELOFIBROSIS: PRELIMINARY SAFETY AND EFFICACY IN A MULTICENTER, OPEN-LABEL PHASE 2 STUDY

F. Passamonti[1], J. Foran[2], A. Tandra[3], V. De Stefano[4,5], M.L. Fox[6], A. Mattour[7], M.F. McMullin[8], A.C. Perkins[9], G. Rodriguez-Macías[10], H. Sibai[11], Q. Qin[12], J. Potluri[12], J. How[13]

[1]Department of Medicine and Surgery, University of Insubria; [2]Mayo Clinic; [3]Indiana Blood and Marrow Transplant; [4]Section of Hematology, Department of Radiological and Hematological Sciences, Catholic University; [5]Fondazione Policlinico Universitario Agostino Gemelli IRCCS; [6]Department of Hematology, Hospital Universitari Vall d'Hebron, Experimental Hematology, Vall d'Hebron Institute of Oncology (VHIO), Vall d'Hebron Hospital Campus; [7]Henry Ford Hospital; [8]Centre for Medical Education, Queen's University Belfast; [9]Australian Centre for Blood Diseases, Monash University and The Alfred Hospital; [10]Department of Hematology, Hospital General Universitario Gregorio Marañón; [11]Medical Oncology and Hematology, Princess Margaret Cancer Centre, University of Toronto; [12]AbbVie Inc; [13]Division of Hematology, McGill University Health Center

Background: Ruxolitinib(RUX), a Janus kinase(JAK) 1/2 inhibitor, is the current standard of care for patients (pts) with myelofibrosis (MF) that improves splenomegaly and disease symptoms with limited impact on disease biology. Many pts lose response over time, highlighting an unmet need for novel therapies. Navitoclax (NAV) is an oral, small-molecule inhibitor of BCL-X_L and BCL-2 that has a synergistic effect when used in combination with JAK inhibitors to enhance apoptosis. This ongoing, open-label, multicenter, phase 2 trial (NCT03222609) is evaluating the efficacy and safety of NAV with/without RUX in pts with MF. Here, we report results from JAK inhibitor-naïve pts treated with NAV+RUX.

Table 1. Key endpoints.

	NAV+RUX n/N (%)
SVR_{35} at wk 24	11/21 (52)
SVR_{35} at any time post BL	16/21 (76)
TSS_{50} from baseline to wk 24	5/16 (31)
TSS_{50} at any time post BL	9/16 (56)
Total anemia response[a]	6/11 (55)
Reduction in bone marrow fibrosis grade from BL by ≥1grade at any time post BL	6/20 (30)

BL, baseline. aTotal anemia response = transfusion independence (TI) in pts with BL Hb<10 g/dl with Hb increase ≥ 2g/dl + TI in those who were transfusion-dependent at BL

Methods: Enrolled pts had primary or secondary MF with splenomegaly (DIPSS ≥INT-1) and did not receive prior JAK-2 therapy or bromodomain and extraterminal motif (BET) inhibitors. Pts initiated NAV at 100 mg QD or 200 mg QD if baseline (BL) platelet count was ≤150 × 10^9/L or >150 × 10^9/L, respectively. RUX was given BID with starting dose based on BL platelet count per local label. The primary endpoint was spleen volume reduction of ≥35% (SVR_{35}) from BL at wk 24. Key secondary endpoints were ≥50% reduction in total symptom score (TSS_{50}), bone marrow (BM) fibrosis reduction, and anemia response. Adverse events(AEs) were monitored throughout the study.

Results: As of Oct 04, 2021, 32 pts received NAV+RUX. Median duration of f/u was 6.1 (range, 1.9 — 18.6) mos. 28 (88%) pts received NAV 200 mg and 4 (13%) received 100 mg OD. Median age was 69 (44 — 83) yrs, and median spleen volume was 1889.08 cm^3 (645.6 — 7339.6). Median NAV and RUX exposures were 24.1 (5.1 — 80.9) and 20.1 (0.1 — 80.1) wks, respectively. 31 (97%) pts reported ≥1 AE (Grade ≥3 AEs, 25 [78%]; serious AEs, 6 [19%]). Most common Grade ≥3 AEs were anemia (34%), thrombocytopenia (31%), and neutropenia (19%). 3 (9%) and 2 (6%) pts reported an AE leading to NAV and RUX discontinuation, respectively, and 2 (6%; 1 PD, 1 cardiac disorder unrelated to NAV) AEs led to death ≤30 days after last NAV dose. SVR_{35} was achieved by 52% of evaluable pts at wk 24 (SVR_{35} in INT-2, 50%; HR, 33%) and by 76% at any time on treatment (Table). Median time to first SVR_{35} was 12.1 (11 — 47) wks.

Conclusions: The combination of NAV+RUX was well tolerated and demonstrated early and robust reductions in spleen volume, anemia, and BM fibrosis in pts without prior JAK-2 inhibitor exposure. SVR_{35}, TSS_{50}, and BM fibrosis improved over time.

C005

NAVITOCLAX MONOTHERAPY IN PTS WITH MYELOFIBROSIS PREVIOUSLY TREATED WITH JAK-2 INHIBITORS: SAFETY AND TOLERABILITY

V. Pullarkat[1], A. Cruz-Chacon[2], S. Gangatharan[3], A. Melnyk[4], G.A. Palumbo[5], M. Bellini[6], S. Tantravahi[7], Q. Qin[8], J. Potluri[8], P. Vachhani[9]

[1]Department of Hematology and Hematopoietic Cell Transplantation, City of Hope National Medical Center; [2]Hospital Centro Comprensivo de Cancer Universidad de Puerto Rico; [3]University of Western Australia, Department of Haematology, Fiona Stanley Hospital; [4]Texas Oncology-Abilene; [5]Dipartimento di Science Mediche Chirurgiche e Tecnologie Avanzate "GF Ingrassia", Università degli Studi di Catania; [6]ASST Papa Giovanni XXIII; [7]University of Utah and Huntsman Cancer Institute; [8]AbbVie Inc; [9]O'Neal Comprehensive Cancer Center at UAB

Background: Navitoclax(NAV) is an oral, small-molecule inhibitor of BCL-X_L and BCL-2 under evaluation in the ongoing, multicenter, multicohort, phase 2 trial(REFINE;NCT03222609). Previous results from REFINE Cohort 1a indicated that addition of NAV to ruxolitinib(RUX) resulted in clinically meaningful outcomes with acceptable safety profile in myelofibrosis(MF) pts with progression or suboptimal response to RUX monotherapy.

Methods: This open-label phase2 trial enrolled MF pts into 4 cohorts according to JAKi experience; all pts provided informed consent. Cohort2 pts had discontinued prior JAKi therapy and received NAV monotherapy orally at the starting dose of 100mg/day(QD) or 200mgQD if baseline(BL) platelet count was 75–150×10^9/L or>150×10^9/L, respectively. Eligible pts had previously received JAKi for≥12W, or≥28days with red blood cell transfusion dependence(≥2 units/mo for 2 mos) or with ≥grade 3 adverse event(AE) of thrombocytopenia or anemia, while on JAKi; all pts had splenomegaly. The primary endpoint was spleen volume reduction ≥35%(SVR_{35}) from BL assessed centrally at W24. Secondary endpoints included change in bone marrow fibrosis grade(per European consensus grading system) and anemia response(per International Working Group criteria). Exploratory endpoints included response duration of SVR_{35} and OS.

Results: As of Oct 4, 2021, 30 enrolled pts received NAV. Table shows BL demographic/clinical characteristics. 14 pts(47%) started NAV at a dose of 100mgQD and 16 pts(53%) started at 200mgQD. The median f/u time was 4.2 mos(range 0.2-15.5). Median duration of NAV exposure was 9.4W(range 0.1–67.1). 27 pts(90%) experienced≥1 AE, the most common being thrombocytopenia(n=16; 53%), diarrhoea(n=9; 30%), nausea(n=8; 27%). 63% of pts experienced grade≥3 AEs: thrombocytopenia(n=11; 37%) and anemia(n=7; 23%) being the most common. 3

pts had serious AEs: dyspnea, hypoxia, and pulmonary hypertension. 15 pts(50%) experienced NAV dose reductions and 16 pts(53%) NAV interruptions . 3 pts had AEs leading to NAV discontinuation(pulmonary hypertension, increased bilirubin and low platelets). 8 pts discontinued NAV due to: AE(n=3), consent withdrawal(n=1), physician decision(n=1), disease relapse(n=1), and PD(n=2). 2 pts died>30 days after the last dose of NAV.

Conclusions: NAV monotherapy in MF pts after prior JAKi had a similar safety profile as previously reported in Cohort 1a. Efficacy analyses are underway to evaluate the activity of NAV monotherapy in MF pts.

Table 1. Baseline demographic and clinical characteristics

Characteristics	Cohort 2 (NAV monotherapy) (N=30)	Cohort 1a (NAV and RUX) (N=34)
Age, median (range), years	68 (55–84)	68 (42–86)
Male	19 (63)	23 (68)
MF type		
Primary MF	14 (47)	16 (47)
Secondary MF	15 (50)	18 (53)
Post-PV	8 (27)	13 (38)
Post-ET	7 (23)	5 (15)
Response to prior RUX at screening		
Refractory	11 (37)	17 (52)
Relapsed	4 (13)	2 (6)
Disease progression	3 (10)	0
Intolerance	6 (20)	0
Other[a]	6 (20)	14 (42)
Unknown	0	1
Duration of prior RUX exposure, median (range), wks	100 (11–496)	91 (19–391)
ECOG PS		
0	8 (27)	16 (47)
1	17 (57)	18 (53)
2	5 (17)	0
Spleen volume, median (range), cm^3	1646 (865–4044)	1695 (466–5047)
Hemoglobin		
<10 g/dL	19 (63)	11 (32)
≥10 g/dL	11 (37)	23 (68)
DIPSS at study entry		
Low	1 (3)	2 (6)
Intermediate-1	5 (17)	16 (47)
Intermediate-2	15 (50)	12 (35)
High	9 (30)	4 (12)

Data are n (%) unless otherwise specified. aIncluded stable disease, PV progressed to MF, ET progressed to MF, not applicable, and other. DIPSS, dynamic international prognostic scoring system; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, essential thrombocythemia; MF, myelofibrosis; PV, polycythemia vera.

Acute myeloid leukemia I

C006

RESULTS OF THE 6-YEAR FOLLOW-UP OF THE GIMEMA AML1310 TRIAL: A RISK- ADAPTED, MRD-DIRECTED THERAPY FOR YOUNG ADULTS WITH NEWLY DIAGNOSED ACUTE MYELOID LEUKEMIA

F. Buccisano[1], A. Piciocchi[2], R. Palmieri[1], V. Arena[2], A. Candoni[3], L. Melillo[4], V. Calafiore[5], R. Cairoli[6], P. de Fabritiis[7], G. Storti[8], P. Salutari[9], F. Lanza[10], G. Martinelli[11,12], M. Luppi[13], S. Capria[14], L. Maurillo[1], M.I. Del Principe[1], G. Paterno[1], M.T. Voso[1], T. Ottone[1], M.A. Irno Consalvo[1], M. Divona[1], S. Lavorgna[1], P. Fazi[2], M. Vignetti[2], W. Arcese[1,15] , S. Amadori[2], A. Venditti[1]

[1]Ematologia, Dipartimento di Biomedicina e Prevenzione, Università di Roma "Tor Vergata", Roma; [2]GIMEMA Foundation, Rome, Italy; [3]Hematology, Azienda Sanitaria Universitaria Integrata di Udine, Udine, Italy; [4]Fondazione IRCCS Casa Sollievo della Sofferenza, UO di Ematologia, San Giovanni Rotondo (FG), Italy; [5]Ospedale Ferrarotto, Catania, Italy; [6]Ospedale Niguarda Ca Granda, Milan, Italy; [7]Ospedale S. Eugenio, Rome, Italy; [8]Azienda Ospedaliera S.G. Moscati, Avellino, Italy; [9]Azienda USL di Pescara, Pescara, Italy; [10]Ospedale S. Maria delle Croci, Ravenna, Italy; [11]Istituto Tumori della Romagna, Meldola, Italy; [12]Policlinico S. Orsola-Malpighi, Bologna, Italy; [13]Dipartimento di Scienza Mediche e Chirurgiche Materno-Infantili e dell'Adulto, Università degli studi di Modena e Reggio Emilia, Modena, Italy; [14]Dipartimento di Biotecnologie Cellulari ed Ematologia, Ematologia Università degli Studi Sapienza, Rome, Italy; [15]Rome Transplant Network, Roma, Italy

In the AML1310 trial, we performed a comprehensive risk assessment, based on the integration of cytogenetic/genetic data and measurable residual disease (MRD) status, to optimize patients' (pts) therapeutic post-remission allocation. According to NCCN2009 risk-stratification, favorable-risk (FR) pts were to receive an autologous stem cell transplant (AuSCT); poor-risk (PR) pts were to receive an allogeneic stem cell transplant (ASCT); intermediate-risk (IR) pts were to receive AuSCT or ASCT based on MRD status, measured by flow cytometry after consolidation therapy. At that stage of analysis, 2-year overall (OS) and disease-free survival (DFS) of the whole series was 56% and 54%, respectively (74% and 61% in the FR category, 42% and 45% in the PR category, 79% and 61% in the IR MRD-negative category, 70% and 67% in the IR MRD-positive category) (Venditti, Blood 2019). With an extended median follow-up of 6 years, we wanted to evaluate the long-term impact on outcome (OS and DFS) of the strategy explored in the AML1310 trial. Three hundred-61/500 pts (72%) achieved a CR, 342/361 completed the consolidation phase and were allocated: 165 (48%) to ASCT (122 PR, 43 IR MRD-positive) plus 23 rescued after salvage therapy; 150 (44%) to AuSCT (115 FR, 35 IR MRD-negative) plus 27 IR pts (8%) with no LAIP. Overall, 110/177 (62%) and 130/188 (71%) AuSCT or ASCT candidates received it. Probability of 6-years OS and DFS of the whole series was 43.6% and 43.1%, respectively (58.5% and 50.1% in the FR category, 35.4% and 38.0% in the PR category; 43.1% and 45.7% in the IR category, 32.5% and 29.1% in the no LAIP one [Figure 1A-B]). Cumulative incidence of relapse (CIR) was 39.7%. Six-year CIR was 42.2%, 37.6% and 35.8% in the FR, PR and IR category, respectively [Figure 1C]. Six-year CIR of no LAIP pts was 50% [Figure 1C]. Six-year CIR and non relapse mortality (NRM) of transplanted pts was 35.6% and 14.9%, respectively [Figure 1D]. With an extended follow-up of 6 years, the present analysis confirms the long-term advantage of a risk- adapted, MRD-driven strategy to implement the post-remission therapeutic decision. For FR or IR-MRD negative

categories, an excess of toxicity was prevented by delivering an AuSCT, whereas the vast majority of PR and IR- MRD positive pts received an ASCT, with a remarkable 6-year OS and DFS benefit. Based on the present knowledge, an MRD- directed approach is being explored also in FR patients, in the GIMEMA AML1819 trial.

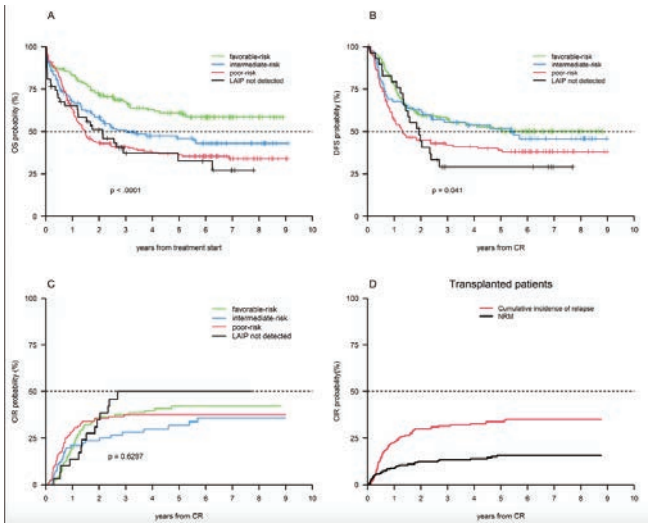


Figure 1.

C007

10-DAY DECITABINE *VS* CONVENTIONAL CHEMOTHERAPY ("3+7") FOLLOWED BY ALLOGRAFTING (HSCT) IN AML PATIENTS ≥60 YEARS: A RANDOMIZED PHASE III STUDY OF THE EORTC LEUKEMIA GROUP, GIMEMA, CELG, AND GMDS-SG

A. Venditti[1], P. Wijermans[2], M. Kicinski[3], S. Chantepie[4], W.Van der Velden[5], R. Noppeney[6], L. Griskevicius[7], A. Neubauer[8], M. Crysandt[9], R.Vrhovac[10], M. Luppi[11], S. Fuhrmann[12], E. Audisio[13], A. Candoni[14], A. Vekhoff[15], R. Foà[16], G. Gaidano[17], D. van Lammeren-Venema[18], W. Posthuma[19], M. Hoogendoorn[20], A. Giraut[21], M. Stevens-Kroef[22], J. Jansen[23], E. Ammatuna[24], J.P. Vilque[25], R. Wäsch[26], H. Becker[26], N. Blijlevens[27], F. Baron[28], S. Suciu[29], S. Amadori[1], G. Huls[30], M. Lübbert

[1]Department of Biomedicine and Prevention, University of Rome Tor Vergata, Rome, Italy; [2]Department of Hematology, Haga Teaching Hospital, 2545 CH, The Hague, The Netherlands; [3]The European Organisation for Research and Treatment of Cancer (EORTC) Headquarters, Brussels, Belgium; [4] Department of Hematology, Centre Hospitalo-Universitaire de Caen, Caen, France; [5]Department of Hematology, Radboud University, Nijmegen, The Netherlands; [6]Universitätsklinikum Essen, Klinik für Hämatologie, Essen, Germany; [7]Department of Hematology, Oncology and Transfusion Medicine Center, Vilnius University Hospital Santaros Klinikos, Vilnius University, Vilnius, Lithuania; [8]Department of Internal Medicine, Hematology, Oncology and Immunology, Philipps University Marburg and University Hospital Gießen and Marburg, Campus Marburg, Marburg, Germany; [9]Department of Hematology, Oncology, Hemostasiology and Stem Cell Transplantation, Medical Clinic IV, University Hospital RWTH Aachen, Aachen, Germany; [10]Department of Haematology, University Hospital Centre Zagreb, Zagreb, Croatia; [11]Dipartimento di Scienze Mediche e Chirurgiche Materno-Infantili e dell'Adulto, University of Modena and Reggio Emilia, Azienda Ospedaliera Universitaria, Modena, Italy; [12]Department of Hematology and Oncology, HELIOS Hospital Berlin-Buch, Kiel, Germany; [13]S.C. Ematologia 2, Torino, Italy; [14]Clinica Ematologica Azienda Sanitaria Universitaria Integrata di Udine, Udine, Italy; [15]Service d'Hématologie Clinique et de Thérapie cellulaire, Hôpital Saint Antoine, APHP, Paris, France; [16]Ematologia, Dipartimento di Medicina Traslazionale e di Precisione, "Sapienza" Università di Roma, Rome, Italy; [17]Division of Hematology, Department of Translational Medicine, Università del Piemonte Orientale and Azienda Ospedaliero-Universitaria Maggiore della Carità, Italy; [18] Department of Hematology, Haga Teaching Hospital, 2545 CH, The Hague, The Netherlands; [19]Department of Internal Medicine, Reinier de Graaf Hospital, Delft, The Netherlands; [20]Department of Hematology, Medical Center Leeuwarden, Leeuwarden, The Netherlands; [21]The European Organisation for Research and Treatment of Cancer (EORTC) Headquarters, Brussels, Belgium; [22]Radboud University Medical Center, Nijmegen, The Netherlands; [23]Radboud Institute Molecular Studies, Radboud University Medical Center, Nijmegen, The Netherlands; [24]University Medical Center Groningen, Groningen, The Netherlands; [25]Institut d'Hématologie de Basse-Normandie, Centre François Baclesse, Avenue général Harris 14000 Caen, France; [26]Department of Hematology, Oncology and Stem Cell Transplantation, Faculty of Medicine, University Medical Center Freiburg, University of Freiburg, Freiburg, Germany; [27]Department of Hematology, Radboud University, Nijmegen, The Netherlands; [28] GIGA-I3 and CHU, University of Liège, Liège, Belgium; [29]The European Organisation for Research and Treatment of Cancer (EORTC) Headquarters, Brussels, Belgium; [30]University Medical Center Groningen, Groningen, The Netherlands; [31]Department of Hematology, Oncology and Stem Cell Transplantation, Faculty of Medicine, University Medical Center Freiburg, University of Freiburg, Freiburg, Germany

Promising outcomes have been reported for the 10-day decitabine (DEC) schedule, suggesting it may be a better treatment prior to HSCT as compared to intensive chemotherapy (IC). To compare efficacy and safety profile of 10-day DEC followed by allografting to IC followed by allografting in older fit AML pts, an international multicenter, open-label randomized phase III trial (NCT02172872) was conducted. DEC was administered 10 days consecutively in cycle 1 (20 mg/m^2), 10 or 5 days in subsequent cycles (depending on bone marrow blast clearance at day 28). IC treatment was daunorubicin 60 mg/m2 x 3 days, cytarabine 200 mg/m2 x 7 days, followed by 1-3 additional chemotherapy cycles. Pts who had an HLA-matched donor and at least stable disease were encouraged to undergo HSCT after ≥ 1 treatment cycle. Pts from the DEC arm not receiving HSCT could continue DEC treatment. Pts were randomized 1:1, and the primary study endpoint was overall survival (OS). Between 12/2014 and 8/2019, 606 pts were randomized, 303 in each arm. Median follow-up was 4.0 yrs. Median age was 68 yrs (range 60-81), 34% of pts were ≥70 yrs old and 57% were male, 21% and 32% had good and adverse ELN 2017 risk profile, respectively. A median of 3 DEC cycles (Q1-3: 2-5) and 2 IC cycles (Q1-3: 1-2) were administered. The CR/CRi rate was 48% with DEC and 61% with IC. HSCT as part of the protocol was performed in 122 pts (40%, 30 of them not in CR/CRi) from the DEC and 118 (39%, 11 of them not in CR/CRi) from the IC arm, and in 52% in both arms at any time. The OS was not significantly different between DEC and IC groups (HR=1.04, 95% confidence interval [CI]: 0.86-1.26; 2-sided p=0.68). The median OS was 15 months (95% CI: 13-18) in the DEC and 18 months (95% CI: 14-22) in the IC group. The OS rates (%) after 1, 2, 3 and 4 years for the DEC and IC groups were 58 *vs* 59, 38 *vs* 40, 30 *vs* 33, and 26 *vs* 30, respectively. Grade 3-5 adverse events reported before HSCT were: febrile neutropenia (37% for DEC *vs* 57% for IC), thrombocytopenia (24% for DEC *vs* 32 % for IC), oral mucositis (2% for DEC *vs* 10% for IC), diarrhea (1% for DEC *vs* 8% for IC), neutropenia (19% for DEC *vs* 13% for IC). The 30-day mortality rate was 3.6% for DEC and 6.4% for IC. The incidence of grade 5 treatment-related adverse events after HSCT was comparable in both treatment arms (25% for DEC and 22% for IC). In conclusion, treatment with DEC resulted in a similar OS and HSCT rate but a better safety profile compared to IC in older AML pts ≥60 yrs, eligible for IC.

C008

METABOLIC SIGNATURE AT ONSET PREDICTS OVERALL SURVIVAL IN AMLS' PATIENTS

N.I. Noguera[1,2], G Catalano[1,2], A. Zaza[1,2], C. Banella[2,3], T. Ottone[1,2], E. Pelosi[4], S. Travaglini[1,2], M. Divona[4], M.I. Del Principe[1], F. Buccisano[1], L. Maurillo[1], E. Ammatuna[5], U. Testa[4], A. Venditti[1], M.T. Voso[1,2]

[1]Department of Biomedicine and Prevention, University of Rome Tor Vergata; [2]Santa Lucia Foundation, I.R.C.C.S.; [3]Department of Health Sciences, University of Florence and Meyer Children's University Hospital; [4]Department of Hematology, Oncology and Molecular Medicine, Istituto Superiore di Sanità; [5]Department of Hematology, University of Groningen, University Medical Center Groningen

We compared Acute Myeloid Leukemias (AMLs) cells metabolism to hematopoietic progenitors and normal maturing bone marrow cells, to acquire useful prognostic information and to uncover actionable therapeutic targets. Analyzed by Seahorse Bioscience XFe96 analyzer, primary AML blast cells feature a lower spare respiratory capacity (SRC) (p=0.02) and lower glycolytic capacity (p=0.02) as compared to early progenitors/precursors (EP/P) from cultured CB CD34+ cells at day 7 of culture (N7, mostly promyelocytes) (Figure 1 a and b).

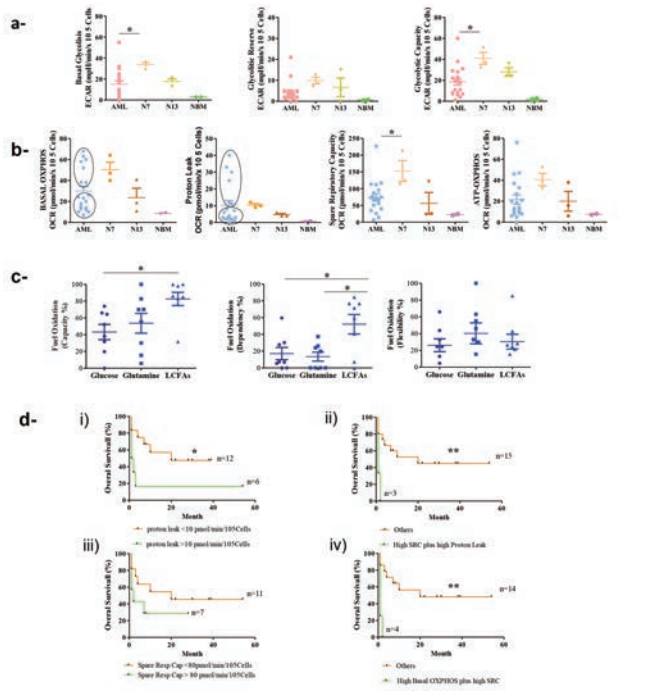


Figure 1. Metabolic characterization in AML primary blast and early progenitors/precursors (EP/P) from cultured normal cord blood CD34+ cells. Profile of the glycolytic activity measured in primary blast from AML patients, EP/P at day 7 (N7, mostly a promyelocyte population) and at day 13 (N13 mostly neutrophil granulocyte) and in normal bone marrow (NBM) (a) Histograms represent basal glycolysis, glycolytic reserve and glycolytic capacity. (b) Histograms represent basal respiration, spare respiratory capacity, proton leak and mitochondrial ATP production. (c) Evaluation of the mitochondrial fuel used by primary blast obtained from AML patients using the XF Myto Fuel Flex Test. The graphs shown dependency, capacity, and flexibility of the cells to oxidize three mitochondrial fuels: glucose (pyruvate), glutamine and long-chain fatty acids (LCFAs). (d) Kaplan-Meier estimates of overall survival in AML patients according to: i) proton leak levels (cut off 10 pmol/min/10^5 cells), ii) high proton leak plus high SRC, iii) SRC levels (cut off 80 pmol/min/105 cells) or high basal OXPHOS plus high SRC. (basal OXPHOS cut off 35 pmol/min/10^5 cells). The tick marks indicate the times at which events (death) were recorded. Data are presented as mean ± SD. Statistical analysis for a, b and c was performed using the Anova t test and Tukey's Multiple Comparison Test. For d we used Log-rank (Mantel-Cox) test. *p ≤ 0.05, *p ≤ 0.005.

Primary AML blasts depend mainly on fatty acids (p<0.05); they display a great flexibility, switching to glucose or glutamine to meet their energetic needs (Figure 1c). We could define two populations (cut off value 10 pmol/min/x105 cells): one with higher (22±12 pmol/min/x10^5 cells) and on with lower (3±2 pmol/min/x105 cells) p<0.0001 levels of proton leak. The cases with higher proton leaks levels presented a reduced, extremely short, overall survival (OS) (p=0.048). We defined two SRC populations (cut off value 80 pmol/min/x105 cells): higher (124±47 pmol/min/x10^5 cells) and lower (52±25 pmol/min/x105cells) levels (p=0.0001). The cases with higher proton leak and SRC levels presented a reduced OS p=0.007. We observed two populations, with higher (54±12 pmol/min/x10^5 cells) and lower (16±6 pmol/min/x105cells) basal OXPHOS levels (p=0.0001). Higher SRC plus higher basal OXPHOS was associated with significant OS shortage (p=0.002), indicating greater aggressiveness and resistance to therapy (Figure 1d). Patients with high mitochondrial respiration had a significantly higher myeloid cell leukemia 1 protein (MCL1) expression. We ascertained that MCL1 directly binds to Hexokinase II (HK2) on the outer mitochondrial membrane (OMM) affecting its stability. We demonstrate that high proton leak and high mitochondrial respiration at onset, arguably with the concourse of MCL1/HK2 action, is significantly linked with a shorter OS in AMLs' patients. Our data describe a new function of MCL1 protein in AMLs' cells, forming a complex with HK2 co-localized to the voltage dependent anion channel (VDAC) on the OMM, promoting glycolysis and OXPHOS, conferring metabolic plasticity and resistance to therapy. The lower spare respiratory capacity and lower glycolytic capacity of AML patients blast respect to normal early hematopoietic precursors suggest a therapeutic window to use glycolytic and mitochondrial inhibitors in resistant AML patients.

C009

ABSTRACT NOT PUBLISHABLE

C010

GIMEMA AML1310 STUDY vs HOVON-SAKK-132 TRIAL FOR YOUNG ADULTS WITH NEWLY DIAGNOSED ACUTE MYELOID LEUKEMIA: AN ANCHORED MATCHING-ADJUSTED INDIRECT COMPARISON OF SURVIVAL OUTCOMES

A. Piciocchi[1], M. Messina[1], V. Arena[1], R. Palmieri[2], M.I. Del Principe[2], L. Maurillo[2], F. Bonifazi[3], P. Fazi[1], M. Vignetti[1], F. Buccisano[2], A. Venditti[2]

[1]GIMEMA Foundation; [2]Ematologia, Dipartimento di Biomedicina e Prevenzione, Università di Roma "Tor Vergata"; [3]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Italy

Introduction: Anchored MAIC (Matching-Adjusted Indirect Comparison) is an ITC (Indirect Treatment Comparison) method adjusting for cross-trial heterogeneity in patient demographic or disease that are believed to be either prognostic or treatment effect modifiers. In this analysis, two trials for young adults with newly diagnosed acute myeloid leukemia (AML) were compared by an anchored MAIC. To this end, the GIMEMA AML1310 (risk-adapted, MRD-directed therapy, Venditti et al – Blood 2019) was weighted for the aggregated patients' characteristics from the experimental arm of the HOVON-SAKK-132 trial (addition of lenalidomide to intensive treatment, Lowenberg et al - Blood Adv 2020). The aim of this pilot analysis was to test the feasibility to compare individual patients' data with aggregated published results.

Methods: Patient-level data from GIMEMA AML1310 (n=500) and aggregated data from HOVON-SAKK-132 (Lenalidomide arm, n=388) trials were used to conduct an anchored MAIC. AML1310 patients were analysed according to the ELN2017 risk classification and patients without risk assessment (n=55) were excluded to align with comparison trial.

Patients from AML1310 study were weighted to balance with baseline characteristics from the Hovon cohort. Accordingly, weighted Overall and Disease-free survival (w-OS, w-DFS) estimates as well as rates of early death within 30 and 60 days were computed.

Results: Four potential effect modifiers were identified and used for adjustment: age, ELN2017 criteria, wbc count and WHO/ECOG performance status. Median follow-up for the AML1310 study was 6 years. Median w-OS and w-DFS were 2.9 (95%CI: 1.7, 5.2) and 2.0 (95%CI: 1.3, 5.7) years, respectively. These estimates were slightly lower than those documented in the most recent report of the AML1310 trial (Venditti et al – ASH2021: median OS 3.8 years and median DFS 3.7 years) (Figure 1) and lower than the results obtained by the Hovon group (median follow-up 41 months, median OS not reached). Weighted early death within 30 and 60 days and observed values were comparable.

Conclusion: The MAIC method allowed a robust comparison of two clinical trials for the treatment of adult AML patients. After adjustment, survival outcomes of AML1310 cohort were slightly lower than the observed estimates. This pilot analysis underlined the potentiality of this statistical method. Indeed, it could be useful to compare with high accuracy studies with strong differences in the selection of patients.

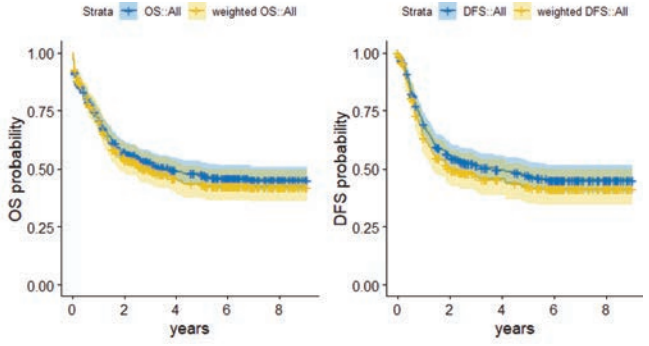


Figure 1. Observed and weighted Overall Survival (OS) and Disease Free Survival (DFS) of the GIMEMA AML1310 study.

Anemias and myelodysplastic syndromes

C011

INHIBITION OF COMPLEMENT C1S BY SUTIMLIMAB IN PATIENTS WITH COLD AGGLUTININ DISEASE (CAD): EFFICACY AND SAFETY RESULTS FROM THE RANDOMIZED, PLACEBO-CONTROLLED PHASE 3 CADENZA STUDY

W. Barcellini[1], A. Röth[2], S. Berentsen[3], S. D'Sa[4], B. Jilma[5], M. Michel[6], I.C. Weitz[7], M. Yamaguchi[8], J. Nishimura[9], J.M.I. Vos[10], M. Storek[11], N. Wong[11], P. Patel[11], X. Jiang[11], D. Vagge[12], M. Wardęcki[13], F. Shafer[11], M. Lee[11], C.M. Broome[14]

[1]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico; [2]Department of Hematology and Stem Cell Transplantation, West German Cancer Center, University Hospital Essen, University of Duisburg-Essen; [3]Department of Research and Innovation, Haugesund Hospital; [4]UCLH Centre for Waldenström's Macroglobulinemia and Related Conditions, University College London Hospitals NHS Foundation Trust; [5]Department of Clinical Pharmacology, Medical University of Vienna; [6]Henri-Mondor University Hospital, Assistance Publique-Hôpitaux de Paris, UPEC; [7]Jane Anne Nohl Division of Hematology, Department of Medicine, Keck School of Medicine of USC; [8]Ishikawa Prefectural Central Hospital, Department of Hematology; [9]Osaka University; [10]Department of Hematology, Amsterdam UMC & Sanquin; [11]Sanofi; [12]IQVIA; [13]Sanofi; [14]Division of Hematology, MedStar Georgetown University Hospital

Introduction: Sutimlimab (SUT), an anti-C1s IgG4 antibody, selectively inhibited the classical pathway, halted hemolysis, and improved hemoglobin (Hb) and quality of life (QoL) in recently transfused patients (pts) with CAD (single-arm CARDINAL study [NCT03347396]). CADENZA (NCT03347422) is a randomized, double-blind, placebo (PBO)-controlled Phase 3 study in CAD pts with no recent transfusions. We report results from Part A (26wks).

Methods: Enrolled CAD pts (screening Hb ≤10g/dL, elevated bilirubin, transfusion independence ≥6 months, ≥1 CAD symptom) were randomized 1:1 to receive SUT (<75kg, 6.5g; ≥75kg, 7.5g; n=22) or PBO (n=20) on d0 and d7, then biweekly. Composite primary endpoint (SUT *vs* PBO) was the fraction of pts with Hb raised ≥1.5g/dL at treatment assessment timepoint (TAT; mean of Wks23, 25, 26) and avoidance of transfusion and study-prohibited CAD therapy (Wks5–26). Secondary endpoints: hemolysis markers, FACIT-Fatigue, pharmacodynamics (PD). Safety was evaluated.

Results: Significantly more SUT pts met the composite primary endpoint: 16 (73%) *vs* 3 (15%) PBO pts (p<0.001). SUT, but not PBO, rapidly increased mean Hb and FACIT-Fatigue and normalized mean bilirubin by Wk1 (Figure 1), and improved additional hemolysis markers up to TAT. The mean (SE) difference at TAT in Hb and FACIT-Fatigue between SUT and PBO was 2.6 (0.4) g/dL and 8.9 (2.5) points (both p<0.001). Improvements with SUT coincided with normalized C4 levels, reduced classical pathway activity and CH50 levels, and no change in C1q levels; PBO arm PD outcomes were unaffected. Solicited anemia symptom incidence fell from baseline to Wk26 for all components with SUT; only weakness and shortness of breath reduced by PBO (Figure 1). 21 (96%) SUT and 20 (100%) PBO pts had ≥1 treatment-emergent adverse event (TEAE); 3 (14%) SUT and 1 (5%) PBO pt had ≥1 serious TEAE; 1 cerebral venous thrombosis was assessed as SUT-related by investigator. Serious infections were reported (0 meningococcal). No serious TEAE of hypersensitivity, anaphylaxis, systemic lupus erythematosus, or death was reported overall. 3 SUT pts (0 PBO) discontinued for TEAE: acrocyanosis and Raynaud's phenomenon (n=1); increased blood IgM (n=1); infusion-related reaction (n=1). TEAEs reported more often with SUT *vs* PBO (difference ≥3 pts): hypertension,

headache, Raynaud's phenomenon, rhinitis, acrocyanosis.

Conclusions: Sutimlimab, but not PBO, halted hemolysis, significantly improved Hb and QoL, and was generally well tolerated.

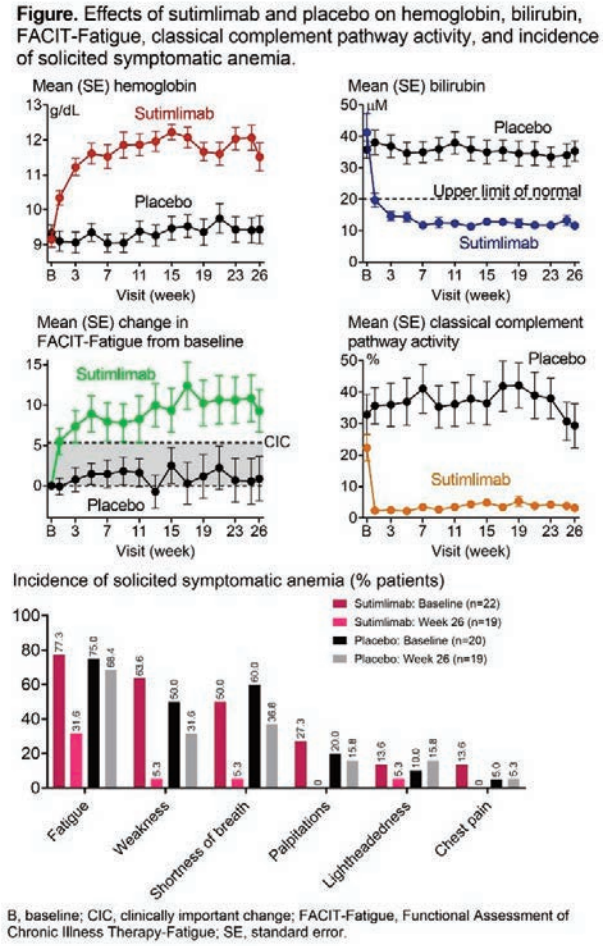


Figure. Effects of sutimlimab and placebo on hemoglobin, bilirubin, FACIT-Fatigue, classical complement pathway activity, and incidence of solicited symptomatic anemia.

B, baseline; CIC, clinically important change; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue; SE, standard error.

Figure 1.

C012

MANAGEMENT OF AUTOIMMUNE HAEMOLYTIC ANAEMIA DURING PREGNANCY AND POST-PARTUM: AN INTERNATIONAL MULTI-CENTRE EXPERIENCE

M. Bortolotti[1], N.N. Fantini[2], A. Glenthoj[3], M. Michel[4], M. Napolitano[5], S. Raso[6], F. Chen[7], V. McDonald[7], I. Murakhovskaya[8], J.M.I. Vos[9], A. Patriarca[10], M.E. Mingot-Castellano[11], D. Prati[2], W. Barcellini[2], B. Fattizzo[1,2]

[1]Department of Oncology and Oncohaematology, University of Milan; [2]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico; [3]Department of Hematology, Copenhagen University Hospital - Rigshospitalet; [4]Centre de Référence Maladies Rares sur les Cytopénies Auto-Immunes del'Adulte, Centre Hospitalier Universitaire Henri Mondor, Assistance Publique-Hôpitaux de Paris, Créteil Université ParisEst Créteil; [5]Haematology Unit, Thrombosis and Haemostasis Reference Regional Center, University of Palermo; [6]Department of Hematology and Rare Diseases, Azienda Ospedaliera Ospedali Riuniti Villa Sofia-Cervello; [7]Clinical Haematology, Barts Health National Health Service Trust, Queen Mary University; [8]Department of Hematology and Oncology, Albert Einstein College of Medicine/Montefiore Medical Center; [9]Department of Hematology, Amsterdam University Medical Center, University of Amsterdam; [10]Department of Translational Medicine, Azienda Ospedaliera-Universitaria "Maggiore della Carità", University of Eastern Piedmont; [11]Servicio de Hematología, Hospital Universitario Virgen del Rocio

Autoimmune haemolytic anaemia (AIHA) during pregnancy is a rare finding, and few is known about its management and maternal and foetal outcomes.

Through a multicentric retrospective study, we identified 38 pregnancies occurred in 28 women from 1997 to 2021 in 10 European centres in Italy, Denmark, France, the Netherlands, USA, and Spain. All included patients had a previous AIHA history or developed/exacerbated AIHA during gestation or postpartum. AIHA was classified according to the direct antiglobulin test and we focused on disease severity, treatment requirement and maternal/foetal outcomes.

Table 1.

N° of observed pregnancies	38
Age at AIHA diagnosis (years); mean (range)	27 (3-39)
Age at pregnancy (years); mean (range)	32 (21-41)
AIHA type	
- warm	10
- warm IgG+C	8
- atypical	5
- mixed	3
- cold	2
Hb at AIHA onset (g/dL); median (range)	6,4 (3,1 – 8,7)
LDH at AIHA onset (UI/L); median (range)	588 (269-1631)
Maternal complications	
- early miscarriages	4
- preeclampsia	2
- placental detachment	1
- PPROM	1
- biliary colic	1
- postpartum infection	1
Foetal complications	
- foetal growth restriction	3
- death	2
- AIHA of the new-born	1
- Preterm birth	1
- Neurologic sequelae	1
- Perinatal respiratory distress	1
AIHA therapies	
- steroids	20
- blood transfusions	10
- immunoglobulins injection	4
- rituximab (post-partum)	4
- cyclosporin (post-partum)	1
Anti-thrombotic prophylaxis	
- with heparin	5
- with ASA	2
- none	18

AIHA, autoimmune haemolytic anaemia; ASA, acetylsalicylic acid; C, complement; Hb, haemoglobin; LDH, lactate dehydrogenase; PPROM, preterm premature rupture of membranes.

We registered 18 warm AIHA, 2 cold agglutinin disease, 3 mixed and 5 atypical forms (Table 1). Mean age at pregnancy was 32 years. AIHA diagnosis predated pregnancy in 15 women and had required at least 1 therapy line in all of them, and >2 lines in 12 (rituximab, N=7; cytotoxic immunosuppressants, N=6; splenectomy, N=5). Among these 15 patients, 6 relapsed during pregnancy, 3 postpartum and 9 were on treatment at pregnancy start (steroids, N=8; cyclosporine, N=1; azathioprine, N=1). A patient with a previous AIHA, relapsed as immune thrombocytopenic purpura during pregnancy. Further 8 patients developed AIHA during gestation and 2 postpartum. A patient had an AIHA onset during the postpartum of the 1st pregnancy and relapsed during the 2nd one. In the 20 women experiencing AIHA during pregnancy/postpartum, median Hb and LDH levels were 6,4 g/dL and 588 UI/L, respectively. Management consisted in blood transfusions (N=10) and prompt establishment of steroid therapy+/-IVIG (N=20), all with response (complete N=13, partial N=7). After delivery, rituximab was necessary in 4 patients and cyclosporine was added in one. Anti-thrombotic prophylaxis was given in 7 patients. Overall, we registered 10 obstetric complications (10/38,

26%), of whom 8 occurred during active haemolysis and treatment for AIHA. Nine foetal adverse events (9/38, 24%) were reported, including 2 perinatal deaths. The latter both occurred in women on active AIHA therapy and were secondary to a massive placental detachment and a symptomatic SARS-CoV-2 infection.

AIHA developing/reactivating during pregnancy or postpartum is rare (about 5%) but mainly severe requiring steroid therapy and transfusions. Importantly, severe maternal and foetal complications may occur in up to 26% of cases mostly associated with active disease, pinpointing the importance of maintaining a high level of awareness.

C013

MDS WITH 5Q-: A REAL-LIFE STUDY OF DETERMINANTS OF OUTCOME AND LONG-TERM RESPONSE TO LENALIDOMIDE ON BEHALF OF GROM-L

C. Gurnari[1,2], A. Piciocchi[3], S. Soddu[3], F. Bonanni[1], E. Scalzulli[4], P. Niscola[5], A. Di Veroli[6], A.L. Piccioni[7], M. Piedimonte[8], G. Maiorana[8], P. Salutari[9], L. Cicconi[10], M. Santopietro[11], S. Gumenyuk[12], C. Sarlo[13], S. Fenu[7], A. Tafuri[8], R. Latagliata[6], L. Fianchi[14], L. Maurillo[1], F. Buccisano[1], M. Breccia[4], M.T. Voso[1,15] on behalf of GROM-L (Gruppo Romano-Laziale MDS)

[1]Department of Biomedicine and Prevention, University of Rome Tor Vergata, Rome, Italy; [2]Department of Translational Hematology and Oncology Research, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH, USA; [3]Italian Group for Adult Hematologic Diseases (GIMEMA) Foundation, Rome, Italy; [4]Department of Translational and Precision Medicine-Az., Policlinico Umberto I-Sapienza University, Rome, Italy; [5]Hematology Unit, Sant'Eugenio Hospital, Rome, Italy; [6]Belcolle Hospital, Viterbo, Italy; [7]Hematology Dep. Az. Osp., San Giovanni-Addolorata, Rome, Italy; [8]Hematology, "Sant'Andrea" Hospital-Sapienza, University of Rome, Roma, Italy; [9]Hematology, Pescara Hospital, Pescara, Italy; [10]Hematology, ASL Roma 1, Rome, Italy; [11]Hematology and Hematopoietic Stem Cells Transplant Unit, AO San Camillo-Forlanini, Rome, Italy; [12]Hematology Unit, Department of Research and Clinical Oncology, IRCCS Regina Elena National Cancer Institute, Rome, Italy; [13]Hematology and Stem Cell Transplantation Unit, University Campus Bio-Medico, Rome, Italy; [14]Department of Hematology, Fondazione Policlinico Universitario Agostino Gemelli-IRCCS, Roma, Italy; [15]Santa Lucia Foundation, IRCCS, Neuro-Oncohematology, Rome, Italy

Lenalidomide (LENA) represents the first example of targeted treatment in MDS. Indeed, patients harbouring 5q- exhibit an exquisite sensitivity to this agent, which derives its therapeutic window from specifically targeting the haploinsufficient CK1α protein, in addition to displaying indirect immunomodulatory effects and upregulating other disease-associated pathways. While clinical trials have shown erythroid responses in up to 80% of 5q-MDS resulting in improved outcomes, specific predictors of response and survival have not been established. Here, we report on a large, real-life cohort of 5q-MDS (n=106) enrolled in the GROM-L observational study between 2002-2021 to unravel clinical determinants of outcomes and response to LENA (Figure 1A).

Overall, patients had a median age at diagnosis of 73 years (47-89) and majority were females (M:F=0.29, Figure 1B). According to the peculiar clinical picture of 5q-MDS, thrombocytosis was noticed in 20% of cases, 5q- was the sole cytogenetic abnormality in 91% of patients, and megakaryocytic dysplasia was present in 80% of marrow evaluations. Based on IPSS-R, virtually all MDS (96%) grouped into very low to intermediate-risk categories.

Patients received LENA at a starting dose of 10mg/day for 21 days/Q28 for a median of 21 cycles (2-131). Hematological and cytogenetic responses were registered in 84% and 79% of cases respectively, with 80% achieving transfusion independence. The occurrence of thrombocytopenia (33%) or neutropenia (51%) required dose adjustments in 45% of cases. With a median follow-up of 5.6 years (1.9-6.9), the 6-year overall survival (OS) and progression-free survival (PFS) were 67% (56-80) and 53% (43-67; Figure 1C-D), respectively. Older age at MDS onset (HR=1.08;p<.001) negatively affected OS, whereas increased creatinine levels (HR=3.18;p=.010) and the occurrence of myeloid toxicity (HR=2.25;p=.013) impacted PFS. Of note, absolute thrombocytopenia (<100x10^9/L) during first cycles reduced the odds of long-term (>36 months) LENA response (OR=0.10;p=.003). At last follow-up, solid malignancies were registered in 7% of our cohort, whereas leukemia progression occurred in 27% of patients at a median of 4 years (0.7-11) from diagnosis, with a lower risk for LENA responders (HR=0.25;p=.001). Our long-term, real-life data confirm the significant advantage of LENA treatment in 5q-MDS observed in the setting of clinical trials, and the association with prolonged survival when compared to the pre-LENA era.

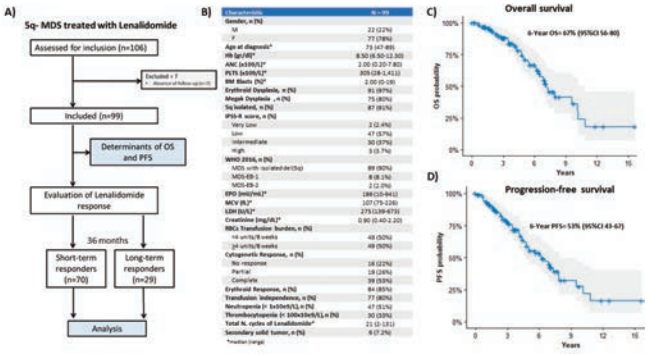


Figure 1.

C014

EXPRESSION OF IMMUNE CHECKPOINT PROTEINS IN BONE MARROW AND PERIPHERAL BLOOD OF MDS/AML PATIENTS: A SINGLE-CENTRE PIVOTAL STUDY

N.L. Parrinello[1], A. Romano[1,2], A. Duminuco[1], S. Marino[1], C. Giallongo[1,3], I. Dulcamare[1], C. Vetro[1], C. Maugeri[1], M. Parisi[1], G. Sapuppo[1], G.A. Palumbo[1,3] F. Di Raimondo[1,2]

[1]UOC Ematologia, AOU Policlinico Rodolico San Marco, Catania, Italy; [2]Dipartimento di Chirurgia e Specialità Medico Chirurgiche, Università degli Studi di Catania, Catania, Italy; [3]Dipartimento Ingrassia, Università degli Studi di Catania, Catania, Italy

Background: Immune checkpoint (IC) inhibitors (ICI) are promising agents with potential effect in myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML). However, there is not enough data on the pattern of IC expression in MDS/AML bone marrow, though this can guide future therapies with ICI.

Aim: To assess the immunosuppressive subpopulation in matched BM and peripheral blood (PB) of newly diagnosed MDS/AML patients.

Methods: We prospectively evaluated 45 newly diagnosed patients from January through December 2021, including 28 MDS (low risk, n=7; INT-1, n=11; INT-2, n=5, high-risk, n=5), 9 therapy-related MDS and 8 AML compared to 8 healthy subjects, after signing informed consent for participation in research. We used a flow-cytometry multi-colour panel in each patient to define IC expression on T- and NK-cells (CD3, CD16), myeloid precursors (CD117, CD34), myeloid-derived suppressor cells (CD15, CD11b, CD14, HLA-DR, CD33, Lox-1). In each population we assessed expression of TIM3, LOX-1 and CD274 (PDL-1).

Results: In BM populations of high-risk MDS, the ligand PD-L1 predominated, with most of the PD-1L ligand expression observed on granulocytes in the process of their differentiation from myeloid precursors.

PDL1 was virtually not expressed on the cells of the monocytic series.

In PB, but not in the BM, the percentage of immunesuppressive LOX-1+granulocytes was increased in high-risk MDS compared to low-INT-1-INT2 and healthy controls (respectively, 2.2 ±0.3 *vs* 1.4 ±0.2 *vs* 0.5 ±0.1 AU, p=0.01). Similarly, the expression of LOX1 was increased on granulocytes in the process of their differentiation from myeloid precursors. Median fluorescence of intensity (MFI) of TIM3 expression on blastswas higher in high-risk MDS and AML (mean MFI ± standard deviation, SD, 2.7 ±0.9) than INT-2 (2.1±0.3) and INT-1/low risk MDS patients (1.5 ±0.5, p=0.002). In high-risk MDS and AML patients, TIM3 expression on T cells was higher than low-INT-1-INT2 and healthy controls (respectively, 1.3 ±0.4 *vs* 0.9 ±0.2 *vs* 0.5 ±0.1 AU, p=0.01), with no significant differences in each individual patient, between BM and PB. Thus, we found that IC system plays a role in high-risk MDS. Moreover, the expression of ligands is mainly realized during maturation of blast cells into granulocytes, which are the main population expressing these inhibitory molecules. The leading role in the suppression of the T-cell response in MDS is played by the PD-1-PDL1 system. Thus, the data obtained justify the trials of dual blockade with anti-PD-1 and anti-TIM3 agents in high-risk MDS.

C015

DIRECT ORAL ANTICOAGULANTS IN β-THALASSEMIA: SINGLE CENTER EXPERIENCE

S. Raso, L. Pitrolo, G. Calvaruso, A. Giangreco, R. Di Maggio, D. Renda, A. Vitrano, G. Carmina, A. Maggio

Department of Hematology and Rare Diseases, Azienda Ospedaliera Ospedali Riuniti Villa Sofia-Cervello, Italy

Patients (PTs) with β-thalassemia (β-T) show a chronic hypercoagulability state due to numerous factors including iron overload, splenectomy and hemolysis. 1 The increased thrombotic risk requires often the use of antiplatelet and/or anticoagulant agents as primary and/or secondary prophylaxis. Despite the extensive use of direct oral anticoagulants (DOACs) during the past years, there is limited experience regarding the use of DOAC in PTs with β-T. The studies on DOACs efficacy and safety have not been conducted in PTs with β-T, however, they may represent a valuable alternative, given the reduced half-life, decreased bleeding risk and incidence of venous thromboembolism (VTE) recurrences and/or stroke respect to Vitamin K antagonist (VKA). Only one study tested the effectiveness of rivaroxaban in a very small group of PTs with β-T and non-valvular atrial fibrillation (NVAF).2 We herein present our experience with the use of DOACs in 17 PTs with β-T: 9 with NVAF and 8 with history of deep vein thrombosis and pulmonary embolism. The characteristics of PTs are reported in Table 1. Data was obtained from review of electronic health records. The median time of treatment was 36 months (IQR, 16-51) and during the follow-up 3 (18%) PTs developed superficial vein thrombosis and 1 (5%) intestinal ischemia while none experienced major bleeding, including PTs treated also with antiplatelet drug. Thrombosis and thromboembolic events were treated with low-molecular-weight-heparin (LMWH). Three of 4 PTs showed increased platelet count at the moment of thrombotic episode. None of PTs with thrombotic complications was switched to another DOAC. Seven out of 17 PTs started DOACs as frontline anticoagulant treatment and 10/17 PTs were shifted from a previous VKA treatment. Rivaroxaban was the drug most often used while dabigatran was unemployed. Frequently PTs with β-T present liver and kidney damage, due both to course of the disease and to hemosiderosis. Therefore, using DOACs could be challenging, as they have been reported to cause hepatotoxicity. However, in our experience there were no adverse events reported and no need of dose modification in any PT. In conclusions, in our experience anticoagulant therapy with DOACs in PTs with βT is well tolerated, apparently safe, without recurrences of thrombotic events and significant bleeding complications. Further studies are therefore needed in order to assess the role of DOACs in PTs with β-T.

References

1. Pennell, D.J.; et al. Cardiovascular function and treatment in thalassemia major: A consensus statement from the American Heart Association. Circulation 2013, 128, 281–308.
2. Apostolou, C. et al. Rivaroxaban Use in Patients with Hemoglobinopathies. Hemoglobin 2017, 41, 223-224.

Table 1. Characteristics of patients who received DOACs

Patients' characteristics	n=17
Age (median, IQR) years	49 (42-55)
Sex M/F	8/9
βTM / βTI	9/8
Time of follow-up (median,IQR) months	36 (16-51)
Laboratory parameters (median, IQR)	
- Hb (g/dl)	9.3 (9.0-9.6)
- Wbc (x 10^3/L)	10 (5.5-14)
- Plt (x 10^3/L)	496(293-573)
- Creatinine (mg/dl)	0.77 (0.59-0.83)
- GOT/GPT (UI/L)	23 (14-33)/22(19-35)
- Bilirubin total (mg/dl)	2.4 (1.8-3.1)
Comorbidity (n°/%)	
- Hypertension	5 (29)
- Cardiopathy	2 (11)
- Diabetes	4 (23)
- Renal impairment	1 (5)
- Respiratory disease	1 (5)
- History of neoplasm	2 (11)
- Pulmonary hypertension	6 (35)
- Hemocromatosis	15 (88)
- Liver disease	8 (47)
βT therapy (n°/%)	
- Transfusion	12 (70)
- HU	5 (29)
- ICT	12 (70)
Splenectomy	8 (47)
Anti-platelet therapy (n°/%)	5 (29)
NVAF (n°/%)	9 (52)
VTE (n°/%)	8 (47)
- DVT	3 (37)
- PE	5 (62)
Type of DOACS (n°/%)	
- Rivaroxaban	8 (47)
- Edoxaban	4 (23)
- Dabigatran	0
- Apixaban	5 (29)

Abbreviation: βTM: β-thalassemia major; β-thalassemia intermedia; Hb: hemoglobin; Wbc white blood cell; Plt: platelets; ICT: iron chlation therapy; HU:hydroxyurea; NVAF:non-valvular atrial fibrillation; VTE: venous thromboembolism. DVT: deep vein thrombosis; PE: pulmonary embolism.

Non-Hodgkin's lymphoma I

C016

MOSUNETUZUMAB MONOTHERAPY IS AN EFFECTIVE AND WELL-TOLERATED TREATMENT OPTION FOR PATIENTS WITH RELAPSED/REFRACTORY FOLLICULAR LYMPHOMA WHO HAVE RECEIVED ≥2 PRIOR LINES OF THERAPY: PIVOTAL RESULTS FROM A PHASE I/II STUDY

P.L. Zinzani[1,2], G. Hess[3], L.E. Budde[4], L.H. Sehn[5], M. Matasar[6], S.J. Schuster[7], S. Assouline[8], P. Giri[9], J. Kuruvilla[10], M. Canales[11], S. Dietrich[12], K. Fay[13], M. Ku[14], L. Nastoupil[15], M.C. Wei[16], S. Yin[16], M.Y. Doral[16], C. Li[16], H. Huang[17], R. Negricea[18], E. Penuel[16], C. O'Hear[16], N.L. Bartlett[19]

[1]IRCCS Azienda Ospedaliero-Universitaria di Bologna Istituto di Ematologia "Seràgnoli"; [2]Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale Università di Bologna; [3]Department of Hematology, Oncology and Pneumology, Johannes Gutenberg-University; [4]City of Hope, 5BC Cancer Centre for Lymphoid Cancer and University of British Columbia; [6]Memorial Sloan Kettering Cancer Center; [7]Lymphoma Program, Abramson Cancer Center, University of Pennsylvania; [8]Jewish General Hospital; [9]Royal Adelaide Hospital; [10]Princess Margaret Cancer Centre; [11]Hospital Universitario La Paz; [12]University Heidelberg; [13]St Vincent's Hospital and Royal North Shore Hospital; [14]St Vincent's Hospital, University of Melbourne; [15]MD Anderson Cancer Center; [16]Genentech, Inc; [17]F. Hoffmann-La Roche Ltd; [18]Roche Products Ltd; [19]Siteman Cancer Center, Washington University School of Medicine

Introduction: Mosunetuzumab (Mosun), a CD20xCD3 bispecific antibody (Ab), redirects T cells to eliminate malignant B cells. During dose-escalation, intravenous (IV) Mosun was highly active and well tolerated in relapsed/refractory (R/R) follicular lymphoma (FL) patients (pts) with ≥2 prior therapy lines (3L+R/R FL). We present pivotal data from a Phase I/II study (NCT02500407), based on a large, single-arm expansion cohort of 3L+R/R FL pts receiving Mosun monotherapy at the recommended Phase II dose.

Methods: Pts had FL Grade [Gr]1–3a, ECOG ≤1 and were R/R to ≥2 prior lines of therapy including an anti (a)-CD20 Ab and an alkylator. Mosun was given IV in 21-day cycles with step-up dosing in Cycle (C)1 (Day [D]1: 1mg; D8: 2mg; D15 and C2D1: 60mg; C3+D1: 30mg). Treatment was completed after C8 (if complete response [CR]) or C17 (if partial response/stable disease after C8). Primary endpoint was independently assessed CR rate.

Results: 90 pts were enrolled (median age 60 years [range: 29–90], 61.1% male, 76.7% stage III/IV FL, 44.4% FLIPI 3–5, 3 median prior therapies [range: 2–10]). 68.9%, 78.9% and 53.3% were refractory to their last therapy, any prior aCD20 Ab and aCD20 Ab+alkylator (double refractory), respectively. 52.2% had disease progression within 24 months (m) from start of initial therapy (POD24). Median time on study was 12.9m (2.0–22.1). Best objective response (ORR) and CR rates were 79% and 58% and were consistent in prespecified subgroups including POD24 (ORR: 83%; CR: 55%) and double-refractory pts (ORR: 69%; CR: 48%). 12m-event-free rates after first response were 65.4% in all responders and 80.1% in CR pts. Median progression-free survival was 17.9m. The most common adverse event (AE) was cytokine release syndrome (CRS; 44.4% of pts), mostly confined to C1 and predominantly low grade; all CRS resolved. Other common AEs: fatigue (36.7%), headache (31.1%), neutropenia and pyrexia (28.9% each), hypophosphatemia (22.2%) and pruritus (21.1%). Common Gr3–4 AEs: neutropenia (26.6%), hypophosphatemia (13.3%), hyperglycemia and anemia (7.8% each), elevated alanine transaminase (5.6%). Two Gr5 AEs occurred, both considered unrelated to Mosun. AEs leading to Mosun discontinuation were rare (4.4%).

Conclusion: Mosun induces deep and durable remissions in 3L+R/R FL pts, including those with POD24 and/or double refractory disease. Mosun has a manageable safety profile, enabling treatment without hospitalization. Mosun represents an active new therapy for 3L+ R/R FL.

C017

GLOFITAMAB (GLOFIT) IN COMBINATION WITH POLATUZUMAB VEDOTIN (POLA): PHASE IB/II PRELIMINARY DATA SUPPORT MANAGEABLE SAFETY AND ENCOURAGING EFFICACY IN RELAPSED/REFRACTORY (R/R) DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL)

P. Corradini[1], M. Hutchings[2], A. Sureda[3], M.J. Terol[4], F. Bosch[5], T.S. Larsen[6], A.R. Dominguez[7], A. Panchal[8], A. Bottos[9], D. Carlile[8], Y. Wang[10], A.F. de L'Etang[9], M. Tandon[8], G. Sellam[9], G. Gritti[11]

[1]University of Milan and Fondazione IRCCS Istituto Nazionale dei Tumori; [2]Rigshospitalet; [3]Universitat de Barcelona; [4]Hospital Clínico Universitario INCLIVA, University of Valencia; [5]University Hospital Vall d'Hebron; [6]Odense University Hospital; [7]Regional and Virgen de la Victoria University Hospitals; [8]Roche Products Ltd; [9]F. Hoffmann-La Roche Ltd; [10]F. Hoffmann-La Roche Ltd; [11]Ospedale Papa Giovanni XXIII

Background: The novel CD20xCD3 T-cell-engaging bispecific antibody glofit has shown promising response rates with manageable safety in R/R B-cell non-Hodgkin lymphoma (B-NHL) patients (pts). NCT03533283 is a Phase Ib/II dose-escalation (DE) and expansion study evaluating glofit + pola or atezolizumab in R/R B-NHL pts. We report preliminary safety and efficacy data for glofit + pola in pts with R/R DLBCL during DE and expansion at the recommended Phase II dose (RP2D).

Methods: A single 1000mg dose of obinutuzumab pre-treatment was administered on Cycle (C) 1 Day (D) 1 alongside step-up dosing (SUD) of glofit on C1D8 and C1D15. Glofit was administered at the target dose from C2D1, every 3 weeks up to C12. Pola was administered at 1.8mg/kg on C1D2 and then on D1 of each cycle up to C6. Primary objective was to establish the RP2D of glofit combined with pola.

Results: As of September 6, 2021 (clinical cut-off date [CCOD]), 59 pts were treated with ≥1 cycle; median follow-up was 3.7 months. A glofit target dose of 30mg was established as RP2D. Of 59 pts, 61% had histology of R/R DLBCL, 15% R/R high-grade B-cell lymphoma and 24% R/R transformed follicular lymphoma. Pts (61% male, median age 59.0 years) received a median of 2 prior lines (range: 1−5); 70% were refractory to their last therapy. The most frequent adverse event (AE) was cytokine release syndrome (42%; 25/59 pts; 24 pts grade (Gr) 1−2 and one patient Gr 5). Gr>3 AEs occurred in 61% of pts; most commonly neutropenia (27%) and anemia (10%). Neurological AEs potentially consistent with ICANS (immune effector cell-associated neurotoxicity syndrome) were reported in 1.7% (one case of Gr 1 somnolence). Peripheral neuropathy (Gr 1/2) due to pola was reported in 19%. Serious AEs occurred in 46%, with two fatal events (one glofit-related CRS, one non-related COVID-19 pneumonia). Study treatment was discontinued in 4 pts due to AEs. At CCOD, 49/59 pts were evaluable for interim response; 7/49 pts had progressive disease and discontinued study treatment. Best overall response rate (ORR) for both dosing cohorts was 80% and complete response (CR) rate 51%. Of 7 pts treated with 2.5/10/10mg SUD glofit, ORR and CR rate were 85% and 71%, and of 42 pts treated with 2.5/10/30 mg SUD glofit, 75% and 45%, respectively. Median CR follow-up was 3.9 months, 23/25 CRs were maintained.

Conclusions: Glofit in combination with pola showed tolerable safety and encouraging preliminary efficacy in R/R DLBCL pts.

C018

A NOVEL DROP-OFF DIGITAL PCR ASSAY FOR CXCR4 MUTATION SCREENING IN IGM GAMMOPATHIES: FIRST DATA FROM THE FONDAZIONE ITALIANA LINFOMI BIO-WM STUDY

M. Ferrante[1], S. Zibellini[2], L. Marcheselli[3], E. Cappello[2], M. Borriero[1], S. Ragaini[1], I. Dogliotti[4], C. Varraso[2], F. Cavallo[1,5], A. Ferrari[6], M. Merli[7], G. Zamprogna[8], L. Laurenti[9], S. Tomasetti[10], E. Cencini[11], G. Loseto[12], S. Finotto[13], M. Marchetti[14], F. Re[15], A. Sica[16], J. Olivieri[17], C. Jimenez[18], N. Puig[18], C. Cavalloni[19], R. García-Sanz[18], M. Varettoni[19], S. Ferrero[1], D. Drandi[1]

[1]Department of Molecular Biotechnologies and health sciencies, University of Torino; [2]Division of Hematology, Fondazione IRCCS Policlinico San Matteo; [3]Fondazione Italiana Linfomi- c/o Centro Oncologico Modenese(COM), Università di Modena e Reggio Emilia; [4]Stem Cell Transplant Unit, University Hospital AOU Città della Salute e della Scienza; [5]Division of Hematology, A.O.U. Città della Salute e della Scienza di Torino; [6]Ematologia, AO Arcispedale Santa Maria Nuova - IRCCS; [7]UOC Ematologia, Ospedale di Circolo e Fondazione Macchi – ASST Sette Laghi; [8]SC Ematologia, ASST Grande Ospedale Metropolitano Niguarda; [9]S.Ematologia, Dipartimento Scienze Radiologiche Radioterapiche ed Ematologiche, Fondazione Policlinico Universitario A Gemelli; [10]Ematologia, Ospedale degli Infermi di Rimini; [11]U.O.C. Ematologia, AOU Senese; [12]U.O.C Ematologia, IRCCS Istituto Tumori Giovanni Paolo II; [13]Oncologia 1 - I.R.C.C.S., Istituto Oncologico Veneto; [14]S.O.S. Ematologia, Ospedale Cardinal Massaia; [15]UO Ematologia e CTMO, Azienda Ospedaliera Universitaria di Parma; [16]Oncologia Medica ed Ematologia, AOU Università degli Studi della Campania Luigi Vanvitelli; [17]Clinica Ematologica, Centro Trapianti e Terapie Cellulari "Carlo Melzi", Azienda Sanitaria Universitaria Integrata di Udine; [18]Hospital Universitario de Salamanca (HUSAL), IBSAL, IBMCC (USALCSIC), CIBERONC; [19]Division of Hematology, Fondazione IRCCS Policlinico San Matteo, Italy

MYD88^{L265P} and CXCR4^{S338X} are the most frequent mutations with clinical implications in Waldenström's Macroglobulinemia (WM). This study evaluates a new sensitive approach based on a drop-off digital PCR (dPCR) assay for CXCR4^{S338X} (p.S388) mutation (CXCR4^{MUT}) detection in WM and IgM monoclonal gammopathies of uncertain significance (IgM-MGUS) patients, enrolled in the FIL-BIOWM trial (NCT03521516). Genomic DNA from bone marrow (BM) and peripheral blood (PB) samples from 240 patients (184 WM, 56 IgM-MGUS) were analyzed from: 51 BM-CD19+ cells, 189 BM and 239 PB, unselected white blood cells (WBC). The drop-off dPCR assay for CXCR4^{MUT} showed a sensitivity of 0,001% measured as allele frequency (AF). 22% (41/184) of WM patients showed CXCR4^{MUT} in BM (median AF 1.6%, [0.14-23.1%]) while only 1% (8/184) were mutated also in PB (median AF: 0.6%, [0.23-35.2%]). Moreover, 95% (39/41) were MYD88^{L265P}. Only 9% (5/56) of IgM-MGUS patients, all MYD88^{L265P}, scored CXCR4^{MUT} in BM (median AF 0.65%, [1.1-0.2%]) and none in PB. 20% (38/189) of BM WBC samples (36 WM, 2 IgM-MGUS) mutated for both CXCR4^{MUT} and MYD88^{L265P} showed correlation in AF between the two mutations (R^2=0.8). Conversely, no correlation was observed in CD19+ cells, between the two mutations (R^2=0.06). Overall, clinical features of CXCR4^{MUT} *vs* wild type (CXCR4^{WT}) patients did not differ significantly, except for lower hemoglobin levels (median 11.6 *vs* 12.8 g/dl, p=0.002) and higher serum IgM monoclonal component (median 1.76 *vs* 1 g/dl, p=0.016). Interestingly, 15/41 WM CXCR4^{MUT} patients who received immediate treatment at the enrollment showed higher disease and mutational burden compared to 26 CXCR4^{MUT} patients still in watch and wait (WW). Indeed, median histologic BM infiltration was 80% *vs* 30% (p<0.001), median IgM monoclonal component was 3.6 g/dl *vs* 1.6 g/dl (p=0.003) and median CXCR4^{MUT} AF was 9.5% *vs* 0.8% (p<0.001), respectively. At the present the median follow-up of the trial is 34 months, and no statistically significant differences in outcome parameters have been recorded among CXCR4^{MUT} and CXCR4^{WT} cases.

In conclusion, we here describe: 1) a sensitive, easily applicable and standardizable approach for CXCR4^{MUT} detection, with no need for CD19+ selection; 2) a lower mutational AF in IgM-MGUS compared to WM; 3) a suboptimal CXCR4^{MUT} detection in PB compared to BM; 4) a statistically significant difference in CXCR4^{MUT} AF, between patients treated at the time of enrollment and those still in WW.

C019

BORTEZOMIB PLUS R-DHAP COMPARED TO R-DHAP IN RELAPSED/REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL) ELIGIBLE TO STEM CELL TRANPLANTATION: FINAL RESULTS OF PHASE II RANDOMIZED TRIAL VERAL12 OF THE FONDAZIONE ITALIANA LINFOMI

A. Chiappella, M. Balzarotti, B. Botto, A. Castiglione, F. Cavallo, S.V. Usai, M. Zanni, C. Califano, F. Re, C. Ghiggi, A. Olivieri, P. Corradini, A.M. Liberati, S. Volpetti, M. Michieli, A. Tucci, G. Gaidano, M. Tani, F. Ciambelli, G. Musuraca, D. Vallisa, F. Merli, A.L. Molinari, A. Tafuri, V.R. Zilioli, D. Marino, C. Stelitano, S.A. Pileri, G. Ciccone, U. Vitolo

Hematology, Fondazione IRCCS Istituto Nazionale dei Tumori. On behalf of Fondazione Italiana Linfomi, Italy

The standard treatment in relapsed/refractory (R/R) DLBCL patients after first line therapy is a cisplatin-containing regimen followed by high-dose chemotherapy and stem cell transplantation (HDC+SCT). Bortezomib had proven activity in aggressive lymphomas. On these bases, the Fondazione Italiana Linfomi designed a prospective, two-arm randomized phase II trial VERAL12 (NCT01805557), aimed at evaluating whether the addition of bortezomib to standard R-DHAP (BR-DHAP) increases complete response (CR) compared to R-DHAP. The primary endpoint was CR after 4 courses of R-DHAP or BR-DHAP, assuming a 30% CR for the standard arm and a 50% CR in experimental arm. Patients aged 18-65 years eligible to HDC+SCT, with R/R DLBCL after first line therapy, were stratified by relapsed or refractory and randomized 1:1 to receive: R-DHAP and subcutaneous 1.5 mg/ms bortezomib on days 1 and 4 of each cycle in addition to R-DHAP. From 2013 to 2018, 107 patients were enrolled and randomized to receive R-DHAP (54) or BR-DHAP (53). Median age was 57 years (IQR: 48;62); stage III/IV 83 patients (78%); IPI risk >2 37 (35%); 53 (50%) relapsed (median time at relapse 10.8 months, IQR: 6.9;20.9) and 54 (50%) refractory (0.9 months, IQR 0.52;1.3). Fifty-two (49%) patients completed the 4 cycles: 55 did not, 42 due to progressive disease. The response after 4 courses was: overall response rate (ORR) 38 (36%), with CR 29 (27%); by arm of randomization, CR 28% for R-DHAP and 26% for BR-DHAP (p-value 0.563). Fifty patients (44%) performed a consolidation with SCT (39 auto-SCT, 11 allo-SCT), 24 in R-DHAP arm and 26 in BR-DHAP arm. Sixty patients died: 49 (82%) due to lymphoma, 1 due to toxicity, 3 due to transplant related mortality, 7 due to other causes. The incidence of adverse events were similar in the two arms, with grade 3-4 haematological toxicities in 96 patients (90%), g3-4 infection in 5 (5%), g3-4 neurotoxicity in 4 (4%). At a median follow-up of 50 months, 2-years PFS was 29% (95%CI: 19.94;41.83) and 41% (27.67;53.84) for R-DHAP and BR-DHAP, respectively; HR 0.65 (0.41;1.02) p 0.062; 2-years OS was 43% (28.98;56.30) and 52% (37.80;64.56) for R-DHAP and BR-DHAP, respectively; HR 0.74 (0.44;1.23) p 0.244. In summary, in the VERAL12 phase II randomized trial, the addition of bortezomib to R-DHAP did not improve the CR rate pre SCT of R/R DLBCL patients eligible to HDC+SCT; a numerically higher 2-yr PFS rate was observed in patients treated with BR-DHAP.

C020

DESIGN OF NEW PERSONALIZED THERAPEUTIC APPROACHES FOR DIFFUSE LARGE B-CELL LYMPHOMA

M. Carella[1,2], V. Stefoni[1,2], G. Musuraca[3], M. Barone[4,5], G. Conti[4,5], M. Fabbrini[4,5], S. Turroni[5], A. Broccoli[1,2], L. Argnani[2], P. Brigidi[4], P.L. Zinzani[1,2]

[1]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli", Bologna, Italy; [2]Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale, Università di Bologna, Bologna, Italy; [3]Hematology Unit, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Meldola, Italy; [4]Microbiomics Unit, Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy; [5]Unit of Microbiome Science and Biotechnology, Department of Pharmacy and Biotechnology, University of Bologna, Bologna, Italy

Although front-line R-CHOP (rituximab-cyclophosphamide, doxorubicin, vincristine, prednisone) can improve clinical outcomes in diffuse large B-cell lymphoma (DLBCL), 20%-25% of patients relapse after initial response, within two years. Recent research on the gut microbiome (GM) in cancer has highlighted its importance in hematology. Indeed, GM can impact the onset and progression of cancer, as well as the outcomes of anticancer therapies and drug side effects.

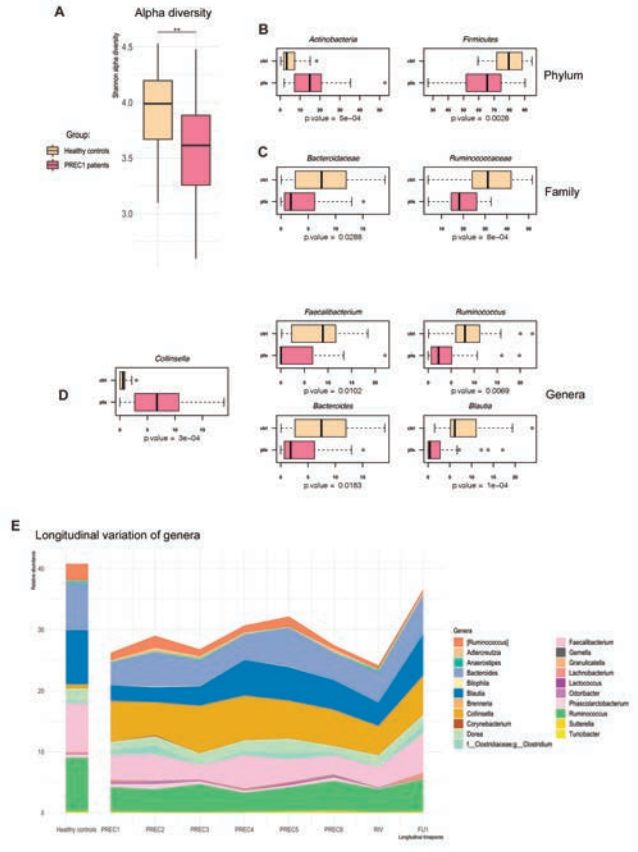


Figure 1.

Fifty DLBCL patients undergoing front-line R-CHOP therapy were enrolled (ClinicalTrials.gov Identifier: NCT03797170, RF-2016-02363730). Feces were collected at baseline, before each therapy cycle and at response assessment (during both therapeutic course and follow-up). GM was profiled by 16S rRNA amplicon sequencing. Patients responding to first line will be followed up for two years after the end of treatment by fecal sampling every 6 months, in correspondence with disease re-evaluation.

The GM of DLBCL patients before starting R-CHOP was compared with already-published data from healthy controls matched by geographical origin (Italy), gender and age. Patients showed less alpha diversity and some changes in composition, including notably an increase in Collinsella and a decrease in typically health-associated taxa, such as Faecalibacterium, Ruminococcus, Blautia and Bacteroides (Figure 1A-D). Concerning the GM dynamics though the R-CHOP therapy cycles (Figure 1E), no significant changes were observed but an overall reduction of several taxa starting from the fourth cycle. The compositional differences reported at baseline persisted until response assessment (following the last therapy cycle), while they partially reversed at the first follow-up (6 months after the end of therapy), with the recovery of healthy-like proportions for Bacteroides, Blautia, Faecalibacterium, Ruminococcus and Collinsella. All but two patients responded positively to therapy.

The GM of DLBCL patients showed a significant alteration even before starting R-CHOP therapy, with reduced richness and dysbiotic compositional features. This imbalance was maintained until the fourth cycle, after which we detected an overall GM shrinkage. Six months after the end of therapy, the dysbiotic signatures were largely reversed, suggesting that GM resilience may be involved in the response to therapy.

Monoclonal myeloma and gammopathies I

C021

HUMORAL AND T CELL IMMUNE RESPONSE TO MRNA COVID-19 VACCINES IN PATIENTS WITH ACTIVE MULTIPLE MYELOMA (MM): RELATIONSHIP WITH DISEASE STATUS AND LINE OF THERAPY

K. Mancuso[1,2], E. Zamagni[1,2], V. Solli[1,2], L. Gabrielli[3], L. Pantani[1], S. Rocchi[1,2], I. Rizzello[1,2], P. Tacchetti[1], S. Ghibellini[2], G. De Cicco[1,2], E. Favero[1,2], M. Ursi[1,2], M. Talarico[1,2], S. Barbato[1], C. Terragna[1], E. Borsi[1], M. Martello[1], A. Poletti[1,2], N. Testoni[1,2], A. Scatà[1], G. Nepoti[1], B. Ruffini[1], T. Lazzarotto[3], M. Cavo[1,2]

[1]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli"; [2]Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale, Università di Bologna; [3]IRCCS Azienda Ospedaliero-Universitaria di Bologna, UO di Microbiologia, Italy

We report the results from an observational prospective monocentric study aimed at assessing the antibody (Ab) and cell-mediated immune (CMI) response (RESP) to mRNA-1273 and BNT162b2 vaccines in patients (pts) with active MM. By study design, anti S-RBD IgG (Elecsys®assay) were measured before vaccination and after 1 (T1), 3 (T3), 6 (T6), 9 (T9) and 12 months (mo) from the second dose (D2). CMI RESP by Interferon-Gamma Release Assays was evaluated at T3 and T12. 102 SARS CoV-2-naïve MM pts (median age: 66) who had received 1 median prior line of therapy (95 on active treatment and 45 with relapsed disease) were enrolled, and Ab RESP was compared with that of 57 health-care workers who received the same mRNA vaccines. Ab RESP at T1 (102 pts), T3 (100 pts), T6 (99 pts) and T9 (96 pts), and of CMI RESP at T1 (99 pts) from D2 are herein reported; T12 results will be presented at the congress. Preliminary results of Ab and CMI RESP at T1 after the third dose (D3) of mRNA-1273 (70 pts) and BNT162b2 (22 pts) vaccines are also reported. At T1, the seropositivity rate (antiS IgG ≥5U/mL) was 88% for MM pts *vs* 100% for controls (p=.004), and the median IgG titer was 411 *vs* 812U/ml, respectively (p=.003). Median IgG titer was 308 at T1 (p=0.1), 240 at T6 (p=.001), and increased up to 2500U/mL after D3 (p<.001); it was significantly higher at all timepoints in pts with ≥CR (p<.0001), previously treated with ASCT (p<.001), on lenalidomide (R) maintenance (p<.0001), and lacking 2-Ig immunoparesis (p.004). Prior exposure to proteasome inhibitors or anti-CD38mAbs resulted in lower Ab titer (p<.0001) at all timepoints. Interestingly, pts who received mRNA-1273 vaccine had higher IgG titer at T1, T3, T6 (p<.001), T9 (p=.01), and after D3 (p=.01). CMI RESP was seen in 34 pts; their median IgG titer was higher *vs* pts without CMI RESP (p<.0001). Only 1 seronegative pt had CMI RESP; both CMI and Ab RESP were absent in 10%. Multivariate analysis confirmed ≥CR (p<.0001), prior ASCT (p=.007) and R maintenance (p=.01) as independent predictors of better Ab RESP, while anti-CD38mAbs had a negative impact (p=.009). COVID-19 was registered in 8 pts (7 after D3, 2 CMI-reactive), with rapid resolution. To conclude, full schedule of mRNA vaccination provided a high seropositivity rate, but lower CMI RESP rate in MM pts. Haematological response and therapy affected Ab RESP. IgG titer strongly declined after 6 mos, but D3 boosted the humoral response. COVID-19 case fatality rate was 0%.

C022

BORTEZOMIB-MELPHALAN-PREDNISONE (VMP) *VS* LENALIDOMIDE-DEXAMETHASONE (RD) IN TRANSPLANT-INELIGIBLE REAL-LIFE MULTIPLE MYELOMA PATIENTS: PRELIMINARY RESULTS OF THE RANDOMIZED PHASE IV REAL MM TRIAL

F. Bonello[1], S. Bringhen[1], N. Giuliani[1], I. Attucci[1], R. Zambello[1], S. Ronconi[1], I.D. Vincelli[1], C. Musolino[1], G. Leonardi[1], R. Ribolla[1], F. Cattel[2], L. Cani[1], P. Galieni[1], A.M. Liberati[1], P. Tosi[1], M.M. Cavalli[1], E. Sciorsi[2], D. Mannina[1], R. Ria[1], F. Patriarca[1], M. Cavo[1], S. Mangiacavalli[1], G. Benevolo[1], G. Ciccone[3], M. Boccadoro[1], A. Larocca[1]

[1]European Myeloma Network Italy; [2]S.C. Farmacia Ospedaliera, A.O.U. Città della Salute e della Scienza di Torino; [3]Unit of Clinical Epidemiology, A.O.U. Città della Salute e della Scienza di Torino and CPO Piemonte, Italy

Background: Bortezomib-melphalan-prednisone (VMP) and lenalidomide-dexamethasone (Rd) represented standards of care for transplant-ineligible (NTE) newly diagnosed multiple myeloma (NDMM) patients (pts) until the introduction of daratumumab in the frontline setting, and remain an option for some pts. The phase IV Real MM trial (funded by the Italian Medicines Agency AIFA, Independent Research) is the first prospective randomized trial comparing safety and efficacy of VMP and Rd in a real-life NTE population.

Methods: NDMM pts who were NTE due to age ≥65 years or comorbidities were randomized 1:1 to 9 VMP cycles *vs* continuous Rd according to standard schedule. Pts were enrolled regardless of performance status, comorbidities, or baseline laboratory values. Pts were stratified according to IMWG frailty score and cytogenetic FISH risk. The primary endpoint was progression-free survival (PFS); key secondary endpoints were response rates, overall survival (OS), and safety.

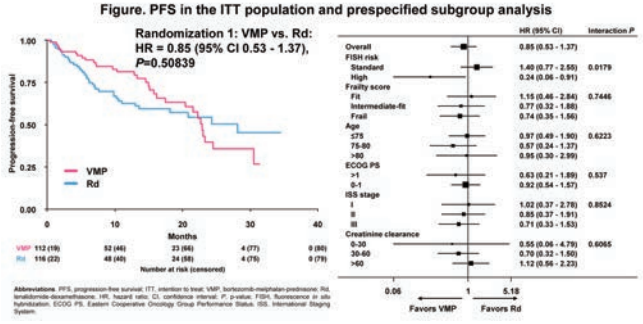


Figure 1.

Results: At the data cut-off (17-12-2021), 228 pts were randomized to receive VMP (n=112) or Rd (n=116). Baseline characteristics were balanced between VMP *vs* Rd arms: median age was 77 *vs* 76 years, respectively; 47% *vs* 48% of pts were frail. In both arms, 18% of pts had high-risk cytogenetics. After a median follow-up of 14 months, the median PFS was 23 *vs* 28 months with VMP *vs* Rd (HR 0.85, 95% CI 0.53-1.37, *P*=0.5). In pts with high-risk cytogenetics, a significant PFS advantage was observed with VMP *vs* Rd (HR 0.24, 95% CI 0.06-0.91, *P*=0.02). No significant difference in PFS between the two arms was detected in standard-risk pts and according to frailty score (Figure 1). Response rates were similar: in the VMP *vs* Rd arms, 82% *vs* 80% of pts reached ≥partial response (PR) and 56% *vs* 48% ≥very good (VG)PR. OS data were immature, after 28 deaths (9 in the VMP *vs* 19 in the Rd arms). Toxicities were consistent with those previously reported with the two regimens. In the VMP *vs* Rd arms, 62% *vs* 63% of pts respectively had ≥1 dose reduction of any drug, including 25% of pts in the VMP arm switching to once-weekly V before cycle 5.

Conclusion: We confirmed the efficacy of VMP and Rd in an older

real-life NTE population including ~50% of frail pts. No PFS advantage of one regimen over the other was observed, except in high-risk pts, who benefited from VMP, suggesting that the doublet Rd is suboptimal in this subgroup. Concerning safety, only ~30% of pts tolerated full-dose VMP or Rd according to schedule.

C023

HIGH LEVEL OF CIRCULATING TUMOUR DNA AT DIAGNOSIS CORRELATES WITH DISEASE SPREADING AND DEFINES MULTIPLE MYELOMA PATIENTS WITH POOR PROGNOSIS

M. Martello[1], A. Poletti[1], D. Bezzi[2], E. Borsi[1], B. Taurisano[1], V. Solli[1], S. Armuzzi[1], I. Vigliotta[1], G. Mazzocchetti[1], I. Pistis[3], L. Pantani[3], S. Rocchi[1], K. Mancuso[1], P. Tacchetti[3], I. Rizzello[1], M. Cavo[1], E. Zamagni[1], C. Nanni[2], C. Terragna[3]

[1]IRCCS - Azienda Ospedaliero Universitaria S. Orsola - Department of Experimental, Diagnostic and Specialty Medicine - University of Bolo; [2]IRCCS - Azienda Ospedaliero Universitaria S. Orsola - Department of Nuclear Medicine; [3]IRCCS - Azienda Ospedaliero Universitaria S. Orsola, Italy

Background: Multiple Myeloma (MM) is a plasma cell (PC) disorder characterized by the presence of skeletal involvement at the time of diagnosis in most of the patients. Recently, cell-free DNA (cfDNA) has been proven to resume the heterogeneity of spatially distributed clones. However, it has to be determined to which extent cfDNA correlates with disease distribution and its possible implications with patients' outcome.

Aims: Aim of this study is to quantitatively and qualitatively evaluate cfDNA at diagnosis and during follow-up in correlation with imaging data to possibly define the integration of this approach with molecular bone marrow (BM) and whole-body residual disease assessment.

Methods: A total of 88 newly diagnosed MM patients were screened at baseline with 18F-FDG PET/CT, and molecularly assessed by Ultra Low Pass-Whole Genome Sequencing (ULP-WGS). For each pts, ULP-WGS was used to characterize both the neoplastic PC clone(s) in the BM (gDNA) and the cfDNA from peripheral blood. Data were analysed by ichorCNA and Clonality R packages.

Results: At diagnosis, the cfDNA tumor fraction (TF) was significantly lower as compared to gDNA TF [median (M) TF: 4.4 *vs* 59.7%, respectively]. Nevertheless, high cfDNA TF levels (> 4.4% cfDNA TF values; range: 4.4-84.3%) correlated with high gDNA TF levels (>65.7% gDNA TF values; range: 65.7-96.7%). This observation was further confirmed by a significant correlation between cfDNA TF and the percentage of BM CD138/CD38 positive plasma cells (r=0.47; p<.0001).

Interestingly, patients with high cfDNA TF at baseline were more likely to present with extramedullary disease (EMD) and a higher number of focal lesions, and also featured a more active tumour metabolism, as compared to pts with low TF (EMD 4/44=9% *vs* 1/44=2.3%, p=ns; M n. PET lesions: 1.7 *vs* 2.5, p= 0.003; SUVmax: 5.2 *vs* 9.6, p = 0.01).

Despite an overall concordance between cfDNA and BM genomic profiles (80/88=90.9%), those patients with high cfDNA TF showed more frequently evidence of spatial heterogeneity (7/8=87.5% of pts with divergent profiles). Finally, high cfDNA TF at diagnosis predicted for poorer prognosis as compared with low cfDNA TF (PFS at 20 months: 67% *vs* 86%, p=0.05; OS at 20 months: 90% *vs* 100%, p=0.04).

Summary/Conclusion: In conclusion, patients with high cfDNA TF displayed imaging data that overall suggested a higher propensity to a metastatic spread of the disease, which finally correlated with poorer prognosis.

Acknowledgements: AIRC IG2019, AIL BOLOGNA ODV.

C024

ABSTRACT NOT PUBLISHABLE

C025

MONOCLONAL GAMMOPATHY OF RENAL SIGNIFICANCE (MGRS): AN ITALIAN MULTICENTRIC RETROSPECTIVE OBSERVATIONAL STUDY ON CLINICAL PRESENTATION AND OUTCOMES

G. De Cicco[1,2], S. Rocchi[1,2], R. Mina[3], C.S. Cartia[4], M.T. Petrucci[5], E. Antonioli[6], A. Gozzetti[7], M. Salvini[8], C. Cerrato[9], P. Deias[10], F. Bigi[1,2], E. Favero[1,2], K. Mancuso[1,2], P. Tacchetti[1], V. Solli[1,2], M. Cavo[1,2], E. Zamagni[1,2]

[1]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli"; [2]Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale, Università di Bologna; [3]SSD Clinical Trial in Oncoematologia e Mieloma Multiplo, Division of Hematology, University of Torino, Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino; [4]UOC Ematologia IRCCS Fondazione Policlinico San Matteo; [5]Azienda Policlinico Umberto I, Sapienza Università di Roma; [6]SODC Ematologia, AOU Careggi; [7]Hematology Unit, Department of Medicine, Surgery and Neurosciences, University of Siena, Siena, Italy; [8]UOC Ematologia, Ospedale di Circolo di Varese; [9]AOU Maggiore della Carità - SCDU Ematologia; [10]Clinica Ematologica e Unità di Terapie cellulari, Azienda Sanitaria Universitaria Friuli Centrale, ASUFC, Italy

Background: Monoclonal gammopathies of renal significance (MGRS) are lymphoproliferative or, most frequently, plasma cell disorders, characterized by renal damage, induced by the deposition of secreted monoclonal immunoglobulins. A kidney biopsy is required for MGRS diagnosis and histopathological classification, whereas bone marrow biopsy let to identify the underlying hematological clone. MGRS therapy regimens were adapted from the ones used for multiple myeloma (MM) and lymphomas.

Materials and method: In this retrospective multicentric observational study we enrolled 60 >18 years patients (pts) diagnosed with MGRS from 2002 to 2020. Pts with MM, multiorgan amyloidosis or MGUS without renal involvement were excluded. The study aimed at describing basal characteristics and treatment approaches and analyzing the impact of different histotypes, first-line therapies, and hematologic response on progression-free survival (PFS) and overall survival (OS).

Results: Among the 60 enrolled pts, 42 (70%) had AL amyloidosis and 28 (30%) non-amyloidosis MGRS. At diagnosis, 33 pts (55%) showed a monoclonal peak, 43 (72%) had imbalanced free light chain ratio, and the median proteinuria value was 3962 mg/die, with higher levels in AL Amyloidosis (v.m. 4530 mg/die) than non-amyloidosis (v.m. 2405 mg/die) pts. Therapies mainly used were: Bortezomib-based regimens followed (18%) or not (42%) by autologous stem cells transplantation (ASCT) (60%), ASCT upfront (14%), rituximab-based regimens (8%) and melphalan-based regimens (18%). After first line therapy 71% pts achieved ≥PR according to the IMWG criteria (16% VGPR, 30% CR) and 68% a renal response ≥PR according to Gerz et al. 2004, regardless of the kind of renal histology. PFS was 62 months, while OS was not yet reached at the median follow-up of 62 months; MGRS histotypes did not correlate with a difference in PFS and OS. Among first-line therapies, only ASCT (both upfront or preceded by a bortezomib-based induction) improved PFS (p=0.011), but not OS. Both VGPR and CR hematologic response resulted in longer PFS (p=0.018 and p=0.015, respectively), but not OS; moreover, hematological response ≥VGPR was associated with renal response ≥PR.

Conclusions: MGRS are rare and complex pathologies, requiring a close collaboration between hematologist and nephrologist. Our results support the use of ASCT, whenever applicable, and highlight the influence of the hematological response on both renal improvement and survival outcomes.

Acute lymphocytic leukemia

C026

IMPACT OF TUMOR BURDEN AND CARCIK-CD19 PEAK ON OUTCOMES IN POST TRANSPLANTATION RELAPSED ACUTE B CELL LEUKEMIA TREATED WITH CARCIK-CD19

G. Rizzuto[1], C.F. Magnani[2], G. Gritti[1], G. Gaipa[2,3], D. Belotti[3,4], B. Rambaldi[1], G.M. Borleri[1], C. Pavoni[1], S. Ferrari[1], G. Cavallaro[1], A. Rapella[1], M. Paganessi[1], S. Tettamanti[2], C. Capelli[1,5], A. Grassi[1], M. Introna[1,5], G. Dastoli[2], A. Rambaldi[1,7], A. Biondi[2,4], F. Lussana[1]

[1]Hematology and Bone Marrow Transplant Unit, ASST Papa Giovanni XXIII; [2]Tettamanti Research Center, Department of Pediatrics, University of Milano - Bicocca/Fondazione MBBM; [3]Laboratorio di Terapia Cellulare e Genica Stefano Verri, ASST-Monza, Ospedale San Gerardo; [4]Department of Pediatrics, University of Milano – Bicocca, Fondazione MBBM; [5]USS Centro di Terapia Cellulare "G. Lanzani"; [6]Department of Oncology and Hematology, Università degli Studi di Milano, Italy

Immunotherapy with chimeric antigen receptor T-cell (CAR-T) represents a novel attractive therapeutic option for relapsed/refractory acute B cell leukemia (B-ALL). Allogeneic CAR-T cells engineered with a non-viral method reduce the costs, overtake the logistical complexity of the viral process, and allow lymphodepleted patients to access CAR-T treatment. We recently examined the feasibility of treatment of BCP-ALL patients relapsed after alloHSCT using donor-derived anti-CD19 CAR T cells (CARCIK-CD19) engineered with Sleeping Beauty (SB) transposon. The purpose of the present study was to evaluate which factors were associated with CARCIK efficacy. From 2018 to 2021, 22 adult patients were screened in a Phase I/IIb study, and 17 were infused. Five patients were enrolled in a subsequent compassionate program. CARCIK in vivo kinetics was studied on peripheral blood using flow cytometry. CARCIK peak (C_{max}) was defined as the maximum concentration of CARCIK, time-to-peak (t_{max}) as the number of days needed to reach C_{max}. Tumor burden (TB) was assessed as bone marrow blasts percentage prior to infusion. An effector-to-target (E:T) ratio was derived by dividing C_{max} to TB. Bridging therapy before CARCIK with inotuzumab (IO) was associated with a favorable response (100% of complete remission (CR) at 28 days post-infusion) compared with other treatments (70%).

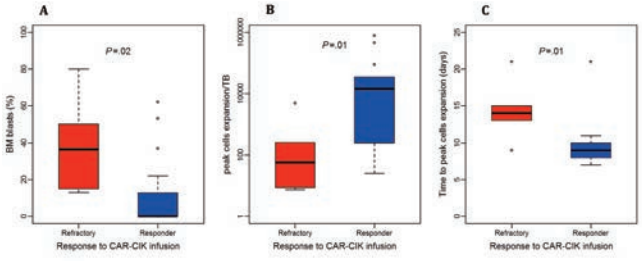


Figure 1.

A lower TB was significantly associated with higher response rate at day 28 (Figure 1A). The E:T ratio was significantly higher in responding patients (Figure 1B). As for post-infusion, t_{max} was found to be significantly shorter in responding patients (Figure 1C). The CR rate accounted for 72% (16/22), with 69% of responders being also MRD-negative. The estimated 12-months OS and PFS -of the whole cohort- were 47% and 20%, respectively. Among patients who achieved CR the duration of response was 41% at 6-months and 24% at 1 year.

CARCIK can induce sustained responses in adult ALL patients relapsed after alloHSCT. A significant clinical benefit was observed among patients who received IO as bridging therapy, effective in reducing the tumor burden by targeting a different B cell restricted antigen. A low TB before infusion, a quick expansion, and an expansion commensurate to TB were all associated with different response rates and therefore could be useful for driving subsequent pre-emptive or prophylactic approaches, such as a second CARCIK infusion or an alloHSCT.

C027

AN ENDOTHELIAL-LEUKEMIA PRE-CLINICAL PLATFORM TO UNCOVER DRUG VULNERABILITIES FOR PERSONALIZED TREATMENTS IN T-ACUTE LYMPHOBLASTIC LEUKEMIA

L.V. Cappelli[1,2], D. Fiore[1], J.M. Phillip[3], L. Yoffe[1,4], F. Di Giacomo[1], Y. Hu[4], C. Kayembe[1], M. Ginsberg[6], L. Consolino[7], J.G. Barcia Duran[5], N. Zamponi[3], A.M. Melnick[3], F. Boccalatte[8], W. Tam[1], O. Elemento[4], S. Chiaretti[2], A. Guarini[2], R. Foà[2], L. Cerchietti[3], S Rafii[5], G. Inghirami[1]

[1]Department of Pathology and Laboratory Medicine, Weill Cornell Medicine; [2]Department of Translational and Precision Medicine, Sapienza University of Rome; [3]Department of Medicine, Hematology and Oncology Division, Weill Cornell Medicine; [4]Institute for Computational Biomedicine & Caryl and Israel Englander Institute for Precision Medicine, Weill Cornell Medicine; [5]Department of Medicine, Ansary Stem Cell Institute, Division of Regenerative Medicine, Weill Cornell Medicine; [6]Angiocrine Bioscience; [7]Department of Molecular Biotechnology and Health Sciences, University of Turin; [8]Department of Pathology, New York University School of Medicine

Background and Aims: T-cell acute lymphoblastic leukemia (T-ALL) is an aggressive disease with few innovative treatments. To investigate novel vulnerabilities/effective compounds and interrogate the leukemia-stromal crosstalk, we generated T-ALL patient-derived-tumor-xenografts (PDX) and implemented a mixed-culture approach using E4ORF1-transduced endothelial cells (ECs) (Seandel M et al, PNAS 2008).

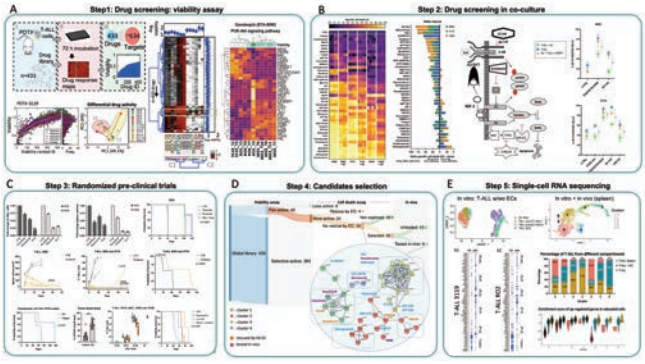


Figure 1.

Results: First, we established a series of 22 T-ALL PDX matching primary samples and we challenged T-ALL cells with a broad drug library (n=433), demonstrating two response clusters based on differential drug susceptibility and linked to specific transcriptomic signatures (Figure 1A). We then defined a group of pan-active compounds across all models (n=40), which we tested with/without ECs in vitro. We found that ECs counteracted the activity of distinct compounds based on T-ALL identity (Figure 1B). Based on the known role of IGF1-IGFR1 as a supportive EC-rescue axis (Medyouf H *et al.*, J Exp Med 2011), we performed the same screening with/without recombinant IGFBP-7 (500 ng/mL), an IGF1 decoy molecule. Remarkably, IGFBP-7 completely or partially abrogated the EC-mediated rescue of selected drugs (Figure 1B) [enzas-

taurin (PKC-b inhibitor), SC144 (GP130 inhibitor), CHIR124 (Chk1 inhibitor) and YM155 (Survivin inhibitor)]. Drugs not rescued by ECs (n=30) were considered positive hits and 5 of them (ruxolitinib, tofacitinib, panobinostat, bortezomib, irinotecan) ultimately proved to be effective in vivo in randomized pre-clinical trials (Figure 1C). We propose a list of compounds that could be readily translated into T-ALL clinical trials (Figure 1D). At single-cell resolution, in vitro interacting T-ALL cells and ECs underwent reciprocal transcriptome changes, with T-ALL shifting towards stemness/undifferentiation and ECs towards tumor-ECs (TECs) phenotypes. Furthermore, in vitro EC-educated T-ALL cells mimicked distinct T-ALL subsets of the leukemic spleen of corresponding PDX mice (Figure 1E).

Conclusions: These data demonstrate that our EC-T-ALL culture system partially recapitulates in vivo conditions, offering a robust platform to study drug response, leukemia-host interactions and cell plasticity. This approach will improve the pre-clinical predictability of novel drugs/combinations for T-ALL and other hematologic malignancies, and propel the development of patient-tailored treatments.

C028

BASELINE GENE EXPRESSION ANALYSIS OF RELAPSED ACUTE B-LYMPHOBLASTIC LEUKEMIA PATIENTS TREATED WITH INOTUZUMAB OZOGAMICIN

C. Sartor[1], I. Vigliotta[2], V. Robustelli[1], G. Cristiano[1], J. Nanni[1], L. Zannoni[1], S. Parisi[2], S. Paolini[2], G. Marconi[1,3], G. Martinelli[3], A. Curti[2], M. Cavo[1,2], C. Terragna[2*], C. Papayannidis[2*]

[1]Istituto di Ematologia "Seràgnoli", Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale, Università degli Studi di Bologna, Bologna, Italy; [2]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli" Bologna, Italy; [3]Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Italy

Inotuzumab ozogamicin (InO) is an anti-CD22 monoclonal calicheamicin-conjugated antibody, approved for relapsed/refractory B-cell acute lymphoblastic leukemia (R/R B-ALL) able to obtain high complete remission (CR) rates but of short duration. Mechanisms underlaying InO resistance are largely unknown. We aimed to characterize the baseline differentially expressed genes (DEGs) in a series of R/R B-ALL patients in relation with patient response to InO to individuate potential pathways involved in resistance. Gene expression profile of 18 R/R B-ALL patient samples was analyzed with RNA-seq, before InO exposure. All patients received at least 1 InO course. Patient population after InO exposure was divided in poor/non-responders (NR=8), defined as either refractory or with a duration of remission (DoR) <3 months after CR achievement, and responders (R=10), defined as DoR ≥3 months after CR. Patient disease characteristics in NR and R groups were homogeneous except for median CD22-fluorescent intensity, that was significantly lower in NR group ($p = 0.04$). The list of significant ($p<0.05$) DEGs whose absolute fold change (FC) was ≥2, was analyzed. P values were corrected with the Benjamini-Hochberg algorithm (false discovery rate; FDR). Gene expression results were analyzed with QIAGEN Ingenuity Pathway Analysis (IPA). Overall, 370 genes were differentially expressed ($p<0.05$) in NR, as compared to R patients of which 32 were significantly differentially expressed: 31 were down- and 1 was up-regulated. DEGs were involved in basophil differentiation, CO_2 transport, erythrocyte and myeloid cell development, heme metabolic and porphyrin-containing compound biosynthetic processes, cation and cellular ion homeostasis. Both IPA upstream regulator and regulator effect analysis identified the serine/threonine homeodomain-interacting protein kinase-2 (HIPK2) as predicted downregulated. HIPK2 inhibition was predicted to be causal upstream condition for the under-expression of six DEGs from the set (FECH, ANK1, SCL4A1, EPOR, GATA1, HBZ) with activation Z score of -2.449 and p value of overlap = 1.02E-09. No difference in terms of HIPK2 expression was appreciated in the two groups, suggesting down-regulation at post-transcriptional level. A unique pattern of gene expression based on HIPK2 downregulation was identified in poor responders to InO, providing potentially important insights in mechanisms of resistance. HIPK2 downregulation needs to be further validated.

C029

NEXT GENERATION SEQUENCING FOR MINIMAL RESIDUAL DISEASE MEASUREMENT IN THE DAILY CLINICAL MANAGEMENT OF PH-NEGATIVE ACUTE LYMPHOBLASTIC LEUKEMIA PATIENTS IS FEASIBLE AND PROVIDES USEFUL CLINICAL DATA

S. Armuzzi[1,2], M. Martello[2], I. Vigliotta[2], B. Taurisano[1,2] V. Robustelli[1,2], E. Borsi[2], V. Solli[1,2], A. Poletti[1,2], G. Mazzocchetti[1,2], I. Pistis[2], J. Nanni[1,2], G. Cristiano[1,2], C. Sartor[1,2], F. Barbato[1,2], A. Curti[2], M. Cavo[1,2], C. Papayannidis[2], C. Terragna[2]

[1]DIMES – Department of Experimental, Diagnostic and Specialty Medicine, Institute of Hematology, University of Bologna; [2]IRCCS - Azienda Ospedaliero-Universitaria di Bologna, Italy

The role of minimal residual disease (MRD) assessment in Ph-Negative Acute Lymphoblastic Leukemia (Ph-neg ALL) has considerably grown in the last few years. MRD results have become critical for risk stratification, patients'(pts) prognosis and as driver of therapeutic decisions. We evaluated next generation sequencing (NGS) as novel approach for MRD assessment in the daily clinical practice of Ph-neg ALL pts, in order to simplify the management of MRD samples and to improve the analysis sensitivity. Clonotypes were defined by NGS of IgH, Igk and T-cell receptor (TCR) genes in 50 newly diagnosed (ND) and 7 relapsed (RE) Ph-neg ALL pts with a median follow-up of 8 (range 1-35) and 2,5 months (range 1-16) in ND and RE pts, respectively. MRD monitoring was performed at the conventional time-points needed for ALL management. MRD analysis was performed both by ASO-qPCR and by NGS. Data were analyzed by Lymphotrack Dx and MRD software. Overall, 49/57 pts (86%) were successfully screened, with 34 IgH, 6 Igk and 45 TCR clonotypes identified. Most pts (29/49) had at least 2 clonotypes. In 4/7 RE pts, clonotypes re-assessment highlighted the emersion of previously undetected, novel rearrangements. To date, MRD was evaluated in 42 pts. In 18/42 pts, 124 MRD measurements were performed by ASO-qPCR, according to the EuroMRD guidelines, with sensitivity $>10^{-4}$ in 10/18 pts. In other 8/42 pts with sub-optimal ASO-qPCR assay, MRD was measured also by NGS to increase both sensitivity and specificity (33 measurements). NGS confirmed 29 (88%) ASO-qPCR results, 17 of which remained undetectable even by NGS, with up to 10^-5 sensitivity and >90% confidence. The remaining 4 results were discordant, with 3 measurements (previously PNQ or neg by ASO-qPCR) precisely quantified by NGS, and 1 (previously PNQ by ASO-qPCR) resulting neg by NGS. In 16/42 pts, MRD was analyzed just by NGS (72 measurements), with sensitivity of 10^{-4} in 39/72 (54%) and of 10^{-5} in 33/72 pts samples (46%). Clonotype assessment by NGS was successful in most cases and, repeated in RE pts, allowed to explore the relatively frequent possibility of clonal evolution in ALL pts. Even though the use of NGS for MRD analysis still requires a standardization and lacks guidelines for the clinical interpretation of the results, it undoubtedly allowed to quantify MRD with higher sensitivity and specificity, thus providing clinicians an important support for the interpretation of ambiguous data (such as PNQ by ASO-qPCR).

C030

DASATINIB PLUS BLINATUMOMAB *vs* HYPER-CVAD PLUS DASATINIB FOR THE FRONTLINE TREATMENT OF PHILADELPHIA CHROMOSOME-POSITIVE ACUTE LYMPHOBLASTIC LEUKEMIA PATIENTS. A MATCHING-ADJUSTED INDIRECT COMPARISON OF CLINICAL OUTCOMES

A. Piciocchi[1], M. Messina[1], S. Soddu[1], P. Fazi[1], M. Vignetti[1], S. Chiaretti[2], R. Foà[2]

[1]GIMEMA Foundation; [2]Hematology, Department of Translational and Precision Medicine, Sapienza University

Introduction: MAIC (matching-adjusted indirect comparison) methods are often required when 1) there is no common comparator treatment to link two clinical trials (unanchored MAIC); 2) there is a common comparator to link two clinical trials, but there are substantial differences in patients' demographics or disease characteristics (anchored MAIC). The premise of the MAIC methods is to adjust for between-trial differences in patients' characteristics. We used an anchored MAIC to perform a sensitive analysis of the results of the GIMEMA LAL2116 (dasatinib plus blinatumomab - Foà *et al.* NEJM 2020) weighted for the aggregated patients' characteristics from the M.D. Anderson Cancer Center (MDACC) trial combining dasatinib with hyper-CVAD (Ravandi et al Cancer 2015). Both trials were designed for the frontline treatment of adult patients with Philadelphia-positive acute lymphoblastic leukemia (Ph+ ALL). The aim of this pilot analysis was to test the method to compare the clinical outcomes of individual patients' data with aggregated published results.

Methods: Patient-level data from the LAL2116 trial (last update submitted to EHA2022 by Chiaretti et al) and aggregated data from the MDACC trial were used to conduct an anchored MAIC. LAL2116 patients (n=63) were weighted to balance with the baseline characteristics from the MDACC cohort (n=72). Weighted overall survival (w-OS) and disease-free survival (w-DFS) estimates, as well as complete molecular response (w-CMR) rates, were computed.

Results: Four potential effect modifiers were used for adjustment: age, gender, WBC and fusion transcript. The LAL2116 w-OS and w-DFS estimates at 48 months were 79% (95%CI: 67%-92%) and 78%(95%CI: 67%-89%), respectively. These survival rates are indeed superimposable to those reported in the LAL2116 trial and significantly higher than the results obtained by the MDACC treatment scheme (Table 1). At both timepoints (+85, blina-C2), the LAL2116 w-CMR rates were similar to the observed values; a comparison with the results of the MDACC trial was not appropriate for differences in methods and timing.

Conclusions: The MAIC method allowed a robust comparison of two clinical trials for the frontline treatment of adult Ph+ ALL and confirmed the greater efficacy of the dasatinib plus blinatumomab combination. This pilot analysis documented the feasibility and potential of this statistical approach, that paves the way to the comparison of studies with differences in patients' features.

Table 1. MAIC results on survival estimates and CMR.

	LAL2116 Observed; Chiaretti et al, EHA 2022	LAL2116 Weighted	MDACC hyper-CVAD plus dasatinib ; Ravandi et al, Cancer 2015
OS at 48 months	78% (66%, 92%)	79% (67%, 92%)	50%*
DFS at 48 months	75% (64%, 87%)	78% (67%, 89%)	50%**
CMR post-C2 blinatumomab	60%	62.9%	-
CMR d +85	28.8%	30.3%	-
CMR at 4 weeks	-	-	65%

*At 47 months
**At 31 months

Infections

C031

EFFECT OF ANTI-SPIKE MONOCLONAL ANTIBODIES ADMINISTRATION ON COVID-19 PROGRESSION AND TIME TO VIRAL CLEARANCE IN PATIENTS WITH HEMATOLOGICAL MALIGNANCIES AND PAUCISYMPTOMATIC SARS-COV-2 INFECTION: THE GIMEMA EMATO0321 STUDY

V. Marasco[1], A. Piciocchi[2], L. Fianchi[3], A. Candoni[4], A. Guidetti[1,5], P. Musto[6,7], M. Bocchia [8], S. Pilerci[9], S. Galimberti[10], E. Coviello[11], R. Bruna[12], A. Visentin[13], M. Turrini[14], A. Tucci[15], C. Selleri[16], E. Crea[2], P. Fazi[2], F. Passamonti[17,18], P. Corradini[1,5]

[1]Divisione di Ematologia e Trapianto di Midollo Osseo, Fondazione IRCCS Istituto Nazionale dei Tumori; [2]GIMEMA Foundation; [3]Dipartimento di Ematologia, Fondazione Policlinico Universitario Agostino Gemelli-IRCCS; [4]Dipartimento di Medicina Specialistica, University of Udine; [5]Università degli Studi di Milano; [6]Dipartimento di Emergenza e Trapianto d'Organo, Università "Aldo Moro"; [7]Unità di Ematologia e Trapianto di Cellule Staminali, AOU Consorziale Policlinico; [8]Unità di Ematologia, Università di Siena, Azienda Ospedaliero Universitaria Senese; [9]Dipartimento di Medicina Sperimentale e Clinica, Università di Firenze; [10]Dipartimento di Medicina Clinica e Sperimentale, Università di Pisa; [11]Unità di Ematologia e Trapianto di Midollo Osseo, Istituto di Ricovero e Cura a Carattere Scientifico Ospedale Policlinico San Martino; [12]Divisione di Ematologia, Dipartimento di Medicina Traslazionale, Università del Piemonte Orientale e Ospedale Maggiore della Carità; [13]Unità di Ematologia e Immunologia Clinica, Dipartimento di Medicina, Università di Padova; [14]Ematologia, Ospedale Valduce; [15]Dipartimento di Ematologia, Azienda Ospedaliera Spedali Civili di Brescia; [16]Ematologia, Ospedale San Giovanni di Dio e Ruggi D'Aragona; [17]Dipartimento di Medicina e Chirurgia, Università dell'Insubria; [18]ASST Sette Laghi, Ospedale di Circolo di Varese, Italy

Patients (pts) with hematological malignancies (HM) have an increased risk of death due to SARS-COV-2 infection. Anti-spike Neutralizing Monoclonal Antibodies (nMoAbs) are indicated for paucisymptomatic COVID-19 pts, but evidence of safety and efficacy among HM pts is lacking. We conducted a multicenter retrospective study (GIMEMA EMATO0321) at 13 centers to assess the effects of nMoAbs on paucisymptomatic HM pts, who were on active anticancer treatment or within 6 months from last therapy. The primary endpoint was the time to molecular naso-pharyngeal swab negativity. Secondary endpoints included hospitalization rate due to COVID-19, intensive care unit (ICU) admission rate, and safety assessment. Overall, 91 paucisymptomatic HM pts (median age 61 yrs) were evaluated. Most frequent diagnosis were non-Hodgkin lymphomas, myeloproliferative diseases, and multiple myeloma, with 42, 16, and 10 cases respectively. Sixty-five of 91 pts were on active treatment, whereas 4 were on a watch and wait strategy and 17 already completed the planned therapy. The most common treatments included chemotherapy in 15 pts, immunotherapy in 17 pts and immuno-chemotherapy in 19 pts. Seventy-two of 91 pts had received at least 1 dose of mRNA vaccine. Detailed pts' characteristics are reported in table 1. Fifty pts received Bamlanivimab/Etesevimab, 28 Casirivimab/Imdevimab, 6 Sotrovimab and 4 Bamlanivimab. Median time between SARS-CoV-2 positivity and nMoAb administration was 3 days (IQR 2-4). Molecular negativity was obtained in 86 pts (95%), with a median time of 18 days (range 1-174). This result is better than the previous finding of 28 days reported in historical group of HM pts not treated with nMoAbs ($p<0.0001$). We did not find any difference in nMoAbs activity according to age, diagnosis, type of treatment, vaccination status or type of nMoAbs. The rate of hospitalization due to COVID-19 progression was 12% (11/91), with a low percentage of ICU admission (2%, 2/91). Ten out of 11 hospitalized HM pts had a lympho-

proliferative disease. Most frequent side effects were chills (4%) and diarrhea (3%); no pts required hospitalization for the management of adverse events. Among paucisymptomatic HM pts the administration of nMoAbs seems to reduce time to swab negativity compared to historical control of HM pts. This result allows to maintain anticancer treatment intensity. Moreover, nMoAbs also reduced the rate of hospitalization due to COVID-19 progression in this high-risk group.

Table 1.

Characteristic	N = 91
Age	62 (19 , 85)
Sex	
M	55 (60%)
F	36 (40%)
Diagnosis	
NHL	33 (36%)
HL	6 (6.6%)
CLL	7 (7.7%)
MM	10 (11%)
Waldenstrom	2 (2.2%)
AML	9 (9.9%)
ALL	3 (3.3%)
Myeloproliferative neoplasm	16 (17.7%)
Other	5 (5.5%)
Response status	
CR	51 (60%)
PR	21 (25%)
PD	7 (8.2%)
Diagnosis	6 (7.1%)
Unknown	6
Hematological therapy	
Active	65 (76%)
Prior	17 (20%)
WW	4 (4.7%)
Unknown	5
Type of last treatment	
CT	15 (17%)
Immunotherapy	17 (20%)
ImmunoCT	19 (22%)
autoSCT	4 (4.6%)
alloSCT	3 (3.3%)
CAR T	2 (2.3%)
Target therapy	11 (13%)
Other	16 (18%)
Unknown	4
Last treatment line	
1	49 (54%)
> 1	35 (38%)
WW	4 (4.4%)
Type of variant	
Alpha (B.1.1.7 and Q lineages)	5 (5.5%)
Delta (1.617.3)	5 (5.5%)
Other	6 (6.6%)
Unknown variant	75 (82.4%)
Symptoms at onset	
Fever	62 (68%)
Cough	60 (66%)
Ageusia/Disgeusia	14 (15%)
Pharyngodynia	14 (15%)
Asthenia	27 (30%)
Headache	13 (14%)
Myalgia	20 (22%)
GE Symptoms	7 (7.7%)
Dyspnea	10 (11%)
Tachypnea	1 (1.1%)
Anosmia	8 (8.8%)
Radiology images showing typical COVID pneumonia	
Yes	5 (5.5%)
No	86 (94.5%)
Type of nMoAbs	
Bamlanivimab/Etesevimab	50 (56%)
Casirivimab/Imdevimab	28 (31%)
Bamlanivimab	4 (4.4%)
Sotrovimab	6 (6.7%)
Unknown	2 (2.2%)
Vaccination status	
Not vaccinated	19 (21%)
1 dose received	10 (11%)
2 doses received	33 (36%)
3 doses received	29 (32%)

NHL = non-Hodgkin lymphoma; HL = Hodgkin lymphoma; CLL = chronic lymphocytic leukemia; MM = multiple myeloma; AML = acute myeloid leukemia; ALL = acute lymphoblastic leukemia; CML = chronic myeloid leukemia; MDS =myelodisplastic syndromes; CR = complete response; PR = partial response, PD = progressive disease; CT =chemotherapy; SCT = stem cell transplantation.

C032

HUMORAL AND CELLULAR IMMUNE RESPONSE IN PATIENTS WITH HEMATOLOGICAL DISORDERS AFTER TWO DOSES OF BNT162B2 MRNA COVID-19 VACCINE: A SINGLE CENTRE PROSPECTIVE OBSERVATIONAL STUDY

E. Bossi[1], A. Aroldi[1,2], L.M. Borin[1], L. Verga[1], F. Cocito[1], B. Manghisi[1,2], G. Rindone[1,2], F. Cavalca[1,2], A. Ripamonti[1,2], E. Inzoli[1,2], M. Raggi[3], S.M.A. Malandrin[3], A. Cavallero[3], L. Antolini[2], D. Bonardi[1], R. Piazza[1,2], C. Gambacorti-Passerini[1,2]

[1]Hematology Division, San Gerardo Hospital; [2]Department of Medicine and Surgery, University of Milano-Bicocca; [3]Microbiology Laboratory, San Gerardo Hospital, Italy

Patients with hematological malignancies have been excluded from the Sars-CoV-2 vaccine trials, despite being at higher risk of severe COVID-19. We performed a single-center observational prospective study in which all the hematological patients followed at the Hematological Division of San Gerardo Hospital, Monza (Italy) deemed to be severely immunosuppressed and with no evidence of previous documented Sars-CoV-2 infection were offered vaccination with two doses of the BNT162b2 vaccine (Pfizer-BioNTech). Evaluation of Sars-CoV-2 IgG specific antibodies was performed between 30 and 60 days after the administration of the second vaccine dose. The T-cell response was analyzed in patients without serological response. Anti-Sars-CoV-2 IgG titers above the cut off value of 33.8 BAU/ml were detected in 303 (80.2%, 95% CI 75.8-94.1) out of the 378 patients enrolled. Patients with lymphoproliferative disorders had a significant lower probability of immunization compared to all other hematological conditions (43.2% versus 88.4%, $p<0.001$). Patients treated with anti-CD20 and Bruton tyrosine kinase inhibitors showed a significantly lower probability of immunization in comparison with all other treatments (21.4% versus 82.6% and 21.1% versus 84%, respectively, $p<0.0001$). Evaluation of cellular immune response was performed in 69 patients who failed seroconversion. Among them, 15 patients (22.7%, 95% CI 14.3-34.2) showed a positive T-cell response. Patients previously treated with anti-CD20 were 2.4 times more likely to test positive for T cell responses than patients treated with other regimens ($p=0.014$). Within a follow-up of 9 months from the second COVID-19 vaccination, symptomatic Sars-CoV-2 infections were reported by 20 patients (5.3%, 95% CI 3.5-8.0) and 4 of them required hospitalization; successful immunization, either serological or T cell mediated, conferred significant protection from developing symptomatic disease. These results indicate that hematological patients can mount an immune response in approximately 85% of cases. Treatment with anti-CD20 antibodies has a negative impact on the serological response but not on the T cell mediated one. Thus, patients with recent or ongoing anti-CD20 treatment who suffer from insufficient humoral immune response after 2 COVID-19 vaccinations might still benefit from vaccination.

C033

SIMULTANEOUS ONSET OF HEMATOLOGICAL MALIGNANCIES AND COVID-19: REAL LIFE DATA FROM THE EUROPEAN HEMATOLOGY ASSOCIATION SURVEY (EPICOVIDEHA)

C. Cattaneo[1], J. Salmanton[2], F. Marchesi[2], S. El-Ashwah[2], F. Itri[2], B. Weinnbergerová[2], M. Gomes Da Silva[2], M. Dargenio[2], S. Martín-Pérez[2], J. Dávila-Vals[2], F. Farina[2], J. Van Doesum[2], T. Valcović[2], C. Besson[2], C.B. Poulsen[2], A. López-Garcia[2], P. Žák[2], M. Schönlein[2], K. Piukovics[2], O. Jaksic[2], A. Cabirta[2], N. Ali[2], U. Sili[2], N. Fracchiolla[2], G. Dragonetti[2], T. Adžić-Vukičević[2], M. Marchetti[2], M. Machado[2], A. Glenthøj[2], O. Finizio[2], F. Demirkan[2], O. Blennow[2], M.C. Tisi[2], A.S. Omrani[2], M. Navrátil[2], Z. Ráčil[2], J. Novák[2], G. Magliano[2], M. Jiménez[2], C. Garcia-Vidal[2], N. Erben[2],

M.I. Del Principe[2], C. Buquicchio[2], R. Bergantim[2], J. Batnić[2], M. Al-Khabori[2], L. Verga[2], T. Szotkowski[2], M. Samarkos[2], I. Ormazabal-Vélez[2], S. Meers[2], J. Maertens[2], L.I. Princzés[2], M. Hoenigl[2], L. Drgoňa[2], A. Cuccaro[2], Y.M. Bilgin[2], A. Aujayeb[2], L. Rahimli[2], S. Gräfe[2], M. Sciumè[2], M. Mladenović[2], G.M. Çolak[2], M.V. Sacchi[2], A. Nordlander[2], C. Berg Venemyr[2], M. Hanáková[2], N. García-Poutón[2], Z. Emarah[2], G. Zambrotta[2], E. Nunes-Rodrigues[2], R. Cordoba[2], G.A. Méndez[2], M.M. Biernat[2], O.A. Cornely[2], L. Pagano[3]

[1]Hematology, ASST-Spedali Civili; [2]Scientific Working Group (SWG) Infection in Hematology of the European Hematology Association (EHA); [3]Hematology Unit Fondazione Policlinico Universitario Agostino Gemelli IRCCS

Patients (pts) with simultaneous diagnosis of hematological malignancies (HM) and COVID-19 are an even greater challenge for Hematologists. We aimed to describe clinical features and long-term follow-up in a large cohort of pts registered in the EPICOVIDEHA registry (Epidemiology of COVID-19 infection in pts with HM: a European Hematology Association survey), with a simultaneous diagnosis of HM and COVID-19, to document the outcome of these pts according to treatment received and to establish the best therapeutic program approach. From Feb-20 to Feb-22, 450 pts with simultaneous HM and COVID-19 have been registered. M/F ratio was 264/186 and the median age was 65y (IQR 53 to 75). Acute myeloid leukemia (AML) was the most frequent HM (35.8%), together with lymphoma (Ly, 34.7%). Median time between HM and COVID-19 diagnosis was 11 days before COVID-19 (IQR -21 to -2). COVID-19 was asymptomatic or mild in 36.5% of cases and severe or critical in the remaining cases. Most of pts were admitted to Hospital during COVID-19 (84.4%). Overall, 343 (76.2%) pts received treatment for HM, which was started before COVID-19 diagnosis in two thirds of pts; median time between HM diagnosis and start of treatment was 7 days (IQR 3 to 19). Treatment was delayed more than one month since diagnosis only in 57/343 pts (16.7%) and 32 (9.3%) pts were treated only with palliative care. A subset of pts did not receive any treatment (23.8%). Among 343 treated pts, an overall response rate was observed in 140 (40.8%) pts after the first line of treatment. After a median follow-up of 35 days (IQR 12 to 168), 273 pts were alive (60.7%). Causes of death were COVID-19 in 78 pts (44%), COVID-19+HM in 73 (41.2%) and HM in 26 (5.8%).

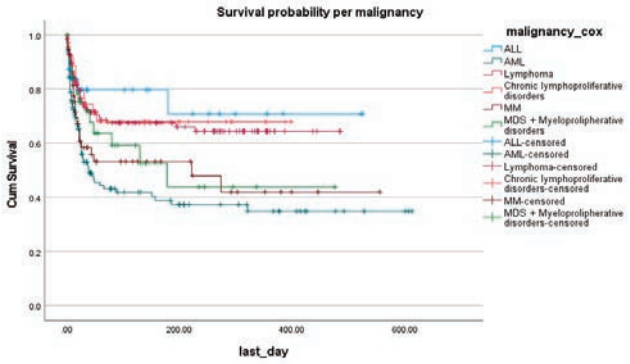


Figure 1.

Survival rate was particularly low in AML, as compared to acute lymphoblastic leukemia (p=0.012), Ly (p<0.0001) and chronic lymphoproliferative disorders (p=0.005) (Figure 1). At multivariable analysis, age (HR 1.037, 95% CI 1.025-1.049), critical COVID-19 (HR 4.607, 95% CI 2.885-7.355), ≥2 comorbidities (HR 1.704, 95% CI 1.109-2.617) and lack of HM treatment (HR 2.719, 95% CI 1.808-4.089) were risks factor for death. Chemotherapy induced neutropenia during acute COVID-19 did not impact on outcome of the entire cohort, except for Ly pts. HM treatment is needed for a favourable outcome in pts with simultaneous diagnosis of COVID-19 and HM. The timing of HM treatment start should be guided by COVID-19 severity, age and type of HM.

C034

ORAL ANTIVIRAL THERAPY IN SARS-COV-2 INFECTED OUT-PATIENTS RECEIVING ANTI-TUMOR TREATMENT FOR HEMATOLOGICAL MALIGNANCIES: A PRELIMINARY MULTICENTER ANALYSIS OF EFFICACY AND SAFETY

C. Minoia[1], D.F. Bavaro[2], G. Loseto[1], C. Pasciolla[1], L. Diella[2], C. Pellegrino[2], V. Totaro[2], V. Spada[2], M. Camporeale[2], I. Attolico[3], T. Perrone[3], F. Di Gennaro[2], P. Musto[3], A. Guarini[1], A. Saracino[2]

[1]Hematology Unit – IRCCS Istituto Tumori "Giovanni Paolo II", Bari; [2]Clinic of Infectious Diseases, Department of Biomedical Sciences and Human Oncology, University of Bari "Aldo Moro", Bari, Italy; [3]Hematology Unit - University of Bari "Aldo Moro", Bari, Italy

Background: Serious complications during SARS-CoV2 infection (63%) and a high mortality rate (up to 30%) were reported in onco-haematological patients; in addition, COVID-19 can also indirectly force the interruption or delay of cancer treatment. Early administration of oral antiviral drugs [molnupiravir (MOL) and nirmatrelvir/ritonavir (NIR/r)] may reduce hospitalization and death. The purpose of this study was to evaluate the possible role of new oral antiviral therapies in the specific setting of onco-hematologic patients with early COVID-19, where real-life data are lacking.

Methods: Outpatients diagnosed with onco-hematologic malignancy presenting COVID-19 were treated with antivirals. Hospitalization and lung failure rate, overall mortality, and safety were analyzed.

Results: Overall, 34 outpatients were prospectively enrolled in the study [median (q1-q3) age of 62 (45 – 68) years. males in 47% of cases). All subjects were affected by B.1.1.529 (omicron) SARS-CoV2 variant. Notably, 29 (85%) were fully vaccinated (3 doses) against SARS-CoV2. A total of 10 (29%) was affected by NHL, 7 (21%) by AML, 5 (15%) by CLL, 3 (10%) by ALL, 3 (10%) by MM, and 2 (5%) by HL, 2 (5%) MDS, 2 (5%) CML. Of those, 8 (24%) were in the follow-up phase, while 26 (76%) were on antineoplastic treatment: importantly, 9/26 (35%) with anti-CD20 therapies and 3/26 (11%) were in bone marrow aplasia. After multidisciplinary evaluation, 20 (58%) and 14 (42%) were treated with NIR/r and MOL, respectively; in addition, 6 patients (3 NIR/r and 3 MOL) underwent a combination therapy with monoclonal antibody against SARS-CoV2 (Sotrovimab) due to concurrent or recent anti-CD20 therapy (5/6) or due to bone marrow aplasia (1/6). Median (q1-q3) time from diagnosis of COVID-19 to therapy was of 1 (1-2) days. During/after therapy 3 (9%) patients were hospitalized due to progression of COVID-19: 1/3 developed severe lung failure and 2/3 died within hospitalization (1 due to COVID-19, 1 due to secondary infections). None reported adverse events any grade during treatment. Median (q1-q3) duration of COVID-19 (first positive to first negative antigenic test) was of 11 (7-17) days.

Conclusions: The early administration of oral antivirals may be safe in onco-hematologic outpatients and could reduce the risk of hospitalization and death due to SARS-COV2 infection. Interestingly, the association with monoclonal antibody could be offered to higher risk patients due to ongoing anti-CD20 therapy.

C035

CLINICAL OUTCOME OF LYMPHOMA PATIENTS RECEIVING CHEMOTHERAPY DURING SARS-COV-2 POSITIVITY

A. Guidetti[1,2], C. Rusconi[1], V. Marasco[1], C. Oltolini[3], F. Taverna[4], M. Canzi[2], A. Dodero[1], L. Farina[1], L. Devizzi[1], M. Di Chio[1], M. Smania[2], F. Mazzon[2], F. Arienti[4], P. Corradini[1, 2]

[1]Divisione di Ematologia e Trapianto di Midollo, Fondazione IRCCS Istituto Nazionale dei Tumori; [2]Università degli Studi di Milano; [3]Dipartimento di Malattie Infettive, Istituto Scientifico San Raffaele; [4]Servizio di Immuno-Ematologia e Medicina Trasfusionale, Fondazione IRCCS Istituto Nazionale dei Tumori, Italy

Patients (pts) with active lymphoid malignancies (LM) infected by SARS-CoV-2 are at high risk of protracted viral shedding and prolonged symptoms duration due to malignancy- and therapy-related immunodeficiency. Discontinuation of chemotherapy (CT) because of viral infection can worsen LM prognosis. Feasibility of CT administration during SARS-CoV-2 infection in LM pts has not been fully investigated so far.

We collected clinical data and results of nasopharyngeal swabs (NFS) for consecutive LM pts treated with CT while positive for SARS-CoV-2, with the aim to describe CT feasibility and to assess the risk of infection worsening. NFS were evaluated based on analysis of cycle threshold of RdRP gene assuming NFS with cycles > 40 as negative. Seven LM pts were treated between January and March 2022 at our center; all pts were positive for Omicron variant of concern and pauci or asymptomatic at COVID-19 diagnosis. Median age was 62 years (41-72). Four pts were affected by Diffuse Large B Cell Lymphoma, 2 by Hodgkin Lymphoma and one by Marginal Zone Lymphoma; at time of infection, 3 pts were receiving first line and 4 a subsequent line of treatment. All pts were previously vaccinated, with 1 (n=1), 2 (n=2) or 3 doses (n=3) of m-RNA vaccines. Two pts received sotrovimab. Patients received a median of 1 cycle of CT (1-3) at a median of 23 days (13-36) from the first SARS-CoV-2 positivity. Four pts received rituximab plus CT, 2 pts CT and one patient ibrutinib. Only one pt (pt 4) developed nasal congestion after CT administration in association with an increase of viral load, whereas two pts developed febrile neutropenia. Five pts achieved a negative NFS for SARS-CoV-2 during CT, while 2 pts remain positive at 65 and 89 days since first detection. Results of NFS were analyzed in terms of cycle threshold for gene RdRP as index of viral load. In 4 pts an increase of viral load was detected (Figure 1), after intensive chemoimmunotherapy with R-CODOX-M/R-IVAC in 2 cases and after ICE and escalated BEACOPP in one case each. Both the two pts with persistent positivity were treated with RCODOX-M/R-IVAC. In conclusion, administration of CT for LM during pauci-symptomatic SARS-CoV-2 infection seems feasible and in our preliminary experience did not induce clinical worsening of COVID-19. However, the increase of viral load observed after CT suggests that treatment with rituximab and high dose CT may temporary increase immunosuppression thus favoring viral replication.

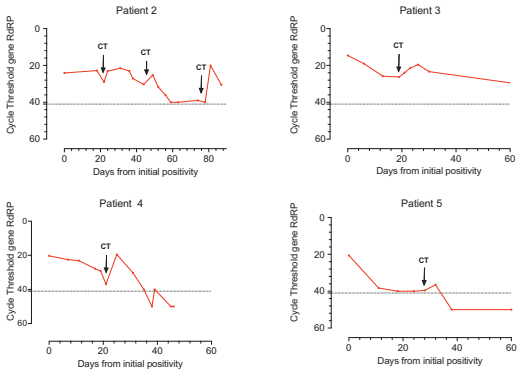


Figure 1.

Allogenic and autologous transplant

C036

NON-RESTRICTIVE DIET DOES NOT INCREASE GASTROINTESTINAL INFECTIONS AND FEBRILE NEUTROPENIA IN PATIENTS WITH NEUTROPENIA AFTER STEM CELL TRANSPLANTATION: RESULTS FROM NEUTRODIET MULTICENTRE PHASE III TRIAL

F. Stella[1,5], V. Marasco[1], G. Levati[1], A. Guidetti[1,2], A. Chiappella[1], G. Perrone[1], M. Pennisi[1], C. Tecchio[3], N. Mordini[4], G. Ferrara[1], G. Gobbi[1], L. Saracino[1], C. Carniti[1], P. Corradini[1,2]

[1]Division of Hematology and Bone Marrow Transplant, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano; [2]Dept. of Oncology and Hematology, University of Milan; [3]Section of Hematology and Bone Marrow Transplant Unit, Department of Medicine, University of Verona; [4]Division of Hematology, Azienda Ospedaliera S. Croce e Carle; [5]Faculty of Medicine, University of Milan, Italy

Background: Preventive measures, including low microbial diet, have been adopted to reduce infections during neutropenia in hematopoietic stem cell transplantation (HSCT) recipients. However, the real effect of a protective diet (PD) has never been explored prospectively. Conversely, there is evidence that PD could negatively affect the quality of life and that a prolonged fasting can increase the incidence of acute gastrointestinal graft-versus-host disease (aGVHD) in allo-HSCT recipients.

Table 1. Patient's characteristics.

	Total =162	Protective = 80	Non restrictive = 82	p-value
Sex (Males)	96 (59%)	47 (59%)	49 (59%)	ns
Age median (range)	56 (22-71)	56 (26-71)	56 (22-71)	ns
Disease type				
- Aggressive lymphoma	60 (37%)	26 (32%)	34 (41%)	ns
- Indolent lymphoma	15 (9%)	10 (12%)	5 (6%)	ns
- Multiple myeloma	70 (43%)	36 (45%)	34 (41%)	ns
- AML	4 (2%)	3 (4%)	1 (1%)	ns
- Other*	13 (8%)	5 (6%)	8 (10%)	ns
Previous lines				
- Median (range)	1 (1-3)	1 (1-3)	1 (1-3)	ns
- >/=3#	79 (49%)	39 (49%)	40 (49%)	ns
Disease status @enrollment				
- CR	80 (49%)	44 (55%)	36 (43%)	ns
- PR	59 (36%)	28 (35%)	31 (38%)	ns
- SD	6 (4%)	1 (1%)	6 (7%)	ns
- PD	7 (4%)	2 (2%)	5 (6%)	ns
- Non applicabile	10 (6%)	5 (6%)	5 (6%)	ns
Antimicrobial prophilaxis				
- Anti-viral	158 (97%)	77 (96%)	81 (99%)	ns
- Anti-bacterical	130 (80%)	65 (81%)	65 (79%)	ns
- Anti-fungal	153 (94%)	76 (95%)	77 (94%)	ns
Reason for admission				
- ASCT	130 (80%)	63 (79%)	67 (82%)	ns
- Allogeneic SCT	32 (20%)	17 (21%)	15 (18%)	ns

Methods: Since July 2016 we are conducting a multicentre randomized interventional study comparing the use of a PD (Arm A) *vs* non-restrictive diet (NRD) (Arm B) in patients aged>18 years hospitalized to receive autologous or allogenic HSCT. Patients received the assigned diet during neutropenia. For PD, foods cooked >80°C and thick peel fruit were considered diet-specific; NRD included fruit and vegetables (adherent to hospital hygiene standards). Primary aim was to assess incidence of infections grade>2 (according to CTCAE4.0) and deaths during neutropenic phase in the two arms. Secondary endpoints included assessment of gastrointestinal infections, fever of undetermined origin (FUO), body weight variations, length of hospitalization, overall survival and cumulative incidence of aGVHD in allo-HSCT recipients.

Results: Overall, 162 patients were analyzed at interim analysis, 80 patients in PD group and 82 in NRD group. Patient's characteristics are summarized in Table 1. We did not observe a significant difference in terms of infections in the two arms: infections grade>2 or death were reported in 35 (43.7%) patients in arm A and in 34 (41.5%) patients in arm

B [relative risk RR=1.05, confidence interval (CI) 95%=0.76-1.4]. Patients developing gastrointestinal infections and FUO during hospitalization was 8 (10%) *vs* 8 (9.8%) [RR=1.01, CI95%=0.57-1.53] and 32 (40%) *vs* 28 (34.1%) [RR=1.13, CI95%=0.82-1.54] in arm A and arm B, respectively. No differences in weight variations from admission to discharge were observed (mean 4.15 kg *vs* 3.66 kg, p=0.3). Average hospitalization length in the two arms was respectively 20.6 *vs* 21.5 days (p=0.4). No deaths were reported at day+30. For 32 allo-HSCT recipients, aGVHD grade >2 incidence at day+100 was 5% *vs* 1.2% in arm A and arm B (RR 1.65, CI95%=0.77-2.19).

Conclusions: Results of this multicentre prospective trial suggest that the use of NRD could be considered for neutropenic patients without risk of more infections.

C037

EXCELLENT OUTCOME WITH FB4 CONDITIONING REGIMEN IN PATIENTS AFFECTED WITH MYELOID MALIGNANCIES OLDER THAN 55 AND WITH HCTI-SCORE <2

D. Avenoso, M. De Farias, H. Alshehri, P. Krishnamurthy, V. Mehra, A. Kulasekararaj, S. Gandhi, A. Pagliuca, F. Dazzi, H. Wood, M. Kenyon, Y. Leung, A. Eaton, M. Cuadrado, A. Gameil, S. Bouziana, P. Hardefeldt, V. Potter

King's College Hospital NHS Foundation Trust, London, UK

Allogeneic haematopoietic stem cell transplant(HSCT)is a curative strategy for acute myeloid leukaemia (AML) and high risk myelodysplastic syndrome(MDS). The calculation of HCT-CI score and the upper limit of 55 years for administering myeloablative conditioning (MAC) are strategies to minimise HSCT non-relapse mortality(NRM). Despite multiple studies performed previously, this remains an area of uncertainty.

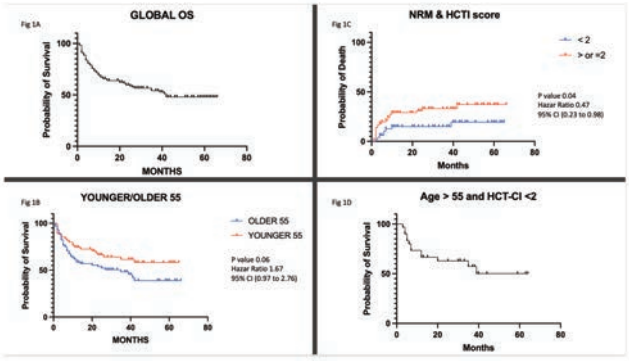


Figure 1.

We report the outcome of patients affected with AML and MDS conditioned with MAC. HSCT was performed with GCSF mobilised peripheral blood stem cells.Conditioning protocol was with fludarabine 30 mg/m^2 days-7,-6,-5,-4,-3 busulfan 3.2 mg/Kg days-6,-5,-4,-3 (FB4); graft versus host disease(GVHD)prophylaxis consisted of thymoglobulin (ATG 5 mg/Kg) or Campath 60 mg (27 and 94 patients, respectively)and ciclosporin 3 mg/Kg until d+56 and then tapered in absence of GVHD. A median of 5.5x10^6 CD34+/Kg was infused (3.1–8). Donors were: 21full matched siblings,76full matched unrelated donors, 24 mismatched unrelated donors. From January 2016 till November 2020, 121 patients (77 AML, 44 MDS) with a median age of 56(19-73)had FB4 conditioning. Patients aged>55 were 64(53%). HCT-CI score <2 and ≥2 was present in 48 and 73 patients, respectively. Two years overall survival(OS)was 55% with a median OS of 42 months (Figure 1A). Median time to neutrophils≥1000/μL was 12days(10-18), and 10days(8-48)to platelets≥20.000/μL. Median CD3 and CD15 chimerism at 1 year were 98% and 100%. Incidence of acute GVHD was 60%(grade III-IV 9%); chronic GVHD rate was 33% (moderate 14%, severe 7%). Relapse rate was 19%.There was no significant difference in OS when patients were stratified according to age (Figure 1B) even if there is a non-significant trend for patients younger than 55.Age at HSCT did not influence NRM but was higher in patients with higher HCT-CI: 10% versus 43% if HCT-CI was <2 and ≥2, respectively(p 0.04 – figure 1C). Two years OS for patients aged ≥55 and with HCTI-CI<2 and for those with HCTI-CI≥2 were 63% (median OS not reached in this group-figure 1D)and 45%, respectively. Two years GRFS for patients aged≥55 and with HCTI-CI <2 and ≥2 were 46% and 20%, respectively. Three years OS was57% and 42%, respectively.This analysis supports the feasibility of FB4 conditioning in patients affected with AML and MDS regardless of age. The decision for myeloablation should rely on comorbidities and disease characteristics rather than chronological age, especially for those with positive MRD at time of HSCT.

C038

PONATINIB AS A PROPHYLACTIC OR PRE-EMPTIVE STRATEGY TO PREVENT CYTOLOGICAL RELAPSE AFTER ALLO-SCT IN PATIENTS WITH PH-POSITIVE ACUTE LYMPHOBLASTIC LEUKEMIA TRANSPLANTED IN COMPLETE CYTOLOGICAL REMISSION

A. Candoni[1] C. Papayannidis[2], D. Lazzarotto[1], C. Skert[3], S. Trappolini[4], C. Sartor[2], R. Bassan[3], A. Olivieri[4], R. Fanin[1]

[1]Clinica Ematologica e Centro Trapianti e Terapie Cellulari, ASUFC, Udine; [2]Istituto di Ematologia Seragnoli, IRCCS Azienda Ospedaliero-Universitaria di Bologna; [3]Ematologia, Azienda Ulss3 Serenissima, Ospedale dell'Angelo, Venezia-Mestre; [4]Clinica di Ematologia, Azienda Ospedaliero-Universitaria, Ospedali Riuniti di Ancona, Italy

The proper administration of TKIs after Allo-SCT in Ph+ ALL remains controversial and the TKI approach (prophylactic, pre-emptive or salvage) is still heterogeneous. In this context, very little is known about the efficacy and safety of third-generation TKIs. Here we present the results of the ongoing multicentre study to analyse efficacy and safety profile of ponatinib (PONA) after Allo-SCT to prevent Ph+ ALL cytological relapse. We report the analysis of the first 32 included patients (pts) with Ph+ ALL (median age 46 years) who received PONA after their Allo-SCT (donors: 21 MUD, 6 siblings HLAId and 3 Haplo). All 32 pts received Allo-SCT while in complete cytological remission (cCR) and 18(56%) had positive minimal residual disease (MRD+) before Allo-SCT. PONA was administered prophylactically (starting with MRD neg) in 21 pts or pre-emptively (starting with MRD positivity post-SCT and without hematological relapse) in 11 pts. The 21 pts treated prophylactically with PONA started treatment earlier, at a median of 4 months (range 1,5-8) after Allo-SCT, than the 11 pts treated pre-emptively, who started PONA at a median of 7,4 months (range 2-31) (p=0,01). The starting dose of PONA was 30 mg/day (range 15-45). Reduction of the initial dose was required in 13/32-41% of cases (mainly in those receiving an initial dose of 45 mg/day), but a permanent discontinuation of PONA, due to toxicity, was required in only 3/32-9,4% pts. No deaths due to PONA-related adverse events were reported. The mean and median follow-up time after Allo-SCT was 34 and 30 months, respectively. At last follow-up, the median duration of PONA therapy was 16 months (range 1-100). Detailed data on safety profile of PONA were collected. In addition to PONA, 6 pts received DLI. The 5-year OS and RFS after Allo-SCT of all 32 pts were 90% and 80%, respectively (Figure 1a and 1b). The 5-year RFS after Allo-SCT of pts who received PONA as prophylaxis was 92% and it was 67% for those who received PONA pre-emp-

tively (log-rank p=0,2). The Preliminary data obtained from this analysis, in a homogeneous population of Ph+ ALL undergoing Allo-SCT while in CcR, support the efficacy and safety of PONA as a maintenance strategy (either as prophylaxis or pre-emptive) after Allo-SCT, resulting in a high probability of OS and DFS and in a low rate of discontinuation due to PONA-related toxicity. However, in the majority of cases where a daily dose of 45 mg was started a dose reduction to 30-15 mg/day was required, which seems to be the appropriate dose to balance efficacy and tolerability.

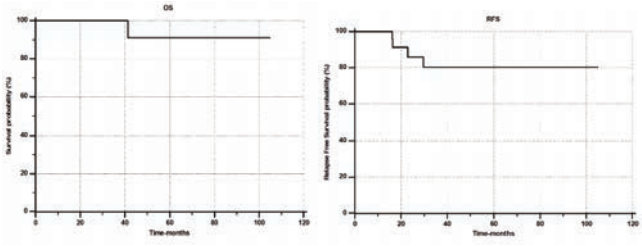


Figure 1. a. Overall Survival after Allo-SCT (90% at 60 months); b. RFS after Allo-SCT-all 32 cases (80% at 60 months). Median follow-up time after Allo-SCT: 30 months.

C039

ALLOGENEIC STEM CELL TRANSPLANTATION AND HLA DONOR-SPECIFIC ANTIBODIES (DSAS): THE IMPACT OF DESENSITIZATION STRATEGY ON ENGFRAMENT

G. Facchin[1], G. Petruzzellis[1], G. Vianello[1], M. Pucillo[1], G. Battaglia[1], C. Savignano[2], V. Miotti[2], M.L. Battista[1], R. Fanin[1], F. Patriarca[1]

[1]Division of Hematology and Stem Cell Transplantation, ASUFC; [2]Department of Transfusion Medicine, ASUFC

Introduction: Haploidentical (Haplo) or mismatched unrelated donors (MMUD) are more and more frequently employed for allogeneic hematopoietic stem cell transplantation. The presence of donor-specific anti-HLA antibodies (DSAs) is associated with risk of primary graft failure independently from graft source, conditioning regimen and other patient and donor factors. Plasma exchange (PEX), intravenous human immunoglobulin (IVIg) and Rituximab represent the backbone of several strategies, however the optimal desensitization schedule remains unclear.

Methods: Patients undergoing haplo- or MMUD-HSCT in our center from 2016 to 2022 were included in the study. DSA were detected using Luminex bead assays at the time of HLA typing, pre-desensitization, post-desensitization, and every week after transplant since engraftment. Results were expressed as Mean Fluorescent Intensity (MFI). Desensitization strategy was performed when pre-transplant DSA levels were higher than 2.000 MFI and include single dose of Rituximab 375 mg/m^2 on transplant day -15, PEX on days -11, -7, -1 and 0 and IVIg 0.4 mg/kg on days -8 and -1.

Results: 11/157 patients (7%) undergoing haplo- or MMUD-HSCT showed high level pre-transplant DSAs. As shown in Table 1, 6/11 (55%), 3/11 (27%), 2/11 (18%) patients presented anti-HLA DSAs class I, II or both, respectively. Median DSA level pre-desensitization was 12458 MFI (2795-24200), of them 7/11 (64%) had DSA >5000 MFI, 4/11 (36%) DSA >20000 MFI. Median DSA level post-desensitization was 6608 MFI (0-22100). After desensitization, DSAs level was no detectable in 4/11 (36%), it has shown at least a reduction of 50% in 5/11 patients and persisted at high level (DSAs > 20000 MFI) in only 1 patient. 9/11 patients (82%) achieved neutrophil engraftment and 2/11 (18%) presented primary graft failure. Both graft failure were associated with high level of anti-HLA DSAs class II (DRB1) pre- desensitization, without a significant reduction after the procedure.

Conclusions: In our study, the desensitization strategy was effective in 9/11 (82%) patients, with reduction of DSAs level and a complete neutrophil engraftment. Presence of high level of anti DRB1 DSAs pre-desensitization without a significant reduction after the procedure seems to be related with graft failure. Future studies are needed to better identify the optimal desensitization strategy in order to reduce the primary graft failure risk.

Table 1. Clinical characteristics.

Age (years), median (range)	60 (55-68)
Sex:	
• male	1/11 (9%)
• female	10/11 (91%)
Diagnosis:	
• Acute myeloid leukemia	9/11 (82%)
• Myelodisplastic syndrome	2/11 (18%)
Disease status before transplant:	
• Complete remission	5/11 (45%)
• Relapsed/Refractory	6/11 (54%)
Donor-Reciplient HLA:	
• haploidentical	8/11 (73%)
• mmUD	3/11 (27%)
ABO mismatch	
• Minor	4/11 (36%)
• Major	4/11 (36%)
• No mismatch	3/11 (27%)
Donor-Recipient sex mismatch:	
• Yes	9/11 (82%)
• No	2/11 (18%)
Median HCT-CI (range)	0,8 (0-4)
Conditioning regimen:	
• Myeloablative	9/11 (82%)
• Non myeloablative	2/11 (18%)
Stem cell source:	
• Peripheral blood	9/11 (82%)
• Bone marrow	2/11 (18%)
Graft composition:	
• Median CD34+/kg infused	5,99 (3,17-7,99)
• Median CD3+/kg infused	30,00 (4,09-49,56)
Antibody specificity	
• DSA class I	6/11 (55%)
• DSA class II	3/11 (27%)
• DSA class I and II	2/11 (18%)
DSA MFI (median)	
• Pre-desensitization	12.458 (2.795-24.200)
• Post-desensitization	6.608 (0-22.100)
• Engraftment	1012 (0-6200)
DSA reduction (pre-post desentization):	
• >50%	6/11 (55%)
• <50%	5/11 (45%)
Engraftment	9/11 (82%)
Graft failure	2/11 (18%)

C040

ESCALATING COMBINATORY FIRST-LINE TREATMENT FOR SEVERE ACUTE GVHD AFTER HEMATOPOIETIC STEM CELL TRANSPLANT

F. Saraceni[1], S. Guerzoni[1], B. Puglisi[1], I. Scortechini[1], G. Mancini[1], A. Fiorentini[1], F.R. Colaneri[1], A. Lotito[1], D. Tancredi[1], I. Federici[1], R. Bencivenga[2], B. Costantini[2], V. Bisraoui Huaman[1], S. Angeletti[1], M. Montanari[2], A. Olivieri[1,3]

[1]Department of Haematology, AOU Ospedali Riuniti Ancona; [2]Transfusion Medicine, AOU Ospedali Riuniti Ancona; [3]Università Politecnica delle Marche, Italy

Acute GVHD is a major cause of morbidity and mortality after HSCT. Steroids remain the standard first-line treatment for severe aGVHD, but less than 40% of patients show a long durable remission. We retrospectively analyzed the outcome of 23 patients who developed grade 3-4

aGVHD and received an escalating combinatory first-line treatment at our institution. Donor was sibling (n=1), UD (n=12) or haploidentical (n=10). Stem cell source was PBSC in 90% of the patients. Conditioning was myeloablative (35%) or reduced-intensity (65%). aGVHD involved skin (87%), GI (83%), and liver (17%). All patients received prednisone or methylprednisolone at a dose >= 1 mg/kg as first treatment. The response was evaluated on the 3rd and 5th days since steroids start. In patients with symptoms progression at day 3 or SD at day 5, extracorporeal photopheresis (ECP) was added (n=12). In all patients with stage >=2 lower GI involvement, Ruxolitinib (Ruxo) 10 mg twice daily was added within 5 days since start of steroids (n=7). ECP schedule included two treatments p/w for 8 weeks with a subsequent individual reduction of treatment frequency. Response to first line treatment was evaluated on day 28 and 56. In patients treated with steroids + ECP the ORR at day 28 was 75% (n=9), with 58% (n=7) achieving CR. In patients treated with steroids + ECP + Ruxo the ORR was 86% (n=6), with 67% (n=4) achieving CR (Figure 1). The durable ORR on day 56 was 58% (n=7/12) in patients treated with steroids + ECP and 71% (n=5/7) in patients treated with steroids + ECP + Ruxo. Median time on steroids was 12 days. ECP shows development of mild thrombocitopenia in 4 patients. 5 patients receiving Ruxo experienced grade 2 anemia or thrombocytopenia, the latter leading to drug discontinuation in 2 patients. 13 patients received ECP and 3 patients received Ruxo as second line treatment for steroid refractory or steroid dependent GVHD. 2 patients with lower GI involvement received vedolizumab as second line therapy. Median time to second line treatment was 24 days. 5 patients died; 4 due to infectious complications secondary to refractory GVHD, 1 of pulmonary embolism with GVHD in CR. Median OS of the global population was 20 months.

In conclusion, an escalating combinatory first-line treatment with a backbone of steroids and ECP, and the addition of Ruxo in patients with lower GI involvement seems feasible and associated with a promising response rate, allowing a rapid steroid taper.

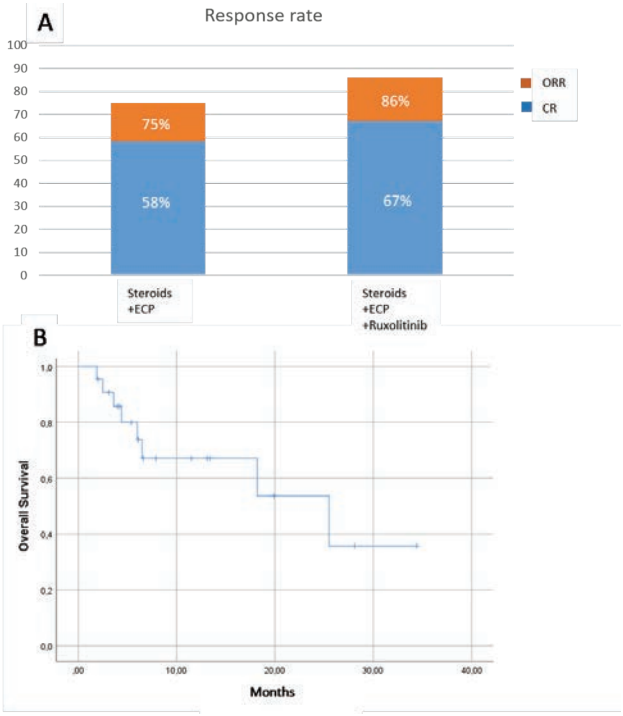


Figure 1.

Myeloproliferative neoplasms II

C041

SF3B1 MUTATIONS IN PRIMARY AND SECONDARY MYELOFIBROSIS: CLINICAL, MOLECULAR AND PROGNOSTIC CORRELATES

G.G. Loscocco[1,2], P. Guglielmelli[1], F. Mannelli[1], B. Mora[3], C. Mannarelli[1], G. Rotunno[1], F. Pancani[1], C. Maccari[1], N. Bartalucci[1], S. Romagnoli[1], G. Coltro[1], F. Passamonti[3], A.M. Vannucchi[1]

[1]Department of Experimental and Clinical Medicine, CRIMM, Center of Research and Innovation of Myeloproliferative Neoplasms, Azienda Ospedaliero-Universitaria Careggi, University of Florence, Italy; [2]Doctorate School GenOMec, University of Siena, Italy; [3]Hematology Unit, Department of Medicine and Surgery, University of Insubria, ASST Sette Laghi-Ospedale di Circolo, Italy

Background: *SF3B1* mutations are uncommon both in primary (PMF) and secondary myelofibrosis (SMF) patients (pts), without a defined impact on prognosis.

Aim and methods: clinical, molecular and prognostic correlates of *SF3B1* mutations in SMF *vs* PMF pts. We analyzed 520 pts annotated for *SF3B1* with a defined 2016 WHO diagnosis; 325 PMF (158 pre-fibrotic/167 overt) and 195 SMF (85 post-PV/110 post-ET).

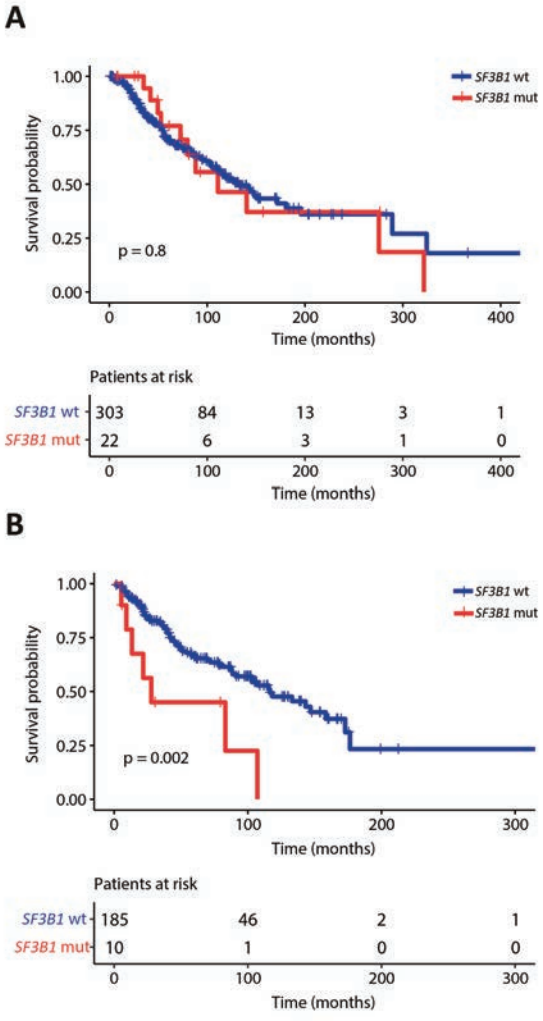


Figure 1.

Results: Median age of PMF pts (58% *JAK2*, 24% *CALR*, 6% *MPL*, and 12% triple negative –TN) was 59 years; 62% were males and median follow-up was 4.5 years. Deaths and leukemic transformations were 121 and 37, respectively. *SF3B1* mutations were detected in 22 pts (7%): 11 K666T/N/M, 7 K700E, 2 H662Q/Y, 1 R625L and 1 N626S. The most frequent non-driver *SF3B1* co-mutated genes included *ASXL1* (n=4) and *TET2* (n=3) followed by *DNMT3A*, *EZH2*, *TP53* (n=2 each). *SF3B1* mutated PMF pts were mostly male (86% *vs* 60%; p=0.01), older (65 *vs* 62 years; p=0.004) and displayed a quite significant higher platelet count (561x10^9/L *vs* 402 x10^9/L; p=0.06), and lower Hb levels (11.3 g/dL *vs* 12.3 g/dL; p=0.09). Among 195 SMF pts (67% *JAK2*, 23% *CALR*, 8% *MPL*, and 2% TN), median age was 63 years and 55% were male; median follow-up was 3.9 years. There were 80 deaths and 27 leukemic progressions. *SF3B1* mutations were detected in 10 pts (5%) and included 4 K666T/N/M, 4 K700E, 1 G751V, 1 G742D. The pattern of most frequent non-driver *SF3B1* co-mutated genes included *TET2* (n=4) followed by *CBL*, *RUNX1* and *TP53* (n=2 each). *SF3B1* mutated SMF pts were older (66 *vs* 62 years; p=0.09) and displayed frequently splenomegaly (p=0.05). *SF3B1* mutations were mostly associated with *CBL* (p=0.004), *RUNX1* (p=0.02) and *KRAS* (p=0.03). Considering PMF pts, *SF3B1* mutations did not impact on OS (Figure 1A, p=0.8) and LFS (p=0.6). Conversely, in SMF, OS was negatively affected by *SF3B1* mutations (Figure 1B,HR 3.1; p=0.002), but not LFS (p=0.9). Univariate analysis identified also age ≥ 65 years (HR 5; p=0.003), leukocytes > 25 × 10^9/L (HR 2; p=0.03), Hb < 11 g/dL (HR 3.1; p<0.0001), platelet count < 150 x10^9/L (HR 2.7; p=0.0003), circulating blasts ≥ 3% (HR 4; p<0.0001), mutations of *CBL* (HR 4; p=0.001), *SRSF2* (HR 8.1; p=0.0006), *U2AF1* (HR 2.7; p=0.02) and *TP53* (HR 2.9; p=0.003) as risk factors for reduced OS. Among these, multivariable analysis confirmed the independent prognostic contribution of mutated *SF3B1* (HR 2.8, p=0.02).

Conclusions: *SF3B1* mutations were independently associated with reduced OS in SMF, but not in PMF.

C042

RUXOLITINIB IN MYELODEPLETIVE MYELOFIBROSIS: RESPONSE, TOXICITY, AND OUTCOME

C. Mazzoni[1,2], D. Bartoletti[1,2], M. Breccia[3], G. Auteri[1,2], E.M. Elli[4], M.M. Trawinska[5], N. Polverelli[6], M. Tiribelli[7], G. Benevolo[8], A. Iurlo[9], A. Tieghi[10], G. Caocci[11], E. Beggiato[12], G. Binotto[13], F. Cavazzini[14], M. Miglino[15,16], C. Bosi[17], M. Crugnola[18], M. Bocchia[19], B. Martino[20], N. Pugliese[21], A.D. Romagnoli[1,2], B. Garibaldi[22], L. Scaffidi[23], A. Isidori[24], D. Cattaneo[9], M. Krampera[23], F. Pane[21], D. Cilloni[25,26], G. Semenzato[13], R.M. Lemoli[15,16], A. Cuneo[14], E. Abruzzese[5], N. Vianelli[1], M. Cavo[1,2], M. Bonifacio[23], G.A. Palumbo[27], F. Palandri[1]

[1]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli"; [2]Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale, Università di Bologna; [3]A.O.UPoliclinico Umberto I, Università degli Studi di Roma "La Sapienza"; [4]Ospedale San Gerardo, ASST Monza; [5]Ospedale S. Eugenio, Università Tor Vergata; [6]ASST Spedali Civili di Brescia; [7]A.O.U. Integrata di Udine; [8]A.O.U. Città della Salute e della Scienza; [9]Foundation IRCCS Ca' Granda, Ospedale Maggiore Policlinico; [10]Azienda USL - IRCCS di Reggio Emilia; [11]Polo oncologico "A. Businco", Università degli studi di Cagliari; [12]Dipartimento di Oncologia, Università di Torino; [13]A.O.U. di Padova; [14]A.O.U. Arcispedale SAnna; [15]IRCCS Policlinico San Martino; [16]Dipartimento di Medicina interna e Specialità mediche, Università di Genova; [17]AUSL di Piacenza; [18]A.O.U. di Parma; [19]Policlinico S. Maria alle Scotte, A.O.U. Senese; [20]A.O. 'Bianchi Melacrino Morelli'; [21]Dipartimento di Medicina clinica e Chirurgia, Università degli Studi di Napoli Federico II; [22]Scuola di Specializzazione in Ematologia, Università degli Studi di Catania; [23]A.O.U. Integrata Verona; [24]A.O. Ospedali Riuniti Marche Nord (AORMN), A.O. San Salvatore; [25]AOU San Luigi Gonzaga; [26]A.O. Ordine Mauriziano di Torino; [27]Dipartimento di Scienze Mediche, Chirurgiche e Tecnologie Avanzate "G.F. Ingrassia", Università di Catania, Italy

Patients (pts) with primary (PMF) or secondary myelofibrosis (SMF) and myelodepletive phenotype (MyD) have more limited therapeutic options and poorer prognosis compared to pts with myeloproliferative (MyP) MF. We explored prognostic correlates of MyD MF in 801 RUX-treated pts included in the "RUX-MF" retrospective study. MyD was defined as: WBC <4×10^9/L and/or Hb <11/<10 g/dL (males/females) and/or PLT <100×10^9/L with no increase of other blood cells (WBC >15×10^9/L, Hb >16.5/>16 g/dL in males/females, PLT >450×10^9/L). Overall, 219 (27.3%) had a MyD MF, including 140 (17.5%) PMF. In PMF pts, MyD was due to leukopenia, anemia and thrombocytopenia in 7.1%, 52.2% and 9.3%, respectively; in SMF, corresponding figures were 5%, 51.9% and 11.4%. Two or more cytopenias were found in 31.4% and 31.7% of PMF and SMF patients, respectively. In multivariable analysis (MVA), lower peripheral blast count (p=0.03), higher TSS (p=0.04) and marrow fibrosis grade ≥2 (p=0.03) confirmed their association with MyD in PMF pts. In SMF, MVA showed correlation of MyD to higher peripheral blast count (p=0.04), higher MYSEC-PM risk (p=0.001), and triple negativity (p=0.03). RUX starting, median at 3 months, and median overall dose was more frequently ≤10 mg BID in MyD than in MyP pts overall, PMF and SMF (p<0.001). Spleen response (SR) rate at 3 and 6 months was comparable in MyD and MyP pts but was lower in pts with PLT<100x10^9/l (p=0.02). In SMF, MyD pts had lower rates of SR at 3 (p=0.004) and 6 months (p=0.05). Symptom response (SyR) was significantly lower in MyD MF at 3 (p=0.01) and 6 months (p=0.008). After a median RUX exposure of 2.3 yrs (0.1-12.6), 364 (45.4%) pts stopped RUX, 110 (13.7%) had a leukemic transformation and 366 (45.7%) died. After competing risk analysis, the cumulative incidence of RUX stop was higher in MyD pts overall (p<0.001) (Figure 1a), only PMF (p=0.03) and only SMF (p<0.001). Incidence of RUX stop was significantly higher in MyD patients with ≥2 cytopenias (p=0.03). Leukemia-free survival was not influenced by MyD/MyP phenotype (Figure 1b). In Cox regression analysis adjusted for DIPSS score, OS was significantly shorter in MyD *vs* MyP MF (p=0.03) (Figure 1c). MyD phenotype is associated with baseline high-risk clinical and molecular features, lower responses to RUX, particularly in case of low PLT count, and higher risk of drug discontinuation and death. Newer strategies are warranted in this setting.

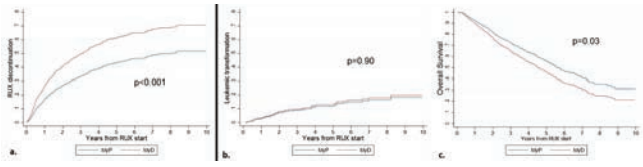


Figure 1.

C043

PREVALENCE OF UBA1 GENE MUTATIONS INVOLVING EXON 3, 4 AND 5 IN A SERIES OF PATIENTS AFFECTED BY MYELOFIBROSIS ASSOCIATED WITH CYTOPENIAS AND/OR INFLAMMATORY DISEASES

R. Stella[1,2], P. Guglielmelli[1], M. Bellini[1], C. Maccari[1], A.M. Vannucchi[1]

[1]Centro di Ricerca e Innovazione per le Malattie Mieloproliferative (CRIMM) - Università degli Studi di Firenze - Azienda Ospedaliero Universitaria Careggi; [2]SC Ematologia Azienda Sanitaria Universitaria Giuliano Isontina, Italy

Recently has been described a new and rare X-linked autoinflammatory disorder called VEXAS syndrome (Vacuoles, E1 enzyme, X-linked,

Autoinflammatory, Somatic), characterized by somatic mutations of the Ubiquitin Like Modifier Activating Enzyme 1 (UBA1) gene. Its main features involve severe autoinflammation (including chondrites, vasculitis and neutrophilic pulmonary and cutaneous inflammation) and hematologic abnormalities. These consist of cytopenias, characteristic vacuoles in myeloid and erythroid precursor cells and dysplastic bone marrow. Since Myelofibrosis (MF) is strictly linked to inflammation, dysplasia and cytopenias, the aim of our research was to examine the prevalence of UBA1 mutations in our court of patients selected for a diagnosis of MF associated with cytopenia and/or inflammatory diseases, also including females. Globally, 259 patients were selected and, among these, 84 had adequate material for UBA1 analysis. Exploratory, in order not to miss rarer variants, besides exon 3 and the site of junction between intron 2 and exon 3, we decided to expand our analysis involving exon 4 and 5 and the exon-intron junction. Eventually, only in one patient (1.2%) was identified an UBA1 mutation, different from mutations reported in VEXAS syndrome and possibly being another rarer variant. It was localized on exon 3 codon 50 predicting the substitution of isoleucine by a lysine: NM_153280.3_C.149T>A_p.Ile50Lys. The patient was a 69-year-old man diagnosed of triple negative overt-Primary MF, had constitutional symptoms, anemia and leucopenia without splenomegaly and common high-risk myeloid mutations. The fact that the patient was negative for driver mutations and high-risk myeloid mutations, while very symptomatic and cytopenic, suggests that his UBA1 mutation may have an important pathogenetic role in his disease. To our knowledge, this is the first investigation of UBA1 mutations in patients affected by MF. Given the tight connection between UBA1 and inflammation and between the latter and MF, it would be interesting to expand this analysis to more MF patients and to other exons of UBA1 gene.

C044

A PROGNOSTIC MODEL TO PREDICT FIBROTIC PROGRESSION IN PATIENTS WITH PREFIBROTIC PRIMARY MYELOFIBROSIS

G. Coltro[1,2], F. Mannelli[1,2], P. Cicogna[1,2], G.G. Loscocco[1,2], C. Mannarelli[1,2], M. Borella[1,2], P. Guglielmelli[1,2], A.M. Vannucchi[1,2]

[1]Department of Experimental and Clinical Medicine, University of Florence; [2]CRIMM, Center for Research and Innovation of Myeloproliferative Neoplasms, Azienda Ospedaliero-Universitaria Careggi, Italy

Background: Prefibrotic primary myelofibrosis (pPMF) recapitulates clinical findings of essential thrombocytopenia. However, outcomes of patients (pts) with pPMF are worse in terms of survival, leukemic evolution, and progression to overt PMF.

Aim and Methods Among 179 patients with WHO-defined pPMF, we sought to identify risk factors predicting fibrotic progression (FP) at 10 years (yrs) and over disease course using logistic regression and Cox proportional hazards models, respectively. FP was defined as previously described (Carobbio *et al.* BCJ 2020). Optimal threshold values for hemoglobin, leukocytes and platelets were computed using ROC analysis with FP as an endpoint.

Results: Median age was 53 (18-90) yrs, 82 (46%) pts were male. A total of 39 (22%) cases of FP were documented after a median time of 16 (11-23) yrs. In univariate analysis, the logistic 10-year risk of FP was predicted by male gender, leukocytes >12×10^9/l, sex-adjusted anemia, absence of thrombocytosis (platelets >450×10^9/l), leukoerythroblastosis, and palpable splenomegaly. Multivariable logistic regression confirmed the independent prognostic contribution of leukocytosis (OR 4.2), absence of thrombocytosis (OR 11.3), and leukoerythroblastosis (OR 7.8). Similarly, in a univariate Cox model, FP-free survival (FPFS) was predicted by leukocytosis, sex-adjusted anemia, absence of thrombocytosis, and leukoerythroblastosis, along with mutated SRSF2. Multivariate Cox analysis confirmed all the previous variables as independent predictors of inferior FPFS, with the only exception of SRSF2 mutation. We then inferred the results of the multivariable Cox analysis with the aim of devising a predictive model for FP, using a HR-weighted point allocation approach: 3 points for absence of thrombocytosis (HR 5.4) and leukoerythroblastosis (HR 4.9) each, 2 points for leukocytosis (HR 3.8), and 1 point for sex-adjusted anemia (HR 2.7). A three-tiered risk model was developed that well stratified pts for the risk of FP: low-risk (0-2 points; n=80), intermediate-risk (3-5 points; n=36), and high-risk (6–9 points; n=6), with median FPFS of 16 (HR 23.9), 8 (HR 6.6), and 2 yrs (HR 4.1), respectively (Figure 1).

Conclusions: In the current study we devised a straightforward, clinical prognostic model that accurately predicted the risk of FP in pPMF. Limitations of the study are its retrospective nature, spanning several years back, and the number of cases, signifying the need of further analysis before firm conclusions.

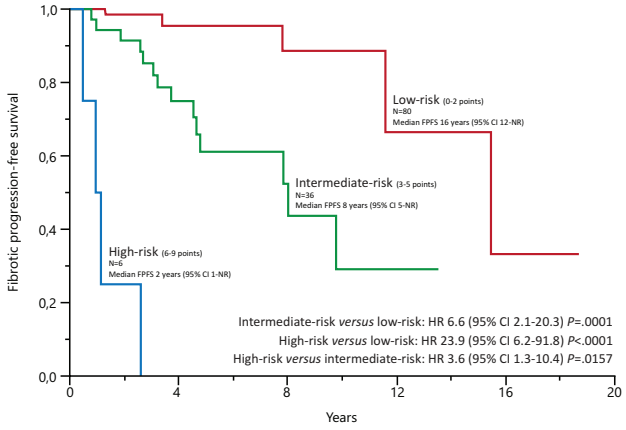


Figure 1.

C045

THE LSD1 INHIBITOR IMG-7289 (BOMEDEMSTAT) MANAGES THROMBOCYTOSIS AND LEUKOCYTOSIS IN PATIENTS WITH ESSENTIAL THROMBOCYTHEMIA (ET)

M. Marchetti[1], F. Palandri[2], D.M. Ross[3], T. Cochrane[4], S.W. Lane[5], S.R. Larsen[6], A.T. Gerds[7], A.B. Halpern[8], J. Shortt[9], J.M. Rossetti[10], K.M. Pettit[11], J. Liang[12], A. Mead[13], A. Vannucchi[14], A. Wilson[15], J.R. Göthert[16], M. Hanna[17], A. Jones[18], J. Peppe[18], G. Natsoulis[18], W. Navarro[18], W-J. Hong[18], W.S. Stevenson[19], C.H. Harrison[20], M. Talpaz[11], N. Vianelli[2], H.Y. Rienhoff[18]

[1]Azienda Ospedaliera Nazionale SS. Antonio e Biagio e Cesare Arrigo; [2]Institute of Hematology "L. & A. Seràgnoli", Sant'Orsola-Malpighi University Hospital; [3]Department of Haematology, Royal Adelaide Hospital and SA Pathology; [4]Department of Haematology, Gold Coast University Hospital; [5]QIMR Berghofer Medical Research Institute, Brisbane; [6]Institute of Haematology, Royal Prince Alfred Hospital; [7]Cleveland Clinic Taussig Cancer Institute, Cleveland; [8]Department of Medicine, Division of Hematology, University of Washington; [9]Monash Haematology, Monash Health; [10]UPMC Hillman Cancer Center; [11]Department of Internal Medicine, Division of Hematology/Oncology, University of Michigan; [12]Middlemore Clinical Trials; [13]MRC Weatherall Institute of Molecular Medicine, University of Oxford; [14]University of Florence, AOU Careggi, CRIMM, Center for Research and Innovation of Myeloproliferative Neoplasms, Italy; [15]University College Hospital, NHS Foundation Trust; [16]Department of Hematology, West German Cancer Center (WTZ), University Hospital Essen; [17]North Shore Hospital. Waitemata District Health Board; [18]Imago Biosciences Inc; [19]Kolling Institute of Medical Research, Royal North Shore Hospital; [20]Guy's and St Thomas' NHS Foundation Trust

Patients with ET often become resistant or intolerant to current treat-

ments underscoring the need for therapies with novel modes of action. Lysine-specific demethylase-1 (LSD1) is an enzyme critical for the self-renewal of malignant cells and for licensing progenitors to mature megakaryocytes. Bomedemstat is an orally active LSD1 inhibitor that in mouse models of MPNs reduced the hallmarks of MPNs in mouse models. IMG-7289-CTP-201 is an ongoing global, open-label, Phase 2b study of bomedemstat in patients with ET who are resistant to or intolerant of at least one standard ET treatment (NCT04254978). Eligible patients report need of cytoreduction, a platelet count (PLT) >450 x 10^9 /L, hemoglobin (Hb) ≥10 g/dL and absolute neutrophil count ≥0.5 x 10^9 /L. The starting dose of 0.6 mg/kg/d is titrated, as needed, to a target platelet count of 200-400x 10^9 /L. Response is defined as PLT≤400x10^9 /L without new thromboembolic events or disease progression. At data cut-off (01Nov'21), 37 patients have enrolled: median age was 68 (42-85) years and 75% were resistant/intolerant to HU, 11% to anagrelide, and 8% to interferon. Twenty-one patients reported a baseline TSS symptom score of 10 or higher. Genotyping by sequencing at screening revealed mutations in JAK2 (36%), CALR (39%), MPL (0%), non-driver mutations (EZH2, ASXL1, SF3B1, TP53)(19%). Median time on study is 28 weeks (0-57). For patients treated >6 weeks, 93% (27/29) achieved a PLT ≤400 x 10^9 /L (see figure). All the patients with elevated WBCs achieved a reduction to <10x 10^9 /L whilst on treatment. All patients maintained a stable Hb. In patients treated for 24 weeks with TSS >0 at baseline (N=17), 47% had a reduction of ≥10 points. The most common AEs were grade 1-2 dysgeusia (49%), constipation (32%), arthralgia, and fatigue (each 24%). 8 SAEs were reported. There have been no safety signals, DLTs, or deaths related to drug. At the time of data cut-off, 84% (31/37) of patients remain on study. To date, in patients resistant or intolerant to at least one standard treatment, bomedemstat has shown in a majority to be well-tolerated, reduce PLT, improve symptoms, and moderate WBC counts while maintaining Hb. For those patients treated ≥6 weeks, 90% achieved a complete response as defined above. Based on this promising data, a Phase 3 study of bomedemstat for the treatment of ET is being planned.

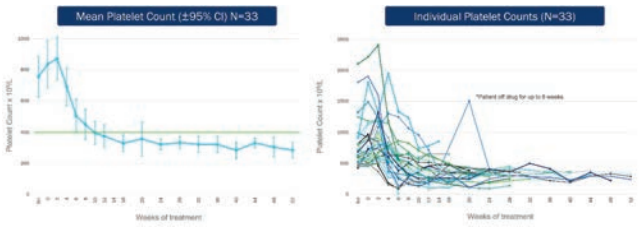


Figure 1.

Haemostasis, thrombosis, thrombocytopenia and platelet disease

C046

RISK OF IMMUNE THROMBOCYTOPENIA RELAPSE AND ONSET RELATED TO SARS-COV-2 VACCINATION AND INFECTION

G. Auteri[1,2], D. Bartoletti[1,2], C. Mazzoni[1,2], M. Biondo[1,2], A.D. Romagnoli[1,2], M. Cavo[1,2], N. Vianelli[1], F. Palandri[1]

[1]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli"; [2]Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale, Università di Bologna, Italy

SARS-CoV-2 infection and vaccination may induce Immune Thrombocytopenia (ITP) onset or relapse. In a monocenter cohort of ITP patients (pts) recorded in the electronical database of the IRCSS S. Orsola-Malpighi Hematology Center, Bologna, from 1982 to 2022, we assessed incidence of ITP onset/relapses following anti-SARS-CoV-2 vaccination/infection, risk factors for ITP relapse after vaccine, and risk factors for COVID19. Information on date/type of anti-SARS-CoV-2 vaccine, platelet (PLT) count before and within 30 days from vaccine and date/severity of COVID19, was collected via phone call or during clinical visits. ITP relapse was defined as a drop in PLT count within 30 days from vaccination that required a rescue therapy OR a dose increase of an ongoing therapy OR a PLT count <30 x10^9/L with ≥20% decrease from baseline. Between Feb2020 and Feb2022, 15 out of 57 (26.3%) new ITP diagnosis was thought to be related to SARS-CoV-2 infection (6 pts) or vaccination (9 pts). Among a total cohort of 1082 pts with ITP diagnosed before Feb 2020, 403 (37.3%) were untraceable or refused to answer questions, and 297 (27.4%) died before Feb 2020 and were excluded from this study. Therefore, 382 ITP pts were included in this analysis and 360 received ≥1 vaccine dose. ITP relapses occurred in 12/360 after the 1st dose (3.3%), 16/342 after the 2nd dose (4.7%) and 17/313 after the 3rd dose (5.4%). Overall, 35/360 (9.7%) pts had a relapse, with 10 (28.6%) pts who experienced multiple relapses, for 45 total relapses. In multivariable analysis (MVA), risk factors associated to ITP relapse after the 1st and the 2nd vaccine dose was active disease (OR 10.8, p=0.002 and OR 6.88, p=0.001, respectively). After booster, both active disease (OR 9.9, p<0.001) and previous relapse (OR 5.33, p=0.01) remained associated to relapse. Overall, 75/382 (19.6%) ITP pts had a COVID19 infection (severe in 9.3%). In MVA, ≥2 vaccine doses were associated with lower risk of infection (SHR 0.08; p<0.001). Both SARS-CoV-2 infection/vaccination represent risk factors for ITP onset. ITP relapse is also frequent after vaccination, with multiple relapses in many pts. Active disease and previous relapse are significantly associated with ITP relapse; in these pts, the completion of the vaccine program and the most appropriate laboratory follow-up after vaccination require case-by-case evaluation. However, having received at least 2 vaccine doses was the most protective factor against COVID19 infection.

C047

FEASIBILITY AND EFFICACY OF LONG TERM USE OF ELTROMBOPAG IN APLASTIC ANEMIA PATIENTS: A SINGLE CENTER REAL LIFE OBSERVATION

M. Carpenedo, A. Zappaterra, B. Ferrari, S. Pezzatti, L. Borin, A. Carrer, L.Verga

U.O Ematologia e Trapianto; ASST Ospedale San Gerardo di Monza, Italy

Introduction: Aplastic anemia (AA) patients benefit from treatment with Antithymocyte globulin (ATG) and cyclosporin (CYA); adding eltrombopag (ELT) to the standard treatment (tx) has led to considerable hemopoietic improvements. Most of published data are based on a maximum of 6 months (mo) of tx with ELT.

Aim: to retrospectively evaluate the efficacy and safety of ELT in our patients with AA treated longer than 6 mo in an attempt to consolidate the response

Results :18 pts (12 female, medium age 50 at diagnosis) 4 non severe AA, 12 severe, 2 very severe (Camitta score) received CyA (all) + ATG (16), and 10 received also ELT. 5 pt had a PNH clone without criteria to introduce anti C5 drug. ELT was given until maximum 150 mg/d then we adjusted the dose according to the response. At 3, 6 and 12 months from ELT start, 10%, 33% and 75% respectively achieved a complete response (CR), and another 30%, 33% and 12.5% achieved transfusion indipendence (TI) at the same time points, even if criteria for CR were not fufilled (Figure 1).

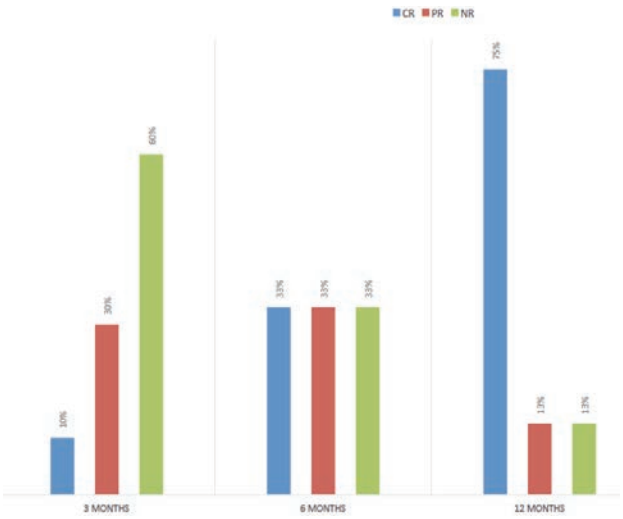


Figure 1.

3/10 pts, non respondent to ATG, CyA and ELT died at a median of 8 mo (4-12 mo) after diagnosis, (median 6 mo after ELT start) due to septic events. Tapering of ELT started at a median time of 12 mo (7-29 mo) after the first administration. With a median fup of 39 mo (20-64) after ELT start, 7/10 are in CR and 2 of them are off therapy since 22 mo. The other 5 are still treated with Cya + ELT in progressive dose tapering according to response, now in CR and dosage of ELT ranges from 100 mg/d to 50 mg once a week in an attempt to stop. No oncological evolution, vascular adverse event or relapse were recorded. 8 pts received only immunosuppressive tx because diagnosis occurred before ELT was licensed for AA in Italy (5) or a CR was reached soon after first line therapy (3). The median age of this group was 26.5 *vs* 53 yr of the previous group, all achieved TI and 6/8 achieved a CR within 6 mo (75% *vs* 33% of pts treated with ATG +CYA + ELT, p< 0.05) probably related to younger age at diagnosis. 2/8 died due to Sars Cov2 infection in CR.

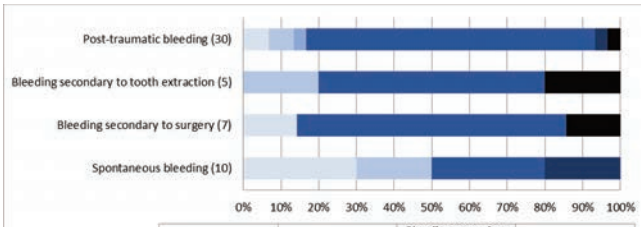
Conclusion: ELT added to CYA and ATG has shown high rate of CR even later than 6 mo of use without any concerning AE. A slow tapering of ELT, started only after a stable CR has been achieved is feasible in order to consolidate the goal. ELT might be useful to obtain a CR especially in AA diagnosed at older age. Lack of earlier response to tx exposes pts to fatal complications

C048

M. Mattana[1], C. Rotolo[1], R. Tomasello[1], C. Cammarata[1], A. Lucchesi[2] , G. Giordano[3], S. Siragusa[1], M. Napolitano[1]

[1]Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties (ProMISE), University of Palermo, Palermo, Italy; [2]IRCCS Istituto Romagnolo per lo studio dei tumori (IRST) "Dino Amadori", Meldola, Italy; [3]Division of Internal Medicine, Hematology Service, Regional Hospital "A. Cardarelli", Campobasso, Italy

Haemophilia is an X-linked recessive disease whose severity depends on the plasma levels of factor VIII (FVIII) in Haemophilia A (HA) or factor IX (FIX) in Haemophilia B (HB). Mild haemophilia (MH) is defined by FVIII or FIX levels between 5% and 40%. There is a paucity of data on MH; clinical evidence and guidelines are derived from severe haemophilia data. The current study aimed to describe clinical, laboratory characteristics and quality of life and illness perception of a cohort of patients affected by MH. We also assessed differences between patients with FVIII:c and FIX:c levels below and above 10%. This retrospective study enrolled all consecutive patients affected by MH A or B, evaluated at our centre from January 1st, 2012, to November 30th, 2021. Age, sex, FVIII and FIX levels, spontaneous or provoked bleeding episodes were collected. Patients were divided into two groups: A with factor levels less than or equal to 10% and B with factor levels greater than 10%. The Chi-square test was used for normally distributed continuous data analysis. A p-value < 0.05 was considered statistically significant. Patients with MH also filled the SF36 and ED-5Q questionnaires to assess health related quality of life and aspects of illness experience and perception, and the results were expressed as a percentage. Forty-two male patients with MH with a mean age of 42.6 +/- 23.4 years were analyzed.



	Spontaneous bleeding (10)	Bleeding secondary to surgery (7)	Bleeding secondary to tooth extraction (5)	Post-traumatic bleeding (30)
Spontaneous resolution	3	1	0	2
Tranexamic acid	2	0	1	2
Desmopressin	0	0	0	1
Factor VIII	3	5	3	23
Haemotransfusion	2	0	0	1
Trattamento chirurgico	0	1	1	1

Figure 1. Haemorrhagic manifestations and treatment.

Of these patients, 14 had FVIII or FIX levels less than or equal to 10%; the remaining had levels greater than 10%. Haemorrhagic manifestations and therapies are shown in Figure 1. The analysis revealed in-group A a statistically significant (p < 0.05) higher incidence of hemarthrosis and spontaneous bleeding than in-group B. There were no statistically significant differences regarding bleeding secondary to trauma or surgery.

SF36 and EQ5D were available for 20 patients: 8 patients from group A and 12 from group B. SF36 questionnaire scored above average (50 SD +/-10) in the area of physical function and below average in the area of emotional aspects, with a 5/6 point difference. The impact of the disease on daily life is thus important and unrelated to Factor levels. The ED-5Q data are congruent with the SF36 data. Perceived health status showed results above 70%. Spontaneous bleeding and hemarthrosis are more frequent in patients with factor levels below 10%. MH has a negative impact on patients' quality of life, especially in their emotional sphere.

C049

PHARMACOKINETIC / PHARMACODYNAMIC (PK/PD) SIMULATIONS GUIDE SELECTION OF THE DOSE FOR ADMINISTRATION OF EFGARTIGIMOD PH20 SUBCUTANEOUSLY IN A PHASE 3 CLINICAL TRIAL IN PATIENTS WITH PRIMARY IMMUNE THROMBOCYTOPENIA

E.N. Oliva[1], W. Ghanima[2], V. McDonald[3], S. Jain[4], A. Hultberg[5], D. Gandini[5], E. Hofman[5], T. Van Bragt[5], W. Parys[5], B. van Hoorick[5], M. Godar[5], F. Rocca[5], Y. Miyakawa[6], C.M. Broome[7]

[1]Haematology Unit, Grande Ospedale Metropolitano; [2]Departments of Medicine, Hematology-Oncology, and Research, Østfold Hospital Trust, Kalnes, and the Department of Hematology, Oslo University Hospital and Institute of Clinical Medicine, University of Oslo, [3]Barts Health NHS Trust, London, England; [4]RUSH University Medical Center, [5]argenx, [6]Saitama Medical University Hospital; [7]Georgetown University

Introduction: Efgartigimod is a human immunoglobulin (Ig) G1-derived Fc-fragment that binds with high affinity to the neonatal Fc receptor (FcRn) in a pH dependent way, resulting in a blockade of FcRn-mediated recycling and degradation of IgGs, including disease-associated autoantibodies. Previous studies in healthy subjects and patients with immune thrombocytopenia (ITP) or myasthenia gravis (MG) have demonstrated that four once-weekly (QW) intravenous (IV) infusions of efgartigimod 10 mg/kg achieves close to maximal IgG reduction and a significant reduction of pathogenic autoantibodies. This dosing schedule was well tolerated in all populations. To allow for subcutaneous (SC) administration, efgartigimod has been co-formulated with a fully human recombinant hyaluronidase enzyme (rHuPH20; efgartigimod PH20 SC). We describe the dose selection process for efgartigimod PH20 SC to identify the most suitable dose of efgartigimod PH20 SC to advance into a Phase 3 study in patients with persistent or chronic ITP.

Methods: Population pharmacokinetic (PK) and pharmacodynamic (PD) modeling data from a Phase 1 study (NCT04564066) were used to predict the efgartigimod PH20 SC dose that would result in a similar PD effect to the efgartigimod benchmark dose from previous studies of 10 mg/kg IV QW. This PK/PD study included 32 healthy subjects who received single SC injections of 750 mg, 1250 mg, 1750 mg or 10 mg/kg efgartigimod co-mixed with rHuPH20.

Results: Weekly SC administration of 1000 mg efgartigimod PH20 SC was predicted to result in comparable maximum total IgG reduction after the fourth SC injection as after the fourth IV infusion of 10 mg/kg administered QW. The area-under-the-curve for total IgG concentration and trough IgG reduction were also predicted to be comparable after four administrations of either formulation. No statistically significant effect of body weight on the PK and PD of efgartigimod PH20 SC was found.

Conclusion: These results informed the dose administration schedule in ADVANCE SC, a Phase 3, multicenter, randomized, double-blinded, placebo-controlled trial (NCT04687072) for evaluation of efficacy and safety of efgartigimod PH20 SC in adults with persistent or chronic primary ITP. Efgartigimod PH20 SC or placebo PH20 SC will be administered QW for four weeks and then either weekly or every other week until Week 24, determined by platelet counts. The primary objective of ADVANCE SC will be to evaluate the sustainable platelet count improvement.

C050

USE OF COVID-19 MRNA VACCINES IN ITP PATIENT: A REAL-LIFE MONOCENTRIC EXPERIENCE

F. Morelli[1], C. Giubbilei[1], S. D'Angelo[1], V. Paradiso[1], A.M. Vannucchi[2], V. Carrai[3]

[1]Hematology Unit, University of Florence; [2]Center for Innovation and Research in Myeloproliferative Neoplasms, Hematology Unit, Azienda Ospedaliera Universitaria Careggi, University of Florence; [3]Hematology, Department of Oncology, AOU Careggi, Italy

Background: COVID-19 pandemic had important implications in hematological patients (pts).As considered fragile individuals, immune thrombocytopenic purpura (ITP) pts were among the first to receive the vaccination. Considering the speed of production and the need of large-scale use of these new vaccines, speculations about their safety were made.Although rare, vaccines such as measles, mumps, and rubella vaccination is a recognized cause of ITP, so it was important to reassure our ps with data about the safety of these new vaccines.

Aims: We conducted this retrospective study to evaluate the safety of mRNA vaccines in a real-life setting of ITP pts followed in our center.

Materials and methods:A cohort of 43 ITP pts was enrolled, characteristics are reported in Table 1.Mentioning the vaccines used, 25 pts received two consecutive *Comirnaty* shots, 17 received two *Moderna* doses while just one received both shots combined. We collected blood samples from March to December 2021, in a time variable between one and two weeks after the vaccine dose. This management was continued until December 2021, when the *GIMEMA-SIE-SISET* recommendations were published.

Results: After the first dose, we observed a platelet drop in 24 pts (56%), with a median drop of 24.000/mmc (1.000-252.000). After the second shot, 23 (53%) pts experienced a platelet drop with a median of 65.000/mmc (2.000-249.000).Only one patient needed rescue therapy with intravenous immunoglobulin after both doses, for platelets less than 30.000/mmc. We did not observe a statistical difference in the median platelets decrease between pts under TPOra treatment and those who were not after the first and second dose, respectively (p=0.08; p=0.84). Time between first and second dose did not impact on platelet drop, with no difference in who received the second shot after 21 or 28 days (p=0.24). No differences in the median decrease was observed in pts with less or more than 50.000/mmc platelets after the first and second dose, respectively (p=0.33; p=0.1).

Conclusion: COVID-19 pandemic is still having an impact on everyone's life, especially for frail pts. In our limited case studies, we observed minimal variation in platelet count in about half of our patients, and only one needed rescue therapy. These real life data help us to confirm the safety of these vaccines in ITP pts, and push us to suggest pts to vaccinate as it remains the safest weapon we have to avoid even serious complications.

Table 1.

PATIENTS CHARACTERISTIC	N/43 pts
Sex (M/F)	18/25
Median age at I vaccine dose(years)	52 (32-86)
TPOra treatment (%)	17 (40%)
Romiplostim (%)	8 (19%)
Eltrombopag (%)	9 (21%)

Chronic myeloid leukemia

C051

PONATINIB IN A REAL-LIFE SETTING: A RETROSPECTIVE ANALYSIS FROM THE MONITORING REGISTRIES OF THE ITALIAN MEDICINES AGENCY (AIFA)

M. Breccia[1], P.P. Olimpieri[2], S. Celant[2], O.M. Olimpieri[2], F. Pane[3], A. Iurlo[4], V. Summa[2], P. Corradini[5], P. Russo[2]

[1]Department of Translational and Precision Medicine, Az. Policlinico Umberto I-Sapienza University, Rome, Italy; [2]Italian Medicines Agency, Rome, Italy; [3]Università degli Studi di Napoli Federico II, Naples, Italy; [4]Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy; [5]Università degli Studi di Milano & Divisione Ematologia, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milano, Italy

The efficacy and safety of ponatinib, a third-generation tyrosine kinase inhibitor (TKI), are mainly reported in sponsored clinical trials. The aim of this study, based on a retrospective analysis from the monitoring Registries of the Italian Medicines Agency (AIFA wMRs), is to provide real-world data on daily practice management, treatment modifications and outcome of a large cohort of chronic myeloid leukemia (CML) patients treated with ponatinib. Information collected through the wMRS included demographic and clinical data, drug prescription and administration data (dose changes, occurrence of adverse events as yes/no dichotomic variable, reasons for treatment interruption and/or discontinuation) and response to treatment. Overall, 666 CML subjects were eligible for analysis: 515 in chronic phase (CP), 50 accelerated phase (AP) and 101 blast phase (BP). Median age at baseline was 58.7 years, male prevalence (57.1%). Median time from diagnosis to start of ponatinib was 2.35 years: 259 (38.9%) subjects had received 2 lines of treatment, 260 (39.0%) 3 lines and 147 (22.1%) 4 or more lines. Mutational status was available for 58.3% of patients (n=388): T315I was reported in 46 (6.9%) patients and other mutations (the most frequent E255K, F317L, Y253H, V299L) in 99 (14.9%) subjects. Overall, 593 patients (89.0%) were evaluable for best response. Ten cases (1.7%, 3 AP/BP and 7 CP) did not achieve molecular response, whereas 58 patients (8.7%, 26 AP/BP patients and 32 CP) reached a BCR/ABL1 ratio between 1% and 10% IS. A MR2 (less than 1%IS) was obtained by 82 subjects (12.3%, 20 AP/BP and 62 CP patients); 128 patients (19.2%, 12 AP/BP and 116 CP patients) achieved a molecular response ranged between MR3 (0.1%) and MR4 (0.01% IS) and 266 (39.9%, 44 AP/BP and 222 CP patients) a deeper molecular response (< 0.01% IS). With a median follow-up of 14.4 months, 136 subjects (20.4%) required at least one dose reduction due to adverse events, while 309 patients (46.4%) decreased in the absence of side effects. Treatment discontinuation occurred in 144 patients (21.6%): intolerance (7.4%), primary resistance (3.5%) and acquired resistance (5.6%). The probability of treatment discontinuation did not significantly differ for ponatinib in second, third or subsequent line of therapy (p=0.58). This real-life investigation shows that ponatinib dose reductions were mainly performed in the absence of reported toxicity rather than owing to the occurrence of adverse reactions.

C052

BCR:ABL1 DIGITAL PCR IDENTIFIES CHRONIC PHASE CML PATIENTS SUITABLE FOR AN EARLY TKI DISCONTINUATION ATTEMPT: A PATIENT-LEVEL META-ANALYSIS

C. Kockerols[1], S. Dulucq,[2] S. Bernardi[3], M. Farina[4], I. Civettini[5], G. Colafigli[6], S. Mori[7], P. Valk,[8] F-X. Mahon[9], C. Gambacorti-Passerini[10], F.E. Nicolini[11], M. Breccia[12], D. Russo[13], P.E. Westerweel[14]

[1]Department of Internal Medicine, Albert Schweitzer Hospital; [2]Laboratory of Hematology, Hôpital Haut Lévêque, University hospital of Bordeaux; [3]Department of Clinical and Experimental Sciences, Hematology 2 and Bone Marrow Transplant Center, University of Brescia, ASST Spedali Civili of Brescia; [4]Department of Clinical and Experimental Sciences, Hematology 2 and Bone Marrow Transplant Center, University of Brescia, ASST Spedali Civili of Brescia; [5]Hematology Division, S. Gerardo Hospital, University of Milano Bicocca; [6]Department of Translational and Precision Medicine, Az. Policlinico Umberto I-Sapienza [7]School of Medicine and Surgery, University of Milano-Bicocca; [8] Department of Molecular Biology, Erasmus Medical Center; [9]Department of Hematology, Institut Bergonié; [10]Hematology Division, S.Gerardo Hospital, University of Milano Bicocca; [11]Department of Hematology, Centre Léon Bérard and CRCL; [12]Department of Translational and Precision Medicine, Az. Policlinico Umberto I-Sapienza University; [13]epartment of Clinical and Experimental Sciences, Hematology 2 and Bone Marrow Transplant Center, University of Brescia, ASST Spedali Civili [14]P.E. Westerweel: Department of Internal Medicine, Albert Schweitzer Hospital

Digital PCR (D-PCR) is an emerging technique that delivers a highly accurate BCR:ABL1 quantification, which is crucial for the selection of patients (pts) who may successfully discontinue TKI therapy. However, it is unclear how its prognostic value relates to time variables such as treatment duration prior to a treatment-free remission (TFR) attempt. Current guidelines suggest aiming for a TKI treatment duration >6 years to increase TFR success rate. We performed an Individual Patient Data Meta-Analysis of different CML cohorts in which BCR:ABL1 was assessed by D-PCR prior to TKI discontinuation. Pts were stratified based on D-PCR and treatment duration. BCR:ABL1 D-PCR was dichotomized based on the study-defined prediction cut-off. Strata were assessed for molecular relapse (MolR) with Kaplan-Meier and multivariable cox regression analysis including a frailty term and confounding variables: age, gender, Sokal score, TKI type, treatment duration, DMR duration and BCR:ABL1 transcript type. MolR was defined as BCR::ABL1 >0,1%IS or 1-log BCR:ABL1 increase in two consecutive analyses. Data were combined from 4 published (STIM2 [Nicolini *et al.*], n=175; ISAV [Diral et al.], n=107; Bernardi *et al*., n=111; Colafigli *et al*., n=50) and 1 unpublished cohort (Dutch; n=40).

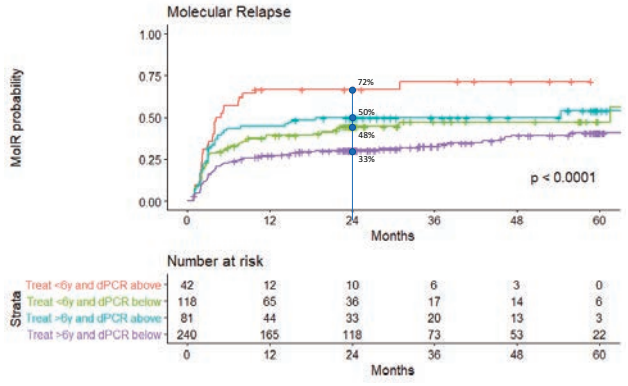


Figure 1.

The pooled dataset comprised 483 pts. 205 pts (42%) experienced MolR with a median time to relapse of 3 months. MolR pts had a significantly shorter treatment duration prior to TKI discontinuation (6.7 *vs* 7.9y, p=0.006) and more often presented a BCR:ABL1 D-PCR above the prediction cut-off (34% *vs* 19%, p<0.001). Interestingly, median treatment durations were similar in pts with a BCR:ABL1 below or above the cut-off (7.0 *vs* 7.5y, p=0.470). The probability of MolR at 24 months was 38% *vs* 58% for pts with a D-PCR BCR:ABL1 below *vs* above the cut-off (p<0.001). In the regression analysis, the HR of D-PCR BCR:ABL1 below the cut-off for MolR was 0.48 (95%CI 0.35-0.66, p<0.001). Pts with a TKI treatment for ≥6 years and low D-PCR result had the lowest MolR rate (Figure 1). Pts treated <6 years and with a low D-PCR result had a rate of 48% at 24 months, while pts treated <6 years and a D-PCR result above the cut-off had the highest MolR rate of 72% at 24 months. These results further support the independent prognostic value of BCR:ABL1 D-PCR in TFR prediction. Importantly, pts with a TKI treatment duration <6 years and a low D-PCR result were found to have a clinically acceptable MolR rate (48%).

C053

APPLICATION OF A NEW PROGNOSTIC SCORE FOR FAILURE-FREE SURVIVAL IN CML PATIENTS TREATED WITH FIRST-LINE IMATINIB

C. Ielo, E. Scalzulli, P. Musiu, C. Luise, S. Pepe, I. Carmosino, M. Martelli, M. Breccia

Hematology, Department of Translational and Precision Medicine, Sapienza University, Italy

Imatinib, the first generation tyrosine kinase inhibitor (TKI), is still widely used in first-line treatment of chronic myeloid leukemia (CML) owing to its efficacy and relatively moderate safety profile. Nevertheless, a widely used prognostic system specifically designed to assess the probability of imatinib failure is lacking and is needed to guide the choice of the appropriate initial TKI treatment. Among the available prognostic scores for CML, the new EUTOS long term survival (ELTS) score is so far the most accurate predictor of survival and response in patients receiving TKI therapy. We carried out a retrospective single-centre study in order to validate the imatinib-therapy failure (IMTF) score recently proposed (Zhang *et al.*, Leukemia 2022). The IMTF model includes five variables (Hb level, WBC count, basophils percentage and ELTS score) and stratifies patients in 5 categories as follows: very low risk, low risk, intermediate risk, high risk and very high risk.

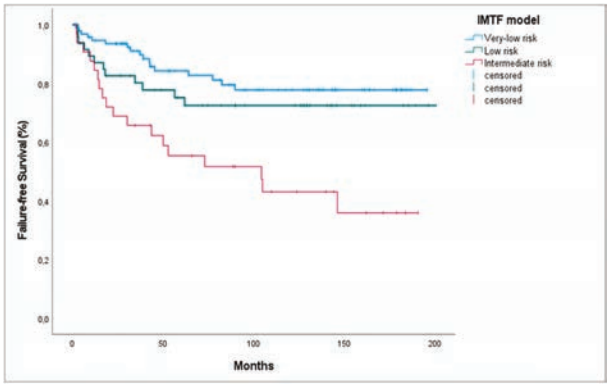


Figure 1.

One-hundred eighty-one CML patients treated with first-line imatinib were included in our analysis, with a median follow-up of 10 years. The median age at diagnosis was 60 years (range 22-87), 57% of patients were males and 43% females. Most of them (91%) had a low risk ELTS score. According to the IMTF score, 53.5% of patients were classified as very low risk, 26.5% as low risk, 18.2% as intermediate risk, 1.1% as high risk and 0.55% as very high risk. Considering the paucity of high and very high risk patients, we evaluated FFS (failure-free survival) restricting the analysis to the three most representative IMTF score subgroups of our cohort (Figure 1). In pairwise comparison we found statistically significant differences between the very low risk subgroup and the intermediate risk subgroup (p <0.001) and between the low risk subgroup and the intermediate risk subgroup (p=0.018). On the other hand, no difference between the very low risk and the low risk subgroup resulted from the analysis. The probability of FFS at 10 years was 77.8%, 72.5% and 43% for the very low, the low and the intermediate risk subgroup, respectively. ROC curves for FFS showed an acceptable performance of the IMTF score with an AUC value > 0.6. In conclusion, despite the unbalanced distribution of our patients in the IMTF risk categories, the proposed scoring system displayed considerable reproducibility in our cohort. IMTF score could be a valid tool to identify patients candidate to alternative treatments.

C054

BOSUTINIB DOSE OPTIMIZATION IN THE SECOND-LINE TREATMENT OF ELDERLY CML PATIENTS: 3-YEAR FINAL RESULTS OF THE BEST STUDY

F. Castagnetti[1], M. Bocchia[2], E. Abruzzese[3], I. Capodanno[4], M. Bonifacio[5], G. Rege-Cambrin[6], M. Crugnola[7], G. Binotto[8], C. Elena[9], A. Lucchesi[10], M. Bergamaschi[11], F. Albano[12], L. Luciano[13], F. Sorà[14], F. Lunghi[15], F. Stagno[16], M. Cerrano[17], A. Iurlo[18], A.R. Scortechini[19], S. Leonetti Crescenzi[20], R. Spadano[21], E. Trabacchi[22], M. Lunghi[23], G. Spinosa[24], D. Ferrero[25], D. Rapezzi[26], M. Ladetto[27], L. Nocilli[28], G. Gugliotta[1], M. Iezza[1], M. Cavo[1], G. Saglio[29], F. Pane[13], G. Rosti[10]

[1]Istituto di Ematologia "Seràgnoli", IRCCS Azienda Ospedaliero-Universitaria di Bologna, Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale, Università di Bologna, Bologna, Italy; [2]Hematology Unit, University of Siena, Siena; [3]Hematology Unit, S. Eugenio Hospital, Tor Vergata University, Roma; [4]Hematology Unit, Azienda Unità Sanitaria Locale-IRCCS di Reggio Emilia, Reggio Emilia; [5]Department of Medicine, Section of Hematology, University of Verona, Verona; [6]Internal Medicine Unit, San Luigi Gonzaga Hospital, Orbassano (TO); [7]Hematology Unit, Azienda Ospedaliero-Universitaria di Parma, Parma; [8]Department of Medicine, Hematology and Clinical Immunology, University Hospital of Padova, Padova; [9]Department of Hematology Oncology, Foundation IRCCS Policlinico San Matteo, University of Pavia; [10]Hematology Unit, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola (FC); [11]Hematology Unit, Policlinico S. Martino-IRCCS, Genova; [12]Hematology Unit, Department of Emergency and Organ Transplantation, University of Bari, Bari; [13]Hematology Unit, Federico II University , Napoli; [14]Hematology Unit, Policlinico A. Gemelli, Università Cattolica del Sacro Cuore, Roma; [15]Hematology and Bone Marrow Transplant Unit, San Raffaele Scientific Institute IRCCS, Milano; [16]Hematology Section and BMT Unit, AOU Policlinico V. Emanuele, Catania; [17]Hematology Unit, AOU Città' della Salute e della Scienza, Torino; [18]Hematology Unit, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano; [19]Hematology Unit, A.O.U. Ospedali Riuniti, Ancona; [20]Hematology Unit, San Giovanni - Addolorata Hospital, Roma; [21]Hematology Unit, Casa Sollievo Della Sofferenza, San Giovanni Rotondo (FG); [22]Hematology and BMT Unit, Department of Hematology and Oncology, Guglielmo da Saliceto Hospital, Piacenza; [23]Hematology Unit, AOU Maggiore della Carità, Novara; [24]Hematology Unit, Azienda Ospedaliero Universitaria Ospedali Riuniti, Foggia; [25]Department of Molecular Biotechnology and Health; Sciences, University of Torino, Torino; [26]Hematology Unit, AO S. Croce e Carle, Cuneo; [27]Hematology Unit, Ospedale SSAntonio e Bi-

agio e Cesare Arrigo, Alessandria; [28]Hematology Unit, Azienda Ospedaliera Papardo, Messina; [29]Divisione Universitaria di Ematologia e Terapie Cellulari, A.O. Ordine Mauriziano, Torino, Italy

The median age of second-line CML patients is > 60 years. Many of them have relevant comorbidities. Bosutinib (BOS) is a second-generation TKI with low incidence of cardiovascular (CV) adverse events (AEs). BOS safety profile may be relevant in elderly patients, but a fixed initial dose of 500 mg may be higher than necessary. To assess the efficacy of low initial BOS dose in the second line treatment of elderly CML patients (> 60 yrs old), with dose increase in absence optimal response (dose optimization), a prospective phase 2 study has been conducted. All patients started BOS 200 mg for 2 weeks, then increased to 300 mg; pts with BCR-ABLIS transcript ≤ 1% at 3 months continued 300 mg, while pts with transcript > 1% further increased to 400 mg. After 12 months (core phase), all pts were followed for additional 2 years (extension phase) to assess long-term efficacy and outcome. The 3-year final analysis is presented here. 63 patients were enrolled; median age: 73 yrs. Reasons for switching to BOS: intolerance 65%, resistance 35%. First-line TKI: imatinib 83%, DAS 11%, NIL 6%. The MR3 rate at 12 mos was 59% (primary endpoint). Median follow-up: 38 mos (3 years minimum). Maximum BOS dose: 400 mg, 21%; 300 mg, 73%; 200 mg, 6%. The probabilities of achieving or maintaining MR3, MR4 and MR4.5 by 36 mos were 78%, 54% and 46%, respectively; lower response rates were observed in resistant pts (64%, 36% and 18%, respectively). Overall, 24%, 33% and 11% of pts had 1 log, 2 logs or > 3 BCR-ABLIS transcript logs reduction from baseline. At 36 mos, 57% were still on BOS, while 27 pts (43%) discontinued the study drug. Events leading to permanent treatment discontinuation: 7 unrelated deaths, 9 AEs, 9 unsatisfactory responses (without transformation), 1 TFR attempt, 1 other reason. The overall survival probability was 81%. Pts with CV AEs: acute coronary syndromes, 6 pts; pericarditis, 2 pts; peripheral arterial thrombosis, 1 pt (all pts had CV risk factors). No pleural effusions were observed. The incidence of GI toxicity was lower than reported elsewhere. 36 pts were still on BOS at the last contact: 6% on 400 mg, 50% on 300 mg, 44% on 200 mg. In conclusion, in elderly pts a progressive BOS dose increase based on molecular response produced high response rates in this setting and most patients remained on 300 mg or less. BOS was well tolerated. An initial use of low dose TKIs, with increase in absence of optimal response, is a promising strategy in all elderly patients.

C055

TREATMENT-FREE REMISSION IN CML: TEN YEARS' EXPERIENCE IN BOLOGNA

M. Iezza[1], F. Castagnetti[1,2], E. Ottaviani[2], M. Mancini[2], C. Monaldi[1], S. De Santis[1], G. Gugliotta[2], N. Testoni[1,2], S. Soverini[1], G. Rosti[3], M. Cavo[1,2]

[1]Dipartimento di Medicina Specialistica Diagnostica e Sperimentale (DIMES), Università di Bologna; [2]Istituto di Ematologia "Seràgnoli", IRCCS Azienda Ospedaliero-Universitaria di Bologna; [3]Hematology Unit, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Italy

Treatment-free remission (TFR) after TKI therapy discontinuation (D/C) has become one of the main and attractive goal for CML patients. Many studies and real-life experiences have shown the feasibility and safety of TFR, but they are confounded by selection bias. In this retrospective analysis, we aimed to describe the outcome of D/C in a real-life context, according to current guidelines (ELN 2020). Adults CP-CML patients (pts) treated with TKI in Bologna between Jan 2000-March 2022 and who subsequently ceased therapy were analyzed. We examined separately the two subgroups of pts diagnosed after and before 2010. We were able to accurately assess deep molecular response (DMR, MR4 or better) by standardized (IS) qPCR since March 2012. Out of 531 pts treated with TKI since 2000, 111 (21%) stopped therapy (from 2013). 43% and 20% of cases met, respectively, the "optimal" and "minimal" criteria for TFR (ELN), 37% less than minimal or undefined (for DMR duration). After a median follow-up (FU) of 48 months (mos) after D/C, 44% of pts lost MR3 (74% within 6, 16% 7-12, 8% 13-24, 2% >24 mos) and 43% resumed therapy (77% at confirmed MR3 loss; 23% at MR2 loss after a 5 mos longer median time); one pt was retreated with BCR-ABLIS >10%, due to pregnancy. After restarting TKI, at least a MR3 was regained in 98% of cases. Out of the pts still in TFR (overall, 12% of our CML pts), 30% didn't meet the ELN eligibility criteria; one is on the second attempt. In all, 81 TFR pts had diagnosis before 2010 (A group) and 30 after (B group). Pts on 1L-IMA, 1L-2GTKI, ≥2L-TKI were (%): 33/13, 25/77, 42/10, respectively. In the A group, 47% of pts didn't fit the ELN eligibility criteria (nearly half due to DMR duration, although stable DMR is difficult to evaluate, given the issue mentioned above); in the B group, 90% were "suitable" for D/C (in particular, 67% fulfilled the optimal criteria). The rates of MMR loss were 42% and 50%, respectively. Therapy duration was longer in the A group (10.2 *vs* 5.3 years). Regarding the B group only, MR3 loss was observed in 73/50/31% of pts with stable DMR within 36/37-48/>49 mos, respectively. Our results confirm TFR is successful only in a small proportion of CML pts and the use of less strict criteria (of eligibility and retreatment) outside clinical trials does not impact the achievement rates. Therapy duration is confirmed a key predictive factor, but larger sample size and longer FU are needed to clarify the real impact of DMR duration.

Non-Hodgkin's lymphoma II

C056

CLINICAL IMPACT OF IMMUNOGLOBULIN HEAVY CHAIN REPERTOIRE IN MANTLE CELL LYMPHOMA: A STUDY FROM THE FONDAZIONE ITALIANA LINFOMI (FIL) PHASE III MCL0208 TRIAL

B. Alessandria[1], E. Genuardi[1], A.M. Civita[1], D. Drandi[1], B. Mantoan[1], M. Ferrante[1], M. Borriero[1], S. Ragaini[1,2], G. Bondielli[1], G.M. Zaccaria[1,3], D. Barbero[1], V. Peri[1,2], S. Hohaus[4,5], G. Musuraca[6], N. Cascavilla[7], C. Ghiggi[8], M. Tani[9], G. Gaidano[10], S. Volpetti[11], S. Veronica Usai[12], N. Di Renzo[13], S. Cortelazzo[14], M. Ladetto[10,15], S. Ferrero[1,2]

[1]Department of Molecular Biotechnologies and Health Sciences, University of Torino; [2]Città della Salute e della Scienza di Torino, Hematology Division, Torino; [3]Unit of Hematology and Cell Therapy, IRCCS-Istituto Tumori 'Giovanni Paolo II', Bari; [4]Dipartimento di Diagnostica per Immagini, Radioterapia Oncologica ed Ematologia, Fondazione Policlinico Universitario A. Gemelli, IRCCS; [5]Dipartimento di Scienze Radiologiche ed Ematologiche, Università Cattolica del Sacro Cuore, Rome; [6]IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Hematology unit, Meldola; [7]IRCCS, Casa Sollievo della Sofferenza, Hematology Division, San Giovanni Rotondo; [8]IRCCS San Martino, U.O. Ematologia e Terapie cellulari , Genova; [9]UOC. Ospedale Santa Maria delle Croci, Hematology Unit, Ravenna; [10]Department of Translational Medicine, University of Eastern Piedmont, Division of Hematology, Novara; [11]Centro trapianti e terapie cellulari, Clinica ematologica, Ospedale Santa Maria della Misericordia-ASUFC, Udine; [12]Ospedale Oncologico Armando Businco, Division of Hematology, Cagliari; [13]Vito Fazzi Hospital, Unit of Hematology, Lecce; [14]Humanitas/Gavazzeni Clinic, Oncology Unit, Bergamo; [15]Azienda Ospedaliera SS Antonio e Biagio e Cesare Arrigo, Struttura Complessa di Ematologia, Alessandria, Italy

Background: Mantle cell lymphoma (MCL) is characterized by a highly restricted immunoglobulin heavy chain (IGH) gene repertoire with stereotyped IGHV CDR3s. Aims: We aimed at characterizing the IGH VDJ repertoire and its putative clinical relevance in the MCL trial. Methods: IGH clonal rearrangements detection was performed by Sanger sequencing on bone marrow or peripheral blood samples collected in FIL MCL0208 trial (NCT02354313). IMGT/V- QUEST tool was used to annotate IGHV-D-J and mutational status (cut-off 98%). Finally, these data were integrated with published clinical, pathological, and mutational data from the trial (current median follow-up 38 months). Results: A clonal IGH productive rearrangement was detected in 209/300 patients (70%), resulting in 159 (76%) unmutated (UM) and in 50 (24%) mutated (M) cases, as expected. Overall, VDJ usage included 29 IGHV families, with IGHV3-21 (#45,22%), 4-34(#33,16%) as the most frequent groups representing the 38% of the analyzed series (Figure 1A). Interestingly, patients carrying IGHV3-21 were often characterized by low Ki-67 index (Ki-67<30%:86%vs64% of other cases, p<0.01) and low risk MIPI score (73%vs43%,p=0.001), while no case of blastoid morphology was registered among the IGHV 4-34 patients (vs89%,p<0.05). Moreover, by grouping together these two rearrangements, statistically significant associations were found with several biomarkers of favorable prognosis (low Ki-67, p<0.01;non-blastoid, p<0.05;absence of TP53 aberrations, p<0.05, or KMT2D mutations, p<0.05, and low-risk MIPI, p<0.0001). Accordingly, both IGHV 3-21 and 4-34 patients showed better long-term outcomes, with longer PFS and OS if compared with all the other cases, both singularly and when grouped together (3 years PFS:75% *vs* 53%,p<0.05;3 years OS:91%vs76%, p<0.01,Figure 1B,C). Finally, these results were independent from IGHV mutational status (p=0.09) and lenalidomide maintenance (p=0.46). Conclusion: This is the first study assessing the clinical impact of VDJ IGH repertoire in a large prospective trial in MCL. As expected, 76% of patients resulted UM, with 3-21 and 4-34 representing 38% of all the IGHV rearrangements. Notably, in our series, no significant correlation between mutational status and outcome was recorded. On the other hand, patients carrying either IGHV 3-21 or 4-34 rearrangements were characterized by favorable clinical and biological known prognosticators and were associated with both PFS and OS improvement.

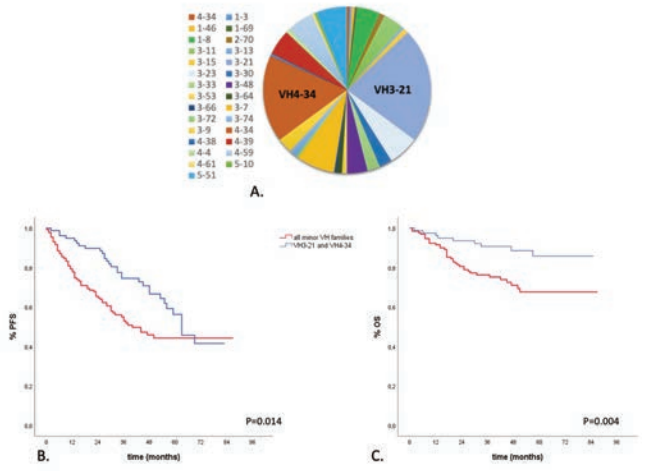


Figure 1.

C057

ZANUBRUTINIB PLUS OBINUTUZUMAB (ZO) VERSUS OBINUTUZUMAB (O) MONOTHERAPY IN PATIENTS WITH RELAPSED OR REFRACTORY (R/R) FOLLICULAR LYMPHOMA (FL): PRIMARY ANALYSIS OF THE PHASE 2 RANDOMIZED ROSEWOOD TRIAL

P.L. Zinzani[1], J. Mayer[2], R. Auer[3], F. Bijou[4], A. de Oliveira[5], C. Flowers[6], M. Merli[7], K. Bouabdallah[8], P. Ganly[9], R. Johnson[10], S. Yuen[11], E. Kingsley[12], G. Tuyman[13], S. Assouline[14], E. Ivanova[15], P. Kim[16], J. Huang[16], R. Delarue[15], J. Trotman[17,18]

[1]Institute of Hematology "Seràgnoli", University of Bologna; [2]Department of Internal Medicine-Hematology and Oncology, Masaryk University and University Hospital; [3]St. Bartholomew's Hospital, Barts Health NHS Trust; [4]Institut Bergonié; [1]nstitut Catala d'Oncologia (ICO) Hospital Duran I Reynals, Hospital; [6]Department of Lymphoma/Myeloma, MD Anderson Cancer Center; [7]Hematology, University Hospital "Ospedale di Circolo e Fondazione Macchi" - ASST Sette Laghi, University of Insubria; [8]Hôpital Haut-Lévêque, CHU Bordeaux; [9]Department of Haematology, Christchurch Hospital; [10]St. James's University Hospital Trust; [11]Calvary Mater Newcastle; [12]Comprehensive Cancer Centers of Nevada; [13]Department of Chemotherapy of Hemoblastosis, Blokhin Russian Cancer Research Center; [14]Jewish General Hospital; [15]BeiGene Switzerland GmbH; [16]BeiGene (Beijing) Co., Ltd., and BeiGene USA, Inc; [17]Concord Repatriation General Hospital; [18]Department of Haematology, University of Sydney

FL is the most common type of indolent non-Hodgkin lymphoma but has limited approved treatment options. In a phase 1b trial, ZO was tolerable and associated with an early efficacy signal. ROSEWOOD (BGB-3111-212) is a phase 2 randomized study to assess efficacy and safety of ZO *vs* O in pts with R/R FL with ≥2 prior therapy lines (ie, anti-CD20 antibody and alkylating agent). Pts were randomized 2:1 to ZO and O arms. O was given on Days 1, 8, and 15 of Cycle 1, Day 1 of Cycles 2-6, then every 8 wks for ≤20 doses. Z (160 mg twice daily) was given

until progressive disease (PD) or unacceptable toxicity; O arm pts with confirmed PD could crossover to ZO. The primary endpoint was overall response rate (ORR) by independent central review. Secondary endpoints were complete response rate (CRR), duration of response (DOR), progression-free survival (PFS), overall survival (OS), and safety. ORR by investigator after crossover was an exploratory endpoint. Primary analysis cutoff was 10/8/2021. In all, 217 pts were randomized to ZO (n=145) or O (n=72). Median follow-up was 12.5 mo; median age was 64 y. 53% (ZO) and 51% (O) had high FL International Prognostic Index scores. The median prior lines of therapy was 3; 28% (ZO) and 25% (O) received >3 lines. Proportion of pts refractory to rituximab, refractory to the most recent therapy line, or with PD within 24 mo of first-line immunochemotherapy initiation was 54%, 32% and 28% (ZO) and 50%, 40% and 32% (O), respectively. The primary endpoint was met; ORR was 68.3% (ZO) *vs* 45.8% (O; P=.0017). CRR was 37.2% (ZO) *vs* 19.4% (O); 18-mo DOR rate was 70.9% (ZO) *vs* 54.6% (O); median PFS was 27.4 mo (ZO) *vs* 11.2 mo (O; hazard ratio [HR], 0.51 [95% CI, 0.32–0.81], P=0.0040). Median time to new anti-lymphoma therapy or crossover was not evaluable (NE; ZO) *vs* 12.1 mo (O; HR, 0.37 [95% CI, 0.23–0.60], P<0.0001). ORR for ZO crossovers (n=29) was 24.1%. Median OS was NE; 18-mo OS was 85.4% (ZO) *vs* 72.6% (O). Most common AEs in the ZO arm were thrombocytopenia (34.3%), neutropenia (27.3%), diarrhea (16.1%), and fatigue (14.0%). Grade ≥3 AEs in >5% of pts with ZO were neutropenia (22.4%) and thrombocytopenia (14.0%); incidence of atrial fibrillation was 0.7% and major bleeding was 1.4%. Incidence of fatal treatment-emergent AEs was 5.6% (ZO) and 9.9% (O). In all, ZO demonstrated superior efficacy to O and had a favorable benefit-risk profile in pts with R/R FL, suggesting that ZO may be a potential combination therapy for pts with R/R FL.

C058

ZANUBRUTINIB (ZANU) IN OLDER PATIENTS (PTS) WITH RELAPSED/REFRACTORY (R/R) MARGINAL ZONE LYMPHOMA (MZL): SUBGROUP ANALYSIS OF THE MAGNOLIA STUDY

A. Tedeschi[1], J. Trotman[2], P.L. Zinzani[3], F. Cavallo[4], R. Marasca[5], A. Liberati[6], B. Hu[7], K. Linton[8], P. McKay[9], H. Chan[10], J. Jin[11], M. Sun[12], M. Sobieraj-Teague[13], M. Coleman[14], P. Browett[15], X. Ke[16], C. Portell[17], C. Thieblemont[18], K. Ardeshna[19], F. Bijou[20], P. Walker[21], E. Hawkes[22], S. Ho[23], K. Zhou[24], M. Co[25], J. Xu[25], J. Huang[25], S. Opat[26]

[1]ASST Grande Ospedale Metropolitano Niguarda; [2]Concord Repatriation General Hospital, University of Sydney; [3]Institute of Hematology "Seràgnoli" University of Bologna; [4]University of Turin, Medical School; [5]Hematology Unit, Department of Medical and Surgical Sciences, University of Modena and Reggio Emilia; [6]Azienda Ospedaliera "Santa Maria"; [7]Levine Cancer Institute/Atrium Health; [8]The Christie Hospital NHS Foundation Trust; [9]Beatson West of Scotland Cancer Centre; [10]North Shore Hospital; [11]The First Affiliated Hospital, Zhejiang University college of medicine; [12]Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College; [13]Flinders Medical Centre; [14]Clinical Research Alliance/Weill Cornell Medicine; [15]Auckland City Hospital; [16]Peking University Third Hospital; [17]University of Virginia Health System; [18]APHP, Hôpital Saint-Louis, Hemato-oncology, Paris University Diderot; [19]University College London Hospitals; [20]Institut Bergonié; [21]Peninsula Private Hospital; [22]Box Hill Hospital; [23]St. George Hospital; [24]Henan Cancer Hospital; [25]BeiGene (Beijing) Co., Ltd., and BeiGene USA, Inc; [26]Monash Health and Monash University

MZL, the second most common lymphoma in older pts, can be challenging to treat due to pt- or disease-related risk factors and treatment toxicity. The next-generation Bruton tyrosine kinase (BTK) inhibitor zanu, which was designed to minimize off-target effects, has received accelerated approval in the United States for R/R MZL. MAGNOLIA (BGB-3111-214; NCT03846427) is a phase 2, multicenter, single-arm study of adults with R/R MZL; here, we present a subgroup analysis of pts ≥65 y. Eligible pts had ≥1 prior therapy (ie, ≥1 anti-CD20 regimen); long-term antiplatelet/anticoagulant use was permitted. Zanu dosing was 160 mg twice daily. Primary endpoint was overall response rate (ORR) by independent review committee (IRC) per Lugano classification. Secondary endpoints were investigator-assessed (INV) ORR, duration of response (DOR), progression-free survival (PFS), and safety. As of 18Jan2021, 68 pts were enrolled (≥65 y: n=40; ≥75 y: n=18); median age was 73 y (range, 65-85). Median number of prior lines was 2 (range, 1-6); 10 pts (25%) were refractory to their last therapy. Most pts had prior rituximab/cyclophosphamide/vincristine/prednisone (48%) or bendamustine/rituximab (30%); 5 pts (13%) had prior rituximab monotherapy. MZL subtypes included extranodal (n=17; 43%), nodal (n=14; 35%), and splenic (n=8; 20%). Median treatment duration was 14.4 mo (range, 0.9-19.6). At a median follow-up of 15.8 mo (range, 2.8-21.8), ORR by IRC was 75% (table). ORRs were 71%, 86%, and 75% for extranodal, nodal, and splenic subtypes, respectively (complete response 41%, 21%, and 0%, respectively). Median DOR and PFS were not reached; 15-mo PFS was 87% and 12-mo DOR was 93%. 63% of pts remain on zanu. Discontinuation (d/c) due to disease progression was 28% by INV. Treatment-emergent adverse events (AEs) in ≥20% of pts were contusion (28%), diarrhea (25%), and constipation (20%). Grade ≥3 neutropenia occurred in 5% of pts. The most common infection was upper respiratory tract infection (10%). 2 pts (5%) had unrelated fatal AEs (COVID-19 pneumonia and myocardial infarction in a pt with preexisting coronary artery disease). Atrial fibrillation/flutter and hypertension occurred in 2 pts (5%) each and did not lead to zanu d/c. No pts required dose reductions, or had major or serious hemorrhage. In summary, zanu was well tolerated in older pts with R/R MZL and had a safety profile consistent with previous findings. High response rates and durable disease control were also observed.

Table 1. Baseline Characteristics, Efficacy, and Safety Outcomes.

	Patients ≥65 Years (n = 40)	Patients ≥75 Years (n = 18)
Baseline Characteristics		
Male sex, n (%)	23 (58)	11 (61)
ECOG PS 0-1, n (%)	35 (88)	15 (83)
Bone marrow involvement, n (%)	18 (45)	9 (50)
Prior lines of therapy, median (range)	2 (1-6)	1 (1-4)
Efficacy (IRC assessment)		
ORR (CR+PR), n (%)	30 (75)	17 (94)
[95% CI]	[58.8, 87.3]	[72.7, 99.9]
CR	10 (25)	4 (22)
PR	20 (50)	13 (72)
SD	7 (18)	1 (6)
PD	3 (8)	0 (0)
Time to response (months), median (range)	2.81 (1.7, 11.1)	2.83 (1.7, 5.6)
Safety		
Any TEAE, n (%)	37 (93)	16 (89)
Grade ≥3 TEAE, n (%)	18 (45)	9 (50)
Serious TEAE, n (%)	16 (40)	8 (44)

CI, confidence interval; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; IRC, independent review committee; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; TEAE, treatment-emergent adverse event.

C059

GLOFITAMAB PLUS R-CHOP INDUCES HIGH RESPONSE RATES WITH MINIMAL CYTOKINE RELEASE SYNDROME (CRS) IN PATIENTS WITH R/R NHL AND PREVIOUSLY UNTREATED DLBCL: PRELIMINARY RESULTS FROM A DOSE-ESCALATION AND SAFETY RUN-IN PHASE IB STUDY

A. Santoro[1], N. Ghosh[2], W. Townsend[3], M. Dickinson[4], M. Topp[5], M. Tani[6], M. Crump[7], F. Morschhauser[8], S. Le Gouill[9], A. Mehta[10], C. Wu[11], M. Barrett[12], K. Humphrey[12], N. Qayum[12], M. Hutchings[13]

[1]Department of Biomedical Sciences, Humanitas University and IRCCS Humanitas Research Hospital, Humanitas Cancer Center; [2]Levine Cancer Institute/Atrium Health; [3]University College London Hospitals BRC Clinical Research Facility; [4]The Peter MacCallum Cancer Centre, Royal Melbourne Hospital and The University of Melbourne; [5]Universitätsklinikum Würzburg; [6]Ospedale Santa Maria delle Croci; [7]Medical Oncology & Haematology, Princess Margaret Hospital; [8]Hôpital Claude Huriez and Centre Hospitalier Régional Universitaire de Lille; [9]CHU Nantes; [10]O'Neal Comprehensive Cancer Center at The University of Alabama at Birmingham; [11]Roche Pharmaceuticals Ltd; [12]Roche Products Ltd; [13]Rigshospitalet

Background: Over a third of 1L DLBCL pts do not respond to, or relapse after, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP). Glofitamab (Glofit) is a novel bispecific antibody binding to CD20 on B cells and to CD3 on T cells. The ongoing NP40126 study is assessing the feasibility and safety of Glofit+R-CHOP in R/R NHL and 1L DLBCL.

Methods: R/R NHL dose-escalation: Pts received Glofit doses in separate cohorts (70µg, 1800µg, 10mg and 30mg) +R-CHOP for 6-8 cycles. To mitigate CRS risk, R- or obinutuzumab (G)-CHOP was given in Cycle (C)1; Glofit was given from C2 onwards. For 70µg and 1800µg cohorts, a fixed-dose Glofit was given. For 10mg and 30mg cohorts, step-up dosing was used to further mitigate CRS risk (2.5mg C2, 10mg C2, target dose C3 and onwards).

1L DLBCL safety run-in: Pts received Glofit 30mg+R-CHOP for 6-8 cycles. Pts received R-CHOP in C1; Glofit step-up dosing began in C2 (2.5mg C2, 10mg C2, 30mg C3 and onwards).

Response rates were assessed by PET-CT (Lugano criteria), and CRS events were graded by ASTCT criteria.

Table 1. Summary of CRS.

	R/R NHL dose-escalation phase (N=31)	1L DLBCL safety run-in phase (N=13)
Any-grade CRS, n (%)	17 (54.8)	1 (7.7)
Grade 1 CRS	10 (32.2)	1 (7.7)
Grade 2 CRS	4 (12.9)	0
Grade ≥3 CRS	3 (9.7)	0

Results: R/R NHL dose-escalation: At data cut-off (June 10, 2021), 31 pts received Glofit+R/G-CHOP. In 31 efficacy-evaluable pts, the overall response rate (ORR) was 90% and complete response rate (CRR) was 77%. Grade (Gr)≥3 adverse events (AEs) occurred in 28 pts, serious AEs in 21 pts and CRS in 17 pts (mostly low grade; majority after the first 2.5mg Glofit dose; Table 1); 1 pt had a Gr5 AE. AEs led to Glofit dose modification/interruption in 2 pts and Glofit withdrawal in 1 pt. Neurologic AEs (NAEs) occurred in 20 pts. Immune effector cell-associated neurotoxicity syndrome (ICANS)-like AEs were uncommon. Neutropenia occurred in 24 pts.

1L DLBCL safety run-in: At data cut-off, 13 pts were enrolled (4 efficacy-evaluable). At interim assessment, CRR was 100%. Of 13 pts, only 1 had a CRS event after the first 2.5mg Glofit dose. Gr≥3 AEs occurred in 8 pts and Gr≥3 AEs related to Glofit in 1 pt only; 1 pt had a serious AE and 1 pt had a Gr5 AE. No AEs led to Glofit or R-CHOP dose interruptions. NAEs occurred in 3 pts (none were ICANS-like) and neutropenia in 6 pts. In both phases median dose intensity was 100% for all R-CHOP components.

Conclusions: Initial data show that Glofit+R-CHOP has tolerable safety in R/R NHL and 1L DLBCL. The very low CRS rate and no neurotoxicity in 1L DLBCL may render Glofit particularly suitable for the outpatient setting without the need for hospitalization.

C060

THE ITALIAN MULTICENTER RETROSPECTIVE OBSERVATIONAL STUDY ON PATIENTS WITH RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA TREATED WITH POLATUZUMAB VEDOTIN PLUS RITUXIMAB (± BENDAMUSTINE) UNDER NAMED PATIENT PROGRAMME

C. Pellegrini[1], L. Argnani[2], A. Morigi[2], A. Fabbri[3], B. Puccini[4], R. Bruna[5], M.C. Tisi[6], F. Masia[7], L. Flenghi[8], M.E. Nizzoli[9], M. Musso[10], M. Salerno[11], P.R. Scalzulli[12], D. Dessi'[13], I. Ferrarini[14], E. Pennese[15], E. Lucchini[16], F.G. Rossi[17], C. Minoia[18], F. Gherlinzoni[19], P. Musto[20], V. Stefoni[1,2], P.L. Zinzani[1,2]

[1]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli"; [2]Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale, Università di Bologna; [3]Uoc ematologia, Azienda ospedaliero-universitaria senese, Siena, Italy; [4]Azienda Ospedaliera Universitaria Careggi, Firenze, Italy; [5]Division of Hematology, Department of Translational Medicine University of Eastern Piedmont and; AOU Maggiore della Carità di Novara, Novara, Italy; [6]Cell Therapy and Hematology, San Bortolo Hospital, Vicenza, Italy; [7]Department of Medicine and Surgery, University of Perugia, Perugia, Italy; [8]Ematologia, Azienda Ospedaliera di Perugia, Perugia, Italy; [9]Ematologia, AUSL/IRCSS Reggio Emilia, Reggio Emilia, Italy; [10]Oncoematologia e TMO, Dip.Oncologico La Maddalena, Palermo, Italy; [11]UOC Ematologia ARNAS Garibaldi, Catania, Italy; [12]IRCCS "Casa Sollievo della Sofferenza" Hospital, SC Ematologia e Trapianto di Cellule Staminali, San Giovanni Rotondo, Italy; [13]Unità operativa di Ematologia e CTMO ospedale Businco Arnas AOB, Cagliari, Italy; [14]Department of Medicine, Section of Hematology, University of Verona, Verona, Italy; [15]UOSD Centro Diagnosi e Terapia dei Linfomi, Dipartimento Oncologico-Ematologico, Presidio Ospedaliero Santo Spirito, Pescara, Italy; [16]SC Ematologia, Azienda Sanitaria Universitaria Giuliano Isontina, Trieste, Italy; [17]Division of Hematology, Fondazione IRCCS Ospedale Maggiore Policlinico, Università degli Studi di Milano, Milano, Italy; [18]Hematology Unit-IRCCS Istituto Tumori "Giovanni Paolo II" Bari, Italy; [19]Azienda ULSS 2 Marca Trevigiana Ospedale Ca' Foncello, Treviso, Italy; [20]Dipartimento dell'Emergenza e dei Trapianti di Organi (DETO) Scuola di Medicina, Università degli Studi "Aldo Moro", Bari, Italy

After the approval by FDA and EMA of the regimen containing polatuzumab vedotin plus rituximab with or without bendamustine (PolaBR), eligible relapsed/refractory diffuse large B-cell lymphoma (DLBCL) patients in Italy were granted early access through a Named Patient Program (NPP) between June 2019 and February 2020. Data from patients treated with PolaBR outside a controlled clinical trial could give additional information about the clinical use, treatment duration, effectiveness, and toxicity of this regimen given to relapsed or refractory DLBCL patients in a real-life context prior to a widespread utilization.

To this aim, an Italian multicentric observational retrospective study was conducted in 19 hematology centers focusing on information about the effectiveness and safety of PolaBR in every-day clinical practice. The decision to add or not bendamustine was at physician discretion as per manufacturer indication. Fifty-five patients who underwent PolaBR through the NPP were enrolled. Briefly, there were 26 females (47.3%),

32 primary refractory patients and 45 ones resulted as refractory to the last therapy prior to PolaBR (median of previous therapies 3, range 2-6). Thirty-six patients underwent PolaBR, whereas 19 ones underwent PolaR. The two groups did not differ for baseline characteristics. The final overall response rate was 32.7% (18.2% complete response rate), with a best response rate of 49.1%.

Median disease-free survival was reached at 12 months, median progression free survival at 5 months and median overall survival at 9 months, respectively. Overall, 88 adverse events (AEs) were registered during treatment in 31 patients, 22 of grade equal or greater than 3. Eight neuropathies occurred, all of grade 1-2 and all judged as related to polatuzumab. The two groups of treatment did not differ for efficacy endpoints (response rate and survivals) but presented statistically significant difference in AEs occurrence, especially in hematological AEs, in AEs of grade equal or greater than 3 and serious AEs. Our data supported the effectiveness of the Pola(B)R regimen in the setting of heavily pretreated DLBCL also in a real-life context. Results also suggested a better tolerability in absence of bendamustine without compromise of efficacy.

Monoclonal myeloma and gammopathies II

C061

PENTA-REFRACTORY MULTIPLE MYELOMA PATIENTS: A REAL-LIFE EXPERIENCE OF MANAGEMENT AND TREATMENT

S. Rocchi[1], F. Bigi[1], K. Mancuso[1], V. Solli[1], P. Tacchetti[2], L. Pantani[2], N. Testoni[1], G. Marzocchi[1], E. Borsi[1], S. Armuzzi[1], G. Mazzocchetti[1], I. Rizzello[1], G. De Cicco[1], M. Ursi[1], E. Favero[1], S. Barbato[2], G. Lazzarini[2], M. Cavo[1], E. Zamagni[1]

[1]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "L. A. Seràgnoli", Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale, Università di Bologna; [2]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "L. A. Seràgnoli", Italy

Despite treatment options for Multiple Myeloma (MM) have dramatically evolved in the last decade due to the increasing availability of PIs, IMiDs and MoAbs, patients (pts) who become penta-refractory (PRMM) are an unmet clinical need. We performed a real-word retrospective analysis of a series of 29 PRMM pts who received at our centre new treatment strategies (chimeric antigen receptor (CAR) T cells, antibody-drug conjugated Belantamab Mafodotin (Belamaf) and SINE inhibitor Selinexor) between 2018 and 2022. At diagnosis their frequency of high-risk MM characteristics, including ISS stage 2-3 and presence of 1 or more of del17p, t(4;14) and t(14;16), was 53% and 55%, respectively. Median (m-) time from diagnosis to penta-refractoriness was 7 years [IQR 4-10] and m-age was 61 years old [IQR 56-69]. The m-number of previous lines of therapy was 5, including ASCT in 86% of pts. Of 29 pts, 9 (31%) were treated with CAR-T cells, 14 (48%) with Belamaf (within EAP and NPP or after AIFA approval) and 6 (21%) with Selinexor (as EAP). Overall, 10 pts (34%) achieved ≥PR (28% ≥VGPR) within a m of 1 month (mo); 9 of these pts (90%) were treated in the CAR-T group. At a m- follow-up (fu) of 5 mos, m-duration of response (DOR) was 2 mos, with 4/9 pts (44%) who are maintaining the response at the last fu. 13/29 pts (45%) died and 18 pts (62%) discontinued therapy due to progressive disease. 10/18 pts who had treatment discontinuation (56%) received a subsequent line of therapy (LOT) (17% ≥ 3 next LOT). M- progression free survival (PFS) and overall survival (OS) were 4 [IQR 2-6] and 5 [IQR 3-12] mos, respectively. Of note, our analysis showed a trend of longer OS for pts who achieved ≥PR during treatment (p=0.067). No warnings about adverse events (AEs) emerged: the most frequent AEs, in addition to the hematological ones (76%, 59% grade≥3) were cytokine release syndrome (100%, 10% grade≥3), ocular (57%, 14% grade≥3) and gastro-intestinal (83%, 17% grade≥3) toxicities for CAR-T, Belamaf and Selinexor group, respectively, without definitive discontinuation. This analysis showed a real-life experience of PRMM pts, with similar reported toxicities profile in comparison with the literature and for whom new strategies with novel mechanism of actions are needed. Particularly, the importance of obtaining a treatment response for longer OS emerged and immunotherapy, despite the small series of pts, can be a valid therapeutic option, which led to promising results.

C062

BEST TREATMENT STRATEGY BEFORE AUTOLOGOUS PERIPHERAL BLOOD STEM CELL TRANSPLANTATION IN POEMS SYNDROME

F. Autore[1], S. Bramanti[2], F. Lessi [3], I. Innocenti[1], A. Piciocchi[4], E. Galli[1], S. Rocchi[5], R. Ribolla[6], D. Derudas[7], S. Oliva[8], P. Stefanoni[9], M. Marcatti[10], A. Schenone[11], G. La Nasa[7], C. Crippa[6], E. Zamagni[5], M. Riva[3], R. Mazza[2], D. Mannina[2], S. Sica[1], A. Bacigalupo[1], L. Laurenti[1]

[1]Fondazione Policlinico Universitario A. Gemelli IRCCS, Roma; [2]Istituto Clinico Humanitas IRCCS, Rozzano; [3]Azienda Ospedale Università Padova, Padova; [4]GIMEMA, Data Centre, Roma; [5]IRCCS Azienda Ospedaliero-Universitaria SOrsola-Malpighi, Bologna; [6]Spedali Civili, Brescia; [7]A. Businco, Cagliari; [8]S. Giovanni Battista, Torino; [9]ASST Papa Giovanni XXIII, Bergamo; [10]San Raffaele, Milano; [11]San Martino, Genova, Italy

We collected clinical and laboratory data of patients with POEMS syndrome from 10 Italian centres. We included all the consecutive patients with POEMS undergoing to aPBSCT from 1998 to 2020. Our data set consisted of 44 patients who underwent aPBSCT with a median follow-up of 77 months (37-169 months). Progression free survival (PFS) and overall survival (OS) rates at 6 years was 65% (49-85) and 92% (84-100), respectively. The cumulative incidence of transplant related mortality and relapse was respectively 4% and 36%. We then divided patients in three subgroups: front-line patients who did not receive any treatment before transplant (15 patients, Group 0), patients treated pre transplant with cyclophosphamide (14 patients, Group 1) and patients treated with other agents such as lenalidomide, chemioterapics or radiotherapy (15 patients, Group 2). The three groups did not show differences in terms of demographic and clinical characteristics. The response rates after transplantation were complete response (CR) in 46%, very good partial response (VGPR) in 23%, partial response (PR) in 18%, stable disease (SD) in 8% and progressive disease (PD) in 5%. The responses (CR *vs* PR/VGPR *vs* SD/PD) showed a significant impact in terms of progression free survival (PFS). When comparing the response rate (CR *vs* PR/VGPR *vs* SD/PD) between the 3 groups any differences was found (p 0.25). When analysing PFS and OS, the 3 groups did not show significant differences (Figure 1); there was a tendency to unfavourable PFS for patients of Group 1 but no variable was found to negatively affect PFS, neither the treatment chosen before transplantation. In 10 cases it was necessary a re-admission in hospital: in 5 cases for relapse and in 5 for infectious complications. We then considered VEGF levels after aPBSCT and we found out that patients with VEGF levels higher than 758 pg/mL were at higher risk of relapse (AUC 0.86, sensibility 78% specificity 86%), with very high potency in Group 1.

This is a large series of patients with POEMS treated with aPBSCT. We show durable and impressive PFS and OS, without significant differences between groups of pre-treated patients and patients who underwent front-line aPBSCT.

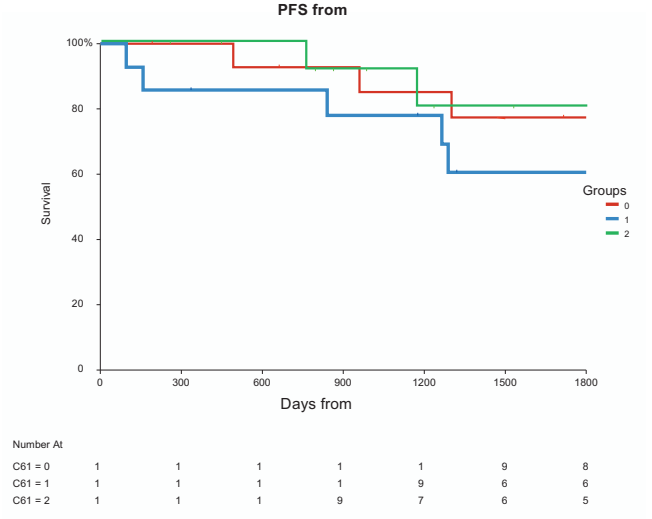


Figure 1. PFS.

C063

MULTIPLE MYELOMA GENOMIC LANDSCAPE EXPLORED BY DIMENSIONAL SCALING TECHNIQUE HIGHLIGHTS THE PRESENCE OF PATIENTS CARRYING 1Q CN GAIN & 13 CN LOSS (1Q&13+) WITH SPECIFIC GENOMIC, TRANSCRIPTIONAL AND CLINICAL FEATURES

C. Terragna[1], A. Poletti[1,2], V. Solli[1,2], M. Martello[1,2], E. Borsi[1,2], E. Zamagni[1,2], L. Pantani[1], I. Vigliotta[1], S. Armuzzi[1,2], B.Taurisano[1,2], G. Mazzocchetti[1,2], P. Tacchetti[1], K. Mancuso[1,2], S. Rocchi[1,2], G. Marzocchi[1,2], N. Testoni[1,2], M. Cavo[1,2]

[1]IRCCS - Azienda Ospedaliero - Universitaria di Bologna; [2]DIMES – Department of Experimental, Diagnostic and Specialty Medicine, Institute of Hematology, University of Bologna, Italy

The risk of Multiple Myeloma (MM) is hardly predictable, due to the complexity of interactions between factors that, at a different extent, might influence patients' (pts) clinical outcome. The up-front identification of early relapsing/refractory pts still represents an unmet clinical need.

We employed descriptive evolutionary statistics and non-linear dimensionality reduction approaches to define biological meaningful MM pts' subgroups and to evaluate the clinical impact of specific genomic configurations, aiming at the definition of biology-based risk stratification models to be implemented in clinical practice.

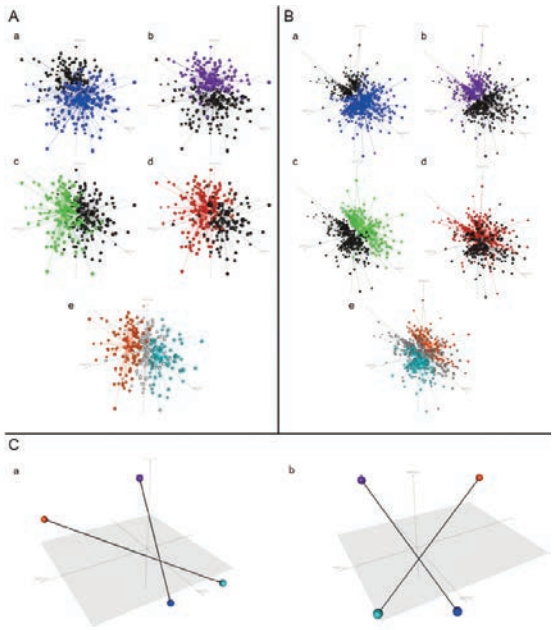


Figure 1. Dimensionality Reduction: tridimensional picture of the complex relationships observed between all MM genomic variants. Each patient was represented by a dot; dots' clusters - representing patients sharing similar genomic backgrounds - located accordingly in the dimensionality-reduced space. Blue, violet, red and green dots represented patients carrying H, t-IgH, del13 and amp1q, respectively. Blue and violet clusters (representing patients carrying H and t-IgH, respectively) located at the horizontal axis' opposed extremities, whereas red and green clusters (representing patients carrying del13 and amp1q, respectively) tended to overlap and to locate along the vertical axis. Panel A: Bologna dataset; panel B: CoMMpass dataset; panel C: resumes the clusters' position within the multidimensional space.

Genomic landscape of 513 newly diagnosed (ND) MM pts was deeply explored by SNPs array and by FISH. Bioinformatics and biostatistics analyses were performed by R language. Results were validated on WGS

and RNAseq data from 840 NDMM pts (CoMMpass dataset). By dimensional scaling techniques, we explored the relationships between all the genomic variables detected in NDMM and clustered pts according to their own genomic complexity, not just according to the presence of the most recurrent aberrations.

Three mains, partially overlapping pts' clusters, placed along crossing axis were generated (Figure 1). The presence of either hyperdiploidy (HD) or t-IgH identified pts in opposite clusters; a third one, perpendicular to the HD-t-IgH axis, included 131 pts carrying both 13q copy number (CN) losses and 1q CN gains (named 1q&13+) suggesting a variance from the well-known HD-t-IgH stratification. Gene expression profiles of 1q&13+ pts highlighted the differential expression of 301 genes, with the most significantly up and down regulated being CCND2 and CCND1, a pattern confirmed also by excluding all pts carrying t-IgH.

1q&13+ pts displayed well-known baseline high-risk features (*e.g.* ISS stage 3, Albumin<3.5 g/dL, high CMMCs count) and their PFS and OS were significantly shorter than those of other pts (5-year PFS: 22% *vs* 37% *vs* 47%, p<0.0001; OS: 50% *vs* 74% *vs* 78%, p<0.001 for 1q&13+, 1q/13, 1q&13- pts, respectively) independently from the presence of either t(4;14)(p16;q32) or del(17p) (multivariate Cox analysis).

In conclusion, the use of dimensionality reduction techniques allowed to elaborate and model all the possible, unsupervised interactions between any MM chromosomal alterations, thus highlighting a previously unrecognized, independent 1q&13+ cluster, characterized by a peculiar expression profile and bad prognosis.

Thanks to: RF2016-02362532

C064

LOW-DOSE CT-BASED BONE MARROW RADIOMIC ANALYSIS FOR CLASSIFICATION AND OUTCOME PREDICTION IN PATIENTS WITH MULTIPLE MYELOMA

C. Botta[1], E. Gigliotta[1], C. Vullo[1], G. Camarda[1]*, C. Rotolo[1], A. Fidenco[2], A. Roppolo[1], C. Spoto[1], A. Rizzuto[1], A. Pirrera[1], F. Plano[1], G. Giannone[1], M. Santoro[1], S. Mancuso[1], M. Napolitano[1], M. Carlisi[1], F. Vernuccio[3], A.M. Florena[1], R. Cannella[2], S. Siragusa[1]

[1]Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties (ProMISE), University of Palermo; [2]Department of Biomedicine, Neurosciences and Advanced Diagnostics (BiND), University of Palermo; [3]Department of Medicine-DIMED, Institute of Radiology, University of Padova, Italy

Multiple myeloma (MM) is a hematologic malignancy characterized by the presence of at least 10% of clonal plasma cells (cPCs) in bone marrow (BM). Considering that up to 80% of MM patients present with bone lytic lesions at diagnosis, low-dose whole body CT (LD-CT) has emerged as the first-choice imaging approach in subjects bearing a monoclonal gammopathy (MG) to evaluate the presence of MM-associated bone disease. Taking advantage from the introduction of innovative radiomic techniques, able to extract additional information (namely "features") from CT images (correlated, among others, with tissue density and heterogeneity), we evaluated LD-CT bone marrow radiomic analysis for the capability of discriminating, among MG, pre-malignant conditions from MM, as well as its ability to predict patients' outcome. To this end we retrieved data from 71 consecutive suspected MG patients admitted to our outpatient service from late 2019 to February 2022 who underwent LD-CD. Of them, 2 were finally not affected by MG, 14 had a premalignant condition, and 55 were affected by MM. 35 radiomic features were extracted from texture analysis performed through LifeX (segmentation was limited to pelvic BM only, on the same side of BM biopsy). Furthermore, CBC count, laboratory tests, disease stage as well as the percentage of BM cPCs were included in the analysis. Unsupervised hierarchical clustering (heatmap and PCA in Figure 1A) identified 2 different groups of patients according to distribution of radiomic features. Interestingly, once restricted to MM patients only, we were able to demonstrate how this classification present predictive/prognostic relevance (Figure 1B; p: 0.04). Next, we evaluated the possible correlation between radiomic features and BM cPCs (Figure 1C and D); surprisingly, as reported in Figure 1C, a linear correlation was found with Grey-Level Run Length Matrix (GRLRM) features, which estimate density homogeneity. Additionally, other features belonging to the GRLRM or Grey Level Co-occurrence Matrix (GLCM) groups were found to be critically associated with an infiltration of plasma cells>60%, allowing us the identification of patients requiring an active treatment (Figure 1D), as well as disease status and Hb values (data not shown). Overall, we provide preliminary evidence of the potential usefulness of CT, beyond bone lytic lesion detection, for the identification of people with increased risk of disease evolution or symptomatic MM.

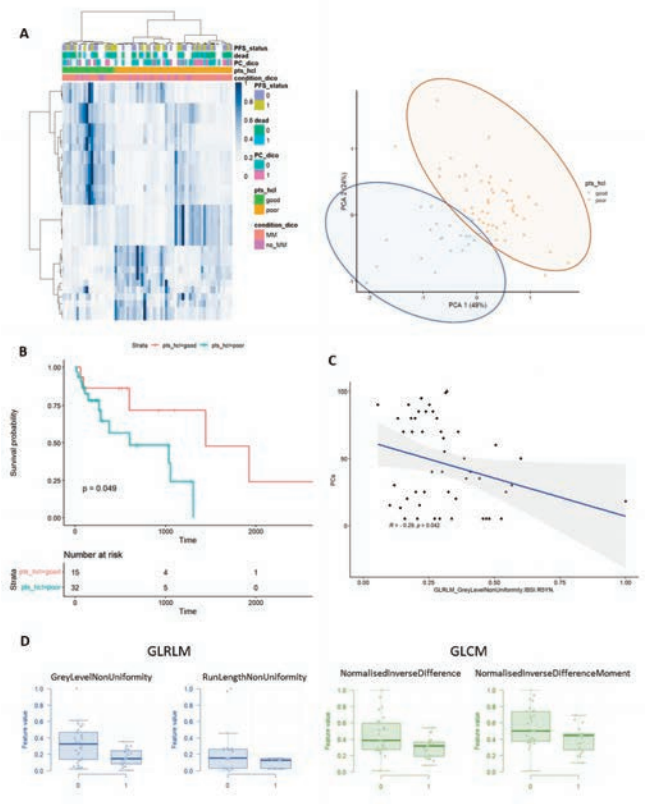


Figure 1.

C065

LENALIDOMIDE MAINTENANCE AFTER VTD INDUCTION AND AUTOLOGOUS STEM CELL TRANSPLANTATION: PRELIMINARY RESULTS OF A REAL-LIFE STUDY INCLUDING 212 PATIENTS

G. Barilà[1], C. Conticello[2], C. Marcon[3], F. Fazio[4], S. Rocchi[5], A. Cellini[6], M. Porrazzo[7], D. Nappi[8], A. Furlan[9], G. Schininà[2], G. De Cicco[5], G. Sapuppo[2], C. Lisi[5], A. Pascarella[1], N. Pescosta[8], E. Zamagni[5], M.T. Petrucci[4], F. Di Raimondo[2], F. Patriarca[3], R. Bassan[1], R. Zambello[5]

[1]U.O.C Ematologia, Azienda ULSS3 Serenissima, Ospedale dell'Angelo; [2]UOC di Ematologia con Trapianto di Midollo Osseo AOU Policlinico G. Rodolico-San Marco; [3]Clinica Ematologica e Unità di Terapie Cellulari, Azienda Sanitaria Universitaria Friuli Centrale (ASUFC), Dipartimento di Area Medica (DAME), Università di Udine; [4]Dipartimento di Ematologia, Oncologia, e Dermatologia, AOU Policlinico Umberto I, Università Sapienza di Roma; [5]IRCCS Azienda Ospedaliero-Univer-

sitaria di Bologna, Istituto di Ematologia Seràgnoli; [6]Dipartimento di Medicina (DIMED), sezione di Ematologia, Università degli Studi di Padova; [7]Struttura Complessa Ematologia, Azienda Sanitaria Universitaria Giuliano Isontina; [8]Ematologia e Centro TMO, Ospedale Centrale Bolzano; [9]U.O.C Ematologia, Ospedale Santa Maria di Ca' Foncello, Italy

According to 2021 ESMO guidelines, treatment of newly diagnosed (ND) transplant eligible (TE) Multiple Myeloma (MM) patients is settled by an induction phase followed by autologous stem cell transplantation (ASCT) and Lenalidomide (Len) maintenance. Before the recent approval of daratumumab-bortezomib-thalidomide-dexamethasone (D-VTD) regimen, VTD induction followed by ASCT and Len maintenance was the standard of care in Italy for ND TE MM patients, however no single perspective trial evaluated this combination.

In this context, the aim of this real-life study was to evaluate the efficacy and the safety of Len maintenance after VTD plus ASCT in ND TE MM patients.

The study cohort included 212 patients (median age 59 years). Baseline features included ISS III in 42/200 (21%) cases and R-ISS III in 26/182 cases (14.3%). FISH analysis was available in 163 patients, with 39 of them (23.9%) displaying high risk (HR) alterations [including t(4;14), t(14,16) and del17p]. Among the remnant 124 patients, information about 1q status was available in 109 cases, with 23 of them showing gain 1q (21.1%). Single or tandem ASCT was performed in 52.8% and 47.2% of cases, respectively.

A median number of 23 cycles of Len maintenance was administered. Complete response (CR) and stringent CR (sCR) rates before starting Len were 26.4% and 14.6%, respectively (overall 41%) and increased with maintenance to 31.7% and 17.3% (overall 49%), respectively. Most importantly 2 years CR and sCR rates were superimposable (30.1% and 19,6% respectively, 49.7% overall). Toxicities were mostly hematological with neutropenia found in 40.6% of cases (grade > or = 3 in 21.2%), while non hematological adverse event were primarily infections and gastrointestinal, mostly of grade 1-2. With a median follow up of 26 months, the 2 years PFS from starting maintenance was 80.7%. Patients with R-ISS >1 show reduced progression free survival (PFS) as compared to patients with R-ISS I (2y PFS 69.2% *vs* 92.3%, p=0.0005). Moreover, patients harboring HR FISH or isolated gain1q displayed reduced PFS with respect to standard risk patients (2y PFS 60.7% *vs* 83.3%, p<0.0001, and 70% *vs* 83.3%, p=0.0339, respectively). To our knowledge, this is the first study evaluating the safety and efficacy of Len maintenance after VTD plus ASCT. Our result provide evidence that patients with clinical and biological low risk disease benefit the most from Len maintenance with a favorable safety profile.

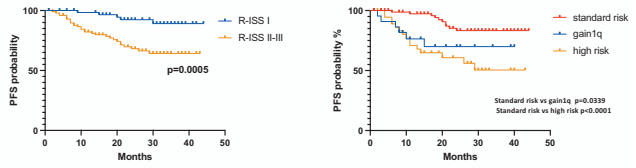


Figure 1.

Cytogenetics and quality of life

C066

SARCOPENIA IS ASSOCIATED WITH SHORTER SURVIVAL IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA TREATED WITH TARGETED THERAPIES. A PROSPECTIVE STUDY

A. Visentin[1], F. Crimì[2], R. Angelone[2], A. Corso[2], C.A. Cavaretta[1], F. Angotzi[1], A. Cellini[1], V. Ruocco[1], S. Pravato[1], E. Quaia[2], L. Trentin[1]

[1]Hematology and Clinical Immunology Unit, Department of Medicine, University of Padova; [2]Radiology Institute, Department of Medicine, University of Padova, Italy

Background: Targeted therapies are broadly active in patients with chronic lymphocytic leukemia including patients with comorbidities, assessed by the CIRS score. Indexes of sarcopenia or adipose tissue assessed by CT scan, are emerging as prognostic markers in cancer patients. Despite CT scan could provide relevant information, it is not recommended by iwCLL guideline. The aim of this study was to assess the impact of muscle and adipose tissue indexes in patients with CLL treated with targeted agents.

Methods: We performed a single center prospective study, REV-CLL01, of CLL patients treated with BTK, BCL2 and PI3K inhibitors out of clinical trials. For each patient baseline unenhanced axial CT scans at L3 vertebra were analyzed with NIH ImageJ software, areas of subcutaneous fat, visceral fat and skeletal muscle were extracted, segmented by a post-processing semiautomatic method. The areas were divided by the square of patient's height, obtaining the skeletal muscle index (SMI), subcutaneous (SATI) and visceral adipose tissue index (VATI).

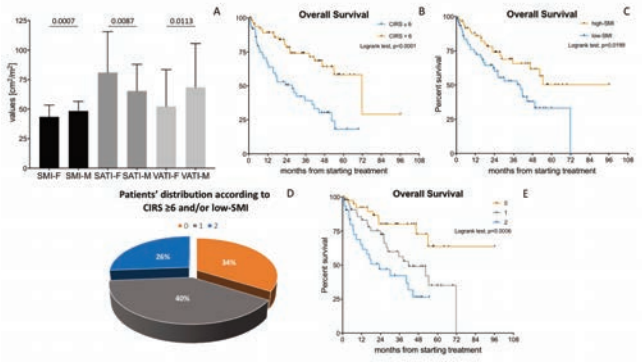


Figure 1.

Results: We included 118 patients, the mean age was 71.6+-8.6 years, 63% were at Rai stage III-IV, 42% had a CIRS >=6, 81% unmutated IGHV, 35% 17p13 deletion, 33% TP53 mutation. The median number of therapies was 3 (range 1-9). 56% patients received ibrutinib, 23% idelalisib+rituximab and 21% venetoclax+-rituximab. We observed that SMI values correlated with SATI (p=0.035) and VATI (p<0.0001). SMI, SATI and VATI were higher in males *vs* females (Figure 1A, p<0.01). By ROC curve we identified 48.3 for male and 42.2. for female as the best cut-offs for sarcopenia. Sarcopenic patients (low-SMI) had a higher number of previous therapies (p=0.027) and CIRS>=6 (p=0.039). All indexes did not correlate with age, stage or biological markers. After a median follow-up of 32m the median OS for the whole cohort was 47m. We found that patients with CIRS>6 (p<0.0001, Figure 1B) and low-SMI had with a shorter OS (median OS 40m *vs* not reached for low-SMI and high-SMI, p=0.0199, Figure 1C). SATI and VATI did not correlate

with OS. Combining data of CIRS>=6 and low-SMI, 34%, 40% and 26% of patients displayed 0, 1 and 2 markers (Fig 1D). The median OS was not reached for score 0, but decreased from 42m to 23m for patients at score 1 and 2 (p=0.0006, Figure 1E).

Conclusion: In this prospective study we found that that basal CT scan identifies sarcopenic CLL patients with low-SMI featured by an adverse prognosis even if treated with targeted oral drugs, in particular when combined with the CIRS score.

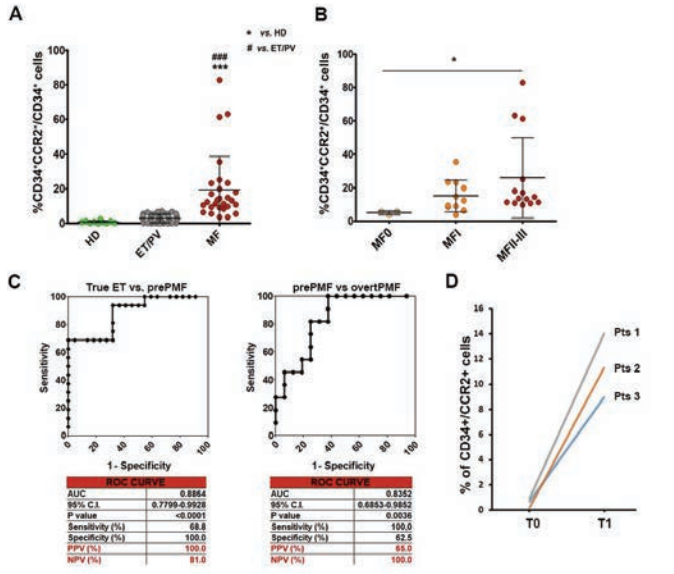
C067

CCR2 FLOW-CYTOMETRIC DETECTION ON CD34+ CELLS IN SUPPORT OF BONE MARROW MORPHOLOGY FOR THE DIFFERENTIAL DIAGNOSIS OF PHILADELPHIA-NEGATIVE MPN SUBTYPES

E. Masselli[1,2], G. Pozzi[1], C. Carubbi[1], S. Bonomini[2], G. Gobbi[1], P. Mirandola[1], M. Vitale[1,2]

[1]Department of Medicine and Surgery, University of Parma; [2]Parma University Hospital, Italy

Bone marrow fibrosis is a key pathological feature of MPN contributing to an impaired microenvironment favoring malignant over normal hematopoiesis. Higher grade of bone marrow fibrosis dictates a more severe disease stage with dismal prognosis and higher risk of leukemic evolution. Therefore, accurate patient allocation into different disease categories and timely identification of fibrotic transformation are mandatory.



(A) CCR2 expression evaluated by flow cytometry (FCM) on immunomagnetically isolated CD34+ cells from healthy donors (HD, n. 10), ET/PV (n.36 of which 16 PV and 20 ET), MF (n.28). Percentages of CD34+CCR2+ cells are normalized to total CD34+ cells (%CD34+CCR2+/CD34+). Data are shown as mean ± SD (***, P<0.001 vs. HD; ###, P<0.001 vs. ET/PV by Kruskal Wallis followed by Dunn's test). **(B)** CCR2 expression evaluated by FCM on immunomagnetically isolated CD34+ cells from MF patients stratified according to grading of bone marrow fibrosis in MF0 (n.3), MFI (n.11) and MFII-III (n.14). Data are shown as mean ± SD (*, p<0.05 vs. MF0 by Kruskal Wallis followed by Dunn's test). **(C) Diagnostic accuracy of CD34+/CCR2+ cell detection by FCM.** Left panel: ROC curve of FCM analysis of CD34+CCR2+ cells in trueET vs. prePMF and summary table reporting: Area under the curve (AUC), confidential interval (CI), *P* value, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). Right panel: ROC curve of FCM analysis of CD34+CCR2+ cells in prePMF vs. overtPMF and summary table reporting: Area under the curve (AUC), confidential interval (CI), *P* value, cut-off value, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). **(D)** % of peripheral blood CD34+/CCR2+ cells in 3 MPN patients during disease progression. Pts 1: T0=ET; T1=accelerated phase with fibrosis 0-I; Pts 2: T0=PV; T1=post-PV MF; Pts 3: T0: MPN-u; T1=MPN-u with fibrosis I.

Figure 1.

Diagnostic strategy still mainly relies on clinical/lab/molecular assessments and bone marrow histopathology, which, however, requires an invasive procedure and frequently poses challenges also to expert hemopathologists. We previously showed that CD34+ cells from primary myelofibrosis patients (PMF) uniquely express C-C Chemokine Receptor 2 (CCR2), which, by contrast, is virtually absent in healthy donors and other MPN subtypes (Masselli E *et al.* Cancers, 2021). Here we tested the diagnostic accuracy of the detection of CCR2+/CD34+ cells to discriminate among MPN subtypes with different degrees of bone marrow fibrosis. CCR2 expression was evaluated by flow cytometry (FCM) on immunomagnetically isolated CD34+ cells from 10 leukapheresis bags (healthy donors, HD) and from peripheral blood /bone marrow of 16 PV, 20 ET and 28 MF (including PMF and secondary MF). We found that MF hematopoietic progenitors significantly overexpress CCR2 as compared to HD, PV and ET (Figure 1 panel A) and that the number of CCR2-expressing cells parallels the degree of bone marrow fibrosis (Figure 1 panel B). Flow-cytometric detection of CCR2 on MPN CD34+ cells has a very good diagnostic accuracy for the differential diagnosis between true ET and prePMF (AUC 0.8864, P<0.0001), and a good diagnostic accuracy for the differential diagnosis between prePMF and overtPMF (AUC 0.8352, P=0.0036) (Figure 1 panel C). Remarkably, longitudinal follow up of 3 MPN patients with evolving bone marrow fibrosis demonstrated that the increase in peripheral blood CCR2+/CD34+ cell % can efficiently track fibrotic changes (Figure 1 panel D). Overall, our data pinpoint flow-cytometric detection of CD34+/CCR2+ cells as an innovative and rapid tool to detect fibrotic changes in MPN and may be envisioned in support of conventional bone marrow histopathology at the time of disease diagnosis in compelling clinical scenarios (i.e., true ET *vs* prePMF) as well as for a non-invasive patient screening (i.e., assessment of circulating CD34+/CCR2+ cells) for subsequent bone marrow biopsy when disease evolution is suspected.

C068

A MULTICENTRIC SURVEY ON THE PERCEPTION OF PALLIATIVE CARE AMONG THE HEALTH PROFESSIONALS WORKING IN HAEMATOLOGY

F. Salmaso[1], S. Di Lorenzo[2], L. Mozzi[3], C. Silvagni[4], S. Soffientini[5], V. Valenti[6], V. Zagonel[7]

[1]Palliative Care Unit, Istituto Oncologico Veneto; [2]Haematology Department of Transplant Center and Cellular Therapies Carlo Melzi; [3]Haematology Unit, Azienda Ospedaliera Ulss 8 Berica, Ospedale San Bortolo; [4]Continuity of Care Center, State Hospital, Istituto per la Sicurezza Sociale; [5]Haematology Unit, Azienda Ospedaliera di Padova; [6]Palliative Care Unit, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST); [7]Department of clinical and experimental Oncology, Medical Oncology 1, Institute of Oncology IOV-IRCCS

Patients with haematological malignancies have less access to Palliative Care (PC) and delayed referrals than patients with solid tumours, although both have complex situations and need support throughout the course of the disease. Which is the reason?

The aim of this survey was to analyse the perceptions of health professionals involved in haematological patients'care on PC, to identify barriers preventing sick persons'access to PC and facilitators that could help this step. A questionnaire was created with specific questions regarding the presence of a hospital PC team, transfusions, multidisciplinary collaboration, education in PC and referral timing of the patients to the PC services. The questionnaire was then submitted to medical and nursing staff of 5 Italian Haematological units and of S. Marino's hospital. Finally, data collected were analysed using quantitative and qualitative methods. Of the 320 questionnaires sent, 142 were completed: 96 by nurses and 46 by physicians.

Analysing specifically the answers:

- only 72 participants have a PC team in their hospital;
- 77 professionals have never attended a PC course, 42 did it on their own initiative outside their hospital, while 23 within their hospital;
- the majority of operators (113) agreed that cooperation between the 2

disciplines benefits both patients and caregivers, but only 100 knew the PC team role;
- on a Likert scale, 70 professionals thought it could be appropriate to refer patients to PC at the beginning of their care pathway, while 75 when the prognosis is less than 3 months and 75 when the symptoms are incoercible;
  most professionals (24/46 doctors and 53/96 nurses) agreed with transfusions even in the last stages of the disease.
  Concerning the facilitators:
- for 93 professionals the presence of a PC team within the hospital is fundamental as for 67 the presence of a dedicated case manager;
  117 health professionals believe the training courses on PC are important.

In conclusion, the attitude of respondents tends to be favourable to the proposed integration of the 2 disciplines. However, they believe that there are few referrals to the PC team because of clinical, cultural, educational, organisational and resource issues. Nevertheless, the interest in the subject is undeniable, as confirmed by the 44,4% response rate, which is satisfactory when compared with that of similar studies conducted abroad.

C069

LONG TELOMERES AT BASELINE AND MALE SEX ARE MAIN DETERMINANTS OF TELOMERE LOSS FOLLOWING CHEMOTHERAPY EXPOSURE IN LYMPHOMA PATIENTS

E. Derenzini, A. Gueli, A. Risso, R. Bruna, D. Gottardi, A. Cignetti, S. Pileri, E.V. Avvedimento, C. Tarella

Onco-Hematology Division, IEO European Institute of Oncology IRCCS, Milan, Italy; Department of Health Sciences, University of Milan, Milan, Italy; Internal Medicine Unit, Ciriè Hospital, Turin, Italy; Division of Gastroenterology, Città della Salute e della Scienza University-Hospital, Turin, Italy; Department of Translational Medicine, University of Eastern Piedmont and Ospedale Maggiore della Carità, Novara, Italy; Hematology and Cell Therapy, A.O.U. S. Giovanni Battista A.O. Mauriziano-Umberto I, Turin, Italy; Hemolyphopathology Division, IEO European Institute of Oncology IRCCS, Milan, Italy; Dipartimento di Medicina Molecolare e Biotecnologie Mediche, Università Federico II, Napoli, Italy

Although chemotherapy (CHT) exposure is an established cause of telomere attrition, determinants of telomere length (TL) dynamics after chemotherapy are poorly defined. In this study, we analyzed granulocyte telomere dynamics in 34 adult lymphoma patients undergoing first-line CHT. TL was measured by southern blot at each CHT cycle and after 1 year from CHT completion. Median age was 59 yrs (range 22-77). Median number of CHT cycles was 6 (range 3-6).

The majority of pts (79%, n=27) experienced TL shortening following CHT exposure. Telomere shortening was observed as early as after 1 cycle of chemotherapy, being significantly decreased after 3 and 6 cycles. Maximal drop in TL was observed at the end of induction therapy, with no significant recovery after 1 year. Telomere shortening was an early event in the chemotherapy course, since 87% of the total telomere loss (mean 586 bp) occurred by the end of cycle 3, and only 13% from cycle 3 to cycle 6. No significant differences in fractional telomere loss were observed in patients treated with chemotherapy regimens with or without anthracyclines or rituximab.

Interestingly, we observed a significant correlation between baseline (pre-treatment) TL and total telomere loss, with a higher degree of telomere shortening following chemotherapy observed in patients harboring the longest telomeres at pre-treatment evaluation. In line with this observation, dividing patients into 2 subgroups based on the median baseline TL (7657 bp, range 4792-12104), significant telomere shortening was observed only among patients with longer telomeres at pre-treatment evaluation. Mean fractional telomere loss by cycle 6 was 14.4% of pre-treatment TL in patients with long telomeres at baseline *vs* 0.3% in patients with short telomeres (p=0.0008). Accordingly, while telomere shortening was negligible in patients with short telomeres, patients with long telomeres experienced a significant telomere loss by cycle 3. Notably, in the long telomere subgroup only male patients experienced significant telomere shortening by cycle 3, as compared to females. Stratifying the analysis by gender and age only young women (<51 years of age) did not show significant telomere shortening following chemotherapy exposure. These findings indicate that gender and baseline TL are major determinants of TL dynamics following chemotherapy exposure in lymphoma patients.

C070

PSYCHOSOCIAL NEEDS AND CHALLENGES IN MANAGEMENT OF ADOLESCENTS AND YOUNG ADULTS WITH HEMATOLOGICAL MALIGNANCIES

E. Sarcletti[1], P. Minetto[2], F. Guolo[2,3], F. Ballerini[2], M. Montanari[3], G. Bartalucci[4], C. Di Grazia[4], M. Gambella[4], A.M. Raiola[4], E. Angelucci[4], R.M. Lemoli[2,3], G. Biffa[1]

[1]U.O. Psicologia Clinica e Psicoterapia, Dipartimento in line Direttore Sanitario, IRCCS Ospedale Policlinico San Martino; [2]U.O. Clinica Ematologica, Dipartimento di Oncologia ed Ematologia, IRCCS Ospedale Policlinico San Martino; [3]U.O. Clinica Ematologica, Dipartimento di Medicina Interna (DiMI), Università degli Studi di Genova; [4]U.O. Ematologia e Terapie Cellulari, Dipartimento di Oncologia ed Ematologia, IRCCS Ospedale Policlinico San Martino, Italy

Introduction: Adolescents and Young Adults (AYAs) patients are generally defined as individuals aged 15 -39 at the time of cancer diagnosis. AYAs from the age of 16 and older are usually referred to adult hematology centers where, however, they represent a minority of the patients.

Cancer in AYAs is a complex life-limiting condition which interferes with biological, psychological and social transitions, typical of this phase of life. Acute leukemias and aggressive lymphomas are among most frequent neoplasms affecting AYAs, requiring intensive and often prolonged therapies, with curative intent. Here we report the results from a multidisciplinary team-work project aimed at hemato-oncological patients, with a special focus on AYAs.

Methods: Since April 2018 we started a specific project aimed at patients affected by hematological malignancies, under the supervision of the Clinical Psychology and Psychotherapy Unit, including: multidisciplinary team discussions, participation in communication of diagnosis and bad news, clinical psychology interviews and psychotherapy for patients and their families.

Results: In the last 4 years, 393 patients with hematological malignancies were enrolled. Approximately 20% were AYAs, aged 16- 39 years (median age 28 years, 58% female, 42% male). One third of them are parents of minor children. Major psychological issues reported and requiring support were specific for age-groups and related to recurrent areas. Younger patients faced challenges about body image, education, peer relationship and sexuality. In older AYAs vocational, economic and family issues emerged. A need for assistance in communicating parent's diagnosis to children was frequent, in order to manage the consequences on the child's daily life. Practical issues often faced included ensuring the continuity of patient's educational activities and providing information about possible socio-economic and employment protection.

Conclusion: AYAs risk to fall into a "no man's land" category between paediatric and adult models of care, thus requiring dedicated sub-units. AYAs patients should be treated by a multidisciplinary team, in order to help them coping successfully with the medical and psychosocial challenges they face due to their condition, including efforts to actively involve the entire family in the supporting process and to help the family itself to adapt to the new situation.

Chronic lymphocytic leukemia and lymphoproliferative syndromes I

C071

PIRTOBRUTINIB, A HIGHLY SELECTIVE, NON-COVALENT (REVERSIBLE) BTK INHIBITOR IN PREVIOUSLY TREATED CLL/SLL: UPDATED RESULTS FROM THE PHASE 1/2 BRUIN STUDY

P. Ghia[1], A. Mato[2], J. Pagel[3], C. Coombs[4] , N. Shah[5], N. Lamanna[6], T. Munir[7], E. Lech-Maranda[8], T. Eyre[9], J. Woyach[10], W. Wierda[11], C. Cheah[12], J. Cohen[13], L. Roeker[2], M. Patel[14], B. Fakhri[15], M. Barve[16], C. Tam[17], D. Lewis[18], J. Gerson[19], A. Alencar[20], C. Ujjani[21], I. Flinn[22], S. Sundaram[23], S. Ma[24], D. Jagadeesh[25], J. Rhodes[26], J. Taylor[20], O. Abdel-Wahab[2], S. Schuster[19], D. Wang[27], B. Nair[27], E. Zhu[27], D. Tsai[27], M. Davids[28], J. Brown[28], W. Jurczak[29]

[1]Università Vita-Salute San Raffaele and IRCCS Ospedale San Raffaele; [2]Memorial Sloan Kettering Cancer Center; [3]Swedish Cancer Institute; [4]University of North Carolina at Chapel Hill; [5]Medical College of Wisconsin; [6]Herbert Irving Comprehensive Cancer Center, Columbia University; [7]Department of Haematology, St. James's University Hospital; [8]Institute of Hematology and Transfusion Medicine; [9]Oxford University Hospitals NHS Foundation Trust, Churchill Cancer Center; [10]The Ohio State University Comprehensive Cancer Center; [11]MD Anderson Cancer Center; [12]Linear Clinical Research and Sir Charles Gairdner Hospital; [13]Winship Cancer Institute, Emory University; [14]Florida Cancer Specialists/Sarah Cannon Research Institute; [15]University of California San Francisco; [16]Mary Crowley Cancer Research; [17]Peter MacCallum Cancer Center, Royal Melbourne Hospital, and University of Melbourne; [18]Plymouth Hospitals NHS Trust - Derriford Hospital; [19]Lymphoma Program, Abramson Cancer Center, University of Pennsylvania; [20]University of Miami Miller School of Medicine; [21]Fred Hutchinson Cancer Research Center; [22]Sarah Cannon Research Institute; [23]Department of Hematology and Medical Oncology, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai; [24]Robert H. Lurie Comprehensive Cancer Center of Northwestern University; [25]Cleveland Clinic; [26]Northwell Health Cancer Institute, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell Health; [27]Loxo Oncology at Lilly; [28]Dana-Farber Cancer Institute and Harvard Medical School; [29]Maria Sklodowska-Curie National Research Institute of Oncology

Background: Covalent BTK inhibitors (BTKi) have transformed management of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), but many patients (pts) will require additional treatment. Pirtobrutinib is a highly selective, non-covalent (reversible) BTKi that inhibits both WT and C481-mutated BTK with equal low nM potency.

Methods: BRUIN is a phase 1/2 multicenter study (NCT03740529) of oral pirtobrutinib monotherapy in pts with advanced B-cell malignancies who have received >2 prior therapies. Primary objective for phase 1: determine the recommended phase 2 dose (RP2D). Primary objective of phase 2: ORR. Secondary objectives included DoR, PFS, OS, safety and tolerability and pharmacokinetics. Response was assessed every 8 weeks from cycle 3, and every 12 weeks from cycle 13, measured according to the iwCLL 2018 criteria, including PR with lymphocytosis (PR-L). Safety was assessed in all pts.

Results: As of 27 Sept 2020, 323 pts with B-cell malignancies (170 CLL/SLL, 61 MCL, 26 WM, 26 DLBCL, 13 MZL, 12 FL, 9 RT and 6 other) were treated on 7 dose levels (25-300mg QD). Among 170 pts with CLL/SLL, median age=69 (36-88) years. Median number of prior lines of therapies=3 (1-11). No DLTs were reported and MTD was not reached (n=323). 200mg QD was selected as RP2D. Fatigue (20%), diarrhea (17%) and contusion (13%) were the most frequent TEAEs regardless of attribution or grade seen in >10% pts. Most common AE of grade ≥3 was neutropenia (10%). 139 CLL/SLL pts were efficacy-evaluable with a median follow up time of 6 months (0.16-17.8+). ORR was 63% (95%CI 55-71) with 69 PRs (50%), 19 PR-Ls (14%), 45 SDs (32%) and 1 PD (1%), and 5 (4%) discontinued prior to first response assessment. Among 121 BTKi pretreated pts, ORR was 62% (95%CI 53-71). Responses deepened over time with an ORR of 86% among pts with >10 months follow-up. ORR was similar in pts who discontinued prior BTKi due to progression (67%), or adverse events or other reasons (52%). Of 88 responding pts, all except 5 remained on therapy (4 progressed, 1 achieved a PR and electively discontinued treatment to undergo transplant).

Conclusion: Pirtobrutinib demonstrated promising efficacy in heavily pretreated CLL/SLL pts and in pts with BTK C481 mutations. Pirtobrutinib was well tolerated and exhibited a wide therapeutic index. Updated data, including approximately 100 new pts with CLL and an additional 10 months since the prior data cut will be presented.

C072

CONSTITUTIVE VLA-4 ACTIVATION IN CHRONIC LYMPHOCYTIC LEUKEMIA (CLL). THE OTHER SIDE OF B-CELL-RECEPTOR (BCR) AUTONOMOUS SIGNALING

E. Tissino[1], R. Bomben[1], P.C. Maity[2], F. Pozzo[1], G. Forestieri[3], A. Nicolò[2], A. Haerzschel[4], T. Bittolo[1], F.M. Rossi[1], M. Datta[2], F. Zaja[5], G. Capasso[1], G. D'Arena[6], A. Chiarenza[7], F. Di Raimondo[7], H. Jumaa[2], D. Rossi[3], G. Del Poeta[8], T.N. Hartmann[4], A. Zucchetto[1], V. Gattei[1]

[1]Clinical and Experimental Onco-Hematology Unit, Centro di Riferimento Oncologico, I.R.C.C.S; [2]Institut für Immunologie, Universitätsklinikum Ulm; [3]Division of Hematology, Oncology Institute of Southern Switzerland; [4]Department of Internal Medicine, Faculty of Medicine, University Medical Center Freiburg, University of Freiburg; [5]DSM, University of Trieste, University of Trieste; [6]IRCCS Centro Di Riferimento Oncologico Della Basilicata, Rionero In Vulture; [7]Divisione di Ematologia, Ospedale Ferrarotto, A.O.U. Policlinico-OVE, Università di Catania; [8]Division Hematology, University of Tor Vergata, Italy

In CLL, VLA-4 (CD49d/CD29), a strong negative prognosticator and key player of microenvironmental interactions, can be rapidly inside-out activated by BCR triggering, such an activation measurable in flow cytometry using the conformation-sensitive anti-CD29 mAb HUTS21 or "real-time" measuring of VLA-4 ligand binding. In CLL, BCR signaling may occur also via autonomous antigen-independent manner but its contribution on VLA-4 activation is still unknown. In 1070/1984 CD49d+CLL (54%;≥30%), 250 (23%) presented an activated VLA-4 conformation (≥20%). The activated VLA-4 was: i) impaired by depletion of plasma from whole blood samples, and reconstituted by sVCAM-1 and fibronectin (FN); ii) impaired by pre-incubation with anti-CD49d HP1/2 blocking mAbs before addition of plasma, sVCAM-1 and FN. By ELISA assay, sVCAM-1 was higher in CD49d+ *vs* CD49d- CLL plasma samples ($p<0.0001$); among CD49d+ cases, sVCAM-1 was lower in activated VLA-4 cases ($p=0.0096$), suggesting ligand sequestration by activated surface VLA-4. CLL with mutated IGHV expressed higher levels of activated VLA-4 compared to unmutated IGHV CLL ($p=0.001$). Higher levels of activated VLA-4 were found in CLL using the IGHV3 and IGHV4 families, compared to cases using the IGHV1 family ($p=0.043$ and $p=0.004$). Moreover, BCR stereotypy analysis highlighted higher VLA-4 activation levels in CLL from subset#2 compared to CLL from subset#1($p=0.02$). To validate these data, the high VLA-4 expressing inducible murine TKO cell model (Dühren-von Minden M, Nature, 2012) was transfected with BCRs derived from 4 CLL with high constitutively activated VLA-4 levels (TKO-high) and 4 CLL with low constitutively activated VLA-4 levels (TKO-low). Compared to TKO-low cells, TKO-high cells showed a higher autonomous BCR signaling ($p=0.03$), and consistently higher VLA-4 affinity ($p=0.01$). In this context, Ibrutinib (IB) treatment impaired both BCR autonomous signaling and VLA-4 affinity. As in TKO, a decreasing constitutive VLA-4 acti-

vation was observed in CLL cells collected at pre-treatment and at day 14-30-60-90 from patients on IB, confirming an IB-dependent impairment of VLA-4 activation via BCR signal. Notably, anti-IgM stimulation induced high Ca++ influx and high VLA-4 affinity state in both TKO and primary CLL cells, irrespective of IB treatment. The presence of a constitutively activated VLA-4 form is observed in a fraction of CD49d+CLL, due to continuous VLA-4 inside-out stimulation derived from autonomous BCR signaling.

C073

ABSTRACT NOT PUBLISHABLE

C074

ZANUBRUTINIB IN ACALABRUTINIB-INTOLERANT PATIENTS WITH B-CELL MALIGNANCIES

P.L. Zinzani[1], M. Shadman[2], I. Flinn[3], E. Kingsley[4], B. Freeman[5], M. Levy[6], J. Cultrera[7], C. Farber[8], A. Chaudhry[9], R. Porter[10], R. Crescenzo[11], A. Idoine[11], X. Zhang[11], A. Cohen[11], K. By[11], J. Sharman[12]

[1]Institute of Hematology "Seràgnoli", University of Bologna; [2]Fred Hutchinson Cancer Research Center, University of Washington; [3]Sarah Cannon Research Institute/Tennessee Oncology; [4]Comprehensive Cancer Centers of Nevada; [5]Summit Medical Group; [6]Texas Oncology-Baylor Charles A. Sammons Cancer Center; [7]Florida Cancer Specialists & Research Institute; [8]Atlantic Hematology Oncology, Morristown Medical Center; [9]Summit Cancer Centers; [10]SSM Health Dean Medical Group; [11]BeiGene (Beijing) Co., Ltd., and BeiGene USA, Inc; [12]Willamette Valley Cancer Institute and Research Center

Bruton tyrosine kinase inhibitors (BTKi) are highly effective against several B-cell malignancies; however, their use is limited by adverse events (AEs), potentially due to off-target kinase inhibition. The next-generation BTKi zanubrutinib (zanu) was designed to minimize off-target effects to prolong treatment duration and limit AEs. In phase 3 trials in WM and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), zanu has consistently shown higher tolerability *vs* ibrutinib (ibr). Previous results from the ongoing, multicenter, single-arm, phase 2 study, BGB-3111-215 (NCT04116437), show that zanu was well tolerated in patients (pts) who discontinued (d/c) ibr and/or acalabrutinib (acala) due to AEs.

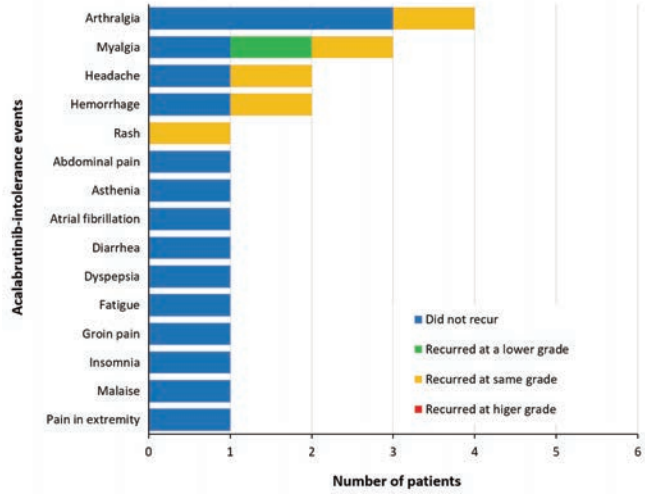


Figure 1. Recurrence and Severity of Acala-Intolerant AEs While on Zanu Treatment.

Here, we report updated results from acala-intolerant pts in BGB-3111-215. Eligible acala-intolerant pts with CLL/SLL, WM, MCL, or MZL were enrolled in cohort 2; progression on prior BTKi was not allowed. Pts received zanu 160 mg twice daily or 320 mg once daily and were evaluated for efficacy and safety, including recurrence of intolerant AEs from prior BTKi. Investigator-assessed responses were recorded every 3 cycles per standard response criteria. As of 6Jan2022, 13 pts received zanu (9 CLL/SLL; 2 WM; 1 MCL; 1 MZL); 10 pts remain on treatment. Median age was 73 y (range 51-83); median treatment duration was 9.2 mo (range 0.5-16.0) and median follow-up was 12.9 mo (range 0.8-16.0). Median number of prior therapies was 2; 62% of pts received ibr before acala, which was the most recent therapy for all. Three pts d/c treatment (myalgia, progressive disease, and withdrawal; 1 each) and withdrew from the study thereafter. 22 acala-intolerant AEs occurred in 13 pts, most commonly, arthralgia (4), myalgia (3), headache (2), and hemorrhage (2). 73% of acala-intolerant AEs did not recur on zanu; 62% of pts had no AE recurrence. 6 AEs recurred: 1 at lower grade, 5 at same grade, and 0 at higher grade (Figure 1). One pt d/c due to recurrence (myalgia, same grade). 3 pts who experienced the same intolerant AEs (pain in extremity, diarrhea, and atrial fibrillation) on ibr and acala did not have recurrence on zanu. Among 10 pts on zanu with ≥90 d of follow-up, 80% had at least stable disease and 70% had a deepening of response. These data suggest that zanu may be a viable therapeutic option for pts who are acala-intolerant–80% of pts received clinical benefit, and most did not experience recurrence of prior intolerant AEs. Enrollment and follow-up are ongoing.

C075

IMMUNE RESPONSE AND CLINICAL EFFICACY OF THE SARS-COV-2 VACCINE IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA: RESULTS OF A PROSPECTIVE, CENTRALIZED, MULTICENTER STUDY

F.R. Mauro[1], D. Giannarelli[2], C. Galluzzo[3], A Visentin[4], A.M. Frustaci[5], P. Sportoletti[6], C. Vitale[7], G. Reda[8], M. Gentile[9], L. Levato[10], R. Murru[11], D. Armiento[12], C. Ielo[1], R. Maglione[1], E. Crisanti[1], S. Pepe[1], A. Cipiciani[6], V. Mattiello[8], V. Gianfelici[10], L. Barabino[13], R. Amici[3], M. Coscia[7], A. Tedeschi[5], L. Trentin[4], S. Baroncelli[3]

[1]Hematology, Department of Translational and Precision Medicine, Sapienza University,[2]. Design and Analysis of Clinical Trials Unit, Scientific Directorate, Fondazione Policlinico Universitario A. Gemelli; [3]National Center for Global Health, Istituto Superiore di Sanità,[4]Hematology and Clinical Immunology Unit, Department of Medicine, University of Padua; [5]ASST Grande Ospedale Metropolitano Niguarda; [6]Institute of Hematology-Centro di Ricerca Emato-Oncologica (CREO), University of Perugia; [7]Department of Molecular Biotechnology and Health Sciences, University of Torino and Division of Hematology, A.O.U. Città della Salute e della Scienza di Torino; [8]Hematology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore, University of Milan; [9]Hematology and Oncology Department, Biotechnology Research Unit; [10]Department Hematology-Oncology, Azienda Ospedaliera Pugliese-Ciaccio; [11]Hematology and Stem Cell Transplantation Unit, Ospedale Oncologico A. Businco, ARNAS,"G. Brotzu."; [12]Hematology, Stem Cell Transplantation Unit, University Campus Bio-Medico; [13]Department of Medical Sciences and Public Health, University of Cagliari, Italy

Reduced response to the SARS-Cov-2 vaccine and high Covid-related mortality have been reported in patients with chronic lymphocytic leukemia (CLL). We carried out a prospective multicenter study to define the rate of immune responses and COVID events after the mRNA SARS-CoV2 vaccine. Between February and August 2021, 200 patients with CLL received the SARS-CoV-2 vaccine. The median age of patients was 70 years, and the median IgG level was 635 mg/dl; 83.5% were previously treated (chemoimmunotherapy only,10%; ibrutinib–based therapy, 36%; venetoclax-based therapy 37.5%). Overall, 135 (77.5%) patients

had been previously treated with rituximab, 33 (16.5%) within 12 months before vaccination. A centralized assessment of the anti-SARS-Cov-2 IgG levels was performed at baseline, after the second and third doses of the vaccine. Four patients were excluded from the analysis (positive test at baseline, 2; lost to the follow-up, 1; Richter syndrome, 1). Seventy-six (39%) patients developed a serologic response after the second dose. A significant increase in the rate of responses, 51.5% (p=0.019), was observed after the booster dose with a response detected in 25% of previously seronegative patients. In multivariate analysis, age (OR: 0.92 [95% CI: 0.92-0.97] p=0.0001), IgG levels (OR: 0.28 [95% CI: 0.13-0.58] p<0.001), and the time between rituximab and vaccination (OR: 0.10 [95% CI: 0.03-0.37] p=0.001), revealed a significant and independent impact on the serologic response. When the analysis was restricted to patients who received targeted therapy, in addition to age (OR: 0.96 [95% CI: 0.92-0.99] p=0.04), IgG levels (OR: 0.31 [95% CI: 0.12-0.79] p=0.014), the time (<18 vs.≥18 months) between the start of ibrutinib or venetoclax-based therapy and vaccination showed a significant and independent impact on response (OR: 0.17 [95% CI: 0.06-0.44], p <0.0001). At present, 160 (82%) patients were COVID-free, while 35 (18%);16 seropositive; 19 seronegative) developed COVID that was lethal in three (1.5%). In conclusion, about half of patients with CLL developed a serological response after the SARS-CoV-2 vaccine. Younger age, IgG levels ≥ 550 mg/dl, ≥12 months from the last rituximab administration, and ≥18 months from the start of targeted therapy were associated with a greater likelihood of achieving an immune response. The SARS-CoV-2 vaccine revealed a clinical benefit in reducing morbidity and mortality COVID-related.

Hodgkin's lymphoma

C076

POST-TRANSPLANT NIVOLUMAB PLUS UNSELECTED AUTOLOGOUS LYMPHOCYTES IN REFRACTORY HODGKIN LYMPHOMA: A FEASIBLE AND PROMISING SALVAGE THERAPY ASSOCIATED WITH EXPANSION AND MATURATION OF NK CELLS

F. Guolo[1,2], P. Minetto[1], S. Pesce[3], F. Ballerini[1], M. Cea[1,2], M. Frello[2], M. Garibotto[2], C. Vernarecci[2], G. Francia[2], E. Montanari[2], M. Greppi[3], M. Bozzo[3,4], M. Miglino[1,2], A. Todiere[1,2], E. Tedone[5], N. Colombo[5], R. Mangerini[5], A. Bo[6], M.R. Ruzzenenti[7], P. Carlier[7], A. Serio[6], S. Luchetti[6], A. Dominietto[1], R. Varaldo[1], S. Candiani[4], M. Mora[5], V. Agostini[7], J.L. Ravetti[5], P. Nozza[5], G. Del Zotto[8], E. Marcenaro[3], R.M. Lemoli[1,2]

[1]Department of Oncology and Hematology (DIPOE), IRCCS Ospedale Policlinico San Martino, Genoa, Italy; [2]Clinic of Hematology, Department of Internal Medicine (DiMI), University of Genoa, Genoa, Italy; [3]Department of Experimental Medicine (DIMES), University of Genoa, Genoa, Italy; [4]Department of Earth, Environment and Life Sciences (DISTAV), University of Genoa, Genoa, Italy; [5]PathologIcal Anatomy and Histology, IRCCS Ospedale Policlinico San Martino, Genoa, Italy; [6]Stem Cell Processing Unit, IRCCS Ospedale Policlinico San Martino, Genoa, Italy; [7]Blood Transfusion Service and Hematology, IRCCS Ospedale Policlinico San Martino, Genoa, Italy; [8]Core Facilities, Area Aggregazione Sevizi e Laboratori Diagnostici, IRCCS Giannina Gaslini, Genoa, Italy

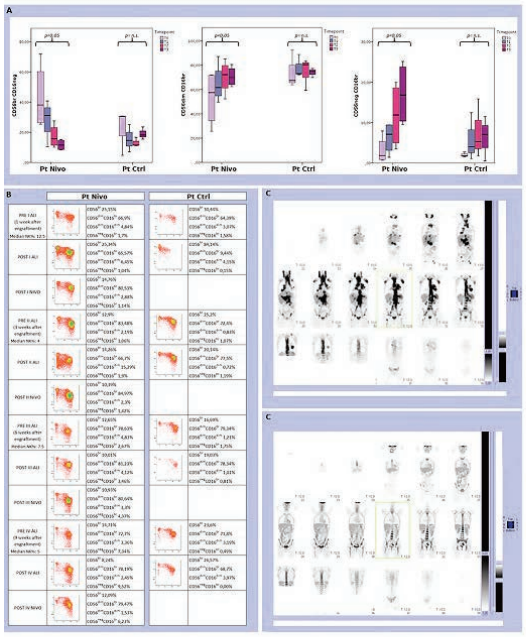
Background: Hodgkin Lymphoma (HL) Hodgkin Lymphoma (HL) is a B-Cell neoplasia characterized by a high degree of response to chemotherapy and an overall favourable outcome in responding patients. Despite the efficacy of first line therapy, however, about 30% of patients affected by HL are either refractory or eventually relapse (R/R) after first or second line therapy followed by autologous hemopoietic stem cell transplantation (ASCT). Immune checkpoint inhibitors (CI) have demonstrated clinical activity in HL patients relapsing after ASCT, although only 20% complete response (CR) rate are usually observed. The efficacy of CI is strictly related to the host immune competence, which is impaired in heavily pre-treated HL patients.

Aims: Here, we aimed to enhance the activity of early post-ASCT CI (nivolumab) administration with the infusion of autologous lymphocytes (ALI) and to investigate the lymphocyte subpopulation involved in the mechanism of response to CI in HL.

Results: Seventeen patients with relapse/refractory (R/R) HL (median age 29 years; range 18-65), underwent lymphocyte apheresis after first line chemotherapy and then proceeded to salvage therapy. Subsequently, 12 patients with progressive disease at ASCT received early post-transplant CI supported with four ALI, whereas 5 responding patients received ALI alone, as a control cohort. Most patients showed CMV seropositivity at the time of enrolment, without signs of active infection (positive anti-CMV IgG, negative IgM and undetectable CMV DNA). No adverse events were recorded, specifically, no immune-related toxicity was observed and none of the patients showed CMV reactivation. All patients receiving ALI + CI (treated patients) achieved negative PET scan CR and 11/12 are alive and disease-free after a median follow-up of 33 months. Four patients underwent subsequent allogeneic SCT and 3 patients are currently waiting for transplantation. Two of the patients in the control arm relapsed. Phenotypic analysis of circulating cells showed a faster expansion of highly differentiated NK cells in ALI plus nivolumab-treated patients as compared to control patients (Figure 1).

Conclusions: Our data show anti-tumour activity with good tolerability of ALI + CI for R/R HL and suggest that this setting may accelerate NK cell development/maturation and favour the expansion of the “adaptive”

NK cell compartment, especially in patients with CMV seropositivity, in the absence of CMV reactivation.



(A) Analysis of the size and distribution of CD56brightCD16neg/dim, CD56dimCD16bright, and CD56negCD16bright NK cell subsets derived from peripheral blood of 4 treated (Pt Nivo) and 3 control (Pt Ctrl) patients at different time points after ASCT (t0: pre-treatment; t1: first post ALI + nivolumab for treated patients and first ALI for control patient; t2: second post ALI + nivolumab for treated patients and second ALI for control patient; t3: third post ALI + nivolumab for treated patients and third ALI for control patients). Data represent the mean ± 95% CI. $p < 0.05$ (B) Comparison of peripheral blood NK cell subsets distribution in two patients representative of the two cohort -patient receiving ALI + nivolumab (Pt Nivo); patient receiving ALI alone (control) (Pt Ctrl)- at the different steps indicated in the Figure. ns, not significant. (C) PET scan from the patient receiving ALI + nivolumab at enrollment (upper panel C) and at end of treatment (EOT) (lower panel C). All the patients shown were seropositive for HCMV, but none of them experienced HCMV reactivation during all study period.

Figure 1.

C077

VENOUS THROMBOEMBOLISM (VTE) IN PATIENTS WITH HODGKIN LYMPHOMA: MONOCENTRIC STUDY OF THROLY AND KHORANA RISK SCORES

G.M. Assanto, A. Serrao, S. Pontecorvo, F. Malfona, G.M. D'Elia, G. Annechini, M. Martelli, A. Pulsoni, I. Del Giudice, A. Chistolini

Hematology, Department of Translational and Precision Medicine, Sapienza University of Rome, Italy

Venous Thromboembolism (VTE) affects morbility of Hodgkin Lymphoma (HL) patients. Thrombosis Lymphoma (ThroLy) and Khorana scores, established for lymphomas and cancer patients, respectively, can be applied to HL to assess basal risk of VTE. We retrospectively evaluated a cohort of HL to validate these scores and evaluate other potential risk factors. 134 patients with newly diagnosed HL (from 2018 to 2020) were included, median age at diagnosis was 42 years (range 18-85), and median follow-up was 23 months (range 6-49). According to Khorana criteria, intermediate-risk (IR) were 80.2% (n=105) while high-risk (HR) were 19.8% (n=26). Regarding ThroLy criteria, low-risk (LR) patients were 16.7% (n=22), IR were 57.6% (n=76) and HR were 25.8% (n=34). All patients received first-line therapy, and 19 (14.4%) subsequently experienced relapse/progression. Central venous catheter (CVC) was implanted in 42.9% (n=57). No patient had previous thrombotic events. Eleven patients (8.3%) were receiving antiaggregant therapy, 17.3% (n=23) received enoxaparine as thrombosis prophylaxis for bulky or mediastinal disease. A total of 22 thrombotic events were observed after a median follow-up of 20 months (range 1-45), 10 were CVC-related. Khorana HR group showed an increased rate of thrombotic events compared to IR, 28% (7/25) *vs* 11.7% (12/103) respectively (p 0.045). Robust association was found between ThroLy risk categories and thrombotic risk: among HR patients, VTE was observed in 32.4% (11/34), against 10.5% (8/76) and 4.55% (1/22), for IR and LR respectively, with an estimated thrombotic EFS of 30 months for HR *vs* 44 for LR (p 0.002 Figure IA). Prophylaxis with enoxaparine abrogated the thrombotic risk in HR patients (p 0.56). Hypertension (HTA) showed a significant association to thrombotic events: among hypertensive patients a higher rate of VTE was observed with 29.6% (8/27) opposed to 12.6% (13/103) in non-hypertensive patients (p 0.038). HTA (HR 2.44, p 0.04 CI1.01-6) and HR ThroLy (HR 2.81, p 0.009 CI1.2-6) were confirmed on multivariate analysis. We then defined a new risk category which included HR ThroLy patients with HTA, which showed inferior estimated EFS *vs* other HR patients (21 *vs* 35 months) with an incidence of 50% of VTE events (6/12) *vs* 22.8% of conventional HR (5/22) (p 0.001 Figure IB). Conclusion: ThroLy score proved its utility in VTE-risk assessment, HTA could be integrated to augment ThroLy predictive power.

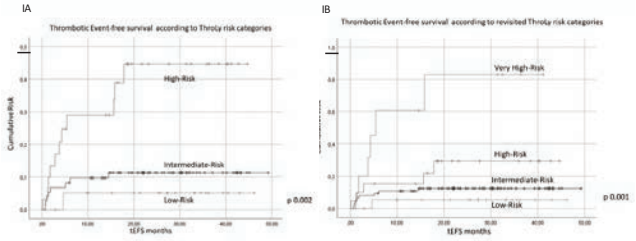


Figure 1. Kaplan-Meier curves showing cumulative incidence of thrombotic events in Hodgkin lymphoma according to ThroLy score (IA) and revisited ThroLy score (with very high-risk patients including ThroLy high-risk + hypertension) (IB).

C078

OUTCOME OF POST-AUTOLOGOUS STEM CELL TRANSPLANTATION RELAPSE IN CLASSICAL HODGKIN LYMPHOMA PATIENTS IN THE ERA OF NEW DRUGS

R. Chiara[1], V. Marasco[1], A. Guidetti[1,2], C. Amodeo[2], M. Smania[2], F. Mazzon[2], A. Dodero[1], L. Farina[1], M. Canzi[2], P. Corradini[1,2]

[1]Divisione di Ematologia e Trapianto di Midollo Osseo, Fondazione IRCCS Istituto Nazionale dei Tumori; [2]Università degli Studi di Milano, Italy

Autologous stem cell transplantation (ASCT) represents the standard of care for patients (pts) affected by relapsed/refractory (R/R) classical Hodgkin Lymphoma (cHL). Pts who can't proceed to ASCT due to refractory disease or who relapse after ASCT present a poor prognosis with an expected median Overall Survival (OS) of less than 24 months. In this setting, a survival improvement is expected since brentuximab-vedotin (BV) and check-point inhibitors (CPI) nivolumab and pembrolizumab have been introduced in the routine clinical practice. We retrospectively analyzed consecutive R/R cHL pts who relapsed post-ASCT from 2004 to 2021 at our center. The aim was to compare OS of pts who relapsed before *vs* after 2012, year of BV availability, and of pts receiving *vs* not receiving allogeneic stem cell transplantation (AlloSCT). Among 93 R/R cHL pts who underwent ASCT, we identified 38 pts who experienced post-ASCT relapse after a median time of 3.5 months (1-71). Median age was 33 years (16-68) and 58% of pts were male. Twenty-eight pts (74%) relapsed within 12 months after ASCT, extranodal involvement was present in 12 (32%) and B symptoms in 2 (6 %) pts. Thirteen pts (34%) relapsed post-ASCT before 2012 whereas 25 pts (66%) , intended as new drugs era. The median number of salvage therapy lines post-ASCT was 2 (1-4). After ASCT, BV and/or CPI as sal-

vage therapy were administered in 27 cases (71%). With a median follow up of 65 months (1-161), the 5-year OS of the whole population was 67%. No statistically significant differences were observed in OS according to period of post-ASCT relapse (p=0,44), 5-year OS being 62% in pts relapsed before 2012 *vs* 70% in pts relapsed after 2012. AlloSCT was performed in 27/38 pts (71%): at alloSCT overall response rate was 92% and 12 pts (44%) were in complete response. Proportion of pts proceeding to AlloSCT was similar in pts treated with BV and/or CPI and BV and CPI naïve pts (73% *vs* 63%, p=0.69). Patients who received AlloSCT had a 5-year OS of 73% *vs* 47% in pts who did not receive AlloSCT (p=0,04, Figure 1). Non-relapse mortality following AlloSCT was 8% at 24 months and 19% at 48 months. In conclusion, with the limitation of a retrospective non randomized trial, the OS we describe is superior to the outcome historically reported in cHL pts relapsed after ASCT.

No significant differences in OS were observed with regard to treatment era, whereas a survival advantage was reported in pts receiving AlloSCT.

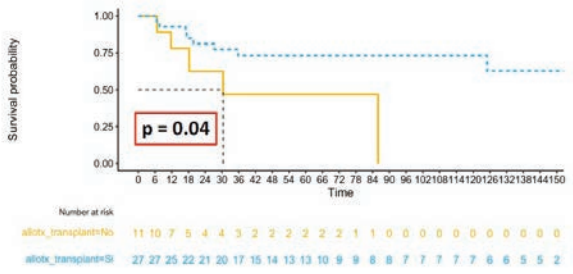


Figure 1.

C079

PREDICTIVE VALUE OF INTERIM-PET IN RELAPSED/REFRACTORY CLASSICAL HODGKIN LYMPHOMA TREATED WITH FOUR BEGEV CYCLES

C. Rusconi[1], V. Marasco[1], V.R. Zilioli[2], A. Guidetti[1], C. Muzi[2], F. Mazzon[3], M. Smania[3], P. Matteucci[1], A. Dodero[1], L. Farina[1], L.F. Devizzi[1], E. Meli[2], A. Chiappella[1], M. Pennisi[1], G. Perrone[1], G. Levati[1], M. Canzi[3], E. Ravano[2], R. Cairoli[2], P. Corradini[1,3]

[1]Division of Hematology and Stem Cell Transplantation, Fondazione IRCCS Istituto Nazionale Tumori Foundation; [2]Division of Hematology, ASST Grande Ospedale Metropolitano Niguarda; [3]University of Milan, Italy

Achievement of complete response (CR) before autologous stem cell transplantation (ASCT) is one of the main predictive factors of outcome in patients (pts) affected by relapsed/refractory (R/R) classical Hodgkin Lymphoma (cHL) eligible to high-dose chemotherapy. The predictive role of interim PET during salvage treatment is well established in pts treated with IGEV or ICE but has not been investigated in pts receiving BEGEV (Bendamustine, Gemcitabine and Vinorelbine).

The aim of the study was to evaluate the predictive value of PET after two cycles (PET2) in pts who completed 4 cycles of BEGEV regardless of interim response.

We retrospectively collected data of 51 consecutive R/R cHL pts eligible to ASCT treated from 2016 to 2021 in 2 Italian centres. Three out of 51 pts were excluded due to missing PET2 and 8 due to BEGEV discontinuation for progressive disease (PD) before or at PET2. Forty pts were analysed: median age at relapse was 42 ys (21-70), 23 pts (57%) were in stage III-IV, 6 pts (15%) had B symptoms and 12 pts (30%) had extranodal involvement (EI). Fifteen pts (38%) were primary refractory, 11 pts (27%) had an early and 14 pts (35%) a late relapse. PET2 was negative [Deauville Score (DS) 1-3] in 30 (75%) and positive (DS 4) in 10 pts (25%). Among adverse risk factors at relapse, only EI correlated with PET2 positivity [Odds Ratio (OR)=6, 95% CI 1.3-23.1, p=0.0041]. All pts completed 4 BEGEV cycles and at final evaluation CR was achieved in 30 (75%), partial response (PR) in 3 (7.5%) and PD in 7 (17.5%) pts. Complete response after 4 BEGEV was obtained in 27/30 (90%) PET2 negative pts and 3/10 (30%) PET2 positive pts (OR=21, 95% CI 3.5-96.6, p=0.0006). ASCT was performed in 36 pts, following the fourth BEGEV cycle in 26 pts (65%) and after further salvage treatments in 10 pts (25%). With a median follow-up of 32 (4-61) months, 3-year overall survival (OS) and progression-free survival (PFS) for the whole study population were 93% and 62% and no significant differences both in PFS and OS were observed accordingly to PET2 result. Conversely, 3-year EFS was significantly superior in PET2 negative *vs* PET2 positive pts [72% *vs* 40%, Hazard Ratio 5,4, 95%CI 1,3-21,6 p=0,015, Figure 1).

In conclusion, interim PET identified chemo-refractory pts during BEGEV salvage treatment; pts with PET2 positive had a low probability to achieve CR after 2 additional BEGEV cycles and should be candidate to new therapeutic strategies before ASCT.

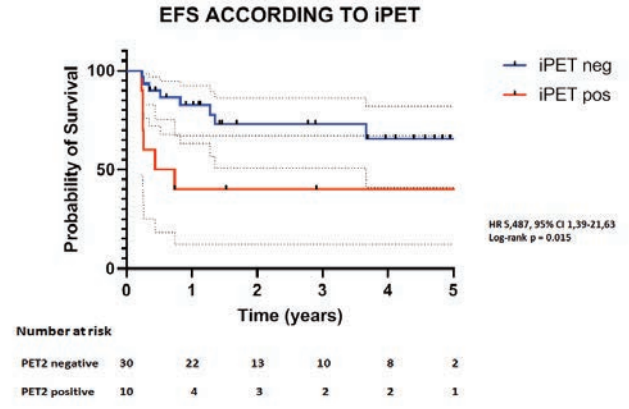


Figure 1.

C080

GERIATRIC-MULTIDIMENSIONAL ANALYSIS AND THERAPEUTIC STRATEGY ARE CLOSELY RELATED TO THE OUTCOME OF ELDERLY PATIENTS WITH HODGKIN LYMPHOMA: A MULTICENTER RETROSPECTIVE STUDY OF THE RTL (RETE TOSCANA LINFOMI)

B. Puccini[1], M. Ciceri[1], E. Cencini[2], I. Romano[1], F. Ghio[3], L. Mannelli[4], S. Moretti[5], G. Lucco Navei[2], D. Dardanis[3], M. Palazzo[1], G. Cervetti[3], A. Fabbri[2], A.M. Vannucchi[1,6,7], L. Nassi[1]

[1]Unit of Hematology, Azienda Ospedaliero-Universitaria Careggi and University; [2]Unit of Hematology, Azienda Ospedaliero-Universitaria Senese and University; [3]Unit of Hematology, Azienda Ospedaliero-Universitaria Pisana and University; [4]SOS Oncoematologia, Ospedale S. Stefano; [5]SOC Ematologia Clinica e Oncoematologia; [6]Department of Experimental and Clinical Medicine, University of Florence; [7]CRIMM, Centro di Ricerca e Innovazione per le Malattie Mieloproliferative, Azienda Ospedaliero-Universitaria Careggi, Italy

Classical Hodgkin lymphoma (cHL) patients (pts) more than 60 years (yrs) old represent approximately 20% of the total population with cHL. Historically, they showed different characteristics and significantly inferior outcomes compared with younger pts. In this retrospective multicenter study, we assessed clinical characteristics, comprehensive geriatric

assessment (CGA), functional status, cumulative illness rating scale (CIRS-G), response to therapy and survival of elderly cHL pts. Methods: We collected data of consecutive older pts with cHL diagnosed from 2009 to 2019 in 4 Tuscan hematological centers. Results: Data from 150 pts were analyzed. Median age was 71 yrs (range 60-90). M:F ratio was 83:67. 71 were nodular sclerosis (47%), 56 mixed cellularity (37%), 19 lymphocite rich (13%), 4 lymphocite depleted (3%). Stage III-IV was present in 69 pts (55%), while 71 pts had B symptoms (45%). CGA assessed at baseline stratified pts in FIT (86 pts; 57%), UNFIT (36 pts; 24%), FRAIL (28 pts; 19%). CIRS-G was analyzed on 75/150 pts, and resulted higher than 3 in 38%.122 pts (81%) were treated with curative intent (CI); 66% were treated with ABVD regime, 15% with VEPEMB, and 8% with VBM. 16 pts (11%) received brentuximab vedotin as single agent or in combination. 87 pts (58%) obtained complete remission, with overall response rate of 70%.After a median follow-up of 54 months (mths), 77 pts (51%) were alive, 30 pts (20%) died for progressive disease, 9 pts (6%) died for treatment-related toxicity and 34 (23%) for other causes. With a median follow-up of 29 mths ((range 2-191), the estimated 5 yrs progression free survival (PFS) rates were 56%. With a median follow-up of 54 mths (range 2-222), the estimated 5 yrs overall survival (OS) rates were 64%. 5-yrs PFS was significantly better in FIT than UNIFIT and FRAIL pts (66% *vs* 47% *vs* 32%; p < 0.000); moreover 5 yrs PFS in pts treated with CI and palliative approach was 63% and 21% respectively (p<0,000) and 5 yrs OS was 70% and 23% respectively (p<0.000). In particular in pts treated with CI PFS was 68% in FIT pts, 55% UNFIT and 28% in FRAIL pts (p<0,05). Conclusions: With the limitations of a retrospective analysis, we can state that both CGA and CI are able to stratify the prognosis of elderly pts with cHL. Larger prospective studies, such as the one currently being conducted by the Fondazione italiana Linfomi (FIL), are needed to confirm these data, possibly also providing correlations with biological markers.

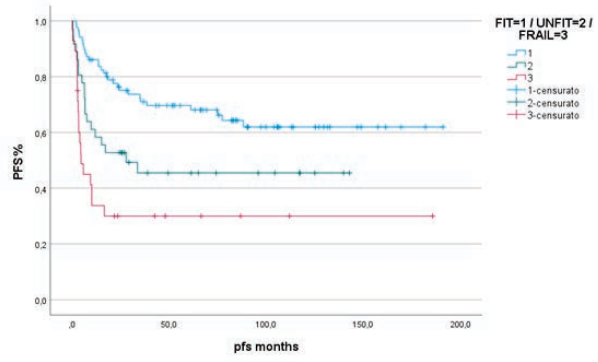


Figure 1.

Monoclonal myeloma and gammopathies III

C081

CD38 EXPRESSION IN EXTRA MEDULLARY DISEASE IN MULTIPLE MYELOMA

L. Notarfranchi[1], F. Accardi[2], C. Mancini[3], E. Martella[3], N. Campanini[3], B. Dalla Palma[4], G. Sammarelli[4], G. Todaro[1], S. Bonomini[4], D. Toscani[1], J. Burroughs Garcia[1], V. Raimondi[1], N.T. Iannozzi[1], P. Storti[1], L. Craviotto[1], N. Giuliani[1, 4]

[1]Department of Medicine and Surgery, University of Parma; [2]U.O. Onco-hematology Azienda Ospedaliera "Ospedali Riuniti Villa Sofia-Cervello"; [3]U.O. Pathological Anatomy, Azienda Ospedaliero-Universitaria di Parma; [4]U.O. Hematology, Azienda Ospedaliero-Universitaria di Parma, Italy

Extramedullary disease (EMD) is a rare clinical manifestation in multiple myeloma (MM) due to plasma cell (PC) proliferation and homing outside of the bone marrow (BM). EMD represents an unmet medical need in MM patients (pts) for the unsatisfactory response to the current treatment, thus a better characterization of PCs of EMD may help to develop appropriate treatments. Pervious works have suggested that the expression modulation of adhesion molecules, including CD44 and CD56, supports clonal PCs migration through the bloodstream. CD38 is a multifunctional transmembrane glycoprotein, expressed by PCs, which also plays a role as adhesion molecule. CD38 is considered a hallmark of MM cells and a therapeutic target for anti-CD38 antibody-based approach, however, CD38 expression profile by extramedullary PCs is still unknown and has been investigated in this study. We investigated 22 MM pts with a biopsy-proven EMD. The expression of CD38 and CD56 and CD44 was evaluated either by flow cytometry at BM level or by immunohistochemistry from both BM and EMD biopsies. Immunohistochemical data were scored using a semiquantitative evaluation of the percentage of CD56, CD44 and CD38, on MM cells on a 5-tiered scale 3 pts presented EMD at diagnosis while 19 pts presented EMD at relapse. Overall, 55% of pts developed multiple plasmacytomas. The most common site was soft tissue and liver/spleen which represents 42% of the total EMD followed by lymph nodes (15%). In 41% the EMD relapse was dissociated from BM relapse. CD56 showed a high score (3-4) in 5 of 22 (23%) EMD samples and was absent in 14 of 22 (64%) pts. Discordant CD56 expression was observed in 18% of samples with a strong down-regulation of CD56 in the EMD samples compared to BM. CD44 showed a high score in 16 of 20 (80%) EMD samples and was absent in 2 of 20 (10%). 4 pts with discordant CD44 expression (27%) showed an up-regulation of CD44 in the EMD samples compared to BM. CD38 had a high score in 16 of 22 BM samples (73%) and was absent in 3 of 22 (14%) EMD samples. Discordant CD38 expression was observed in 26% of samples with a down-regulation of CD38 in the EMD samples compared to BM. In conclusion, our data indicate that discordant expression of CD56, CD44 and CD38 may occur in EMD lesions compared to BM. The possible lack of CD38 expression in EMD was highlighted for the first time and it could have a critical therapeutic impact.

C082

PREDICTIVE RELEVANCE OF SUSTAINED MINIMAL RESIDUAL DISEASE (MRD) AND EARLY LOSS OF MRD NEGATIVITY DURING MAINTENANCE THERAPY AFTER AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCT) IN NEWLY DIAGNOSED MULTIPLE MYELOMA PATIENTS. A SINGLE CENTER EXPERIENCE

R. Ribolla[1], A. Belotti[1], C. Crippa[1], M. Chiarini[2], V. Giustini[2], V. Cancelli[1], S. Ferrari[1], A. Peli[1], C. Bottelli[1], C. Cattaneo[1], A. Roccaro[3], G. Rossi[1], A. Tucci[1]

[1]Division of Hematology, ASST Spedali Civili di Brescia; [2]Chemistry Laboratory, Diagnostic Department, ASST Spedali Civili di Brescia; [3]Clinical Research Development and Phase I Unit, ASST Spedali Civili di Brescia, Italy

Introduction: The predictive relevance of sustained MRD negativity in multiple myeloma (MM) is emerging in clinical trials. We analyzed outcome according to sustained MRD negativity in MM patients (pts) treated with autologous stem cell transplantation (ASCT) at our Institution.

Methods: We retrospectively analyzed the outcome of 85 newly diagnosed MM pts (median age 60 yrs) diagnosed at our center between Jan 2015 to Dec 2020 in ≥VGPR after ASCT (median follow up: 46 months). Bone marrow samples were collected for 8-color FCM marrow MRD evaluation (sensitivity 10^{-5}) at day +100 after ASCT, before maintenance. Sustained 1-year MRD negativity was also evaluated and the outcome according to MRD status was analyzed.

Results: Of 85 pts, 30 (35%) were ISS stage 3 and 18 (21%) had high risk (HR) cytogenetics. Induction regimens were: VTd 59, VRd 5, D-VRd 6, D-VCd 2, KRd 11, KCd 2. Single ASCT was performed in 52 pts (61%), whereas 33 pts (39%) received double ASCT. Response rates were VGPR 28%, CR 26% and sCR 46%, 69% with MRD negativity before maintenance. 1-year sustained MRD negativity was documented in 51 pts (60%), whereas early loss of MRD negativity was observed in 8 (9%). Better PFS was observed in pts with sustained MRD negativity compared to MRD positive pts before maintenance: median NR *vs* 51.3 mo, p <0.0001, HR 0.20 (0.077-0.53). The worst PFS (25.6 mo) was observed in pts with early loss of MRD negativity (<1 year) and was significantly inferior if compared both to pts with sustained MRD negativity (p <0.0001, HR 0.06; 0.008-0.54) and to MRD positive pts before maintenance (p 0.01, HR 0.36; 0.11-1.09), with significantly different outcome of the 3 subgroups (p < 0.0001). Different median OS was observed among the 3 subgroups: NR in sustained MRD negative and MRD positive pts, 36.6 mo in pts with early loss of MRD negativity (p 0.0004). Considering sustained MRD negativity, cytogenetics, ISS and induction treatment (VTD *vs* novel combination therapies), variables that independently affected PFS were the early loss of MRD negativity (p <0.0001, HR 0.07; 0.02-0.25) and HR cytogenetic profile (p 0.022, HR 0.28; 0.09-0.84) whereas OS was independently influenced by the presence of HR cytogenetic disease (p 0.021, HR 0.05; 0.004-0.63) on a multivariate analysis.

Conclusion: Our data confirms the predictive value of sustained 1-year MRD negativity. The detection of early loss of MRD negativity identifies a subgroup of pts with a particularly poor prognosis.

C083

REAL-WORLD DATA OF ATTRITION RATES BY SUBSEQUENT LINES OF THERAPY IN MULTIPLE MYELOMA PATIENTS TREATED IN A TERTIARY CARE ITALIAN CENTRE

M. Offidani[1], S. Morè[1], L. Corvatta[2], V.M. Manieri[1], A. Olivieri[1]

[1]Clinica di Ematologia Azienda Ospedaliero-Universitaria Ospedali Riuniti di Ancona; [2]U.O.C. Medicina, Ospedale Profili, Italy

Background: Despite therapeutic progress leading to a significant improvement of outcome, most Multiple Myeloma (MM) patients relapse and require subsequent lines of therapy (LOTs). A recent real-world experience reported attrition rates (ARs), defined as the ratio of patients who did not have record of a subsequent LOT, ranging from 21% to 57% across all LOTs (Fonseca et al, BMC Cancer 2020).

Methods: We examined treatment patterns and ARs across all LOTs in newly diagnosed MM patients recorded in our database from 2011 to 2021, evaluating potential factor affecting AR by Cox regression analysis. We then evaluated ORR, CR and survival rates of each line of therapy.

Results: We analyzed 413 patients with a median age of 69 years (range 30-93), 61.5% older than 65 years, with PS ≥ 2 in 22% and 118 (30%) who had more than 2 comorbidities. R-ISS stage 2-3 and renal failure were detected in 74% and 18% of patients respectively. Median follow-up was 48.7 months (range 6-140). In LOT-2 the most frequently used regimens were lenalidomide (L)-based (35%) and bortezomib (B)-based (33%). In LOT-3 patients received mainly L- (21.5%), pomalidomide (P)- (20.5%) and B-based (18%) regimens whereas both carfilzomib (K)- and antiCD38 MoAbs-based regimens were given to 14% of patients. In LOT-4 and LOT-5 P-based regimens were the most used (26.5% and 32%, respectively). Rate of patients receiving therapy from LOT1 to LOT-5 and AR rates are summarized in the Table. In univariate analysis age >65 years, ISS 2-3, > 2 comorbidities, no transplant, response < VGPR and no maintenance were significantly associated with AR but regression analysis selected only age > 65 years [HR 7.4 (3.3-16.5)] and > 2 comorbidities [HR 2.5 (1.5-5.6)] as factors affecting AR. Of note, in patients < 65 years AR was 16% *vs* 53% in older, whereas it was 30% *vs* 63% in patients with < 2 and ≥2 comorbidities, respectively. ORR and CR rates, TTNT and OS throughout the lines of therapy are reported in the Table 1.

Conclusions: In our real-life experience near half of patients received a 2nd line of therapy. AR was lower than 25% in the first 3 LOT, becoming 33% for LOT-4 and 50% for LOT-5 suggesting that the best available therapies should be given early. Advanced age and comorbidities remain a challenge since they are the main reasons of AR. However, access to new therapeutic regimens with higher safety/efficacy profile will allow to treat a higher number of patients further improving their outcome.

Table 1.

	LOT-1	LOT-2	LOT-3	LOT-4	LOT-5
Patients, n (%)	413	200 (48.4)	92 (22.5)	45 (11)	25 (6)
Relapsed, n	270	145	68	40	24
Ongoing or in response, n (%)	143 (34.6)	55 (27.5)	24 (26)	5 (11)	1 (4)
Next LOT, n (%)	200 (48.4)	92 (46)	45 (49)	25 (55.5)	12 (48)
Attrition rate (%)	17	26.5	25	33.3	48
ORR (%)	85	70	52	31.5	9.5
CR (%)	37	25	16.5	8	0
TTNT, median, months	40.5	19.5	10.3	6	4.7
OS, median, months	83	38.3	24	12.2	10.5

C084

INCIDENCE AND CLINICAL OUTCOME OF SARS-COV-2 INFECTION AFTER TWO AND THREE VACCINATION DOSES IN PATIENTS WITH MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE (MGUS)

N. Sgherza[1], P. Curci[1] , R. Rizzi[1,2], D. Roccotelli[2], M. Croce[2], M. Avantaggiato[2], L. Ruga[2], A. Vitucci[1], A. Palma[1], D. Di Gennaro[2], M. Chironna[3], S. Tafuri[3], P. Musto[1,2]

[1]Hematology and Bone Marrow Transplantation Unit, AOUC Policlinico; [2]Department of Emergency and Organ Transplantation, "Aldo Moro" University School of Medicine; [3]Department of Biomedical Sciences and Human Oncology, "Aldo Moro" University School of Medicine, Italy

Vaccination against SARS-CoV-2 is the main strategy to prevent adverse outcome of COVID-19. In this regard, immune dysregulation detected in subjects with MGUS might let to speculate a suboptimal clinical response to vaccine (Konishi, Cancer Cell 2022). Aiming to specifically address the effects of anti-SARS-CoV-2 vaccines in this subset of patients, we compared incidence and outcome of this viral infection observed in a previously described cohort of 1,454 not vaccinated MGUS patients (91 of whom were SARS-CoV-2 positive) (Sgherza, Haematologica 2022), with those recorded in a comparable population during the national vaccination campaign. Specifically, we collected new retrospective data from 86 SARS-CoV-2 positive individuals among 1,060 COVID-19-naïve MGUS patients evaluated after at least two doses of anti-SARS-CoV-2 vaccine received between April 2021, and January 2022 . The most frequent MGUS-isotype was IgG (74.4%), followed by IgM (16.3%), IgA (7%), and biclonal (2.3%).

Table 1. A) Characteristics of MGUS patients with SARS-CoV-2 infection before and after vaccination. B) Effects after two and three vaccine doses.

A	Pre-vaccination*	Post-vaccination	P-value
Mean age, years +/- SD (range)	65.6 +/- 13.3 (29-89)	65.9 +/- 13.4 (31-90)	0.8437
Gender (male/female)	42/49	53/33	0.05
Total SARS-CoV-2 positive MGUS, n. (%)	91/1,454 (6.2)	86/1,060 (8.1)	0.0727
COVID-19 outcome			
Presence of symptoms, n. (%)	54 (59.3)	23 (26.7)	<0.0001
Hospitalization, n. (%)	19 (20.9)	2 (2.3)	0.0001
Hospitalization in ICU, n. (%)	10 (11.0)	1 (1.2)	0.0097
Death due to COVID-19, n. (%)	8 (8.8)	1 (1.2)	0.035
Mean number of days from last vaccine dose to SARS-CoV-2 infection, +/- SD (range)	NA	103 +/- 80.3 (2-285)	NA
B	**Two doses**	**Three doses**	
Vaccine sequence in SARS-CoV-2 positive MGUS pts, n.	BNT162b2 mRNA x 2, **31** ChAdOx1 nCoV-19 x 2, **9** mRNA-1273 x 2, **2**	BNT162b2 mRNA x 3, **28** ChAdOx1 nCoV-19 x 2/mRNA-1273, **7** BNT162b2 mRNA x 2/mRNA-1273, **4** ChAdOx1 nCoV-19 x 2/BNT162b2 mRNA, **3** mRNA-1273 x 2/ BNT162b2 mRNA, **2**	NA
SARS-CoV-2 infection according to vaccine doses received, n. (%)	42/156 (26.9)	44/904 (4.9)	*<0.0001*
COVID-19 outcome			
Presence of symptoms, n. (%)	17/42 (40.5)	6/44 (13.6)	0.007
Hospitalization, n. (%)	0	2 (4.5)	NA
Hospitalization in ICU, n. (%)	0	1 (2.3)	NA
Death due to COVID-19, n. (%)	0	1 (2.3)	NA
Mean number of days from last vaccine dose to SARS-CoV-2 infection, +/- SD (range)	47.3 +/- 41.9 (2-245)	171 +/- 60.8 (2-285)	*<0.0001*

Abbreviations: NA: not applicable; pts: patients; ICU: intensive care unit; * Data extracted by Sgherza N et al. Haematologica. 2022 Feb 1;107(2):555-557.

Most of patients (96.5%) were at low or low-intermediate risk, according to Mayo Clinic prognostic model. Variant of concern was available in 25 vaccinated patients: n. 2 Alfa (8%), n. 4 Delta (16%), n. 19 Omicron BA.1 (76%). Table 1 summarizes the results observed. Overall, incidence of SARS-CoV-2 infection was not different between not vaccinated and vaccinated patients, though it was higher in the smaller group of patients vaccinated with two doses respect to those receiving three doses. Rates of symptoms, hospitalization, hospitalization in Intensive Care Unit and rate of deaths were significantly lower in vaccinated patients. The presence of SARS-CoV-2 related symptoms (but not rates of hospitalizations and deaths) was higher among patients after 2 doses than in those treated with 3 doses, while the mean number of days between the last dose of vaccine and infection was inferior. No relevant/unexpected vaccine-related side effects were recorded. Our data indicate that the incidence of SARS-CoV-2 infection is not reduced in fully vaccinated MGUS patients, probably because of a different pandemic scenario characterized by higher diffusion capacity of the recently recognized variants and fewer restriction measures applied in the last months. However, the clinical outcome of COVID-19 appears to be significantly improved by vaccines, supporting extensive vaccination programs also in patients with MGUS.

C085

REAL-WORLD DATA ON SAFETY AND EFFICACY OF UPFRONT DARATUMUMAB-BASED THERAPY IN PATIENTS WITH LIGHT CHAIN (AL) AMYLOIDOSIS AND HIGH PLASMA CELL BURDEN EVALUATED AT 3 MONTHS

C. Bellofiore[1,2], R. Mina[3], S. Mangiacavalli[4], P. Milani[1], L. Cani[3], M. Basset[1], P. Benvenuti[1], C. Cartia[4], M. Nanci[1], G. Pagani[4], M. Nuvolone[1], A. Foli[1], C. Conticello[2], G. Merlini[1], F. Di Raimondo[2], L. Arcaini[5], S. Bringhen[3], G. Palladini[1]

[1]Amyloidosis Research and Treatment Center, Foundation "Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Policlinico San Matteo", Department of Molecular Medicine, University of Pavia, Italy; [2]Division of Hematology, AOU "Policlinico G. Rodolico-San Marco", University of Catania, Catania, Italy; [3]Division of Hematology, University of Torino, Torino, Italy; [4]Division of Hematology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; [5]Division of Hematology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy and Department of Molecular Medicine, University of Pavia, Pavia, Italy

Background: The anti-CD38 monoclonal antibody daratumumab is a powerful anti-plasma cell agent. Since it has been approved in the frontline setting for newly diagnosed multiple myeloma patients, it became accessible to AL amyloidosis patients with high plasma cell burden. The phase III clinical trial ANDROMEDA shown that the addiction of daratumumab to the upfront therapy with cyclophosphamide, bortezomib and dexamethasone (D-CyBorD) improves both hematologic and organ response rate in AL amyloidosis and led to the first ever-approved regimen for AL amyloidosis by FDA and EMA.

Aim: To evaluate the efficacy and safety of daratumumab combinations as upfront treatment in AL amyloidosis patients in a real-world setting.

Methods: Our maintained dataset was searched for newly diagnosed AL amyloidosis patients treated with daratumumab-based therapy in 2021. Hematologic and organ responses were assessed according to the International Society of Amyloidosis criteria 3 months after treatment initiation.

Results: Fifty-six consecutive patients were included in the study, Table 1. Nineteen (34%) patients were treated with daratumumab in combination with lenalidomide (D-RD), 31 (56%) with bortezomib [21 (38%) associated with melphalan and dexamethasone and 10 (18%), with off label use of D-CyBorD], six patients (11%) received daratumumab monotherapy due to their frailty (stage IIIb). Grade ≥3 adverse events occurred in 5 (9%) patients: anaemia, thrombocytopenia, pneumonia, deep vein thrombosis and bradycardia. Median follow-up of living patients was 9 months (range: 6-13 months), the median number of cycles administered was 2 (range: 2-6) and the median time to response was 2 months (range: 1-3 months). Nine (16%) patients died due to progressive

disease. Treatment is still ongoing in 37 (66%). The overall hematologic response rate was 78% (CR 14%, VGPR 46%, PR 18%). Cardiac and renal response were observed in 9 (19%) and 7 (19%) patients respectively. Comparing patients who would not have been eligible for ANDROMEDA clinical trial (36%) with the eligible ones, the hematological response rate was lower but not significantly different (ORR 75% *vs* 81%; ≥VGPR 60% *vs* 61%).

Conclusion: Treatment with daratumumab-based regimens in patients with AL amyloidosis and high plasma cell burden is effective and feasible. Early deep haematological responses are frequent and organ responses are seen in 20% patients at three months.

Table 1.

Patients charatcteristics (n=56)	Median (IQR) n (%)		Median (IQR) n (%)
Median age	64 (56 – 72)	**Mayo Cardiac stage**	
Male sex	32 (57)	I	1 (2)
Involved light-chain type		II	27 (48)
K : λ	12 (21) : 44 (79)	IIIa	9 (16)
dFLC (mg/L)	301 (100 – 520)	IIIb	14 (25)
Bone marrow plasma cells	19 (13 – 28)		
Involved/uninvolved≥ 100	5 (9)	NYHA class≥ 3	11 (20)
CRAB	8 (14)	PS-ECOG≥ 2	15 (27)
Organ involvement			
Heart	50 (91)	**Renal stage**	
Kidney	38 (68)	I	17 (30)
Liver	7 (13)	II	18 (32)
PNS	7 (13)	III	3 (5)
ANS	9 (16)	Dialysis at diagnosis	1 (2)
>2 organs	16 (29)		

Acute myeloid leukemia II

C086

IMMUNE RESPONSE TO A THREE-DOSE REGIMEN OF BNT162B2 MRNA COVID-19 VACCINE IN PATIENTS WITH ACUTE MYELOID LEUKEMIA

S. Sciabolacci[1], G. Perta[1], V. Cardinali[1], S. Bozza[2], L. Brunetti[4], P. Bondi[2], A. Graziani[2], B. Falini[1], I. Gionfriddo[1], C. Mecucci[1], M.G. Cusi[3], A. Mencacci[2], M.P. Martelli[1]

[1]Hematology, Centro Ricerche Emato-Oncologiche (CREO), Department of Medicine and Surgery, University of Perugia; [2]Microbiology and Clinical Microbiology, Department of Medicine and Surgery, University of Perugia; [3]Microbiology and Virology Unit, Department of Medical Biotechnologies, University of Siena; [4]Hematology, Department of Medicine and Surgery, A.O.U Ospedali Riuniti Ancona, Italy

Introduction: Patients with acute myeloid leukemia (AML) are at higher risk for severe illness related to SARS-CoV-2 infection compared with the general population. The three-dose regimen of BNT162b2 mRNA COVID-19 vaccine has been proven to be effective in the general population, preventing COVID-19 infection in the range of 95%. The "booster" prevents the wane of protection and broadens neutralizing antibody responses against emerging SARS-CoV-2 variants, such as Omicron. Data regarding the efficacy of mRNA vaccines in AML patients are still not available.

Materials and Methods: Patients and control subjects were studied both after the second and the third dose of vaccine. Antibody titers were measured by LIAISON SARS-CoV-2 TrimericS IgG (DiaSorin) and NeutraLISA test (EUROIMMUN); cell-mediated immune response was detected through Interferon Gamma Release Assay (SARS-CoV-2 IGRA ELISA, EUROIMMUN). Neutralization patterns were analyzed through microneutralization assay on infected cells (wild-type, WT versus Omicron variant).

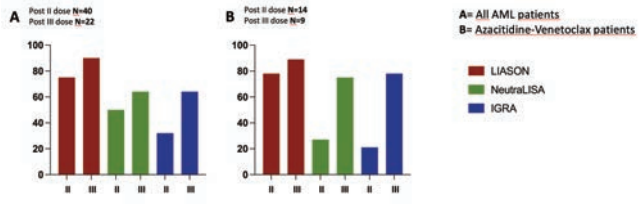


Figure 1.

Results: Forty AML patients and 20 controls were studied after the 2nd dose. Of these, 22 AML patients and 11 controls were studied after the 3rd dose. After the 2nd and 3rd dose of vaccine SARS-CoV-2 anti-S IgG antibodies were detected in 30/40 (75%) and 20/22 (90%) AML patients, respectively (vs 95% and 100% of control group). In responding patients, neutralizing activity was detected in 15/30 (50%) after the 2nd dose and in 14/20 (70%) after the 3rd dose (vs 94% of control subjects). Cell-mediated immune response was detected in 13/40 (32%) and 14/22 (64%) patients (vs 100% of control subjects). Among patients undergoing the 3rd dose, 14 (63%) were on active therapy (2 CTx, 9 aza-ven, 2 azacitidine, 1 experimental therapy) and 8 (36%) were off-therapy (4 in complete remission, 4 with progressive disease). In these patients neutralizing activity and cell-mediated responses were considerably higher after the "booster". Furthermore, after the 3rd dose, Omicron variant cross-neutralization was observed in 11 out of 17 (65%) patients with neutralizing activity against WT SARS-CoV-2.

Conclusion: In AML patients, the "booster" significantly improved

neutralizing activity and cell-mediated immunity (80% *vs* 25%), in particular in patients in complete or partial remission, with no significant differences in patients treated with CTx or aza-ven. The "booster" dose allows protection against the Omicron variant in about half of the AML patients.

C087

REPURPOSING OF ANTIBIOTICS INHIBITING MITOCHONDRIAL TRANSLATION IN COMBINATION WITH VENETOCLAX IN ACUTE MYELOID LEUKEMIA: FROM PRECLINICAL MODELS TO CLINICAL PRACTICE

V. Amato[1], S. Fusani[1], A. Rossi[1], A. Maraglino[1 2], S. Sammassimo[1], F. Gigli[1], E. Todisco[1], C. Tarella[1], E. Derenzini[1 3]

[1]Divisione di Oncoematologia, IEO Istituto Europeo di Oncologia IRCCS; [2]Sezione di Ematologia, Dipartimento di Scienze Radiologiche ed Ematologiche, Università Cattolica del Sacro Cuore; [3]Dipartimento di Scienze della Salute, Università di Milano, Italy

The introduction of the BCL-2 inhibitor Venetoclax (VEN) in combination with chemotherapy or hypomethylating agents (HMA) represents a major advancement in Acute Myeloid Leukemia (AML) therapy. However, VEN resistance is still an unmet clinical need. In this light, pharmacological disturbance of mitochondrial respiratory chain is a promising strategy to circumvent VEN resistance. Tigecycline (Tig) and Linezolid (Lin), two antibiotics largely used in AML patients (pts), inhibit mitochondrial respiration in preclinical models. With the aim of characterizing the in vitro activity of Tig and Lin in combination with VEN, we first assessed cell viability in two BCL-2 positive AML cell lines, MOLM-13 and MV4-11, using the cell Titer-Glo assay™. Tig and Lin inhibited cell viability in a time and dose dependent manner at clinically achievable concentrations. Tig and Lin treatment led to downregulation of COX1, indicative of respiratory chain inhibition. Notably, the antiproliferative effects of these antibiotics were enhanced by co-treatment with VEN, with synergistic interactions assessed with the Chou-Talalay method. Following these preliminary observations, we retrospectively reviewed all AML pts treated with VEN at our Institute between 2018 and 2022 (n=43), focusing on concomitant antibiotic therapy with Lin and/or Tig given in the context of infective complications occurring during the normal clinical practice. Five AML pts were treated with concomitant Lin 600 mg bid (n=4) and/or Tig 50 mg bid (n=1) during VEN-based regimens. Median age was 54 y.o. (36-75), median time of exposure to combination treatment was 15 days (7-24). Two heavily pretreated pts died of sepsis shortly after treatment (unrelated to Lin). Three pts achieved CR after combination treatment: 1 pt with complex karyotype received Lin in combination with cytarabine+VEN as third-line; 1 pt with MLL rearrangement received Lin in combination with first-line HMA+VEN; 1 pt with trisomy 8 and IDH1 mutation received Tig in combination with first-line HMA+VEN. Two of these pts underwent allogeneic stem cell transplantation. Notably, in the last 3 pts we did not observe any renal, liver toxicity or delayed hematologic recovery.

These data suggest that mitochondrial translation inhibitors such as Lin or Tig could enhance VEN efficacy in preclinical AML models. These findings and preliminary clinical data provide rationale for repurposing of this class of drugs in combination with VEN in AML.

C088

INTERIM REPORT ON PHASE II STUDY ON VENETOCLAX (VEN) PLUS DECITABINE (DEC) (VEN-DEC) FOR ELDERLY (≥60 <75YEARS) PATIENTS WITH NEWLY DIAGNOSED ACUTE MYELOID LEUKEMIA (AML) ELEGIBLE FOR ALLOGENEIC STEM CELL TRANSPLANTATION: VEN-DEC GITMO STUDY

D. Russo[1], N. Polverelli[1], M. Vezzoli[2], S. Bramanti[3], A. Curti[4], S. Santarone[5], R. Sorasio[6], M. Bernardi[7], E. Borlenghi[8], M. Farina[1], P. Galieni[9], L. Castagna[10], V. Mancini[11], A.M. Carella[12], E. Terruzzi[13], C. Vetro[14], A. Leoni[1], S. Bernardi[1], S. Calza[2], A. Gheorghiu[15], M. Malagola[1], M. Martino[15,16], F. Ciceri[7]

[1]Unit of Hematology 2 and Stem Cell Transplant, ASST Spedali Civili, University of Brescia, Italy; [2]Department of Molecular and Translational Medicine, University of Brescia, Brescia, Italy; [3]Bone Marrow Transplant Unit, IRCCS Humanitas Research Hospital, Rozzano, Italy; [4]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli", Bologna, Italy; [5]Dipartimento Oncologia Ematologia, Terapia Intensiva Ematologica, Ospedale Civile, Pescara, Italy; [6]SC Ematologia, Azienda Ospedaliera S Croce e Carle, Cuneo, Italy; [7]Hematology and Bone Marrow Transplantation Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy; [8]Unit of Hematology, ASST Spedali Civili di Brescia, Brescia, Italy; [9]Hematology and Cell Therapy Unit, Ospedale C. e G. Mazzoni, Ascoli Piceno, Italy; [10]Haematology Department, United Hospitals of Palermo, Palermo, Italy; [11]Dipartimento di Ematologia ed Oncologia, Niguarda Cancer Center ASST Grande Ospedale Metropolitano, Milano, Italy; [12]SSD Hematologic Intensive Care and Cell Therapy Unit, Department of Medical Sciences, "Casa Sollievo della Sofferenza" Foundation, San; Giovanni Rotondo, Italy; [13]Hematology Unit, San Gerardo Hospital, Monza, Italy; [14]Division of Hematology, A.O.U. Policlinico "G. Rodolico-San Marco", Catania, Italy; [15]GITMO trial office; [16]Division of Stem Cell Transplantation and Cellular Therapies, Grande Ospedale Metropolitano "Bianchi-Melacrino-Morelli", Reggio Calabria, Italy

VEN-DEC GITMO trial is a no profit, prospective, phase II, multicentre, non-randomised, uncontrolled, single group assignment, open label study to evaluate the safety and efficacy of the "chemo-free" combination Venetoclax plus Decitabine (VEN-DEC) as "bridge" to allo-SCT in elderly (≥ 60 - < 75 years) AML patients. Primary endpoint is the proportion of elderly AML patients who get allo-SCT in CR/CRi/MLFS with the "chemo-free" combination Venetoclax plus Decitabine (VEN-DEC) Venetoclax and Decitabine will be administered for 2 cycles. In case of CR/CRi/MLFS according to ELN criteria, patients will undergo allo-SCT within 2 months. In case of NR or PR after the 2nd Cycle VEN-DEC, 2 additional cycles will be administered and patients achieving CR/CRi/MLFS will undergo allo-SCT within 2 months. Patients with NR or PR will be treated according to single center policy. The study is designed as a Simon optimal two-Stage Phase II clinical trial, including a planned futility check. If there are 3 or fewer patients submitted to allo-SCT in the first 30 enrolled patients, the trial will be terminated for futility. Otherwise, considering an overall 12% of drop-out rate, 70 additional patients will be accrued for a total of 100 patients.

At 1st April 2022, 33 pts were enrolled by 24 Italian Gitmo Transplant Centers. Two patients did not fulfil inclusion/exclusion criteria according to study protocol and were excluded as screening failure. The remaining 30 patients received at least 1 cycle of VEN-DEC treatment in-patient, from the 2nd cycle onwards 26 cases were treated outpatient. Study treatment was discontinued in 4 out of 30 patients (13.3%) before transplant. The reasons for discontinuation were infectious complications (2 cases), no response after cicle 4 (1 case), unknown (1 case). At data cut-off, 6 out of 30 treated patients ended study treatment and 5/6 (83%) were successfully submitted to transplant.

According to study design, the first step was met, and additional 70 patients will be enrolled.

The preliminary results of VEN-DEC GITMO trial appear promising in allowing elderly AML patients to be submitted to allo-HCT.

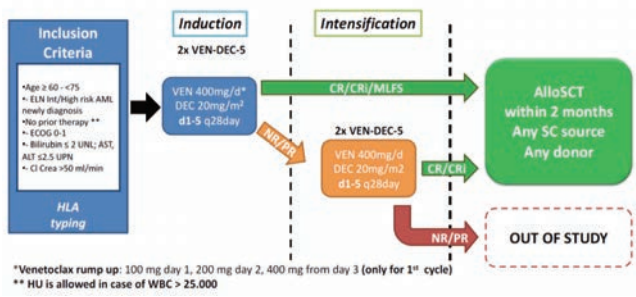


Figure 1.

C089

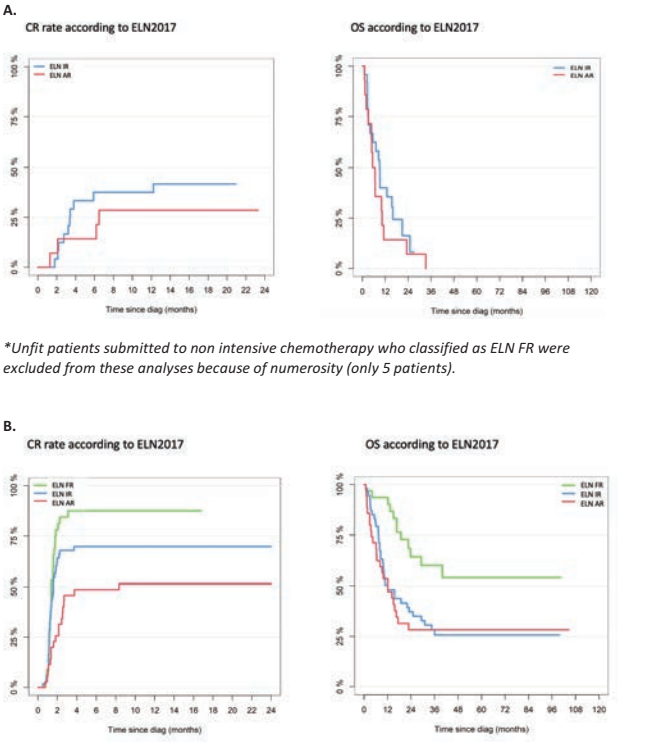
REAL LIFE FEASIBILITY OF A COMBINED CLINICAL AND BIOLOGICAL FITNESS ASSESSMENT IN PATIENTS WITH ACUTE MYELOID LEUKEMIA

R. Palmieri[1], S. Iacobelli[2], G. Paterno[1], F. Moretti[1], E. Buzzatti[1], A. Savi[1], E. Meddi[1], G. Trotta[1], M.I. Del Principe[1], L. Maurillo[1], M.T. Voso[1], A. Venditti[1], F. Buccisano[1]

[1]Ematologia Dipartimento di Biomedicina e Prevenzione Università di Roma "Tor Vergata"; [2]Dipartimento di Biologia Università di Roma "Tor Vergata", Italy

Fitness assessment plays a crucial role in the process of treatment allocation for patients (pts) with acute myeloid leukemia (AML). Among the available scores, the SIE, SIES and GITMO criteria were intended to describe novel definitions of unfitness to intensive chemotherapy (IC) or non-intensive chemotherapy (N-IC). Since these criteria were not designed to include disease-related genetic/cytogenetic status, we investigated whether an integrated fitness (according to SIE/SIES/GITMO criteria) and biological (according to ELN2017 risk stratification) assessment could help re-defining risk-category assignment of our pts, and better discriminating their outcome. This retrospective analysis includes 285 consecutive pts with AML, diagnosed at our institution between 2013 and 2021. Median age was 68 years (range 21-93); 142 (49.8%) pts qualified as fit (Fi-P), 57 (20%) unfit (UF-P) and 86 (30.2%) frail (Fr-P); 46 (16.1%) pts were classified as favorable [ELN-FR], 107(37.5%) intermediate [ELN-IR] and 69 (24.2%) adverse risk [ELN-AR]. Sixty-3 (22.2%) pts were not classifiable due to the lack of molecular data. One-hundred thirty-2 (46.6%) pts received IC, 65 (22.8%) N-IC, 88 (30.9%) best supportive therapy (BST), with an overall 93% concordance rate between clinical fitness status and treatment received (90.1% of Fi-P received IC, 91.2% of UF-P N-IC and 97.7% of Fr-P BST, respectively). Such a concordance improved over the time (87.8% in 2013 up to 95.2% in 2021). In the UF-P group, 12-months complete remission (CR) rate was similar between ELN-IR (37.5%) and ELN-AR (28.6%) pts, with no difference in terms of median overall survival (OS) between the 2 groups (9.1 months *vs* 6.6 months for IR and AR, respectively). Among Fi-P, 12-months CR rate was commensurate with ELN2017 risk (87.5% *vs* 69.7% *vs* 51.4% for ELN-FR, ELN-IR, and ELN-AR, respectively; p=0.0012), with an OS advantage for ELN-FR pts over ELN-IR and ELN-AR ones (median: not reached for ELN-FR *vs* 12.2 months for ELN-IR and ELN-AR, respectively; p=0.0051).

In conclusion, a real-life therapeutic allocation relying on a comprehensive [SIE/SIES/GITMO criteria and ELN2017 risk] assessment is feasible. Pts unfit for N-IC may be candidate to an active, non-intensive approach, even if belonging to the ELN-AR category. For Fi-P belonging to the ELN-IR and ELN-AR categories, there is room for further improvement of clinical outcome by taking advantage of new strategies (targeted agents, biomarker driven approaches)



**Unfit patients submitted to non intensive chemotherapy who classified as ELN FR were excluded from these analyses because of numerosity (only 5 patients).*

Figure 1. CR rates and OS stratified according to ELN2017 risk in the Unfit patients/non intensive chemotherapy group (A*), and in the Fit patients/intensive chemotherapy one (B).

C090

CPX-351 INDUCTION IN SECONDARY ACUTE MYELOBLASTIC LEUKEMIA: EXTENDED FOLLOW UP FROM THE ITALIAN COMPASSIONATE USE PROGRAM

F. Guolo*[1,2], P. Minetto*[1,2], L. Fianchi[3], M. Cea[1,2], M. Gottardi[4], E. Mauro[4], S. Galimberti[6], G. Rizzuto[7], M. Sciumé[8], M. Rondoni[9], G. Bertani[10], M. Dargenio[11], A. Bilio[12], B. Scappini[13], P. Zappasodi[14], A.M. Scattolin[15], F. Grimaldi[16], G. Pietrantuono[17], P. Musto[17,18], M. Cerrano[19], S. D'Ardia[20], E. Audisio[21], A. Cignetti[22], C. Pasciolla[23], F. Pavesi[24], A. Candoni[25], C. Gurrieri[26], M. Morselli[27], C. Alati[28], N. Fracchiolla[29], G. Rossi[30], M. Caizzi[31], F. Carnevale-Schianca[32], A. Tafuri[33], G. Rossi[8], F. Ferrara[34], L. Pagano*[3] R.M. Lemoli*[1,2]
*equally contributed

[1]IRCCS Ospedale Policlinico San Martino, Genoa, Italy; [2]Clinic of Hematology, Department of Internal Medicine (DiMI), University of Genoa, Genoa, Italy; [3]Istituto di Ematologia, Fondazione Policlinico Universitario A. Gemelli, IRCCS, Rome, Italy; [4]Onco Hematology, Department of Oncology, Veneto Institute of Oncology IOV, IRCCS, Castelfranco Veneto, Italy; [5]Ospedale Ca' Foncello, Treviso, Italy; [6]UO Ematologia, Dipartimento di Medicina Clinica e Sperimentale, Università di Pisa, Italy; [7]Hematology and Bone Marrow Transplant Unit, ASST Papa Giovanni XXIII, Bergamo, Italy; [8]SC Ematologia e Dipartimento di Oncologia Clinica, A.O. Spedali Civili, Brescia, Italy; [9]U.O.C. di Ematologia, Azienda Unità Sanitaria Locale della Romagna, Ravenna, Italy; [10]S.C. Ematologia, ASST Grande Ospedale Metropolitano, Niguarda Ca' Granda Milano, Milan, Italy; [11]Ospedale Vito Fazzi, Lecce, Italy; [12]Ospedale di Bolzano, Bolzano, Italy; [13]Dipartimento di Oncologia-SODc Ematologia, Azienda Ospedaliero - Universitaria Careggi, Florence, Italy; [14]Clinica Ematologica, Fondazione IRCCS Policlinico

San Matteo, Pavia, Italy; [15]Unità Operativa di Ematologia, Ospedale dell'Angelo, Mestre-Venezia, Italy; [16]Dipartimento di Medicina Clinica e Chirurgia, AOU Federico II di Napoli, Naples, Italy; [17]IRCCS Centro Oncologico della Basilicata, Rionero in Vulture (Pz), Italy; [18]Unit of Hematology and Stem Cell Transplantation, AOU Policlinico Consorziale, "Aldo Moro" University, Bari, Italy; [19]Department of Molecular Biotechnology and Health Sciences, Division of Hematology, University of Torino, Turin, Italy; [20]Institute for Cancer Research and Treatment, University of Turin-School of Medicine, Turin, Italy; [21]S.C. Ematologia2, Dipartimento di Ematologia e Oncologia, AO Città della Salute e della Scienza di Torino, Turin, Italy; [22]Divisione Universitaria di Ematologia e Terapie Cellulari, A.O. Ordine Mauriziano, Turin, Italy; [23]Haematology Unit, IRCCS Istituto Tumori "Giovanni Paolo II", Bari, Italy; [24]Hematology and Bone Marrow Transplantation Unit, San Raffaele Scientific Institute, Milan, Italy; [25]Clinica Ematologica, Centro Trapianti e Terapie Cellulari, Azienda Sanitaria Universitaria Integrata di Udine, Udine, Italy; [26]U.O. Ematologia ed Immunologia Clinica, Azienda Ospedaliera di Padova, Padova, Italy; [27]Department of Medical and Surgical Sciences, Section of Hematology, University of Modena and Reggio Emilia, Azienda Ospedaliero Universitaria Policlinico, Modena, Italy; [28]A. O. Bianchi-Melacrino-Morelli, Reggio Calabria, Italy; [29]Oncoematologia, IRCCS Ca' Granda Ospedale Maggiore Policlinico and University of Milan, Milan, Italy; [30]U.O. Ematologia, Casa Sollievo della Sofferenza IRCCS, San Giovanni Rotondo (Fg), Italy; [31]S.C. Ematologia Azienda Sanitaria Universitaria Integrata di Trieste, Ospedale Maggiore, Trieste, Italy; [32]Medical Oncology, Hematopoietic Stem Cells Unit, Turin Metropolitan Transplant Center, Candiolo Cancer Institute-FPO, IRCCS, Candiolo, Italy; [33]Department of Clinical and Molecular Medicine & Hematology, Sant'Andrea - University Hospital - Sapienza - University of Rome, Rome, Italy; [34]Division of Hematology, Cardarelli Hospital, Naples, Italy

Background: The outcome of patients with acute myeloid leukemia (AML) secondary to myelodisplastic syndrome (MDS) or therapy-related (s-AML) receiving conventional treatment and allogeneic stem cell transplantation consolidation (HSCT) is poor. CPX-351 is composed by liposomal encapsulated cytarabine and daunorubicin, at a fixed molecular ratio of 5:1 and showed superior results, compared to standard 3+7 induction, in a phase III trial (Lancet et al, JCO 2018) in patients affected by sAML. We recently published results from CPX-351 Italian Compassionate Use Program (CUP) (Guolo et al, Blood Cancer J. 2020) showing that CPX-351 is an effective and well tolerated induction regimen for high risk AML patients treated with a curative aim. With a limited follow up, our data suggested the good activity and tolerability of CPX-351, especially as a bridge therapy to allogeneic stem cell transplantation (HSCT). Here we report the results from the extended follow up analysis of the Italian CUP.

Methods: Seventy one patients were treated between December 2018 and June 2019 in a compassionate use program (CUP) in 31 Italian Hematology Centers. Median age was 65.5 years (52-79). Sixty-two (88%) patients had at least one relevant comorbidity upon enrolment. Six patients (9%) presented with ECOG 3-4 upon enrolment.

Results: CR was achieved in 50/71 patients (70%), whereas HSCT consolidation was performed in 20/50 CR patients (40%). After a median follow up of 28 months (24.6 – 32.9 95% IC), median overall survival (OS) was 13 months. Two-years OS was 28.6% in the whole cohort. In order to confirm the positive impact of HSCT in first complete remission (CR) and the correlation with the other variables, a landmark model was applied, including only patients alive and in CR at day 90. In landmark analysis, HSCT performed in first CR after CPX-351 was the only significant predictor of longer survival: median OS was not reached for patients transplanted in first CR *vs* 12 months for patients who did not undergo HSCT, $p < 0.05$, Figure 1). Two-year OS for patients who received HSCT was 57.6% *vs* 15.8% for patients who did not undergo HSCT.

Conclusions: Results from the extended follow up of Italian CPX-351 CUP confirm the good activity and good tolerability of CPX-351 in sAML patients. Thanks to the low risk of adverse events, despite high frequency of comorbidities and old median age in our cohort, many patients were able to proceed to HSCT, thus significantly improving survival.

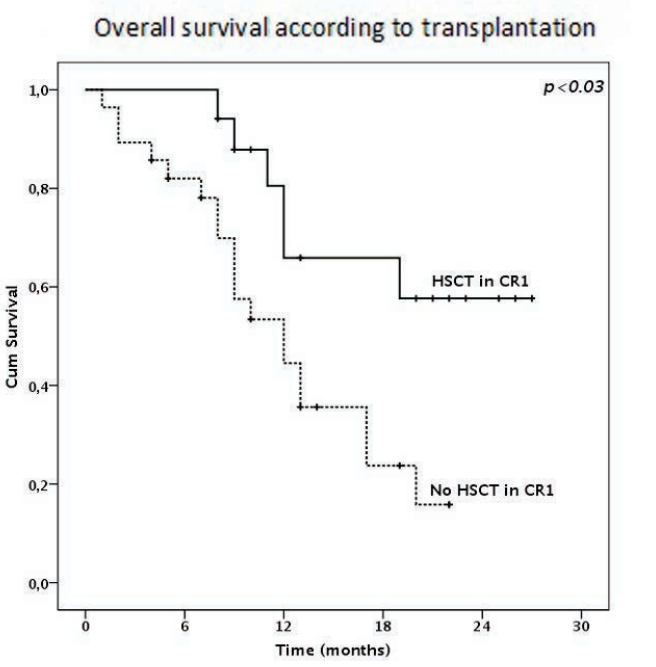


Figure 1.

Chronic lymphocytic leukemia and lymphoproliferative syndromes II

C091

CLINICAL IMPACT OF TP53 DISRUPTION IN CHRONIC LYMPHOCYTIC LEUKEMIA PATIENTS TREATED WITH A BCR INHIBITOR. A CAMPUS CLL EXPERIENCE

R. Bomben[1], F.M. Rossi[1], F. Vit[1], T. Bittolo[1], A. Zucchetto[1], R. Papotti[2], E. Tissino[1], F. Pozzo[1], M. Degan[1], E. Zaina[1], I. Cattarossi[1], P. Nanni[1], R. Marasca[3], G. Reda[4], L. Laurenti[5], J. Olivieri[6], A. Chiarenza[7], L. Ballotta[8], A. Cuneo[9], M. Gentile[10,11], F. Morabito[11,12], A. Tafuri[13], F. Zaja[14], R. Foà[15], F. Di Raimondo[7], G. Del Poeta[16], V. Gattei[1]

[1]Clinical and Experimental Onco-Hematology Unit, Centro di Riferimento Oncologico di Aviano (CRO) IRCCS, Italy; [2]International PhD School in Clinical and Experimental Medicine, University of Modena and Reggio Emilia, Modena, Italy; [3]Hematology Unit, Department of Oncology and Hematology, Azienda-Ospedaliero Universitaria (AOU) of Modena, Policlinico, Modena, Italy; [4]Division of Ematologia, Fondazione IRCCS Ca'Granda Ospedale Maggiore Policlinico di Milano, Milano, Italy; [5]Fondazione Universitaria Policlinico A Gemelli di Roma, Roma, Italy; [6]Clinica Ematologica, Centro Trapianti e Terapie Cellulari "Carlo Melzi" DISM, Azienda Ospedaliera Universitaria S. Maria Misericordia, Udine, Italy; [7]Division of Hematology, Policlinico, Department of Surgery and Medical Specialties, University of Catania, Catania, Italy; [8]Dipartimento Clinico di Scienze Mediche, Chirurgiche e della Salute, University of Trieste, Trieste, Italy; [9]Hematology Section, Department of Medical Sciences, University of Ferrara, Ferrara, Italy; [10]Hematology Unit AO of Cosenza, Cosenza, Italy; [11]Biothecnology Research Unit, AO of Cosenza, Cosenza, Italy; [12]Hematology Oncology Department, Augusta Victoria Hospital, East Jerusalem, Israel; [13]Department of Clinical and Molecular Medicine and Hematology, Sant'Andrea - University Hospital - Sapienza, University of Rome, Rome, Italy; [14]Department of Medical, Surgical and Health Sciences, University of Trieste, Italy; [15]Hematology, Department of Translational and Precision Medicine, 'Sapienza' University, Rome, Italy; [16]Division of Haematology, University of Tor Vergata, Rome, Italy

Background: In the chemo-immunotherapy (CIT) settings, *TP53* deletion and mutations mostly co-occur and are considered equal prognosticators, nevertheless the impact of isolated or concomitant mutations and deletions remains unclear in the context of targeted agents.

Methods: In the framework of an institutional Italian multicenter working group on CLL (Campus CLL), a retrospective analysis of 229 CLL patients treated with ibrutinib was analyzed for del17p by FISH and *TP53* mutations by NGS, on samples within 6 months prior the start of ibrutinib. The median follow-up from ibrutinib treatment was 36.3 months (95% CI 29.5-41.5 months).

Results: In the CLL cohort, 74 patients with del17p showed significant inferior OS (P=0.0355) and PFS (P=0.0065) respect to wt cases (Figure 1A). With regard to *TP53* mutations, 296 *TP53* mutations were found in 126 patients (range of mutations/patients 1-11). As with CIT, TP53-mutated patients, irrespective of VAF (Figure 1B), experienced a significantly worse OS and PFS than wt cases also by univariate analyses (P=0.0160, and P=0.0378, respectively). After combination of del17p with *TP53* mutation data, only patients with concomitant *TP53* mutations and del17p experienced significantly shorter OS and PFS compared to *TP53*wt cases (Figure 1CD). The simultaneous presence of *TP53* mutations and del17p remained an independent predictor factor both for OS and PFS by multivariate analysis, together with the previous therapy lines (0-1 *vs* >1), and anemia. The evolution of TP53-mutated clones was assessed in 38 patients with longitudinal PB samples. Among relapsed cases, 7 showed a prominent expansion of the TP53-mutated clone, 8 remained stable, and the remaining displayed an evident decrease (Figure 1E). In non-relapsed patients, 3 cases presented an increase of *TP53* mutations, 13 remained stable, and 6 showed a reduction (Figure 1F), with no significant difference compared to relapsed cases (P=0.0623). *BTK* and *PLCG2* mutations were found in 9/16 (56%) relapsed cases and in 3/22 (14%) patients still on ibrutinib (P=0.0492). Of note, only 3/7 relapsed cases that presented a positive selection for *TP53* mutations showed the presence of *BTK* mutations at the time of relapse.

Conclusions: This retrospective study indicates that only the concomitant presence of *TP53* mutations and deletion is an independent negative prognostic factor for OS and PFS in patients with CLL on ibrutinib treatment.

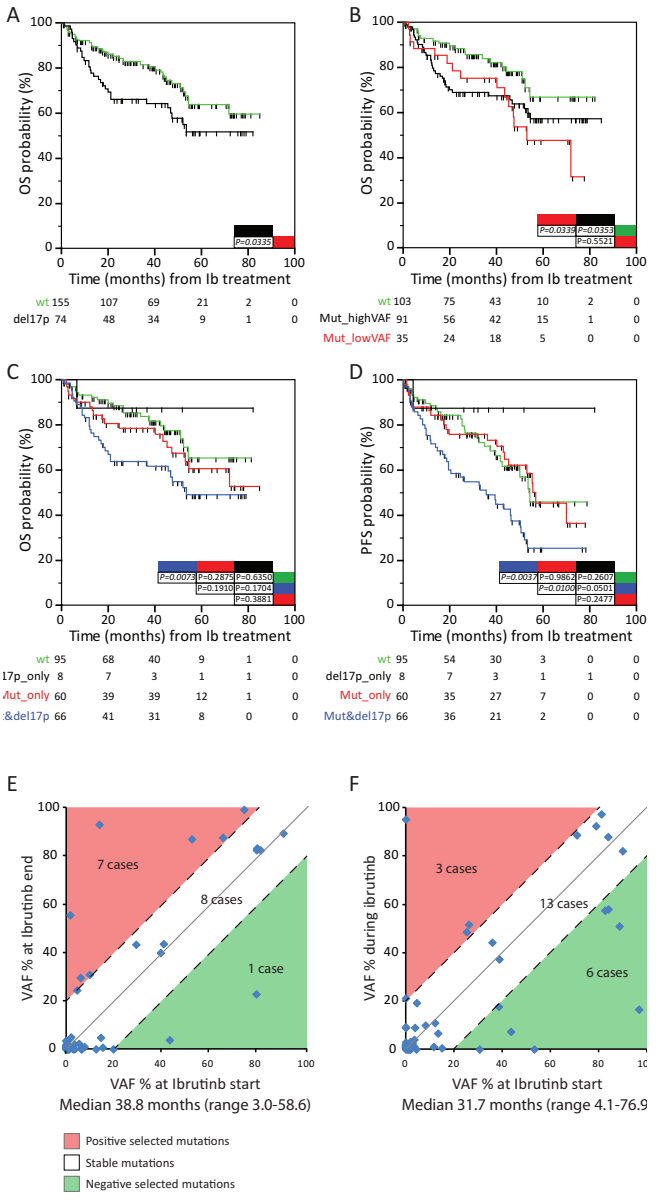


Figure 1.

C092

OUTCOME OF FIRST-LINE TREATMENT WITH IBRUTINIB IN 747 PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA WITH TP53 ABERRATIONS INCLUDED IN THE PRODUCT REGISTRY OF THE ITALIAN MEDICINES AGENCY (AIFA). A GIMEMA-AIFA STUDY

*G.M. Rigolin[1],*P. Russo[2], P.P. Olimpieri[2], V. Summa[2], S. Celant[2], L. Scarfò[3], L. Tognolo[1], M.P. Ballardini[1], A. Urso[1] , M. Sessa[1], S. Gambara[1],**P. Ghia[3],**A. Cuneo[1] * contributed equally as first author ** contributed equally as last author

[1]Hematology unit, Department of Medical Sciences, University of Ferrara; [2]Italian Medicines Agency; [3]Università Vita-Salute San Raffaele and IRCC Ospedale San Raffaele

Background: Although the efficacy of ibrutinib in previously untreated CLL carrying TP53 disruption is well documented few real-world data in this subset of CLL data are available.

Aims: To analyze the effectiveness of ibrutinib in all CLL patients carrying 17p-/TP53 aberrations who received ibrutinib as first line treatment in Italy.

Methods: CLL with 17p-/TP53 aberrations included in the AIFA web platform who started ibrutinib between 2016 and 2020 were included in our analysis. The minimum potential follow-up was 15 months. The primary endpoint was time to treatment discontinuation (TTD). i.e. the time between the first administration and the date of ibrutinib discontinuation for any cause, the secondary endpoint was overall survival (OS).

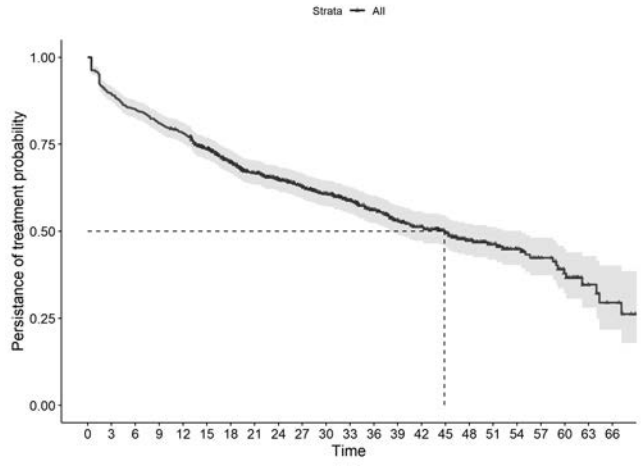


Figure 1. Time to treatment discontinuation n 747 patients with CLL and 17p-/TP53 aberrations.

Results: 747 patients were included. Median age was 71 years, 56.4%, 36.8% and 6.8% of the cases had ECOG PS 0, 1, ≥2, respectively. Rai stages 0-II and III-IV were reported in 54.9% and in 45.1% of the patients, respectively; previous atrial fibrillation in 3.3%; lymph node >5 cm, lymphocyte >25X10^9/L and/or or splenomegaly in 73.1%; renal impairment in 9.1% and use of anticoagulants in 4.0% of patients. The median follow-up (FU) was 23.9, months (IQR 13.2-38.4), the median FU for patients without events was 32.5 months (IQR 22.3-45.5). 45.9% of the patients discontinued ibrutinib, with a median TTD of 44.9 months (Figure 1) [95% C.I.: 38.0-54.6 months]. At 15 months the overall response rate was 77.4%. The analysis of OS and the effect of site expertise is ongoing.The multivariable analysis on 338 events of discontinuation (146 due to progression/death) showed that a shorter TTD was associated with age ≥70 *vs* <65 years [HR 1.76; 95% C.I. 1.34- 2.32]; ECOG 1 *vs* 0 [HR 1.26; 95% C.I. 1.00-1.58]; ECOG 2-3 *vs* 1 [HR 2.06; 95% C.I. 1.41-3.00]. A normal renal function had protective effect on TTD [HR 0.71; 95% C.I. 0.50-1.00].

Summary/conclusion: We observed an excellent treatment retention rate (54.1%) with ibrutinib in this predominantly elderly patient population entirely representative of the real-world practice in our country, a figure that appears superimposable with that observed in a pooled analysis of 4 trials, where a median TTD of 45.9% was observed in a younger patient population including 89 patients (median age 65) (Allan JN, BJH 2022:947). The median TTD of 44.9 months in this unbiased patient population was influenced by age, ECOG PS and renal function.

C093

RITUXIMAB AS AN EFFECTIVE SALVAGE THERAPY IN PRETREATED HAIRY CELL LEUKEMIA PATIENTS: THE BOLOGNA EXPERIENCE

A. Broccoli[1,2], L. Argnani[1,2], L. Nanni[1,2], G. Bagnato[1,2], M. Carella[1,2], B. Casadei[1,2], P.E. Coppola[1,2], G. Gugliotta[1,2], G. Lolli[1,2], A. Morigi[1,2], C. Pellegrini[1,2], V. Stefoni[1,2], P.L. Zinzani[1,2]

[1]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli"; [2]Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale, Università di Bologna, Italy

Hairy cell leukemia (HCL) patients usually experience multiple disease relapses during the course of their disease. The CD20 antigen is highly expressed on the surface of hairy cells. Single-agent rituximab can be a suitable treatment option in patients relapsing after repeated courses of purine analogs, if purine analogs are contraindicated (*e.g.* in case of poor bone marrow cellularity, high disease infiltration predicting long-lasting aplasia), especially if newer agents (such as moxetumomab or vemurafenib) are not easily available (as it happens in several countries). Our institutional series of HCL patients receiving single-agent rituximab as salvage therapy was retrospectively reviewed. Patients received rituximab at the standard dose of 375 mg/sqm weekly for 4 weeks. The main study objectives were overall response rate (ORR), time-to-next treatment (TTNT), progression-free survival (PFS) and overall survival (OS). Responses have been categorized according to the Consensus Resolution Criteria. Thirty-three patients received 39 courses of rituximab (4 patients received it twice, one patient three times), in median as third line of therapy (range 2-8). First rituximab was given at a median age of 61 years and at a median time from disease diagnosis of 65 months. Out of 39 courses, a complete response was obtained in 28.2% of cases, a partial response in 23.1% and a minimal response in 20.5%, yielding an ORR of 71.8%. In 28.2% of patients we observed no response. Median TTNT was reached at 33 months (65% at 2 years), while median PFS was reached at 24 months (51% at 2 years). Median OS resulted of 154 months (22% at 20 years). Among the 5 patients receiving rituximab more than once, all responded after the first course, although the ORR after the second or later course was only 50%. Median TTNT following the first rituximab was 38.5 months in these patients, ranging from 15 to 205 months. To our knowledge, this is the widest series of HCL patients receiving single-agent rituximab for disease relapse. Rituximab is an effective salvage therapy in pretreated HCL patients after failure of purine analogs, as it permits an adequate disease control with considerably long TTNT periods. It may be repeated if no alternatives are available, although it seems to reduce its efficacy in the following courses.

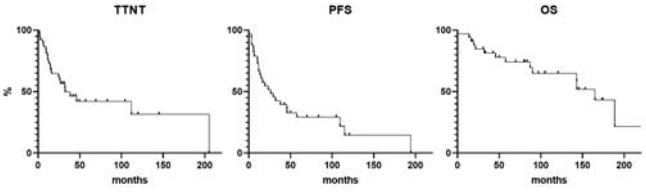


Figure 1.

C094

SHORT TIME TO FIRST TREATMENT IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA AND BORDERLINE MUTATED IGHV STATUS: A SINGLE CENTER EXPERIENCE

F. Angotzi, A. Cellini, V. Ruocco, C. Cavarretta, S. Pravato, E. Pagnin, M. Facco, F. Piazza, L. Trenti, A. Visentin

Hematology and Clinical Immunology Unit, Department of Medicine, University of Padova, Italy

Background: The immunoglobulin heavy variable region (IGHV) mutational status is a pivotal prognostic marker in chronic lymphocytic leukemia (CLL). Patients have classically been divided into mutated IGVH (M-IGHV) and unmutated IGHV (U-IGHV) subsets based a 98% threshold of identity to the germline sequence. In the last years, new evidence emerged suggesting that patients with borderline IGHV (BL-IGHV) show different disease characteristics, albeit with conflicting results. Moreover, the impact of different treatments on BL-IGHV still unclear. Our aim was to investigate the impact of BL-IGHV mutational status in CLL patients treated at our institution.

Methods: We retrospectively reviewed 655 patients with CLL from Padova university hospital, with productive IGHV rearrangement according to the ERIC guideline. Patients were divided into 5 groups based on IGHV mutational status: fully-unmutated (FU-IGHV, identity 100%, n=183), unmutated (U-IGHV, 99.99–98.00%, n=90), borderline (BL-IGHV, 97.99–97.00%, n=31), mutated (M-IGHV, 96.99–90.00%, n=309) and heavily-mutated (HM-IGHV, <90%, n=42). Most common BCR stereotypes were assessed by ARResT. Univariate analysis was performed with the Kaplan-Meier model, multivariate analysis according to the Cox proportional-hazards model for time to first treatment (TTFT) and overall survival (OS).

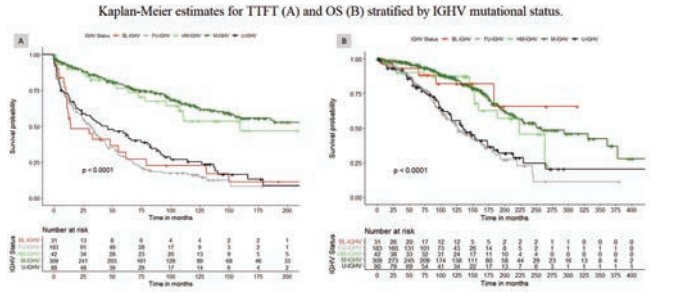


Figure 1.

Results: The BL-IGHV group was enriched in BCR subset #2 (12.9%, p<0.0001) and presented with more advanced stage at diagnosis than M-IGHV patients (p<0.0001 for both RAI II-IV and BINET B-C stages). No age difference was found between all groups. In both univariate and multivariate analysis (adjusting for age, FISH categories and stage) patients with BL-IGHV status showed a TTFT shorter than U-IGHV patients (median 14.3m *vs* 45.7m, HR 1.94, p=0.026), and even than FU-IGHV patients (14.3m *vs* 31.4m, HR 1.81, p=0.022). This difference remained significative even when excluding subset #2 patients from the BL-IGHV group. However, OS of BL-IGHV patients resembled M-IGHV patients (median NR *vs* 285 months, HR 0.67, p=0.44) and was longer than FU and U-IGHV cases (NR *vs* 127 and 135 m respectively, p <0.0001).

Conclusions: Patients with BL-IGHV represent a heterogeneous group, with likely yet unknown patient and disease-specific factors that influence their prognosis. While TTFT may be reduced, the favorable OS suggests a good response to therapy. Multicenter studies including large numbers of BL-IGHV patients may help clarify these points.

C095

MONITORING OF MINIMAL RESIDUAL DISEASE IN CHRONIC LYMPHOCYTIC LEUKEMIA PATIENTS TREATED WITH VENETOCLAX: FIRST RESULTS OF A PROSPECTIVE MULTICENTER REAL LIFE EXPERIENCE

L. Farina[1], V. Bellani[1], A. Aiello[2], L. Vittoria[2], M. Motta[3], A. Ferrario[4], F.L. Bozzi[2], G. Levati[1], L. Scarfò[5], G. Reda[6], C. Monfrini[1], M. Deodato[7], G. Pruneri[2], C. Carniti[1], G. Gaidano[8], P. Corradini[1,9]

[1]Hematology, Fondazione IRCCS Istituto Nazionale dei Tumori; [2]Department of Pathology, Fondazione IRCCS Istituto Nazionale dei Tumori; [3]S.C. Ematologia, ASST Spedali Civili; [4]Hematology, ASST dei Sette Laghi-Ospedale di Circolo; [5]Strategic Research Program on CLL, Università Vita-Salute San Raffaele and IRCCS Ospedale San Raffaele; [6]Hematology, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico; [7]Hematology, Niguarda Cancer Center, Niguarda Hospital; [8]Hematology, Department of Translational Medicine, University of Eastern Piedmont; [9]University of Milan, Italy

The Bcl-2 inhibitor Venetoclax achieves deep responses in chronic lymphocytic leukemia (CLL) patients, including undetectable minimal residual disease (uMRD). We report the first results of a multicenter prospective MRD monitoring study in CLL patients treated with Venetoclax in the real-life setting.

Forty-two patients were enrolled from April 2019 until March 2022. Three patients died before the first MRD assessment due to adverse events and were excluded from the analysis. At the last follow-up 34 patients (M/F,19/15) have both clinical and MRD available data. MRD samples were centralized and assessed by 8-colour flow cytometry (FC) on peripheral blood (PB) every 3 months and samples with 10-4 CLL cells were considered as undetectable, according to the iwCLL guidelines. PB-uMRD patients were evaluated on bone marrow (BM).

Median age was 70 years (range,47-84), median number of previous lines were 2 (range, 0-4), 22 patients were relapsed after B-cell receptor (BCR)-inhibitors. Patient characteristics were as follows: unmutated immunoglobulin-heavy-chain-rearrangement 82%, 17p deleted (17pdel) 44%, TP53 mutated 24%, 11p deleted 32%, complex karyotype in 11 out of 20 evaluated patients, Binet stage A 6%, B 53%, C 41%, bulky disease 41%. In 21 patients Venetoclax was combined with Rituximab. Median follow-up was 348 days (range 30-1078).

One-hundred and three tests were performed on PB and 44 on BM; median number of tests per person was 3 on PB and 1 on BM. uMRD on PB was as follows: 15/31 (48%) at 3 months, 17/24 (71%) at 6 months, 15/19 (79%) at 9 months, 13/16 (81%) at 12 months, 8/10 at 15 months, 4/7 at 18 months. uMRD on BM in PB-uMRD patients was as follows: 5/12 at 6 months, 5/9 at 9 months, 4/10 at 12 months. At 9 months the rate of PB uMRD in Rituximab-treated *vs* Venetoclax monotherapy, 17pdel-positive *vs* negative and BCR-inhibitor-treated *vs* naïve patients were not significantly different. At the last follow-up 4 MRD-positive patients progressed of whom 2 died of transformed disease; 2 uMRD patients died of infection.

The continuous improvement of CLL treatment with the use of time-limited and combined targeted therapies will make the MRD assessment in clinical practice increasingly appropriate. This study showed the feasibility of FC MRD evaluation in a multicenter real-life setting and the initial results of Venetoclax-based therapy showed a high rate of uMRD in high-risk and BCR-inhibitor-treated patients.

Non-Hodgkin's lymphoma III

C096

LONG TERM SAFETY AND EFFICACY OF CRIZOTINIB IN RELAPSED/REFRACTORY ALK+ LYMPHOMAS: A MONOCENTRIC ANALYSIS

G. Rindone[1,2], A. Aroldi[1,2], E. Bossi[1,2], L. Verga[1], G.P.M. Zambrotta[1,2], S. Tarantino[1,2], R. Piazza[1,2], L. Mussolin[3], R. Chiarle[4,5], C. Gambacorti-Passerini[1,2]

[1]Hematology Division, San Gerardo Hospital; [2]Department of Medicine and Surgery, University of Milano-Bicocca; [3]Department of Woman's and Child's Health, University of Padova; [4]Department of Molecular Biotechnology and Health Sciences, University of Turin; [5]Department of Pathology, Boston Children's Hospital and Harvard Medical School

Anaplastic large T-cell lymphoma (ALCL) is an aggressive disease with a 3-years overall survival (OS) of 82% if complete remission (CR) is achieved with standard chemotherapy. More than 50% of patients relapse and need 2nd line therapies, such as anti-CD30 immunoconjugate Brentuximab Vedotin (BV) and consolidation with autologous stem cells transplantation. Nevertheless, a significant proportion of patients eventually relapses, with rapidly progressive disease and death. Around 50% of ALCLs and some cases of diffuse large B-cell lymphoma and plasmablastic lymphoma show anaplastic lymphoma kinase (ALK) protein expression because of a chromosomal translocation involving ALK gene. Crizotinib is an ALK inhibitor recently approved by FDA in ALK+ ALCL in paediatric and young adult patients. We herein present the long-term efficacy and safety data in the 27 patients affected by ALK+ lymphomas followed in Monza's San Gerardo Hospital and treated with crizotinib monotherapy.

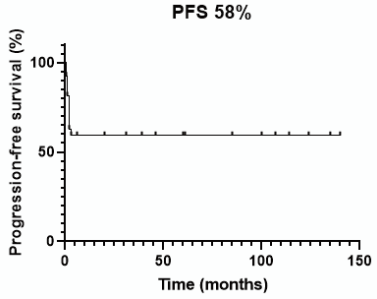


Figure 1.

Patients were treated with a median of 2 therapeutic lines before crizotinib. CT or PET/CT scan and real time polymerase chain reaction (RT-PCR) assay for ALK transcripts in peripheral blood (PB) were assessed 1 and 3 months after crizotinib introduction and every 3 to 6 months thereafter. Crizotinib was started at standard dose of 250 mg BID. Among 25 evaluable patients, overall response rate was 80% after one month of therapy (20/25, 95% CI 61%-91%). Among 17 patients with positive RT-PCR at baseline, 10 (59%, 95% CI 36%-78%) had negative RT-PCR after one month of therapy. The 15 patients who achieved CR after 3 months of therapy are still alive today in CR. Progressions always developed within 3 months. Neutropenia (usually G3/4), gastrointestinal disturbances, visual disturbances, peripheral oedema, paraesthesia, muscle cramps (usually G1/2) were the most frequently reported adverse events, usually temporary or manageable with support therapy or short therapy interruptions or dose reduction down to 250 mg/die. Median follow-up in alive patients is 61 months (range 6-140). Progression-free survival (PFS) and OS are 58% (Figure 1) and 59%. Crizotinib is an effective and safe therapeutic option for long term therapy of ALK+ R/R lymphomas. Early crizotinib introduction seems crucial to increase the possibilities of achieving early radiological and molecular responses, that might be predictive of long-term remission. Crizotinib is now available in 648 for R/R ALK+ lymphomas not eligible for BV.

C097

EFFICACY AND SAFETY OF ZANDELISIB ADMINISTERED BY INTERMITTENT DOSING (ID) IN PATIENTS (PTS) WITH RELAPSED OR REFRACTORY (R/R) FOLLICULAR LYMPHOMA (FL): PRIMARY ANALYSIS OF THE GLOBAL PHASE II TIDAL STUDY

P.L. Zinzani[1], W. Jurczak[2], V. Ribrag[3], K. Linton[4], G. Collins[5], J. Lopéz-Jimenéz[6], A. Mengarelli[7], T. Phillips[8], G. Musuraca[9], O. Sheehy[10], J. Li[11], W. Xu[11], M. Azoulay[12], R. Ghalie[11], A. Zelenetz[13]

[1]University of Bologna; [2]MSC National Research Cancer Institute; [3]Institut Gustav Roussy; [4]Manchester Cancer Research Centre; [5]GenesisCare; [6]Hospital Universitario Ramon y Cajal; [7]Regina Elena National Cancer Institute; [8]University of Michigan Health System; [9]Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori I.R.S.T; [10]Belfast Health and Social Care Trust; [11]MEI Pharma Inc; [12]Kyowa Kirin; [13]Memorial Sloan Kettering Cancer Center

Zandelisib is a PI3Kδ inhibitor with high target binding affinity and tumor retention, administered by intermittent dosing (ID) on days 1-7 of 28-day cycles to potentially allow repopulation of regulatory T-cells and reduce the risk of immune-related adverse events (irAEs) seen with continuous PI3Kδ inhibition. In a Phase Ib study of 37 R/R FL pts, daily (QD) zandelisib dosing for two 28-day cycles followed by ID led to an 87% overall response rate (ORR; 78% single agent; 95% with rituximab), with <10% of pts reporting Grade 3+ irAEs and discontinuations due to drug-related AEs (Pagel ICML 2021). Zandelisib was further evaluated as a single agent in R/R FL in the global Phase II TIDAL study (NCT03768505). Eligible pts were ≥18y with Grade I-IIIA FL and progressive disease after ≥2 prior therapies and no prior PI3K inhibitor. Consenting pts received zandelisib 60 mg QD for 2 cycles followed by ID.. The primary efficacy population (PEP) consisted of the first 91 treated pts of 120 planned. Primary endpoint was independent review committee-assessed ORR (Lugano criteria), analyzed after ≥6 months follow-up. Among 91 PEP pts of 121 enrolled, median number of prior therapies was 3 (range, 2-8), 21 (23%) had prior stem cell transplant, 42 (46%) were refractory to last therapy, 31 (34%) had tumors ≥5 cm, and 51 (56%) were POD24. ORR was 70.3% (64/91; 95% CI: 59.8%, 79.5%), and complete response (CR) rate was 35.2% (32/91; 95% CI: 25.4%, 45.9%). Responses occurred early, with 87.5% (56/91) at end of Cycle 2 and 75% (24/91) of CRs at end of Cycle 4. Data were immature to accurately estimate duration of response. At median follow-up of 9.4 months (range, 0.8-24) for all pts, 12 (9.9%) discontinued treatment due to any treatment-related AE. Grade 3 AEs of special interest (AESI) occurred in 18 pts: diarrhea (n=6), colitis (n=2), rash (n=4), stomatitis (n=3), and AST and ALT elevation and non-infectious pneumonitis (n=1 each); most Grade 3 AESI (15/18 [83%]) occurred during daily dosing in cycles 1-3. Consistent with the Phase Ib study, zandelisib on ID was associated with high ORR and CR rates in heavily pretreated FL pts, with <10% discontinuing due to treatment-related AEs/ and low incidence of Grade 3 AESI. The combination of zandelisib plus rituximab *vs* chemoimmunotherapy in R/R FL and MZL is currently being evaluated in the global registrational COASTAL Phase III study (NCT04745832).

C098

SUBCUTANEOUS EPCORITAMAB + R-CHOP AS FIRST-LINE TREATMENT IN PATIENTS WITH HIGH-RISK DLBCL: PHASE 1/2 UPDATE

L. Falchi[1], F. Offner[2], D. Belada[3], J. Brody[4], K.M. Linton[5], Y. Karimi[6], R. Cordoba[7], S. Snauwaert[8], A. Abbas[9], L. Wang[9], J. Wu[10], B. Elliott[9], M.R. Clausen[11]

[1]Lymphoma Service, Memorial Sloan Kettering Cancer Center; [2]Universitair Ziekenhuis Gent; [3]; 4th Department of Internal Medicine – Hematology, University Hospital and Faculty of Medicine; [4]Icahn School of Medicine at Mount Sinai; [5]The Christie NHS Foundation Trust and Manchester Cancer Research Centre; [6]University of Michigan Comprehensive Cancer Center; [7]Fundacion Jimenez Diaz University Hospital, Health Research Institute IIS-FJD; [8]Department of Hematology, AZ Sint-Jan Hospital; [9]Genmab,[10]AbbVie; [11]Vejle Hospital

Patients (pts) with newly diagnosed high-risk diffuse large B-cell lymphoma (DLBCL) have a poor prognosis when treated with standard immunochemotherapy and may benefit from novel treatments. Epcoritamab (epco) is a bispecific CD3xCD20 antibody that demonstrated meaningful antitumor activity and a manageable safety profile as a single agent. Presented here are updated results from phase 1/2 EPCORE NHL-2 (NCT04663347) arm 1 exploring subcutaneous epco with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in adults with previously untreated $CD20^+$ DLBCL and an International Prognostic Index (IPI) of 3–5. Pts received epco + R-CHOP every 21 d for 6 cycles, followed by epco monotherapy in 28-d cycles to complete up to 1 y of therapy. Epco was dosed: QW, cycle (C) 1–4; Q3W, C5–6; Q4W, C≥7. To mitigate CRS, corticosteroid prophylaxis and epco step-up dosing were mandated. As of December 1, 2021, 33 pts had received epco + R-CHOP (epco 24 mg, n=4; 48 mg, n=29). The median time from diagnosis to first dose was 25 d (range, 5–70), and the median number of total cycles initiated was 5 (1–13). Overall, 31 pts (94%) remained on treatment with a median follow-up of 3 mo (range, 0–9.7). Neutropenia (48%; febrile neutropenia in 9% of all pts), CRS (45%), infections (42%), anemia (39%), and injection-site reactions (36%) were the most common treatment-emergent AEs (TEAEs). There was no treatment discontinuation due to TEAEs. CRS events mainly occurred in C1; 87% of pts with a CRS event had CRS associated with the first full dose. CRS was generally of low grade (G; 42% G1/2, 3% G3) and resolved in a median of 2 d (range, 1–11); 4 pts were treated with tocilizumab. G3 tumor lysis syndrome and G2 ICANS occurred in 1 pt each, and there were no fatal TEAEs. In the 25 efficacy-evaluable pts, PET-CT showed an overall response rate (ORR) of 96% (24/25) and a complete metabolic response (CMR) in 68% of pts (17/25). In the 10 pts who completed 6 cycles of R-CHOP by the data cutoff date, the ORR was 100% and the CMR rate was 90%; each of these pts remained in response at data cutoff, with the longest duration of response being 7.1 mo and ongoing. Updated results will be presented. Epco is the first subcutaneous bispecific antibody to be assessed with standard of care R-CHOP in pts with previously untreated DLBCL. Epco + R-CHOP had a manageable safety profile and high response rates in this population, with no relapses as of the data cutoff date.

C099

DEVELOPMENT OF A GENE-EXPRESSION BASED SIGNATURE TO TRANSCRIPTOMICALLY OPTIMIZE MEDIASTINAL GRAY ZONE LYMPHOMA DIAGNOSIS

G. Gargano[1], M.C. Vegliante[1], F. Esposito[2], G. Opinto[1], G. Zaccaria[1], S.A. Pappagallo[1], P. Mondelli[1], G. Loseto[1], C. Minoia[1], E. Sabattini[3], C. Agostinelli[3], V. Tabanelli[4], S.A. Pileri[4], L. Nassi[5], A. Guarini[1], S. Ciavarella[1]

[1]Hematology and Cell Therapy Unit, IRCCS-Istituto Tumori 'Giovanni Paolo II', Bari, Italy; [2]Department of Mathematics, University of Bari 'Aldo Moro'; [3]Haematopathology Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna and Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna, Bologna, Italy; [4]Division of Hematopathology, European Institute of Oncology, IRCCS, Milan, Italy; [5]Department of Hematology, Careggi Hospital and University of Florence, Florence, Italy

Non-Hodgkin Lymphomas with intermediate features between Diffuse Large B-cell Lymphoma (DLBCL) and classical Hodgkin Lymphoma (cHL) – also known as Gray Zone Lymphomas (GZL) - represent a unique, diagnostically challenging entity. Among GZL, those involving the mediastinum (mGZL), typically exhibit discordant features between cHL and Primary Mediastinal Large B-cell Lymphoma (PMBCL), and are characterized by a high degree of diagnosis reclassification and consequent therapeutic failure. Therefore, there is an urgent need for tools applicable to routine clinical practice allowing deeper molecular characterization of mGZL and selection of the optimal treatments. We applied a deconvolution algorithm named CIBERSORTx to public gene expression profiling (GEP) data comprising 50 cHL (GSE17920) and 31 PMBCL (GSE11318) defined as a training set. This approach purified GEP from tumor and microenvironment (ME), then the Non-Negative Matrix Factorization (NMF) method was used to identify a set of genes better discriminating the two lymphoma subtypes. Finally, an ensemble of feature selection techniques allowed to lower the number of genes identifying a final molecular signature. We tested this signature using an independent in-silico cohort of 34 cHL (GSE17920) and 20 PMBCL (GSE87371) (testing set) and a real-life set of cHL, PMBCL as well as mGZL samples. CIBERSORTx and NMF allowed the selection of 2,913 genes related to both tumor and microenvironment characterizing either cHL or PMBCL. The expression of these genes allowed a correct discrimination of the two lymphomas subtypes. The subsequent feature selection provided a final signature of 168 genes and an unsupervised hierarchical clustering confirmed their discriminating capability on both training and testing sets. More importantly, when applied to an independent cohort of real-life cases, the 168 gene panel allowed the successful clustering of mGZL to either cHL or PMBCL groups on a transcriptomic ground. We described the development of a robust gene expression-based signature capable of distinguishing cHL from PMBCL, and transcriptomically categorizing mGZL based on the expression of selected tumor- and microenvironment-related genes. If validated on formalin-fixed paraffin-embedded (FFPE) samples (es. by NanoString Technology), the signature could be of promising translation into routine clinical practice or diagnostic purposes.

C100

CAR-T CELL THERAPY IN AGGRESSIVE LYMPHOMAS: THE UPDATED REAL-LIFE EXPERIENCE OF "L. E A. SERÀGNOLI" INSTITUTE OF BOLOGNA

B. Casadei[1,2], S. Guadagnuolo[1], C. Pellegrini[1], V. Stefoni[1,2], A. Broccoli[1,2], L. Nanni[1,2], A. Morigi[1,2], M. Carella[1,2], G. Lolli[1,2], P.E. Coppola[1,2], G. Bagnato[1,2], M. Gentilini[1,2], S. Rizzi[1], C. Tassi[3], E. Maffini[3], M. Dicataldo[3], L. Argnani[2], F. Bonifazi[3], P.L. Zinzani[1,2]

[1]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli", Bologna, Italy; [2]Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale, Università di Bologna, Bologna, Italy; [3]IRCCS Azienda-Ospedaliero Universitaria di Bologna, Bologna, Italy

After three years of real-life experience with the two anti-CD19 chimeric antigen receptors (CAR) T- cell therapies, axicabtagene ciloleucel (axi-cel) and tisagenlecleucel (tisa-cel), in relapsed/refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal B-cell lymphoma (PMBCL), we have more data in terms of efficacy, safety and (long-term) outcome.

One hundred and six patients (pts) were screened, 71 of whom underwent leukapheresis and, to date, 53 pts received CAR T-cells.

At time of writing, 51 pts are evaluable for analysis (44 DLBCL and 7 PMBCL). Thirty-one pts received axi-cel and 20 ones received tisa-cel, based on slot production availability and histology.

Median age at therapy was 58 years (range 20-71), 37 (72.5%) were males, 33 (64.7%) in stage III/IV, 7 with bone marrow involvement. Bulky disease was present in 26 pts (50.9%). The median number of previous therapies was 2 (2-7); 13 pts (25.5%) failed a previous autologous transplantation, and 48 (94.1%) ones were refractory to the most recent therapy. Thirty-nine pts (76.5%) received a bridging therapy. The median time from apheresis to CAR-T infusion was 48 days (29-123). All pts received lymphodepletion with fludarabine and cyclophosphamide.

At one months after the infusion, responses were as follows: 19 (37.3%) complete responses (CR) and 14 partial responses (PR), with an overall response rate (ORR) of 64.7%.

At three months after infusion 36/51 pts were evaluable for response: 61.1% CR and 13.9% PR, with an ORR of 75%. Twelve out of 13 pts evaluable at 1 year were still in CR (9 DLBCL and 3 PMBCL). Median progression free survival was reached at 6 months, whereas disease free survival at 15 months. Sixteen patients underwent at least 1 subsequent therapy, and all but one (in PR) showed progression of disease at the latest follow-up (7 deceased).

Regarding toxicity, 42 (82.4%) pts developed cytokine release syndrome of any grade (9.8% grade 3 or higher). Immune cell-associated neurotoxicity syndrome of any grade occurred in 33.3% of patients (13.5% grade 3 or higher).

Our real-life experience on CAR-T confirms the efficacy reported in clinical studies and the manageability of the related toxicity. However, hematologists must question which is the best strategy for patients relapsing after CAR-T, also in the view of the upcoming indications.

POSTERS

Autologous - allogeneic transplantation and infections

P001

THE HAEMATOLOGICAL RELAPSE IN LAM-NPM1+ ADULT PATIENTS AFTER ALLOGENEIC STEM CELL TRANSPLANT CAN BE PREDICTED BY THE IDENTIFICATION OF A CORRELATION BETWEEN CHIMERISM AND NPM1 QUANTITATIVE VALUES

M. Caputo[1], S.M. Muggianu[1], M. Celentano[1], S. Marotta[1], I. Migliaccio[1], M. Pedata[1], C. Riccardi[1], R. Peluso[1], C. Falco[2], A. Viola[3], F. Ferrara[3], A. Picardi[1,4]

[1]Stem Cell Transplant Program, AORN A. Cardarelli; [2]Collection Facility of Transplant Program, AORN A. Cardarelli; Hematology, AORN A. Cardarelli; [3]Departement of Biomedicine and Prevention; Tor Vergata University, Italy

The main risk factor in term of transplant outcome in adult patients with Acute Myelogenous Leukemia (AML) is the relapse after allogeneic stem cell transplantation (SCT), but the NPM1 positivity cut-off related to the relapse is unclear. The aim of our study was to analyze, prospectively, the correlation between chimerism and NPM1, after allogeneic SCT in AML-NPM1+ adult patients, in order to identify a predictive cut off for haematological relapse. From 2019 and 2021, 57 allogeneic SCT were performed at AORN Cardarelli Single Transplant Program in Naples. Indication to allogeneic SCT was AML in 29 cases, of whom 14 NPM1+ (7/14 males, median age 42.5, range 22-64), associated with Flt3ITD+ (N=10) or TKD+(N=2) in 12 cases. Reduced conditioning regimen (RIC) was used in 6/14 allogeneic SCT procedures, the donor was an HLA identical sibling (7/14), haplo-identical (4/14) or unrelated (3/14). Disease status at transplant was: 1st CR (10/14), 2nd CR (3/14) or active (1/14) disease. RIC or myeloablative conditioning regimen was used in all patients whereas GVHD prophylaxis depended on the donor's type. Overall, 258 bone marrow samples were analysed using quantitative RT-PCR to detect chimerism (N=128) and type A NPM1 mutation (N=130). The time points for monitoring chimerism and NPM1 analyzed were: before allogenic SCT, every month along 24 months and, then, every 3 months until 5 years after transplant. Overall, 13 patients are alive and in CR after a median follow up of 18 months (range 1-30) while 1 died for relapse. Concerning the relationship between chimerism and NPM1, the analysis has shown that day +30 after allogeneic SCT is a too early time point not reliable for prognostic purpose. Conversely, time points included between day +60 and +180 show linear correlation between NPM1 and recipient chimerism (r-value close to 1). Long term median follow-up is necessary to evaluate recipient chimerism and NPM1 mutation relationship after day 180. Moreover, recipient chimerism>1% associated with NPM1>100 copies led to haematological relapse whereas recipient chimerism values ≥1% with NPM1 copies < 100 did not. The contemporary monitoring of recipient chimerism and NPM1 values, after allogeneic SCT, could led to a better selection of patients who can benefit from immunomodulation and relapse pre-emptive therapy. From these preliminary data, the association between recipient chimerism>1% with NPM1>100, may be identified as a risk factor for haematological relapse.

P002

THE UNIQUE CGVHD GENE EXPRESSION PROFILE EVALUATED BY NANOSTRING TECHNOLOGY IN COMPARISON WITH OTHER SKIN IMMUNE-MEDIATED FIBROSING DISEASES: SCLERODERMA AND MORPHEA

E. Marinelli Busilacchi[1], R. Giannini[2], G. Tossetta[3], E. Molinelli[1,4], D. Marzioni[3], G. Goteri[5], S. Galimberti[6], G. Mancini[7], A. Campanati[1,4], A. Offidani[1,4], G. Moroncini[1,8], A. Olivieri[1,7]

[1]Department of Clinical and Molecular Sciences, Università Politecnica delle Marche; [2]Department of Surgical, Medical, Molecular Pathology and Critical Area (Anatomical Pathology Section), University of Pisa; [3]Department of Experimental and Clinical Medicine, Università Politecnica delle Marche; [4]Dermatology Unit, AOU Ospedali Riuniti di Ancona; [5]Pathology Unit, AOU Ospedali Riuniti di Ancona; [6]Department of Clinical and Experimental Medicine, University of Pisa; [7]Hematology Unit, AOU Ospedali Riuniti di Ancona; [8]Clinica Medica, AOU Ospedali Riuniti di Ancona, Italy

Introduction: Graft Versus Host Disease (GVHD), diffuse cutaneous scleroderma (SSc) and morphea, or localized scleroderma (LS), are fibrotic immune-mediated diseases characterized by excessive extracellular matrix deposition around inflamed or damaged tissue. While in SSc the fibrotic pathway involves autoantibodies with profibrotic cytokine overexpression, in LS specific mechanisms have not been fully elucidated. In cGVHD both macrophages and fibroblasts contribute to fibrosis through IL-17 dependent mechanism. We compared the gene expression profiles of these distinct fibrotic diseases, characterized by some clinically overlapping features, to explore the pathology-specific pathways involved in the fibrotic process.

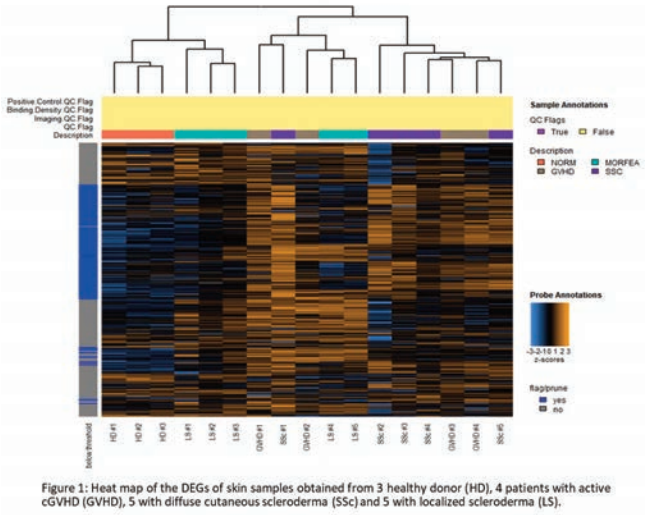


Figure 1: Heat map of the DEGs of skin samples obtained from 3 healthy donor (HD), 4 patients with active cGVHD (GVHD), 5 with diffuse cutaneous scleroderma (SSc) and 5 with localized scleroderma (LS).

Figure 1.

Materials And Methods: Skin samples were obtained from 3 healthy donors (HD), 4 patients with active cGVHD, 5 with SSc and 5 with LS. We used NanoString (nCounter) technology to study gene expression profile up to 770 RNA targets to identify differentially expressed genes (DEGs), either upregulated (UP) or downregulated (DOWN); p value adjusted ≤ 0,05 were considered statistically significant.

Results: The three distinct fibrotic diseases had 6 DEGs in common without significant network interactions. String analysis "cGVHD *vs* HD" returned 21 DEGs (9 UP and 12 DOWN) that are involved in Th17, Th1 and Th2 cell differentiation stimulated by inflammatory cytokines "SSc *vs* HD" found 46 DEGs (6 UP and 40 DOWN) implicated in Th17, Th1 and Th2 cell differentiation and in TNF signaling pathway. "LS *vs*

HD" showed 16 DEGs (11 UP and 5 DOWN) common to systemic lupus erythematosus and genes active in Toll-like receptor signaling. "cGVHD *vs* SSc" shared 10 DEGs (3 UP and 7 DOWN): all genes participate in response to stress. Instead,3 DEGs downregulated are involved in Th17, Th1 and Th2 cell differentiation. "SSc *vs* LS" found 8 DEGs (3 UP and 7 DOWN) all belonging to FoxO signaling pathway; instead, "cGVHD *vs* LS" did not show DEGs.

Conclusions: These preliminary data suggest that these three skin fibrotic diseases have distinct DEGs compared to normal skin, with common pathological cluster contributing to the pathogenesis of skin fibrosis Our study provides new insights into the molecular mechanisms of SSc, GVHD and LS, highlighting possible shared and distinctive pathways driving fibrosis and tissue remodeling in these different pathological conditions.

P003

CENTRAL VENOUS ACCESS AND PERIPHERALLY INSERTED CENTRAL CATHETERS IN HEMATOPOIETIC STEM CELL TRANSPLANTATION: A RETROSPECTIVE COMPARISON OF POSSIBLE COMPLICATION RATES

A. Mele, E. Prete, R. De Francesco, G. Greco, A. Greco, L. Tonialini, S. Sibilla, F. Donatelli, F. Martella, A. Cannoletta, S. Citiso, F. Ciardo De Marti, M.R. Morciano, G. Rizzo, A. Orlando, V. Pavone

Department of Hematology and Bone Marrow Transplant, Hospital Card. G. Panico, Tricase, Italy

Introduction: Central Venous access devises(CVAD) and peripherally inserted central catheters (PICC)are essential for the managing of patients undergoing hematopoietic stem cell transplantation (HSCT).The aim of this retrospective study is to evaluate the incidence of complications associated to vascular accesses.

Method: A total of 127 patients,undergoing HSCT at our Hospital between Jan 2019 and Dec 2021,were analyzed.Vascular accesses were successfully insered in all patients.The Broviac and dual-lume PICC was implanted in 85 and 42 patients, respectively. SPSS™ v22 was used to perform the descriptive analysis of the main variables using a confidence interval of 95%.The student's t-test was used to compare the means of two independent samples assuming unequal variances.

Results: The baseline characteristics of patients,underling disease and different phases of the HSCT are listed in Table 1.The clinical characteristics between the two populations are not balanced since the PICC has been used essentially in autologous patients (93%) and 38 of these were MM.Broviac was placed in both allogenic(53%) and autologous (47%)HSCT. The catheter-related blood stream infections(CRBSI) occurred in 17% (n=14) and in 5% (n=2) of Broviac and PICC, respectively(p= 0,04). The different pathogens associated to CRBSI were reported in Table 1. Broviac and PICC were removed for infections in 5%(n=4) and in 3% (n=1) of patients, respectively. The catheter related thrombotic complications (CRTC) was recorded only in PICC (n=7; 17%), p 0,003.None of the catheters was removed early due to thrombotic episodes.After the thrombotic episode,all patients were treated with low-molecular-weight heparin (LMWH) while the catheter remained in place;in case of PLTs $<50\times10^9$/l low dose LMWH were used.No fatal event related to the CRTC was observed.Broviac and PICC remained without problems throughout the HSCT procedure in 91% (n=73) and 93% (n=39),respectively.Univariate analyses of variables associated to vascular complications were analyzed.Only a lower number of CD34 infusion($<4x10^6$/Kg) resulted significantly associated to a higher incidence of PICC-CRTC,p 0,03,while mucositis was statistacally predictive of CRBSI in patients with Broviac (100% *vs* 80%, p 0,01).

Conclusions: In our experience,Broviac was associated with an increased risk of bloodstream infections.Thrombotic episodes were observed in PICC.No fatal events were observed.Further prospective studies are needed to confirm these data.

Table 1.

Table 1. Patients characteristics, underling disease and different phases of the HSCT; Number and rate of catheter-related complications

	BROVIAC	PICC	
	85	42	P
Allogeneic HSCT, N (%)	45 (53)	2 (5)	0,0001
Autologous HSCT, N (%)	40 (47)	26 (93)	
Disease at HSCT			
Lymphoma, N (%)	35 (44)	2 (5)	
Multiple Myeloma, N (%)	12 (14)	38 (91)	0,001
Acute Leukemia, N (%)	27 (32)	//	
Others, N (%)	8 (9%)	2 (3)	
Responsive disease at HSCT, N (%)	74 (87)	38 (90)	0,57
Median age at transplant, (range)			0,51
> 65 years, N (%)	11 (13)	7 (17)	
>2 lines of prior CHT , N (%)	29 (34)	4 (10)	0,008
>12 months prior HSCT, N (%)	38 (45)	5 (72)	0,001
Median CD34 infused (range)			0,05
> 4x10^6/Kg, N (%)	46 (54)	15 (36)	
Engraftment			
Days to Neut>500/microL			
>12 days, N (%)	36 (56)	7 (17)	0,03
Days to PLT > 20000/microL			
>14 days, N (%)	25 (34)	8 (19)	0,09
Diarrhea, N (%)	49 (58)	20 (48)	0,25
Mucosite, N (%)	70 (83)	33 (79)	0,51
Febrile Neutropenia, N (%)	60 (72)	23 (55)	0,06
Number and rate of catheter-related complications			
CRBSI, N (%)	14 (17)	2 (5)	0,04
Pathogens			
Coagulase-negative staphylococci	4	/	
Escherichia Coli	5	2	
Klebsiella Pneumoniae	3		
Others	2		
CRTC, N (%)	0	7 (17)	0,003

Abbreviations: HSCT: hemopoietic stem cell transplantatio; CHT: Chemotherapy; Neut: Neutrophyl; PLT_ Platelets; CRBSI: catheter-related blood stream infections; CRTC: catheter related Thrombotic complications

P004

REDUCING AUTOGRAFTING POST-INFUSIONAL TOXICITIES TROUGH DMSO REMOVAL BEFORE PERIPHERAL BLOOD PROGENITORS INFUSION

M. Antonacci[1], V. Filipponi[1], M.C. Scerpa[2], U. Coppetelli[2], S. Perrone[2], N. Cenfra[2], S. Mecarocci[2], L. Fiori[2], F. Brinchi Giusti[2], P. Giovangrossi[3], F. Equitani[3], E. Ortu La Barbera[2], G. Cimino[1,2]

[1]Department of Translational and Precision Medicine, Hematology, Sapienza University of Rome; [2]Hematology Unit Santa Maria Goretti Hospital; [3]Immunohematology and Trasfusion Medicine Service Santa Maria Goretti Hospital, ASL Latina, Latina, Italy

Background: Hemopoietic stem cells storage requires cryoprotectants like dimethyl sulfoxide (DMSO). Washing out DMSO before autografting seems to reduce infusional toxicity rate and not impact on cell viability and engraftment potential of peripheral blood progenitors. Up to date few data are available.

Aims: The aim of the study was comparing autografting-related toxicities during and after CSE infusion, between patients who received cells with or without DMSO.

Methods: We retrospectively analysed 55 consecutive patients (Table 1) underwent HDCHT-ASCT at S.M.Goretti Hospital Hematology Unit (Latina, IT) from January 2019 to December 2021. Thirty patients (17 Multiple Myeloma, 6 Hodgkin's Lymphoma, 7 Non Hodgkin's Lymphoma) received unmanipulated autograft (Group1-G1), while Twenty-five patients (12 Multiple Myeloma, 13 Non Hodgkin's Lymphoma) had DMSO-free stem cells infusion (Group2-G2).

Results: Harvested and infused CD34+ number/kg was not influenced by DMSO removal before infusion, as well as the average time of engraftment ($N\geq 0.5 \times 10^9$ /L: 10.4 days G1 *vs* 10.1 days G2; $PLTs\geq 20 \times 10^9$/L: 11.7 days G1 *vs* 12.5 days G2) and the blood component transfusion requirement. No grade 3-4 infusion reaction was observed in any case and no significant differences in febrile neutropenia incidence, FUO, sepsis or other sources of infection were detected (44 *vs* 57%, p=0.28). By contrast a lower rate of grade 3 mucositis (37% *vs* 4%, p=0.003) and nausea and vomiting episodes (40% *vs* 8%, p=0.007) was

found in Group 2, together with a shorter hospitalization length (16.8 days *vs* 14.2 days, p=0.0059).

Conclusion: Our data strongly support DMSO removal in CSE-autografting to reduce severe post-infusion gastrointestinal adverse events, leading to shorter hospitalization. Further and larger studies are required to confirm benefits from this procedure.

Table 1.

	Group 1	Group 2	P-value
Clinical characteristics			
Number of patients	30	25	
Age [year]	57(21-69)	59(33-70)	ns
Sex			0.0006
M	15	22	
F	15	3	
Conditioning regimen			
FEAM	13	13	
HD-Melphalan	17	12	
Diagnosis			
MM	17	12	
NHL	7	13	
HL	6	0	
Biological parameters			
CD34+ before thawing (#)	359±198	336±162	ns
CD34+ after thawing (#)	328±176	321±129	ns
CD34+ recovery (%)	91±88	95±76	ns
Viable CD34+ after thawing (%)	98±7	86± 4	not comparable*
Engraftment			
WBC > 1x10^9/L (days)	10.2(9-12)	10.6(9-15)	ns
N > 0.5x10^9/L (days)	10(8-11)	10.4(8-14)	ns
PLTs > 20x10^9/L (days)	11.7(8.18)	12.5(8-22)	ns
Hospitalization after infusion (days)	16.8(11.24)	14.2(10.27)	0.0059
RBC unit (#)	0.4(0-2)	0.5t(t0-3)	ns
PLTs unit (#)	1.6(0-5)	1.5(0-7)	ns
Post-infusion AEs			
GI syntomps	27/30(90%)	21/25(84%)	ns
Mucositis	15(50%)	15(60%)	ns
G1-2	12/40%)	14(56%)	ns
G3	11(37%)	1(4%)	0.003
Nausea	0	7(28%)	0.002
Nausea and vomiting	12(40%)	2(8%)	0.007
Diarrhea	18(60%)	17(68%)	ns
Fever			
T≥38°	17/30(57%)	11/25(44%)	ns
≥48h	3(10%)	3(12%)	ns
FUO	11(37%)	9(36%)	ns
Sepsis	3(10%)	1(4%)	ns
Other infectious foci	3(10%)	1(4%)	ns

*different ISHAGE protocols have been used to evaluate cells viability (lower threshold in Group2).
ns= not statistically significant. FEAM: fotemustine, etoposide, cytarabine, melphalan.
MM: multiple Myeloma. NHL: Non Hodgkin's Lymhoma. HL: Hodgkin's Lympoma. AEs: adverse events

P005

THIOTEPA-TREOSULFAN-FLUDARABINE (TTF) AS CONDITIONING REGIMEN IN PATIENTS UNDERGOING ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION (ALLOHSCT) FOR MYELOFIBROSIS OR MYELODYSPLASTIC SYNDROME: A SINGLE CENTER EXPERIENCE

F.A. Canale[1,2], G. Porto[1,2], V. Chiara[1,2], B. Loteta[1,2], G. Irrera[1,2], V. Naso[1,2], T. Moscato[1,2], G. Console[1,2], R.E. Saladino[3], M. Francone[3], G. Pucci[2], M. Pellicanò[2], M. Martino[1,2]

[1]Stem Cell Transplantation and Cellular Therapies Unit, Onco-Hematology Department, Grande Ospedale Metropolitano, "Bianchi-Melacrino-Morelli"; [2]Transplant Program CIC 587, Onco-Hematology Department, Grande Ospedale Metropolitano, "Bianchi-Melacrino-Morelli"; [3]HLA Tissue Typing Laboratory Unit, Grande Ospedale Metropolitano, "Bianchi-Melacrino-Morelli"

AlloHSCT remains the only potentially curative treatment for myelofibrosis (MF) and myelodysplastic syndromes (MDS), but there is no consensus on the best conditioning treatment. Treosulfan as alkylating agent in a RIC regimen demonstrated low toxic profile and the combination of two alkylating agents seems to increase the chance of achieving engraftment with full donor chimerism in MF patients. Therefore a dual alkylator regimen with treosulfan, thiotepa and fludarabine (TTF) could be a promising toxicity-reduced but myeloablative conditioning regimen for a setting of patients characterized by advanced median age and at high risk for relapse and transplant-related mortality. To date no data about TTF are reported in this setting. We analyzed retrospectively 10 patients (median age: 61) affected by MF (60%) or MDS (40%) who underwent alloHSCT with TTF as conditioning regimen. The median time from diagnosis to alloHSCT was 10.5 months (range, 6-158). Graft source was peripheral blood stem cells in all patients. Donor type was HLA-matched related (n=3), matched unrelated (n=4), mismatched unrelated (n=2) and haploidentical (n=1). Graft-versus-host disease (GVHD) prophylaxis consisted of a calcineurin inhibitor plus methotrexate and ATG for 8 patients, while combination of cyclosporine with micophenolate mofetil and post-transplant cyclophosphamide was used in two cases: one haploidentical and a mismatched unrelated donor. Full donor early engraftment was achieved in all patients except 2, who died during aplasia. The median time to neutrophil recovery was 16 days (range, 16-21). The median time to achieve platelet engraftment >20 G/L was 22 (range, 15-40) days. Median follow-up was 8.2 (range, 1-15) months. Complications after HSCT included mucositis grade 3-4 in 3 patients, one diarrhea grade 3, one grade 3 systolic disfunction, neutropenic fever. Two patients early died: 1 for cerebral hemorrhage and 1 due to acute kidney disease and subsequent multi-organ failure. Two patients experienced grade II acute GVHD, while mild chronic GVHD occurred in another patient. No relapse was seen. A trend towards better survival was observed for patients who underwent alloHSCT before the median time period of 24 months (p=0.06). These data suggest feasibility and efficacy of TTF regimen for MF/MDS patients, with excellent early full donor engraftment and manageable transplant related toxicity. Larger cohort and longer FU are needed for survival analysis.

P006

OUTCOMES OF REDUCED DOSE TEAM (THIOTEPA, ETOPOSIDE, CYTARABINE, MELPHALAN) PRIOR TO AUTOLOGOUS STEM CELL TRANSPLANTATION FOR HODGKIN AND NON-HODGKIN LYMPHOMA: A MONOCENTRIC EXPERIENCE

S. Barbato[1], S. Di Folca[1], V. Marafioti[1], S. Avilia[1], F. Grimaldi[1], A. Severino[1], M. Picardi[1], L. Luciano[1], G. Battipaglia[1], F. Pane[1]

[1]Hematology - Department of Clinical Medicine and Surgery, Federico II University, Italy

Combination of carmustine, etoposide, cytarabine, melphalan (BEAM) is a commonly used regimen for autologous stem cell transplantation (auto-SCT) in lymphomas. Replacement with thiotepa (TEAM) has been done due to a shortage of carmustine and to reduce its pulmonary toxicity. In our center, to reduce gut toxicity, namely mucositis, since 2015 we use a reduced dose of etoposide and cytarabine.

We retrospectively analyzed transplant outcomes of adult patients undergoing auto-SCT conditioned with TEAM (thiotepa 5 mg/kg/12h on day -7; etoposide 100 mg/m^2/12h and cytarabine 100 mg/m^2/12h on days -6 to -3; melphalan 140 mg/m^2 on day -1).

Thirty-nine patients (males, n=24; females, n=15) underwent auto-SCT between 2015-2021. Median age was 43 (range 22-65) years. Twenty-seven patients were transplanted for refractory (n=10) or relapsed (n=15) disease. The most frequent histology was diffuse large B-cell lymphoma (n=15) followed by Hodgkin lymphoma (n=10), follicular lymphoma (n=5), mantle cell lymphoma (n=5) and primary mediastinal B-cell lymphoma (n=4). The median number of chemotherapy lines prior to transplant was 2 (range 1-5). Disease status at auto-SCT was complete response (CR) in 37 and partial response (PR) in 2 patients. All but 1 patient engrafted. Median median time to neutrophil

and platelet engraftment was 11 (range 8-16) and 19 (range 9-40) days, respectively. Toxicities included mucositis in 32 patients (82%) (grade 1-2, n=29; grade 3, n=3; grade 4, n=0), febrile neutropenia in 26 patients (67%), resolutive pneumonia in 1 patient. Five patients (13%) underwent maintenance therapy (brentuximab, n=3; rituximab, n=1; ibrutinib, n=1). Twelve patients relapsed with a median time after auto-SCT of 5.5 (range 3-19) months and 1-year cumulative incidence of relapse of 38% [95% CI 20-56]. Two patients underwent allogeneic SCT. The 100-day and one-year non-relapse-mortality (NRM) was 2.5% [95% CI 0.2-11]. Eight patients died: 1 for septic shock; 5 for disease progression and 2, after disease relapse, for suicide and cerebral hemorrhage, respectively. At last follow-up, 29 patients (81%) were in CR. With a median follow-up of 21 (range 3-77) months, 2-year progression-free and overall survival were 59% [95% CI 38-75] and 81% [95% CI 74-88], median progression-free and overall survival were 14 (range 0-77) and 17 months (range 0-77). Reduced TEAM is a feasible conditioning regimen with low toxicity and NRM and acceptable survival rates.

P007

TREOSULFAN-BASED REDUCED INTENSITY CONDITIONING IN T-CELL REPLETE HAPLOIDENTICAL STEM CELL TRANSPLANTATION: A SINGLE CENTER EXPERIENCE

F.A. Canale[1,2], G. Porto[1,2], V. Chiara[1,2], B. Loteta[1,2], G. Irrera[1,2], V. Naso[1,2], T. Moscato[1,2], G. Console[1,2], R.E. Saladino[3], M. Francone[3], G. Pucci[2], M. Pellicanò[2], M. Martino[1,2]

[1]Stem Cell Transplantation and Cellular Therapies Unit, Onco-Hematology Department, Grande Ospedale Metropolitano, "Bianchi-Melacrino-Morelli"; [2]Transplant Program CIC 587, Onco-Hematology Department, Grande Ospedale Metropolitano, "Bianchi-Melacrino-Morelli"; [3]HLA Tissue Typing Laboratory Unit, Grande Ospedale Metropolitano, "Bianchi-Melacrino-Morelli"

Haploidentical hematopoietic stem cell transplantation (HSCT) with post-transplantation cyclophosphamide (PTCy) has been validated as standard option using both reduced-intensity (RIC) and myeloablative conditioning (MAC). In a non-inferiority phase 3 trial Beelen et al showed that treosulfan-fludarabine RIC regimen ensures low non-relapse mortality (NRM) and excellent engraftment in the in the HLA-matched setting. On the other hand, data regarding feasibility and efficacy of treosulfan-based RIC schedule are lacking for haploidentical platform. We explored an initial retrospective cohort of 5 hematological patients, investigating feasibility and safety of haploidentical HSCT made with a treosulfan-fludarabine RIC regimen, followed by PTCy. Patients underwent HSCT between January 2021 and April 2022 and were affected by acute myeloid leukemia (n=2), non-Hodgkin lymphoma (n=2), Hodgkin disease (n=1). The median age of patients was 58 years, while the median time from diagnosis to transplant was 49 months (range, 6-81). Graft source was peripheral blood stem cells in all patients. Treosulfan cumulative dose was 30g/m^2 in 80% and 36g/m^2 in 20% of patients. Graft-versus-host disease (GVHD) prophylaxis consisted of PTCy plus combination of cyclosporine with micophenolate mofetil. Donor engraftment occurred in all patients, with full donor chimerism achieved by day 30. The median time to neutrophil recovery and platelet engraftment was 16 days (range, 13-21) and 21 days (range, 14-36), respectively. The median follow-up was 9.1 (range, 0.8-15.2) months. The only grade III non-hematologic toxicity was a HHV6 associated encephalitis, no deaths after HSCT were seen. One patient affected by mantle-cell lymphoma experienced grade I acute GVHD, followed by a moderate cutaneous chronic GVHD. Donor lymphocyte infusions (DLI) were started in patient with AML who experienced mixed chimerism (88% donor) at day +257. No disease relapse occurred. In conclusion, our initial data show early full donor engraftment and manageable transplant related toxicity with treosulfan-fludarabine conditioning. Therefore, treosulfan-based RIC represents a feasible and safe strategy also in haploidentical HSCT, optimal for various setting of hematological malignancies (AML with advanced age, MDS, lymphomas, etc.). We will further evaluate this platform with a larger cohort and longer follow-up, which are essential requisites for analysis of GVHD incidence and survival estimate.

P008

THE LOSS OF VITALITY IN STEM CELLS AFTER THAWING : RETROSPECTIVE EVALUATION OF PLT AND NEUTROPHILS IN HPCA PRODUCTS

F. Culurgioni, R. Floris, M. Orrù, A. Piras, G. La Nasa

S.C. Ematologia e CTMO, Ospedale Oncologico "A. Businco", ARNAS "G, Brotzu", Italy

Several scientific evidences suggest that a loss of cell vitality during the post-manipulation and thawing processes of peripheral or medullary stem cells is often associated with apheresis collections that provide an high quantity of wbc neutrophils as well as of platelet range. Consequently, an increase in the collecting of stem cell is required in order to contrast the excessive losses; more specifically, significant collecting processes lead to use a larger amount of DMSO during the thawing procedure, and, consequentially, to the administration to the patient by cell transplantation.

This study, focuses on the identification of those critical points that might interfere with the indicators analysis (post manipulation/thawing of CD34 cell vitality).

The analysis conducted in the current study relies on a sample of 154 HPCA collections (from 2018 to 2020) and is focused on the gradual retardation in the time of implementation of neutrophils and platelets during 2018-2019.

The analysis is based on the study of HPCA collection, divided by pathology in that year in which the high retardation has been discovered. The results show that the post manipulation vitality of the myeloma group (37,1% samples) in the chosen period of time reached 75,62%, while the vitality of the LAL group (2,8% samples) was 81,7%; concerning the lymphoma group (51,2% samples), the vitality percentage was 94,68%. Moreover, it has been discovered that the same happened, proportionately, in the vitality evaluation of a thawed product.

The HPCA collecting derived from myelomas have a higher percentage and absolute value than WBC neutrophils and platelets. This result is related to the lower rate of vitality of thawed and post manipulation products.

The settlement of these difficulties and the improvement of these processes has resulted in the reduction of implantation time and in the time of hospitalisation, in the diminishing of possible problems derived from infections, in the lower range of DMSO given to the patient and in a smaller damage from DMSO.

Is possible to affirm that the retardation in the implantation time, due to the use of thawed apheresis products, occurs both in the paediatric patients as well as in adults along with a significant loss of post manipulation vitality. Particularly, this condition is present especially in those patients suffering from multiple myeloma rather than those suffering from lymphoma, acute leukaemia and other kinds of pathologies.

P009

THE ROLE OF FLOW CYTOMETRY IN THE COUNTING AND IN EVALUATION OF CD34+ HEMATOPOIETIC STEM CELLS (HSCS) VIABILITY IN AUTOLOGOUS STEM CELL TRANSPLANT (ASCT)

R. Nuccorini, S.P. Pascale, M. Giuseffi, A. Amendola, D.M. Caputo, I. Chitarrelli, M. Cimminiello, S. Coluzzi, K. Ferrara, N.B. Filardi, R. Iula, A. Matturro, D. Vertone, M. Pizzuti

UOC Ematologia-AOR San Carlo di Potenza, Italy

Background: Autologous Stem Cell Transplant (ASCT) is frequently used as a strategy of treatment for various hematological malignancies and some solid tumors. Flow cytometry (FC) play an important role in clinical decisions since it acts like a "bridge" between haematology and transfusion medicine. FC is present in different moments during HSCT: CD34+ cells monitoring and collection; qualitative stem cells assessment by viability (before conditioning therapy and at the time of infusion); evaluation of immunological recovery.

Methods: We studied CD34+ cell enumeration and viability using a reference FC procedure employing STEM-KIT Beckman coulter and modified International Society of Hematotherapy and Graft Engineering (ISHAGE). For viability evaluation we used a cutoff of 20% according to JACIE procedures.

Patients: We studied 21 patients (pts) with different diagnoses (10 lymphoma, 8 multiple myeloma and 3 amyloidosis); with median age of 52 years (range 29-74), 19 pts underwent to ASCT after first-line therapy and 2 after second-line.

Results: All pts were mobilized collecting a median 6,2X10^{6}CD34$^+$/Kg (3-18) in a median number of 1 aphereses (1-2). Viability pre-conditioning therapy was evaluated in 18 pts with a median value of 51% (30-72). 6 pts performed a double ASCT according to clinical decision (total transplantation procedures: 27). Bed-side viability was evaluated in 24 cases. Engraftment was achieved at day 12 for neutrophils (8-16) and at day 16 for platelets (10-22). At 12 months of follow up all pts are alive without disease progression. Stratifying pts according to their age (>60 *vs* <60 years) and diagnosis we didn't observe significant differences in terms of viability, CD34+cells count and engraftment.

Conclusions: From data analysis stratified by age, older pts had pre-conditioning and bed-side viability values not significantly different from the results obtained by younger pts (median: 53% *vs* 50% and 65% *vs* 63% respectively). This suggests that even in older pts HCSC maintain their characteristics and are able to mobilize and reconstitute the marrow in the same time frame as young pts. Further studies will be needed to improve the standardization of the method for assessing viability and to clarify which is the cutoff to use to define the quality of the apheresis and to integrate into clinical practice.

P010

FEASIBILITY OF CASPOFUNGIN PROPHYLAXIS IN THE PRE-ENGRAFTMENT PERIOD IN PATIENTS UNDERGOING ALLOGENEIC HEMATOPOIETIC TRANSPLANTATION

A. Fiore[1], A. Vincenzi[1], F. D'Agostino[1], R. Iannotta[1], F. Grimaldi[1,2], L. Ammirati[3], C. Califano[3], A. Camera[4], L. Luciano[1], S. Avilia[1], A. Severino[1], M. Picardi[1,2], F. Pane[1,2], G. Battipaglia[1,2]

[1]Federico II University of Naples, Hematology Department, Naples, Italy; [2]Department of Clinical Medicine and Surgery, Federico II University of Naples, Naples Italy; [3]Onco-Ematologia Ospedale Pagani, Salerno; [4]Hematology Unit, Sant'Anna e San Sebastiano Hospital, Caserta, Italy

Invasive fungal infections (IFIs) prophylaxis with azoles is hampered by pharmacological interactions and hepatic toxicity. Conversely, caspofungin is an echinocandin with a manageable pharmacologic profile.

We report 20 patients (13 females, 7 males) transplanted in our Center (july 2020-march 2022) and receiving off-label caspofungin in the pre-engraftment period (from neutropenia until engraftment).

Transplant indications were: AML (n=14), ALL (n=1), MDS (n=1), MDS/MPN (n=1), HL (n=1), BP-CML (n=1) and NHL/SCID (n=1). Median age at transplant was 54 (range 25-70) years. Median interval from diagnosis to transplant was 8 (IQR 6-15) months.

Fourteen patients were transplanted in complete remission, 6 with active disease. Two patients had a Sorror score >2. Stem cell source was PB in 9 and BM in 11 cases.

Donors were HLA-identical siblings in 6, unrelated 10/10 in 5 and 9/10 in 2, Haploidentical in 7 cases. Conditioning regimen was myeloablative or reduced-intensity in 12 and 8 patients, respectively. Graft-versus-host disease (GVHD) prevention consisted of Cyclosporine A alone (n=1), with methotrexate (n=5) or mycophenolate mofetil (n=14). Antithymocyte globulin or post-transplant cyclophosphamide were used in 10 and 9 patients, respectively. Median duration of hospitalization for allo-HCT was 30 (15-56) days. Median duration of caspofungin prophylaxis was 17 (8-26) days with no toxicities and no need to switch to other antifungal agents. No IFIs were registered during hospitalization. All but one patient engrafted. Median time to neutrophil and platelet engraftment were 15 (range 9-23) and 17 (range 8-44) days. One patient developed a possible IFI (radiological findings) at 36 days after allo-HCT, successfully treated with antibiotics and voriconazole.

Three patients experienced grade II-IV acute GVHD (2 grade II, 1 grade IV), resolutive in all but one patient, dying at 125 days after allo-HCT. At 100 days transplant-related mortality was 5% (one death due to veno-occlusive disease). One patient died due to disease relapse 75 days after allo-HCT. Molecular relapse occurred in two patients, treated with DLI + decitabine in one and + gilteritinib in another. With a median follow-up of 7 (range 1-21) months, 6-months overall and progression-free survival were 88±8% and 82±10%, respectively, while GVHD/relapse-free survival was 82±9%.

Prophylaxis with caspofungin is feasible, with low toxicity and no IFIs during the pre-engraftment period.

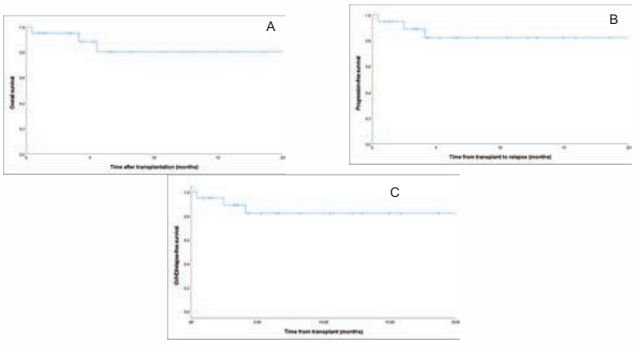


Fig.1 (A) 6-mo OS:80±10%. (B) 6-mo PFS: 89±7%. (C) 6-mo GRFS: 89±7%.

Figure 1.

P011

CHARACTERISTICS AND CLINICAL OUTCOME OF SARS-COV-2 INFECTION IN 83 FULLY VACCINATED PATIENTS WITH LYMPHOID NEOPLASMS DURING THE PANDEMIC "THIRD WAVE"

T. Perrone[1], P. Masciopinto[2], V. Strafella[2], A. Giordano[1], F. Gaudio[1], M.C. Longo[1], E. Arcuti[2], C. Presicce[2], L. Ruga[2], M. Croce[2], L. Strippoli[2], O. Battisti[2], G. Brindicci[3], A. Saracino[3], P. Stefanizzi[4], S. Tafuri[4], F. Albano[2], P. Musto[2]

[1]Unit of Hematology and Stem Cell Transplantation A.O.U.Policlinico; [2]Department of Emergency and Organ Transplantation, University School of Medicine; [3]Clinic of Infectious diseases, AOUC Policlinico; [4]Department of Biomedical Sciences and Human Oncology, University School of Medicine

Patients with lymphoid malignancies (LM) look particularly vulnerable to SARS-CoV-2 infection, with increased COVID-19-related mortality and low rates of seroconversion after receiving anti- SARS-CoV-2 vaccines. In this single center, retrospective study, we evaluated COVID-19 outcome in 83 consecutive and fully vaccinated patients affected by LM who experienced SARS-CoV2 infection between December, 2021, and April, 2022, during the so-called "third wave" of pandemic. Fifty-one patients had B-cell non-Hodgkin lymphomas (NHLs) (29 follicular, 12 diffuse large B-cell, 7 marginal zone and 3 mantle cell histology, respectively), 17 chronic lymphocytic leukemia, 11 Hodgkin lymphoma, 3 T-cell NHLs, and 1 hairy-cell leukemia. All patients had received two doses of anti-SARS-CoV-2 mRNA vaccines and 77.1% of them a further, booster dose. Median age was 57.8 years (range 18-94) and M/F ratio was 52/31. Within the last 12 months, 61 patients (72.2%) had received a treatment for their LM before SARS-CoV-2 infection: 19 of them (22.9%) were on treatment with immuno-chemotherapy (ICT), 13 (15.6%) on anti-CD20 maintenance, 14 (16.8%) on chemotherapy only, 12 (14.4%) on ibrutinib, and 3 (3.6%) on check-point inhibitors. Twenty-three patients (27.7%) needed hospitalization; among them, 4 (4.8%) were admitted to intensive care units (ICUs) and 7 (8.4%) died. Thirty-three (39.8%) patients received antiviral drugs, while 4 (4.8%) hospitalized patients received monoclonal antibodies for COVID-19 treatment. Median time to reach a negative test for SARS-CoV-2 was 17 days (range 3-86). However, at the time of analysis, 16 patients (28%) were still positive after 5-to-61 days. At univariate analysis, treatment with ICT or ibrutinib (p=0.008) and diffuse, large B-cell or mantle cell NHLs (p=0.022) were significantly associated to a worse overall survival (OS), while maintenance therapy with anti-CD20 monoclonal antibodies as single agents did not. Booster dose and antiviral treatments did not influence time to SARS-CoV-2 negativity and OS, though a favorable trend was observed with the use antiviral drugs. In conclusion, during the current phase of pandemic, we observed a lower number of patients who required hospitalization in ICUs or died than previously reported in LM, supporting the effective role of vaccination. Type of treatment and histology had prognostic impact. The role of a third vaccine dose and that of antiviral treatments warrant further investigation.

P012

COVID-19 IN ADULT ACUTE MYELOID LEUKEMIA PATIENTS: A LONG-TERM FOLLOW-UP STUDY FROM THE EUROPEAN HEMATOLOGY ASSOCIATION (EPICOVIDEHA)

F. Marchesi[1], J. Salmanton-García[2], Z. Emarah[2], K. Piukovics[2], M. Nucci[2], A. López-García[2], Z. Ráčil[2], F. Farina[2], M. Popova[2], S. Zompi[2], E. Audisio[2], M.P. Ledoux[2], L. Verga[2], B. Weinbergerová[2], T. Szotkovski[2], M. Gomes Da Silva[2], N. Fracchiolla[2], N. De Jonge[2], G. Collins[2], M. Marchetti[2], G. Magliano[2], C. García-Vidal[2], M.M. Biernat[2], J. Van Doesum[2], M. Machado[2], F. Demirkan[2], M. Al-Khabori[2], P. Žák[2], B. Víšek[2], I. Stoma[2], G. Méndez[2], J. Maertens[2], N. Khanna[2], I. Espigado[2], G. Dragonetti[3], L. Fianchi[3], M.I. Del Principe[2], A. Cabirta[2], I. Ormazabal-Vélez[2], O. Jaksic[2], C. Buquicchio[2], V. Bonuomo[2], J. Batinić[2], A.S. Omrani[2], S. Lamure[2], O. Finizio[2], N. Fernández[2], I. Falces-Romero[2], O. Blennow[2], R. Bergantim[2], N. Ali[2], S. Win[2], J. Van Praet[2], M.C. Tisi[2], A. Shirinova[2], M. Schönlein[2], J. Prattes[2], M. Piedimonte[2], V. Petzer[2], M. Navrátil[2], A. Kulasekararaj[2], P. Jindra[2], J. Sramek[2], A. Glenthøj[2], R. Fazzi[2], C. De Ramón-Sánchez[2], C. Cattaneo[2], M. Calbacho[2], N.C. Bahr[2], S. El-Ashwah[2], R. Cordoba[2], M. Hanakova[2], G. Zambrotta[2], M. Sciumè[2], S. Booth[2], R. Nunes Rodrigues[2], M.V. Sacchi[2], N. García-Poutón[2], J-A. Martín-González[2], S. Khostelidi[2], S. Gräfe[2], L. Rahimli[2], E. Ammatuna[2], A. Busca[2], P. Corradini[2], M. Hoenigl[2], N. Klimko[2], P. Koehler[2], A. Pagliuca[2], F. Passamonti[2], O.A. Cornely[2], L. Pagano[3]

[1]Hematology Unit IRCCS Regina Elena National Cancer Institute; [2]Scientific Working Group (SWG) Infection in Hematology of the European Hematology Association (EHA); [3]Hematology Unit Fondazione Policlinico Universitario Agostino Gemelli IRCCS

Patients with acute myeloid leukemia (AML) are at high risk of mortality from coronavirus disease 2019 (COVID-19). The optimal management of AML patients with COVID-19 has not been established. Our multicenter study included 388 adult AML patients with COVID-19 diagnosis between February 2020 and October 2021. The vast majority were receiving or had received AML treatment in the prior 3 months. COVID-19 was severe in 41.2% and critical in 21.1% of cases. The chemotherapeutic schedule was modified in 174 patients (44.8%), delayed in 68 and permanently discontinued in 106. After a median follow-up of 325 days, 180 patients (46.4%) had died; death was attributed to COVID-19 (43.3%), AML (26.1%) or to a combination of both (26.7%), whereas in 3.9% of cases the reason was unknown.

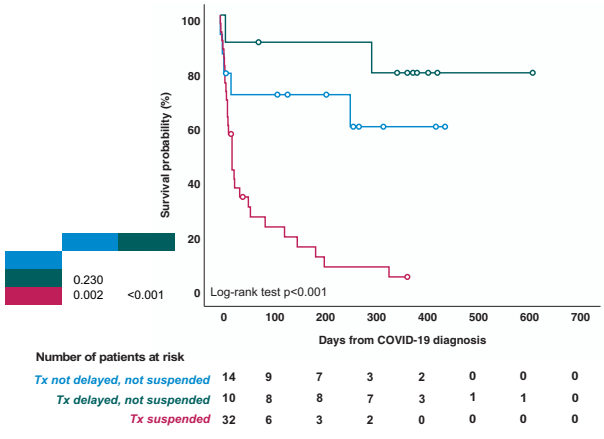


Figure 1.

At multivariable analysis, active leukemia [HR 4.197, 95% CI: 2.196-8.020; p<0.001], older age [HR 1.016, 95% CI: 1.004-1.028; p=0.012],

and treatment discontinuation [HR 4.417, 95% CI: 2.306-8.460; p<0.001] were associated with death, whereas AML treatment delay was protective [HR 0.367, 95% CI: 0.151-0.891; p=0.027]. Seventy-nine patients had a simultaneous AML and COVID-19 diagnosis, with an improved survival when AML treatment could be delayed (80%; p<0.001, Figure 1). Overall survival in patients with COVID-19 diagnosis between January 2020 and August 2020 was significantly lower than those who were diagnosed between September 2020 and February 2021 and between March 2021 and September 2021 (39.8% *vs* 60% *vs* 61.9%, respectively; p=0.006). COVID-19 in AML patients was associated with a high mortality rate and modifications of therapeutic algorithms. The best approach to improve survival was to delay AML treatment, whenever possible.

P013

SEROLOGICAL RESPONSE TO SARS-COV2-19 VACCINE IN PATIENTS WITH HEMATOLOGICAL MALIGNANCIES: RESULTS OF THE STUDY "CERVAX"

S. Mohamed[1], E. Lucchini[1], F. Sirianni[3], M. Porrazzo[1], L. Ballotta[1], M. Ballerini[1], G.M. De Sabbata[1], E. De Bellis[1], I. Cappuccio[1], M. Granzotto[3], B. Toffoletto[3], M. Ruscio[3], A. Russignan[4], M. Krampera[4], L. Torelli[2], F. Zaja[1,2]

[1]SC Ematologia, Azienda Sanitaria Universitaria Giuliano Isontina; [2]Dipartimento di Scienze Mediche, Chirurgiche e della Salute, Università di Trieste; [3]SC Laboratorio Analisi, Azienda Sanitaria Universitaria Giuliano Isontina; [4]Dipartimento di Medicina, sezione Ematologia, Università di Verona, Italy

mRNA-COVID19 vaccines such as BNT162b2 became available in late 2020, also for hematological malignancies patients (HM pts). However, vaccine efficacy in this group was not evaluated in registration trials. Usually, HM pts are poor responder to vaccines, due to the lasting and deep immunosuppression induced by the disease/treatment. Therefore, a prospective, multicenter, observational study (CERVAX) to assess the post-vaccine serological response in a cohort of COVID19-negative HM pts, was developed. Pts with lymphomas (NHL), chronic lymphocytic leukemia (CLL) and multiple myeloma (MM), off therapy for at least 3 months, in watch-and-wait or, in treatment with ibrutinib, venetoclax, IMIDs were included. IgG, CD4 cells and IgG anti-SARS-CoV2 were evaluated at baseline (T0). Different time points were considered to assess the serological response to vaccine: before the second dose (T1), at 3-6-12 months after first dose (T2-3-4, respectively). The SARS-CoV2 IgG II Quant Assay has been used. Also, SARS-CoV2-reactive T cells analysis was evaluated through interferon gamma release assays (IGRAs). Since March 2021, 39 pts have been enrolled: 15 (38%) NHL, 12 (31%) CLL and 12 (31%) MM. Clinical and biologic features are shown in Table 1. Most of pts received ≥ 1 line of treatment (77%). A seroconversion was observed in 13/39 (33%) pts at T1; an increase of serological response was registered after the second dose (T2) (22/39 pts, 56%). This response was maintained after 6 months from the first dose (T3) (22/39 pts, 56%). Non-responders at T3 were 13/39 (33%): 2/15 NHL (13%), 2/12 MM (16%), 9/12 CLL (75%). Ten of non-responders were on therapy (2 IMIDs, 3 ibrutinib, 5 venetoclax). Moreover, only 3/39 pts developed a mild symptomatic COVID19 infection after first dose (1 non-seroconverted) and second dose (2 seroconverted). Considering the exploratory nature of our study and the small number of cases, no correlation between IgG, CD4 values at T0 and the seroconversion was found (p value 0.25 and 0.48, respectively). T4 and SARS-CoV2-reactive T cells analysis are still ongoing. Despite the limit of a small cohort, according to our data, CLL and venetoclax/ibrutinib seems to be related to a lower seroconversion. In conclusion, our study supports the efficacy of mRNA vaccine in HM pts, demonstrating the seroconversion even in subsets of heavily immunocompromised pts and the importance to continue the vaccine program even in non-responders after the first dose.

Table 1. Clinical and Biological Patients' Features.

Features (tot. Pts 39)	N (%)			
Gender				
F	19 (49)			
M	20 (51)			
Age (median) [range]	77 [52-88]			
F	81 [52-87]			
M	76 [52-88]			
Hematological Malignancies		**T1 seroconverted**	**T2 seroconverted**	**T3 seroconver**
LNH	15 (38)	7	12	
CLL	12 (31)	0	1	
MM/MGUS/MM smouldering	12 (31)	6	9	
Therapy				
On Therapy (ibrutinib, venetoclax, IMIDs)	16 (41)			
None	23 (59)			
Previous therapy lines				
0	9 (23)			
≥ 1	30 (77)			
Disease status (T0)				
CR, PR, SD, VGPR	36 (92)			
PD	3 (8)			
IgG status at T0				
< 500 mg/dl	11 (28)			
≥ 500 mg/dl	28 (72)			
CD4+ at T0				
< 400/mmc	16 (41)			
≥ 400/mmc	23 (59)			
CD8+ at T0				
< 400/mmc	16 (41)			
≥ 400/mmc	23 (59)			
Seroconversion SARS-CoV2 IgG T1				
Negative	26 (67)			
Positive	13 (33)			
Seroconversion SARS-CoV2 IgG T2				
Negative	14 (36)			
Positive	22 (56)			
Not done *	3 (8)			
Seroconversion SARS-CoV2 IgG T3				
Negative	13 (33)			
Positive	22 (56)			
Not done *	4 (11)			
Status at last Follow Up				
Alive	39 (100)			
Dead	0			

* due to an ongoing COVID19 infection during study, or lost to follow-up

P014

RESULTS OF AN INNOVATIVE PROGRAM FOR SURVEILLANCE, PROPHYLAXIS AND TREATMENT OF INFECTIVE COMPLICATIONS FOLLOWING ALLOGENEIC STEM CELL TRANSPLANTATION IN HEMATOLOGICAL MALIGNANCIES (BATMO PROTOCOL)

M. Malagola[1], A. Turra[1], L. Signorini[2], S. Corbellini[3], N. Polverelli[1], L. Masina[1], G. Del Fabro[2], S. Lorenzotti[2], B. Fumarola[2], M. Farina[1], E. Morello[1], S. Bernardi[1,4], F. Re[1,4], A. Caruso[3], F. Castelli[2], D. Russo[1]

[1]Chair of Hematology, University of Brescia, Bone Marrow Transplant Unit, ASST Spedali Civili; [2]Department of Infectious and Tropical Diseases, University of Brescia and ASST Spedali Civili; [3]Department of Molecular and Translational Medicine, Section of Microbiology and Virology, University of Brescia Medical School; [4]Centro di Ricerca Ematologico – AIL, ASST Spedali Civili, Italy

Background: Infective complications represent a relevant cause of morbidity and mortality in patients undergoing allogeneic haematopoietic stem cell transplantation (Allo-SCT). The BATMO (Best-Antimicrobial-Therapy-TMO) is an innovative program for infections prevention and management, adopted in our Center since 2019.

Methods: Data on infective complications of 116 transplanted before BATMO protocol (cohort A; 2016 - 2018) were compared with those of 84 patients transplanted following BATMO protocol (cohort B; 2019 - 2021). The clinical and transplant characteristics of the 2 cohorts were well comparable, even though patients of cohort B were at higher risk of developing bacterial, fungal and CMV infections due to a significantly higher proportion of myeloablative regimens and haploidentical donors.

Results. No change in the incidence of infections with organ localization was observed between the two cohorts. A significant reduction in Clostridioides difficile infections by day +100 was observed in cohort B

(47% *vs* 15%; p=0.04). At day +30, a higher incidence of Gram negative BSIs was observed in cohort B (12% *vs* 23%; p=0.04). By day +100 and between day +100 and +180, neither the incidence of BSIs and of the various etiological agents, nor the mortality from Gram negative bacteria, nor the incidence of invasive fungal infections was different in the two cohorts. The incidence of CMV reactivations by day +100 dropped drastically in patients of cohort B, following letermovir registration (51% *vs* 15%; p=0.00001).

Discussion: The results of this study suggest that the BATMO program is safe. In particular, the choice to avoid prophylaxis with fluoroquinolone was associated with an increase in Gram negative BSIs by day +30, but this did not translate into a higher mortality. Moreover, this strategy was associated with a significantly reduction of Clostridiodes difficile infections. Anti-CMV prophylaxis with letermovir confirmed its efficacy in significantly reducing CMV reactivation. Even though patients of cohort B were at higher risk of developing fungal infections (more haploidentical transplants with more myeloablative regimens), the extensive use of posaconazole for prophylaxis balanced this risk and no increase in the incidence of fungal-associated complications was observed.

P015

EVALUATION OF SEROLOGICAL RESPINSE TO ANTI-SARS-COV-2 MRNA VACCINATION IN HAEMATOLOGICAL PATIENTS

S.P. Pascale[1], R. Nuccorini[1], T. Pierri[2], R. Di Mare[1], L. Fabio[1], E. Lerose[1], M.A. Merlino[1], P. Schiavo[1], A. Amendola[1], G. Brucoli[2], M.D. Caputo[1], I. Chitarrelli[1], M. Cimminiello[1], S. Coluzzi[1], N. Filardi[1], A. Matturro[1], D. Vertone[1], M. Poggiaspalla[5], F. Malaspina[5], G. Musuraca[5], G. Coralluzzo[1], C. Mannarella[3], C. Musto[2], A.P. Bellettieri[4], G. Martinelli[5], C. Cerchione[5], M. Pizzuti[1]

[1]UOC di Ematologia, Azienda Ospedaliera Regionale "San Carlo", Potenza, Italy; [2]UO di Medicina Trasfusionale, Azienda Ospedaliera Regionale "San Carlo", Potenza, Italy; [3]UOS di Ematologia, Presidio Ospedaliero "Madonna delle Grazie", Matera, Italy; [4]Direzione Sanitaria, Azienda Ospedaliera Regionale "San Carlo", Potenza, Italy; [5]Direzione Scientifica, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Meldola, Italy; [6]UO di Ematologia, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Meldola, Italy

Introduction: In immunocompromised patients, SARS-COV-2 mRNA vaccine has been used in Italy from the beginning of vaccination campaign, but several studies have shown that serological response of onco-hematological patients was reduced compared to healthy subjects, due to the state of immunosuppression because of both underlying disease and administered therapy.

Methods: We evaluated the association of anti-SARS-COV-2 spike IgG titer in 215 haematological patients with clinical and demographic variables to verify if it was possible to identify predictive parameters of serological response, as well as using a control group, consisting of healthy health workers of San Carlo Hospital in Potenza. IgG titers anti-SARS-CoV2 were evaluated after 30-45 days post booster using chemiluminescent microparticle immunoassay technology.

Results: Patients with hematological malignancies, compared with the control arm, had both a mean concentration of anti-SARS-CoV2 IgG significantly lower and a seroconversion rate numerically lower. All Chronic Lymphatic Leukemia patients showed levels of antibody titer below the mean concentration, also in only clinical surveillance patients . Comparing serological response in hematological malignancies, only Acute Leukemia patients had highest seroconversion rate among the patients cohorts and a mean antibody concentration greater than control arm. Patients treated with steroids and Rituximab showed a lower level of anti-SARS-COV-2 spike IgG. Differences of anti-spike IgG levels among Chronic Myeloid Leukemia patients stratified according to TKI therapy and molecular response were observed and they could have interesting implications on the evaluation of the effects of these drugs on the immune system, but, having not reached statistically significance at the moment. The cohort of patients who received a stem cell transplant was very heterogeneous because it included different hematological malignancies and different types of transplant, however a mean concentration of anti-SARS-CoV2 IgG greater than the control arm was reported. Indeed among patients who performed a transplant for over 6 months only one had a spike IgG titer below the cutoff.

Conclusions: Our data confirm reduced serological response in haematological patients after anti-SARS-COV-2 vaccination. However, we found a great diversity of response according to types of pathologies and therapies.

P016

FEVER OF UNKNOWN ORIGIN AND MULTIDRUG RESISTANT ORGANISM COLONIZATION IN AML PATIENTS

L. Guarnera, G.E. Trotta, V. Boldrini, L. Cardillo, I. Cerroni, V. Mezzanotte, G. Pasqualone, A. Savi, B. Borsellino, E. Buzzatti, R. Palmieri, G. Paterno, L. Maurillo, F. Buccisano, A. Venditti, M.I. Del Principe

Department of Biomedicine and Prevention, University of Rome Tor Vergata, Rome, Italy

Background: Colonization by multidrug resistant organisms (MDRO) is an ever more frequently described condition in hematologic departments, which puts the patients at risk of life-threatening bacterial sepsis. Fever of unknown origin (FUO) is a condition related to the delivery of chemotherapy in hematologic malignancies, in which the use of antibiotics is debated. The incidence and risk factors for these conditions in patients with acute myeloid leukemia (AML) during the treatment are not clearly defined.

Table 1. Characteristics of study population.

	All admissions	MDRO colonization		FUO	
Number of admissions (n, %)	103 (100)	31 (30)		55 (53)	
Age (median, range)	59 (24-90)	61 (26-75)	p= 0.7	59 (24-81)	p= 0.7
Male sex (n, %)	47 (45)	14 (45)	p= 1	21 (38)	p= 0.1
ECOG (median, range)	0 (0-4)	0 (0-3)	p= 0.7	0 (0-3)	p= 0.09
Intensive chemotherapy/Non intensive treatment/Support care (n, %)	64 (62) 30 (29) 9 (8)	18 (58) 13 (42) 0 (0)	**p= 0.03**	35 (63) 18 (33) 2 (4)	p= 0.1
Previous intensive chemotherapies (median, range)	1 (0-6)	2 (0-6)	**p= 0.04**	1 (0-6)	p= 0.9
Previous non intensive treatments (median, range)	0 (0-33)	0 (0-4)	p= 0.2	0 (0-33)	p= 0.2
Previous admissions to hematology departments (median, range)	1 (0-6)	2 (0-5)	p= 0.1	1 (0-5)	p= 0.8
Previous exposure to Piperacillin/Tazobactam (n, %)	57 (55)	18 (58)	p= 1	32 (58)	p= 0.8
Previous exposure to Vancomicin (n, %)	20 (19)	12 (39)	**p= 0.003**	14 (25)	p= 0.1
Previous exposure to Carbapenems (n, %)	31 (30)	16 (52)	p= 0.07	22 (40)	p= 0.8
Previous MDRO colonization (n, %)	24 (23)	14 (45)	**p= 0.002**	11 (20)	p= 0.3
Hemoglobin (mean, range)*	9.4 (5.5-13)	8.7 (5.5-12.8)	**p= 0.03**	8.8 (6-13)	p= 0.1
Neutrophils (mean, range)*	3.430 (0-39.340)	2.340 (10-6950)	p= 0.1	2.790 (10-39.340)	p= 0.2
Lymphocytes (mean, range)*	2.350 (30-18.390)	1.410 (30-5420)	**p= 0.01**	2.420 (30-15.390)	p= 0.8
Lactate dehydrogenase (mean, range)*	423 (86-2848)	401 (19-1477)	p= 0.9	412 (103-2161)	p= 0.3
Neutrophils<500µ/L (n, %)	87 (84)	26 (84)	p= 0.7	51 (93)	**p= 0.04**
Days of Neutrophils<500µ/L (median, range)	13 (0-39)	13 (0-39)	p= 0.8	15 (0-39)	**p= 0.02**
> 10 days of Neutrophils<500µ/L (n, %)	61 (59)	20 (64)	p= 0.6	40 (73)	**p= 0.008**
Neutrophils<100µ/L (n, %)	64 (62)	19 (61)	p= 0.8	35 (64)	p= 0.5
Days of Neutrophils<100µ/L (median, range)	5 (0-30)	7 (0-30)	p= 0.5	8 (0-30)	**p= 0.01**
Mucositis (n, %)	21 (20)	10 (32)	p= 0.1	14 (25)	p= 0.2
Days of hospitalization (median, range)	28 (3-145)	39 (7-145)	**p= 0.02**	31 (7-67)	p= 0.2

* at time of admission.

Methods: We retrospectively analyzed 103 consecutive admissions for a total of 55 patients (29 males/26 females) of non- promyelocytic AML patients at the Hematology Unit of University Tor Vergata in Rome, between June 2019 and February 2022. AML diagnosis and treatment schedules were defined according to the European LeukemiaNet guidelines. MDRO screening was performed in all patients on the same day of admission and once weekly thereafter. Patients with at least one positive swab for MDRO were defined as colonized. FUO was defined as temperature >38.3°C recorded on at least one occasion in patients in whom infection was not manifest.

Results: Of 103 consecutive hospitalizations of patients with AML, MDRO colonization were observed in 31 (30%). The most frequently isolated organism was Klebsiella pneumoniae KPC (71%). MDRO colonization was related to non-intensive treatment (p=0.03), previous MDRO colonization (p=0.002), number of previous intensive chemotherapies (p=0.04), previous exposure to vancomycin (p=0.003), days of hospitalization (p=0.02), hemoglobin and lymphocytes at the time of the admission (p=0.03 and p=0.01). FUO occurred in 55 cases (54%) and correlated with neutropenia (Table 1). In multivariate analysis, FUO was related to days of neutropenia (<500/µL, p=0.02) while MDRO colonization to days of hospitalization (p=0.006), previous MDRO colonization (p=0.01), hemoglobin and lymphocytes at the admission (p=0.03 and p=0.05).

Conclusion: In our experience, MDRO colonization is frequent and difficult to eradicate. This condition seems to occur more often in patients undergoing non intensive treatment and in those heavily pretreated. The appropriate use of antibiotics, especially in the case of FUO, and the contraction of hospitalization length, when applicable, could represent measures to tackle further spread of MDRO.

P017

PREVENTION OF SARS COV2 INFECTION IN HEMATOLOGY CLINICAL SETTING: A MONOCENTRIC EXPERIENCE FROM F. SPAZIANI HOSPITAL

M. de Muro, F. Saltarelli, A. Carbone, L. Cardarelli, L. De Padua, N. Frattarelli, D. Gangemi, L. Malandruccolo, V. Martini, L. Petriccione, R. Porrini, L. Quattrocchi, L.A. Solinas, G. Tomei, S. Vaccarini, A. Abballe, R. Sala

Department of Hematology, Fabrizio Spaziani Hospital, Frosinone, Italy

Background: Dramatic spread of coronavirus disease 2019 (COVID-19) is caused by a novel coronavirus 2 (SARS-CoV-2), responsible of an acute respiratory syndrome rapidly expanded all over the world causing thousand of deaths; we consider prevention of SARS-CoV-2 infection fundamental in haematological patients receiving treatment or follow up. Despite majority of patients are vaccinated we know vaccines are not always effective in preventing infection in immunocompromised patients.

Method: From January 2021 to December 2021, 3100 patients attended hematological Day Hospital (DH) and 166 patients were admitted in the hematology ward. On admission in DH patients were requested to fill an evaluation form about symptoms and/or contacts with positive people and to show a rapid antigenic swab result, temperature was recorded. Wearing an FFP2 mask was mandatory for all patients during their stay. All the rooms were ventilated every hour and no companions were allowed in DH. Admission in hematology ward required initially a negative antigenic swab and every patient was placed in a single room until results of a new molecular swab was available. Visitors were not allowed to enter the ward unless in case of depressed or terminal patients.

Results: We identified 16 positive swabs among 14 patients (two patients infected twice in 12 months) in DH; patients were all vaccinated with two doses; 14 were asymptomatic, 2 showed t 37.5 C; 3 patients were affected by Non Hodgkin Lymphoma, 1 by Chronic Lymphocytic Leukemia, 5 by Multiple Myeloma, 1 by Acute Myeloid Leukemia, 2 by Paroxysmal Nocturnal Hemoglobinuria , 2 by Myelodysplasia. 13 patients were receiving active treatment, 1 was on follow up. 2 positive patients/166 were identified in Hematology ward after admission: 1 affected by Acute Myeloid Leukemia and 1 with Aplasia, both feverish and vaccinated with two doses; 50 visitors were tested and were found negative; no infections were recorded among patients who received visits.

Conclusions: Sars-Cov-2 positive patients in the ward were isolated and transferred to covid center within 12 hours; in our opinion this prevention strategy was effective leading to avoid outbreaks in Hematology Unit (patients and operators) and allowing prompt identification of positive patients to refer to Covid Center or to proper home care therapy (antiviral, monoclonal antibody).

Table 1.

Pathology	Number of Patients	Number of Infection	Active Therapy	Follow Up
Non Hodgkin Lymphoma	3	3	3	0
Multiple Myeloma	5	7	5	0
Myelodysplasia	2	2	2	0
Paroxysmal Nocturnal Hemoglobinuria	2	2	2	0
Acute Myeloid Leukemia	2	2	2	0
Chronic Lymphocytic Leukemia	1	1	0	1
Aplasia	1	1	0	0

Chronic lymphocytic leukemia and other lymphoproliferative syndromes

P018

LYMPH NODE AS A PROGNOSTICATOR OF PROGRESSION DURING VENETOCLAX TREATMENT IN CHRONIC LYMPHOCYTIC LEUKEMIA. A CAMPUS CLL STUDY

F. Autore[1], I. Innocenti[1], G. Reda[2], A. Visentin[3], C. Vitale[4], A. Piciocchi[5], A. Fresa[1], M.M.A. Leone[6], L. Farina[7], G. Quaresmini[8], C. Baratè[9], A. Giordano[10], A. Ferrari[11], I. Angeletti[12], M.R. De Paolis[13], L. Malerba[14], F. Chiurazzi[15], G. Loseto[16], G. Catania[17], P. Sportoletti[18], I. Scortechini[19], R. Moia[20], M. Gentile[21], G.M. Rigolin[22], V. Mattiello[2], V. Gattei[23], M. Coscia[4], L. Trentin[3], R. Foà[24], A. Cuneo[22], L. Laurenti[1]

[1]Fondazione Policlinico Universitario A. Gemelli IRCCS, Roma; [2]Fondazione IRCCS Ca' Granda Ospedale Maggiore, Milano; [3]Università degli Studi di Padova, Padova; [4]A.O.U. Città della Salute e della Scienza di Torino, Torino; [5]Fondazione GIMEMA, Roma; [6]A.O. Ospedali Riuniti Villa Sofia-Cervello, Palermo; [7]Fondazione IRCCS Istituto Nazionale dei Tumori, Milano; [8]Ospedale Papa Giovanni XXIII, Bergamo; [9]A.O.U. Pisana, Pisa; [10]A.O.U. Consorziale Policlinico di Bari, Bari; [11]Arcispedale Santa Maria Nuova IRCCS, Reggio Emilia; [12]Ospedale S. Maria di Terni, Terni; [13]A.O. Vito Fazzi, Lecce; [14]A.O. Ospedali San Salvatore di Pesaro, Pesaro; [15]Università Federico II, Napoli; [16]IRCCS Oncologico di Bari, Bari; [17]A.O.N. SS Antonio e Biagio e C. Arrigo, Alessandria; [18]Centro di Ricerca Emato-Oncologica (CREO), Università di Perugia, Perugia; [19]A.O.U. Ospedali Riuniti di Ancona, Ancona; 20 Università del Piemonte Orientale, A.O.U. Maggiore della Carità, Novara; [21]AO di Cosenza, Presidio Ospedaliero Annunziata, Cosenza; [22]A.O.U. Arcispedale S. Anna, Università di Ferrara, Ferrara; [23]Centro di Riferimento Oncologico di Aviano IRCCS, Aviano; [24]Policlinico Umberto I, Università Sapienza, Roma.

Clinical or biological parameters useful to predict progression during treatment with ibrutinib, idelalisib and venetoclax in chronic lymphocytic leukemia are poorly defined. We conducted a multi-center retrospective study on patients treated with ibrutinib and/or idelalisib who were switched to venetoclax for progression or due to adverse events.

Of all the 128 evaluable patients, 81 had received ibrutinib prior to switching to venetoclax, 35 had received idelalisib and 12 both. When comparing the three subgroups, we did not notice any statistical difference in terms of clinical or biological features. Also the curves of progression-free survival (PFS) and overall survival (OS) on kinase inhibitors were comparable (p=0.018 and p=0.93, respectively).

In the ibrutinib group, 57 (70.4%) patients showed progression during treatment after a median PFS of 27.6 months. The analysis of the variables did not find any significant prognosticator at baseline and at different time points during the follow-up (at 6, 12, 18 and 24 months). There were no differences when considering the cause of discontinuation (progression versus adverse event, p 0.7). No variable was found to predict progression nor to have significance for PFS also in the idelalisib group and in subgroups according to the line of treatment.

When considering treatment with venetoclax we conducted the analysis on all 128 patients who were treated for a median of 14.3 months (range 0.7-44.1). In this group, the diameter of the largest lymph node reached significance and was found as prognosticator for progression (Figure 1). Thus, the progression during venetoclax could be predicted by the larger diameter of the biggest lymph node which was significantly different between the 28 (22%) patients who progressed and the others who did not. By ROC analysis, we found 56.5 mm of diameter of the larger lymph node at baseline to identify patients who progressed.

In this study, we find useful parameters to predict progression and for this we analyzed a population of progressed patients. These data could therefore not be compared with other studies in which patients who continued BCR inhibitors for a longer follow-up were also included.

The lymph node prognostic role as a predictor of progression during venetoclax treatment is a new parameter that deserves to be investigate in future studies.

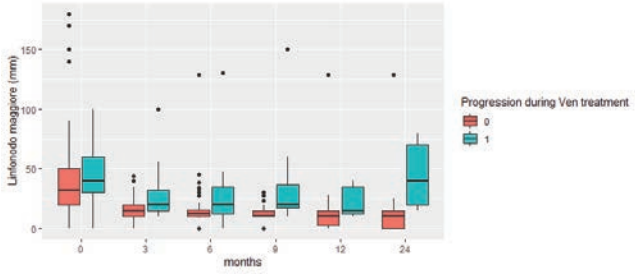


Figure 1. Comparison of lymph node diameters between patients who did not progress (group 0) and patients who progressed during venetoclax treatment (group 1).

P019

ABSTRACT NOT PUBLISHABLE

P020

IBRUTINIB IN OVER-EIGHTIES PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA: A MULTICENTER ITALIAN COHORT

V. Mattiello[1], G. Reda[1], A. Frustaci[2], A. Visentin[3], F.R. Mauro[4], I. Innocenti[5], M. Gentile[6], D. Giannarelli[7], A. Noto[1], R. Cassin[1], A. Barone[8], A. Neri[1], L. Laurenti[5], A. Tedeschi[2]

[1]Hematology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico; [2]Department of Haematology, Niguarda Cancer Center, ASST Grande Ospedale Metropolitano Niguarda; [3]Hematology and Clinical Immunology unit, Department of Medicine University of Padua; [4]Hematology, Department of Translational and Precision Medicine, 'Sapienza' University, Rome; [5]Dipartimento Scienze Radiologiche ed Ematologiche, Divisione di Ematologia Fondazione Policlinico universitario A Gemelli, Roma; [6]Azienda Ospedaliera of Cosenza; [7]Biostatistic Unit, Scientific Directorate, Fondazione Policlinico Universitario A. Gemelli; [8]Department of Oncology and Hemato-Oncology, University of Milan, Italy

In this multicenter retrospective study, we aimed to assess the activity and safety of ibrutinib in a cohort of 60 patients with CLL aged ≥80 years at therapy start. The primary endpoint was safety evaluation. Key secondary endpoints were overall response rates (ORR) according to iwCLL 2018, median progression free survival (PFS) and overall survival (OS). After a median follow up of 27 months, at least one adverse event occurred in 68.3% patients, leading to treatment discontinuation in 23.3%. The most common grade ≥3 events were infections (23%) and neutropenia (6%). Cardiovascular (CV) events occurred in 31.6% of patients, with an incidence of atrial fibrillation (AF) and arterial hypertension (AH) both increasing over time (16% at 24 months). Although no significant increase in incidence of CV events was noted among patients with concomitant CV risk factors or previous events, baseline echocardiographic characteristics could predict AF occurrence. Bleeding was the most frequent AE, occurring in 36.6% of patients, with a median time to event of 24 months and predominantly in patients assuming concomitant antiplatelet or anticoagulant drugs. A total of 23 infective events was registered, mostly in the first 12 months, leading to drug permanent dis-

continuation in 5 patients. The obtained ORR was 88.2%, with 21.7% of patients achieving CR and 66.7% PR; median PFS was 51.8 months (95% CI: 47.4-56.2). No significant difference in PFS was observed comparing TN to R/R patients (p=0.83), or IGHV mutated and unmutated patients (p=0.45). Furthermore, no difference emerged comparing PFS data of patients with TP53 dysfunction (del17 and/or TP53 mutation) to patients without TP53 dysfunction (p=0.13). Patients achieving a response during ibrutinib experienced a prolonged PFS compared to patients achieving SD as best response to treatment (p<0.0001). Drug withholding for more than 7 days due to ibrutinib-related toxicities reduced PFS with a trend to statistical significance (p=0.07). Median OS was 53.2 months (95% CI: 43.3-63.0). In conclusion, a high proportion of patients had an ORR to ibrutinib and the risk-benefit profile was favourable, providing further evidence for use of ibrutinib in this subset of elderly and unselected patients. Safety profile remains consistent with literature data with no emergent adverse events, thus making ibrutinib an attractive therapeutic possibility even in patients with advanced age and multiple comorbidities.

P021

EARLY CLEARANCE OF HAIRY CELL LEUKEMIA IN BONE MARROW SPECIMENS AFTER FIRST-LINE TREATMENT WITH PURINE ANALOGS PREDICTS FAVORABLE OUTCOME

S. Ligia[1], G.M. Assanto[1], M. Passucci[1], G.M. D'Elia[1], G. Annechini[1], I. Del Giudice[1], M. Martelli[1], E. Tiacci[2], A. Pulsoni[1]

[1]Hematology, Department of Translational and Precision Medicine, Sapienza University of Rome; [2]Hematology, Department of Medicine, University and Hospital of Perugia, Italy

Hairy cell leukemia (HCL) is a rare B-cell malignancy. Nowadays standard first line treatment includes the use of purine nucleoside analogs (PNAs), either Cladribine or Pentostatin, with high complete response (CR) rates and long-term responses. Patients in CR should have near normalization of peripheral blood counts (hemoglobin >11 g/dL, platelets >100 000/mL, absolute neutrophil count >1500/mL), regression of splenomegaly and <5% of HCL cells on both the peripheral blood smear and the bone marrow (BM) examination.

In the Consensus Guidelines for HCL it is recommended that a post-treatment bone marrow biopsy should be performed at least 4–6 months after PNAs.

We retrospectively analyzed a total of 43 patients diagnosed with HCL from our institution. All patients were primary treated with PNAs and the response assessment was performed both 2 and 6 months after therapy, in order to evaluate the clinical and prognostic value of an earlier response assessment.

Median follow-up was 121 months (SD 56.2), median age at diagnosis was 54 years (SD 10.28) and 33/43 were males (76.7%). At diagnosis the mean neutrophil count was 880/mmc, mean platelets count was 97.700/mmc and 36/43 patients (83.7%) had an enlarged spleen. HCL bone marrow infiltration was >50% in 38/43 patients (88.4%).

After treatment 31/43 patients (71.1%) and 41/43 patients (95.3%) achieved a hematologic response at 2 and 6 months, respectively. At follow-up PFS was 67.5%.

In BM specimens at 2 months, univariate analysis showed an estimated mean PFS of 190 months for patients with <=5% HCL *vs* 120 months (PFS 83% *vs* 58.6%) for patients with >5% HCL infiltration (p=0.05); same comparison was performed at 6 months without significancy (p=0.9) (figure I). This finding was confirmed in patients with spleen involvement (p=0.05).

Furthermore, a bone core biopsy Hairy Cell Index (HCI) was calculated by multiplying the percent marrow cellularity by the percent of hairy cells in the marrow, at 2 and 6 months. A significant trend was evidenced in the comparison between 2 and 6 months HCI (0.06 *vs* 0.043, p=0.065). As well neutrophils count increase was significant between 2 and 6 months (2370 *vs* 2876/mmc, p=0.03), confirming delayed timing to achieve hematologic response after PNAs.

Our data suggest a favorable prognostic impact of early HCL clearance from BM in patients treated with PNAs. Given our sample size, a larger cohort study should be conducted in order to validate the value of 2-months BM evaluation.

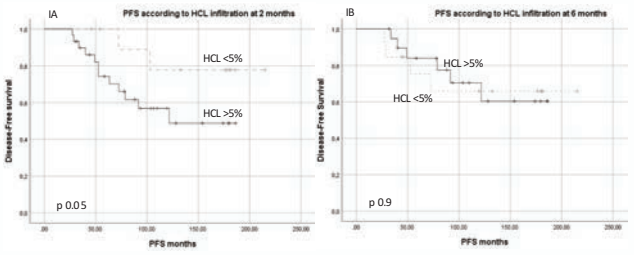


Figure 1. PFS according HCL infiltration in bone marrow specimen at 2 (IA) and 6 months (IB). Early clearance shows superior outcome when compared to late clearance. PFS, Progression free Survival; HCL, Hairy Cell Leukemia.

P022

COVID-19 VACCINATION IN CHRONIC LYMPHOCYTIC LEUKAEMIA PATIENTS TREATED OR NAÏVE. A MONOCENTRIC REAL-LIFE EXPERIENCE

I. Innocenti[1], G. Benintende[2], A. Mosca[2], L. Stirparo[2], A. Tomasso[2], F. Vuono[2], A. Fresa[2], F. Autore[1], L. Laurenti[3]

[1]Sezione di Ematologia, Dipartimento di Diagnostica per Immagini, Radioterapia Oncologica ed Ematologia, Fondazione Policlinico Universitario A. Gemelli IRCCS; [2]Sezione di Ematologia, Dipartimento di Scienze Radiologiche ed Ematologiche, Università Cattolica del Sacro Cuore; [3]Sezione di Ematologia, Dipartimento di Diagnostica per Immagini, Radioterapia Oncologica ed Ematologia, Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Italy

Background: Chronic Lymphocytic Leukaemia (CLL) patients (pts) have decreased response to SARS-CoV-2 vaccination, with a highly heterogeneous response, depending on baseline features, disease and treatment status, types of therapy, vaccine administered, and immunoglobulin level at time of vaccination.

Aims: This study evaluates the antibody responses after Covid-19 vaccination, stratifying CLL pts according to treatment status and type of treatment, including chemo-immunotherapy (CIT), BTK or anti-Bcl2 inhibitors, monoclonal antibodies (MoAb).

Patients and methods: Baseline demographics, treatment history and laboratory parameters prior to first dose of COVID-19 vaccine were collected and pts were tested for SARS-COV2 anti-spike Ig at different time point. 100 CLL pts received two/three dose of mRNA vaccine between January 2021 and March 2022. Median age was 69 years, and 51% pts were males. Median IgG level at baseline was 733 mg/dL, 78% of pts had IgG > 500 mg/dL. 71% pts received at last ≥ 1 prior therapy, CIT or inhibitors; 44% were actively treated; no patient changed or stopped treatment. All pts were vaccinated: 76% with BNT162b2, 16% with mRNA-1273, 8% with two BNT162b2 and mRNA-1273 booster (Table 1).

Results: No CLL patient experienced SARS-COV2 infection. At first serologic testing, at a median of 131 days after the 2nd dose, 53% pts tested negative and 47% positive. Among pts who did not develop immunity, 58% were on treatment with CIT or inhibitors, alone or in association with MoAb. Among pts who developed immunity, 38% were naïve and 30% were off therapy. All pts who received MoAb in the previous six months failed to develop immunity; those who received MoAb more than 6 months before, 28% did not develop immunity, while 72%

did. At second serologic testing, at a median of 46 days after the booster, 66% pts tested positive, with a 31% rate of seroconversion (Table 1).

Conclusions: We confirms low humoral response in CLL, due to both disease and therapy related factors. Pts who, at vaccination, were either naïve or off therapy yielded better results. The timing of MoAb strongly influences the response. BTK inhibitors impair the humoral response to vaccination against any pathogen, including SARS-COV2. Data show that the 3nd dose confers higher rates of response. In conclusion, vaccination is recommended to all CLL pts, due to immune dysregulation, and it is important to evaluate the timing of vaccination and maintain safety measures at any time.

Table 1.

Patient's features: Clinical and Biological characteristics 100 pz (January 2021-March 2022)			
Sex M/F, %		51/49	
Median age, years (range) age≤ 65 years, n, % Age> 65 years, n, %		69 (40-86) 74 (74%) 26 (26%)	
Comorbidities, %		40% hypertension 8% diabetes and hypertension 5% lung disease 2% diabetes 6% lung disease and hypertension 39% others	
Rai stadium,%	A B C	59 31 10	
FISH,%	Normal Kariotype Del 17p Del 13q Del 11q Trisomy 12 Trisomy 12 and Del 13q	36 7 28 13 13 3	
IgVH mutational status,%	mutated unmutated	56 (56%) 44 (44%)	
Median IgG at baseline, mg/dl (normal range 700-1600) IgG ≤ 500 mg/dl, % IgG > 500 mg/dl, %		733 (257 – 2185) 22 78	
CLL Treatment			
Therapy status at baseline	- 29% treatment naive - 27% off therapy - 44% ongoing therapy	44% pts Ongoing therapy at baseline	- 30% chemoimmunotherapy - 54% inhibitors BTK - 5% inhibitors Bcl-2 - 11% inhibitors plus MoAb
Timing of vaccination with respect to MoAb (46/85 pts)		46% never MoAb 20% received a MoAb > 12 months before the vaccination 56% received a MoAb between 6 to 12months before the vaccination 24% received MoAb <6 months from the vaccination	
Vaccination features			
Type of vaccine, %	- 76% Pfizer (three doses) - 16% Moderna (Three doses) - 8% Pfizer plus booster Moderna		
Median time between vaccination and serology testing after second dose	131 days (20 days – 252 days)	Median time between vaccination and serology testing After third dose	46 days (12 days – 155 days)
Serologic result after two doses,% (100 pts)	53% negative		
	➢ 18% treatment naïve	➢ 24% Off therapy	➢ 58% On treatment	- 26 % CIT - 53% inhibitors BTK - 9% inhibitors Bcl-2 - 12% inhibitors plus AbMo
	47% positive		
	➢ 38% treatment naïve	➢ 30% Off therapy	➢ 32% On treatment	- 32% CIT - 58% inhibitors BTK - 10% inhibitors plus AbMo
Serologic result after booster, % (56/100 pts)	34% negative (69% persistently negative) 66% positive (31% rate of seroconversion)		

Table 1: Patient's features and Covid-19 vaccination response.

P023

TREATMENT WITHIN THE FIRST 24 MONTHS FROM DIAGNOSIS IS A MARKER OF SHORTER SURVIVAL IN ASYMPTOMATIC PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA AT BINET A STAGE. A CLL CAMPUS STUDY

A. Visentin[1], G. Reda[2], F. Autore[3], M. Corbanese[1], A. Tomasso[3], S. Pravato[1], R. Cassin[2], C.A. Cavarretta[1], F. Angotzi[1], A. Cellini[1], V. Ruocco[1], L. Laurenti[3], R. Foà[4], F.R. Mauro[4], A. Cuneo[5], L. Trentin[1]

[1]Hematology and Clinical Immunology Unit, Department of Medicine, University of Padua; [2]Hematology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore; [3]Hematology Institute, Fondazione Policlinico Universitario Agostino Gemelli IRCSS; [4]Department of Translational and Precision Medicine, Hematology unit, 'Sapienza' University, Rome, Italy; [5]Hematology Section, Department of Medical Sciences, Azienda Ospedaliera-Universitaria, Arcispedale S. Anna, University of Ferrara, Ferrara, Italy

Introduction: Chronic lymphocytic leukemia (CLL) is characterized by a wide heterogeneity from long-lasting asymptomatic subjects to patients needing treatment within a few months from diagnosis. International prognostic score (IPS) and alternative IPS (AIPS) have been developed to predict time to first treatment (TTFT) in asymptomatic Binet A stage patients with CLL. In addition, ongoing clinical trials are investigating whether early treatment of high-risk patients, with targeted drugs, would provide clinical benefits. This study was aimed at characterized patients with early progressions and the accuracy of prognostic scores in identifying them.

Methods: Binet A CLL patients at stage at diagnosis were recruited. IPS score was calculated as the sum of palpable lymph nodes, absolute lymphocyte count (ALC)>15,000/uL and unmutated IGHV; while AIPS as the sum sum of palpable lymph nodes, ALC>15,000/uL, deletion of 11q23 and/or 17p13. Time to first treatment (TTFT) and overall survival (OS) were estimated using the Kaplan-Meier.

Results: Eight-hundred nineteen Binet A patients were included in this study, 58% were males, the median age at diagnosis was 63+-11 years, 39% had palpable lymph nodes, 30% ALC>15,000/uL, 65% were IGHV mutated, 41% del(11q) and/or del(17p). After a median follow-up of 8.6 years the median TTFT and OS were 11 and 27 years. Using the ROC curve analysis, we identified need of treatment within 24 months from diagnosis (T24) as a reliable cut-off of survival (Area 0.7982, p<0.0001). 130 (18%) patients were T24; the median OS for T24 patients and those who progressed after 24 months was 14 and 29 years (Figure 1A). T24 patients had a 4-fold higher-risk of death than other patients (HR 3.8, p<0.0001). An increasing rate of the 24-month cumulative incidence of treatment was observed according to the IPS score from 0 to 3, 2.8%, 9.3%, 34% and 60%, respectively (Figure 1B, p<0.0001). While, according to AIPS the 24-month TTFT was 5.4%, 15%, 40% and 65% (Figure 1C, p<0.0001). IPS revealed a higher prediction accuracy that AIPS with a higher c-index (TTFT:0.949 *vs* 0.40; OS:0.684 *vs* 0.662) and a lower Akaike information criteria (AIC, TTFT:3,033 *vs* 3,647; OS:1,026 *vs* 1,329).

Conclusions: We found that among Binet A staged patients T24 patients is associated with an adverse outcome, well-identified by the IPS score. Given the higher risk of death for T24 subjects, early treatment during the asymptomatic phase might improve the outcome of score 3 patients.

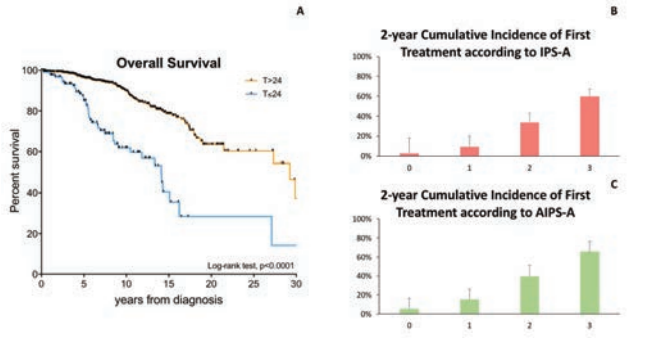


Figure 1.

P024

VALIDATION OF AN INFECTION RISK SYSTEM IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA TREATED WITH THE IDELALISIB-RITUXIMAB REGIMEN

C.A. Cavarretta[1], A. Visentin[1], A. Cellini[1], C. Vitale[2], A. Sanna[3], F. Chiurazzi[4], E. Crisanti[5], M. Gentile[6], L. Laurenti[7], L. Nocilli[8], J. Olivieri[9], C. Patti[10], R. Murru[11], M. Foglietta[12], P. Sportoletti[13], A. Gozzetti[14], F.M. Quaglia[15], M. Coscia[2], R. Foà[5], A. Cuneo[16], L. Trentin[1], F.R. Mauro[5]

[1]Hematology and Clinical Immunology Unit, Department of Medicine, University of Padua; [2]Division of Hematology, A.O.U. Città della Salute e della Scienza di Torino and Department of Molecular Biotechnology and Health Sciences, University of Turin; [3]Hematology Unit, Careggi Hospital; [4]Division of Hematology, Cardarelli Hospital; [5]Hematology unit, Department of Translational and Precision Medicine, "Sapienza" University; [6]Hematology Unit, Hematology and Oncology Department; [7]Hematology Institute, Fondazione Policlinico Universitario Agostino Gemelli IRCSS; [8]Division of Hematology, Department of Human Pathology in Adulthood and Childhood, University of Messina; [9]Division of Hematology and Stem Cell Transplantation, University of Udine; [10]Hematology Unit, Ospedale V. Cervello; [11]Hematology and Stem Cell Transplantation Unit, Ospedale A. Businco, ARNAS "G.Brotzu"; [12]Division of Hematology, AO S. Croce e Carle; [13]Institute of Hematology-Centro di Ricerca Emato-Oncologica, Department of Medicine, University of Perugia; [14]Hematology Unit, Department of Medicine, Surgery and Neurosciences, University of Siena; [15]Department of Medicine, Section of Hematology, University of Verona; [16]Hematology Unit, Department of Medical Sciences, St. Anna University Hospital

Background: Idelalisib, the first in class PI3K inhibitor, plus rituximab (IDL-R) is an effective targeted therapeutic option for relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL) but limited by treatment-related adverse events (AEs). In particular, an increased rate of infections has been described in patients treated with IDL-R. Recently, a prognostic score to define the infectious risk has been developed in patients treated with ibrutinib therapy, based on the previous history of pneumonia, ≥ 2 lines of therapy and the presence of chronic obstructive pulmonary disease (COPD).

Aims: This study was aimed at defining the incidence, prognostic impact of infections and the infection risk score in CLL patients treated with IDL-R.

Methods: We included 109 CLL patients who received IDL-R diagnosed and managed in 16 Italian CLL campus centers between 2013 and 2020. All patients were treated with IDL-R. Infectious events considered were bacterial pneumonia (PN), grade ≥ 3, non-opportunistic infections (NOIs) and opportunistic infections (OIs).

Results: The median age of patients was 71 years, Rai stage III-IV was present in 53.2% of patients, unmutated IGHV in 63.3%, and TP53 disruption (del17p, and or TP53 mutation) in 55%. Sixty-one % of patients received ≥ 2 prior treatments; 31.2% of patients had a severe infection in the year before starting IDL-R and 29.4% a COPD. Pneumonia or a severe infectious event was recorded in 44% of patients. Patients who experienced PN or a severe infection showed a significantly inferior overall survival (OS) than those infection-free (p=0.0371). According to the scoring system, 59%, 16% and 26% of patients were included in the low (LRG), intermediate (IRG) and high-risk group (HRG), respectively The score system identified patients with an increasing rate of infections: 30% in the LRG (3% PN, 16% NOI, 11% OI), 41% in the IRG (24% PN, 12% NOI, 6% OI) and 79% in the HGR (54% PN, 14% NOI, 11% OI). The infection rate of patients in the HRG was significantly higher than that of the LRG (p<0.001) and IRG (p=0.023). The 3-year OS from start IDL-R was 66.6%, 58.7% and 42.5% for LRG, IRG and HRG, respectively (p=0.0371).

Summary/conclusion: IDL-R was associated with the development of a relevant number of infectious events, which negatively impacted on the outcome of patients. The infection risk score developed in patients treated with ibrutinib could identify patients who might better benefit from IDL-R therapy.

P025

OUTCOME OF PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA WHO DEVELOPED COVID: CLINICAL IMPACT OF THE SARS-COV2 VACCINE

C. Luise[1], R. Maglione[1], E. Crisanti[1], C. Ielo[1], M. Salvatori[1], S. Ligia[1], F. Malfona[1], S. Pepe[1], G.C. Galluzzo[2], S. Baroncelli[2], D. Giannarelli[3], F.R. Mauro[1]

[1]Hematology, Department of Translational and Precision Medicine, Sapienza University; [2]National Center for Global Health, Istituto Superiore di Sanità; [3]Design and Analysis of Clinical Trials Unit, Scientific Directorate, Fondazione Policlinico Universitario A. Gemelli, Italy

Patients with chronic lymphocytic leukemia (CLL) show variable degrees of humoral and cellular immunodeficiency associated with an increased risk of infections and impaired immune response to vaccines. Several studies described inadequate serologic responses to the SARS-CoV-2 vaccine and high mortality rates in patients with CLL who have been affected by Covid. We carried out a single-center observational study to compare the clinical outcome of patients with CLL who developed Covid before or after receiving the mRNA SARS-CoV2 vaccine. Between February 2020 and March 2022, 80 CLL patients with CLL followed at our institution experienced Covid, 36 (45%) before the introduction of the SARS-CoV2 vaccine and 44 (55%) after vaccination (two doses, 7; three, 37). The median age of patients was 66 years (range, 39-91), and the median IgG level was 710 mg/dl. Fifty-four% of patients were IGHV unmutated, and 14% showed TP53 disruption. Forty patients were treatment-naïve, and 40 were previously treated (chemoimmunotherapy only, 10 patients; ibrutinib–based therapy, 23; venetoclax-based therapy, 7). Twenty-seven (34%) patients had previously received rituximab, 2 (7%) within 12 months before vaccination. No significant differences in the clinical and biologic characteristics of vaccinated and not vaccinated patients were observed, except for a higher proportion of cases with del11q in the vaccinated group. Twenty of the 44 (45%) vaccinated patients who developed Covid had a prior serologic response. As compared to vaccinated patients, not vaccinated required more frequently hospitalization (47% *vs* 30%; p= 0.11), intensive cares (28% *vs* 5%; p= 0.0048) and showed a significantly lower survival after Covid (10-month survival: 83% *vs* 98%; p<0.05). Four of the seven patients who died due to Covid showed progressive disease. After Covid, we observed a serologic response in 21/32 (66%) patients not previously vaccinated and in 6/7 (86%) seronegative after prior vaccination. In conclusion, the emergence of different SARS-CoV-2 strains and, or the decrease in the levels of specific antibodies over time could explain the lack of a protective effect of the vaccine in patients with a prior serologic response. Covid induced a high rate of serologic responses in not vaccinated patients and those seronegative after the previous vaccine. Our results suggest that the SARS-CoV-2 vaccine had a beneficial impact in mitigating the severity and mortality of Covid in CLL patients.

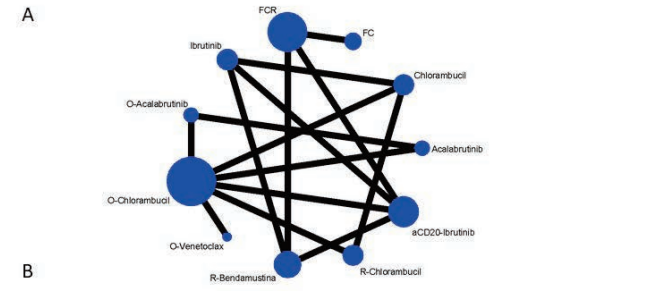
P026

NETWORK META-ANALYSIS OF FIRST LINE TREATMENT FOR CHRONIC LYMPHOCYTIC LEUKEMIA: DO WE STILL NEED CHEMOTHERAPY?

C. Botta[1], A. Rizzuto[1], A. Pirrera[1], E. Gigliotta[1], C. Vullo[1], G. Camarda[1], C. Rotolo[1], A. Roppolo[1], C. Spoto[1], M. Santoro[1], S. Mancuso[1], M. Napolitano[1], M. Gentile[2], S.M. Siragusa[1]

[1]Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties (ProMISE); University of Palermo, Palermo, Italy; [2]Hematology Unit, "Annunziata" Hospital of Cosenza, Cosenza, Italy

The treatment of chronic lymphocytic leukemia (CLL) currently relies on the use of chemo-immunotherapy (bendamustine, chlorambucil, fludarabine in combination with rituximab), Bruton's tyrosine kinase inhibitors (BTKi, ibrutinib or acalabrutinib) or BCL2 inhibitors (venetoclax) alone or combined with an anti-CD20 (aCD20) monoclonal antibody (mAb) (rituximab or obinutuzumab). However, the availability of multiple choices for the first line setting and a lack of direct head-to-head comparisons, pose a challenge for treatment selection. To overcome these limitations, we performed a systematic review and a network meta-analysis (NMA) on published randomized clinical trials performed in the first line treatment setting of CLL. For each study we retrieved data on progression free survival (PFS) (according to del17/P53 and IGHV status), overall response rate (ORR), complete response (CR) and incidence of most frequent grade 3-4 adverse event. We identified 9 clinical trials encompassing 11 different treatments, with a total of 5288 CLL patients evaluated (Figure 1A).



B

	del17/TP53 mutated	del17/TP53 WT	IGHV somatic hypermutation	IGHV germline	CR	ORR	G34AE	mean SUCRA
O-Acalabrutinib	90,9	96,8	99,2	97,5	96,0	81,2	52,2	87,7
aCD20-Ibrutinib	93,6	68,3	79,8	65,8	68,4	55,6	60,1	70,2
Acalabrutinib	62,5	87,0	65,1	85,4	75,6	10,2	99,6	69,3
O-Venetoclax	42,2	81,6	86,4	69,4	82,9	81,3	36,3	68,6
Ibrutinib	78,0	52,8	57,4	78,6	46,1	27,4	85,2	60,8
R-Bendamustina	45,3	36,6	53,0	50,0	21,7	76,2	61,8	49,2
O-Chlorambucil	25,0	48,4	42,0	31,1	62,6	49,2	22,9	40,2
FCR		24,9	35,5	34,6	20,7	83,9	13,5	35,5
R-Chlorambucil	12,5	29,9	17,2	12,9	51,2	27,6	40,1	27,3
FC		20,2	14,0	21,1	5,6	51,3	0,3	18,8
Chlorambucil	0,0	3,6	0,4	3,6	19,2	6,0	78,0	15,8

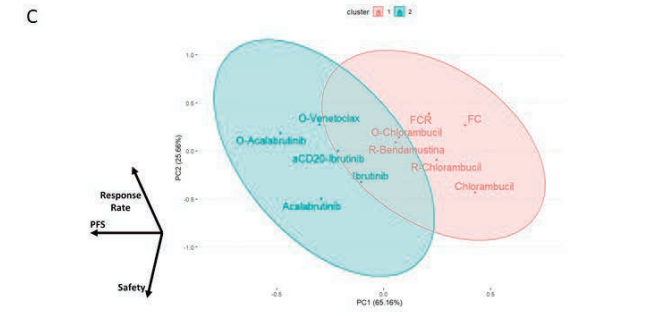


Figure 1.

We systematically performed separated NMAs to evaluate the efficacy/safety of each regimen in the conditions previously described to obtain the surface under the cumulative ranking curve (SUCRA) score, subsequently used to build separated ranking charts (Figure 1B). Interestingly, the combination of obinutuzumab with acalabrutinib (O-acala) reached the top of the chart in each subanalysis performed, with the exception of the del17/P53mut setting, where it was almost on pair with the aCD20 mAbs/ibrutinib combination (SUCRA aCD20-ibrutinib and O-acala: 93.5% and 91%, respectively), and of the safety evaluation, where monotherapies (acalabrutinib in particular) gave better results. Finally, taking into account that NMA and SUCRA work for single endpoints only, we performed a principal component analysis to recapitulate in a cartesian plan the SUCRA profiles of each schedule according to the results obtained in each sub-analysis (Figure 1C), confirming again the superiority of aCD20/BTKi or BCL2i combinations in first line setting. Overall, here we demonstrated that: 1) a chemotherapy-free regimen such as the combination of aCD20 with a BTKi or BCL2i should be the preferred treatment choice despite biological/molecular characteristics (preferred regimen O-acala); 2) there is less and less room for chemotherapy in the first line treatment of CLL.

P027

FAMILIAL CHRONIC LYMPHOCYTIC LEUKAEMIA: ITALIAN MONOCENTRIC EXPERIENCE AS STARTING POINT FOR FUTURE UNDERSTANDING OF PREDICTIVE BIOMARKERS

G. Benintende[1]*, I. Innocenti[2]*, A. Fresa[2], A. Tomasso[1], F. Vuono[1], A. Mosca[1], L. Stirparo[1], F. Autore[2], E. Sangiorgi[3,4], L. Laurenti[5]
*The two authors contributed equally to the study

[1]Sezione di Ematologia, Dipartimento di Scienze Radiologiche ed Ematologiche, Università Cattolica del Sacro Cuore; [2]Sezione di Ematologia, Dipartimento di Diagnostica per Immagini, Radioterapia Oncologica ed Ematologia, Fondazione Policlinico Universitario A. Gemelli IRCCS; [3]Istituto di Medicina Genomica, Università Cattolica del Sacro Cuore; [4]Fondazione Policlinico Universitario A. Gemelli IRCCS; [5]Sezione di Ematologia, Dipartimento di Diagnostica per Immagini, Radioterapia Oncologica ed Ematologia, Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Italy

Background: Chronic lymphocytic leukaemia (CLL) is the most common leukaemia, with a 1.1% incidence in 2021, according to SEER 13, and an 87% 5-years mortality. The median age at diagnosis is 70 years old and it is twice more common for man. Family history of hemopathy is the strongest risk factor for CLL, with first degree relatives having an 8.5-fold increased risk of CLL. Data from the literature report a 14% prevalence of family history of blood disease and a 7% of CLL itself in CLL patients. Some authors described an anticipation phenomenon in second generation patients. Little is known about the biological characteristics of familial CLL compared to sporadic cases.

Aims: Our monocentric experience investigates the epidemiology of familial CLL, the presence of predictive biomarkers and the occurrence of genomic alterations that would predispose relatives to develop such disease.

Methods: Our dataset includes 41 familial cases, defined as patients with a first degree relative affected by CLL, on a total of 471 cases. The clinical and biological characteristics were collected retrospectively from medical records. Statistical analysis was performed by NCSS 2020 software.

Results: In our cohort, the prevalence of familial CLL was 9.4%. 38% patients were males and 62% females, contrarily to sporadic cases. The median age of familial CLL cases at diagnosis was 55 years old, with substantial anticipation compared to literature reports from sporadic cases (70 years old). FISH at diagnosis showed a 5% prevalence of 17p deletion, 24% 13q deletion, 8% 11q deletion and 5% trisomy 12, while 35% patients presented no alteration. IgHV mutational status showed

40% mutated patients and 38% unmutated patients. Regarding molecular alterations, TP53 was mutated in 8% of patients; NOTCH1 was mutated in 22% of patients, a number which is consistently higher than sporadic cases. Familial CLL patients' biological characteristics are in table 1.

Conclusions: Our cohort presented peculiar characteristics, in line with previous observational studies on familial CLL and discordant to literature reports on sporadic cases. Further investigations are needed to clarify the presence of biomarkers, and the study will be extent to more centers. Genome analysis could be a key feature to shade light on pathogenesis and predisposition to CLL in this subgroup of patients.

Table 1. Familial CLL patients' biological characteristics compared to sporadic patients' characteristics.

	Familial CLL in our court	*Sporadic CLL in literature*
Median age at onset	55 years old (38-83)	70 years old
FISH	5% del17p 24% del13q 8% del11q 45% no mutation 18% not done	7% del17p 50% del13q 18% del11q 25% no mutation
IgHV mutational status	40% mutated 38% unmutated 22% not done	68% mutated 32% unmutated
Molecular biology	8% TP53 22% NOTCH1 32% no mutation 38% not done	5-10% TP53 5-10% NOTCH1 80-90% no mutation or others

P028

RETROSPECTIVE STUDY OF THE IMPACT OF CHEMO-IMMUNOTHERAPY AND TARGET THERAPY IN PATIENTS WITH CHRONIC KIDNEY DISEASE AND CHRONIC LYMPHOCYTIC LEUKEMIA

C.M. Rapolla[1], F. Morelli[1], A.M. Vannucchi[2], A. Sanna[3]

[1]Hematology Unit, University of Florence; [2]Center for Innovation and Research in Myeloproliferative Neoplasms, Hematology Unit, Azienda Ospedaliera Universitaria Careggi, University of Florence; [3]Hematology, Department of Oncology, AOU Careggi, Italy

Introduction: Chronic lymphocytic leukemia (CLL) is the most common leukemia in elderly patients and the treatment decision should include an assessment of IGVH and TP53 status as well as comorbidities and patient-related factors. Chemo-immunotherapy (Fludarabine Cyclofosfamide and Rituximab (FCR), bendamustine plus rituximab (BR), chlorambucil plus Obinutuzumab(G)), BTKs inhibitors (ibrutinib, acalabrutinib), BCL-2 inhibitors (venetoclax), PI3K inhibitors (idelalisib) are the possible therapeutic options. The incidence of chronic kidney disease (CKD) is about 15%, and it increases with elderly and comorbidities.

Aim: This study was aimed to evaluate the management of CLL patient with CKD, in particular the impact of therapy on renal function in patients with increased creatinine (>1.2 mg/dl) at the beginning of therapy and the management of patient with immune mediated glomerulopathy (IMG).

Methods: The retrospective study included 47 consecutive CLL patients (43 male; 4 female), treated in Careggi Hospital in Florence between 2014-2021. Two had IMG diagnosticated by biopsy, we also evaluated 3 more patients with IMG without increase of creatinine. Median age of patients was 72 (40-90).

Results: Mean creatinine before treatment was 1.46 mg/dl (1.2-2.46). Patients were treated with FCR (6.4%), oral FCR (2.1%) chlorambucil (8.5%), G-chlorambucil (4.3%), rituximab alone (6.4%), BR (8%) R-CVP (2.1%) or BTKs inhibitors (27.7%), PI3K inhibitors (6.4%) or BCL-2 inhibitors (6.4%). No dose adjustments were made based on renal function. 72% were on first line treatment, 14.9% in second line, 12.8% after the second line. The results show that there is no worsening of renal function after treatment (creatinine before treatment 1.46mg/dl *vs* after treatment 1.49 mg/dl, p=0.34). Five patients with IMG were treated with: 1 oral FCR, 1 FCR, 2 rituximab and 1 BR. 4/5 responded to treatment, mean proteinuria before treatment was 3593 mg/24h (1400-6000), post treatment 996,8 mg/24h (171-3170) ($p<0.05$). The non-responding patient previously treated with rituximab received oral FCR with significant reduction of proteinuria (3170-376).

Conclusion: Our preliminary data showed that active treatment in CLL patients with mild CKD is feasible. Maybe proteinuria should be included in the routinary CLL assessment. In this category of patients, further studies with wider cohorts are needed to confirm them and it could be interesting to analyze the impact of target drugs in this setting.

P029

MANAGEMENT OF MOGAMULIZUMAB TREATMENT IN PATIENTS WITH AGGRESSIVE REFRACTORY SÉZARY SYNDROME AND MYCOSIS FUNGOIDES: A REAL LIFE REPORT

C. Giordano[1], A. Giordano[2], A. Severino[1], A. Cacace[1], I. Conversano[1], G. Donnarumma[1], M. Viscovo[2], L. Pagano[2,3], F. Pane[1]

[1]Department of Clinical Medicine and Surgery, Hematology Unit, Federico II University; [2]Department of Hematology, Fondazione Policlinico Universitario A. Gemelli; [3]Department of Hematology, Fondazione Policlinico Universitario A. Gemelli -IRCCS- Universita Cattolica del Sacro Cuore, Italy

Advanced mycosis fungoides (MF) and Sézary syndrome (SS) are forms of cutaneous T-cell lymphoma (CTCL) characterized by poor prognosis. Mogamulizumab is a defucosylated humanized monoclonal antibody that selectively binds CCR4, highly expressed on malignant T cells, making it an ideal molecule for targeted therapy.

In this single center retrospective case series study we report the efficacy and safety outcome of 4 patients treated in the Hematology Department of Federico II University of Naples and A. Gemelli of Rome. All patients had an aggressive refractory advanced stage CTCL and received a median of 3 (range 2-5) skin-directed/systemic treatments before mogamulizumab (Table 1).

Table 1.

Pt n°	Sex	Age	Disease	DOD	Clinical stage at baseline*	Treatment received before Mogamulizumab	Mogamulizumab infusions total, n	Best Global Response to Moga	Time to global best response (months)	Mogamulizumab-related toxicity
1	M	68	SS	18/08/2020	T4N0M0B1 (IVA1)	bexarotene, MTX, ECP (1st); brentuximab (2nd) and gemcitabine (3rd)	13, on going	CR	1	None
2	M	71	SS	06/02/2020	T3N0M0B1 (IVA1)	brentuximab (1st), gemcitabine (2nd), IFN-MTX (3rd)	11, on going	CR	2	None
3	M	57	MF	08/04/2020	T3N3M0B0 (IVA2)	pegylated liposomal doxorubicin (1st); bexarotene (2nd)	4	SD	1	MAR
4	M	64	MF	14/05/2021	T4N3M0B0 (IVA2)	bexarotene (1st); ECP (2nd)	4, on going	SD	1	MAR

***According to International Society for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task force of the European Organization of Research and Treatment of Cancer (EORTC) Revision 2007. Bexarotene: 300mg/m² orally every day until toxicity or progression; ECP: extracorporeal photoaferesis; MTX: low dose methotrexate s.c injections at 10mg/m² weekly; IFN: pegylated interferon 2a 135 ug s.c injection weekly; brentuximab 1.8 mg/m² e.v for each cycle of 21 days; gemcitabine 1000 mg/m² at day 1, 8 and 15 of 28 days cycle; pegylated liposomal doxorubicin 20 mg/m² e.v for each cycle of 21 days. All patients received intravenous infusions of mogamulizumab at 1.0 mg/kg on the standard 28-day cycle schedule given on days 1, 8, 15 and 22 of the first cycle and then on days 1 and 15 of subsequent cycles. MAR: mogamulizumab associated rash.**

Two male patients of 68 and 71 years received a diagnosis of SS in February 2020 and August 2020, respectively. They both presented erythroderma and hitchy skin lesions and skin biopsies showed dermal lym-

phocytic infiltrate with aberrant phenotype. Blood flow cytometric analysis detected 77% pathologic T-lymphocytes and 55%, respectively, with SS phenotype and positive T-cell receptor ϒ gene rearrangement. Patients achieved a complete remission in the blood compartment since the 3rd infusion of Mogamulizumab and a partial response in the skin since the 6th infusion and for both patients treatment's still on going. No side effects were recorded. In order to reduce the pruritus both patients also received PUVA therapy but in one case was promptly discontinued due to photo-distribution rash while for the other a mild improvement was reported.

The remaining two cases represent two male patients of 57 and 64 years, respectively, with MF. Due to disease progression after treatment with local and systemic treatment, mogamulizumab was started. They both received 4 cycles of treatment resulting in stable disease as best responses, rapidly lost for one patient that after initial improvement progressed at 3 months and he's now being treated with gemcitabine. As adverse events Mogamulizumab related rash (MAR) was reported for both patients qualified as a grade 1-2 skin toxicity under the CTCAE v.5 criteria, but no treatment discontinuation was performed. Additionally, no patients experiencing MAR received parallel treatment with mogamulizumab and MAR-directed therapies (treat-through-strategy).

In our small series we show Mogamulizumab employment in four patients with aggressive SS/MF refractory to multiple lines of treatment and confirm the hypothesis that in patients with SS may achieve a better response with minor toxicity than in MF. In conclusion, mogamulizumab represents a valuable therapy for advanced MF/SS as it can produce prolonged responses, particularly within the peripheral blood.

P030

IMMUNE SEROLOGIC RESPONSE AND COVID IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA AND HYPOGAMMAGLOBULINEMIA

R. Maglione[1], E. Crisanti[1], A. Visentin[2], A.M. Frustaci[3], C. Luise[1], C. Ielo[1], G. Schiaffini[1], S. Pepe[1], M.C. Galluzzo[4], S. Baroncelli[4], A. Tedeschi[3], L. Trentin[2], D. Giannarelli[5], F.R. Mauro[1]

[1]Hematology, Department of Translational and Precision Medicine, Sapienza University; [2]Hematology and Clinical Immunology Unit, Department of Medicine, University of Padua; [3]ASST Grande Ospedale Metropolitano Niguarda; [4]National Center for Global Health, Istituto Superiore di Sanità; [5]. Design and Analysis of Clinical Trials Unit, Scientific Directorate, Fondazione Policlinico Universitario A. Gemelli, Italy

Hypogammaglobulinemia (HGG) was found to be an unfavorable factor in achieving an adequate antibody response to the SARS-CoV-2 vaccine in patients with chronic lymphocytic leukemia (CLL). We carried out a retrospective study to evaluate the serologic response and the outcome of CLL patients with HGG who received the SARS-CoV-2 vaccine. Between March 2021 and April 2022, 49 patients with CLL and IgG levels <550 mg/dl, managed at three Hematology institutions (Rome, Padova, Milan), received the SARS-CoV-2 vaccine. The median age of patients was 72 years (range, 48-89), and the median IgG level before vaccination was 416 mg/dl. Three patients were treatment naïve, and 46 were previously treated (chemoimmunotherapy, 15 patients; ibrutinib-based therapy, 21; venetoclax-based therapy, 10). Thirty-seven patients had been previously treated with rituximab, two within 12 months before vaccination. At the time of vaccination 16 (33%) patients were on subcutaneous immunoglobulins (Igs) replacement and showed at baseline a significantly higher level of lgG than those without an Igs support (393 *vs* 668 mg/dl; p<0.0001). No significant difference in the number of patients who received the third dose of vaccine was observed in the two groups (94% *vs* 81% p=0.31). After vaccination, we recorded adequate levels of anti-SARS-CoV-2 antibodies in a significantly higher proportion of patients on Igs replacement (75% *vs* 42%; p= 0.038). Eight (16%) patients developed Covid. Two patients experienced a second event of Covid. Covid events were recorded in 3/25 (12%) seropositive patients and 5/23 (22%) seronegative patients (p=0.45). A similar proportion of patients with or without Igs support developed Covid (17% vs.15%; p=1). Three of the eight patients with Covid patients were hospitalized while 5 received home cares. All patients recovered. In conclusion, more than half of patients with CLL and HGG developed a serologic response to the SARS-CoV2 vaccine. Although the serological response did not significantly impact on the development of Covid, the favorable outcome of patients suggests a clinical benefit of the SARS-CoV2 vaccine in this patient population. The increased levels of anti-SARS-CoV-2 antibodies detected after vaccination more frequently in patients on Igs replacement could be due to the presence of specific antibodies in the Igs lots obtained from seropositive donors after Covid or vaccination.

P031

IBRUTINIB TREATMENT AND ITS IMPACT ON CIRCULATING IMMUNE CELLS IN CHRONIC LYMPHOCYTIC LEUKEMIA PATIENTS

F. Morelli[1], C.M. Rapolla[1], A.M. Vannucchi[2], A. Sanna[3]

[1]Hematology Unit, University of Florence; [2]Center for Innovation and Research in Myeloproliferative Neoplasms, Hematology Unit, Azienda Ospedaliera Universitaria Careggi, University of Florence; [3]Hematology, Department of Oncology, AOU Careggi, Italy

Background: Chronic lymphocytic leukemia (CLL) is a B-cell malignancy characterized by immune dysregulation, infections represent a cause of mortality and morbidity in CLL patients (pts).Ibrutinib (IBR) is a Bruton's tyrosine kinase inhibitor very effective on CLL, but this treatment is burdened by infective complications especially within the first months of therapy.The decline of infections could suggest that immune competence may be restored by IBR directly or by reductions in CLL burden.

Aims: This monocentric prospective study evaluates immunophenotypic changes in circulating immune cells in CLL pts treated with IBR.We collected peripheral blood samples at baseline,3,6 months of therapy;new samples at 12 and 24 months will be collected.

Material and methods: We collected clinical and biological data of 20 pts treated with IBR in our Centre since January 2021.Multiparametric flow cytometry was used to characterize immune cells.Median age at IBR start was 74(50-84) years and only 3 were female.Nine pts were treatment-naive, 7 patients were on second-line therapy. The other 4 have already received at least 2 previous lines.In particular, 11 pts received a previous chemo-immunotherapy(CIT).

Results: The only correlation between clinical-biological data and an impact on baseline immune cells was found between a previous exposure to CIT and CD3+HLA-DR+cells(median 1x10^9/L *vs* 6x10^9/L in chemo-naïve pts;p=0.025).No differences observed in who have received a chemo-free therapy prior to IBR or based on the previous number of therapy lines.

In Table 1, we report the median values at different timepoints.We observed a statistical difference between baseline and after 6 months as expected for CD19+(p= 0.04).Another difference was found in the decrease of CD3+CD4+count(p=0.04).Also, the CD3+ count was influenced by IBR(p=0.04).The last statistically significant difference was observed in the decrease of NK cells(p=0.04). An infectious complication was observed in 8 pts(40%). In particular 4 pts experienced COVID-19, 4 pneumonia and one single patient experienced both and a complicated urinary tract infection.

Conclusion: These preliminary data shows an early reduction of CD4+T-cell subset, dysfunctional in CLL.NKT cells, that mediate tumor immunosurveillance, at baseline were higher than expected but with IBR they decrease by 59% in 6 months.Further data are needed, but these

could suggest an impact of IBR on immune system that could help on infective complications.

Table 1.

MEDIAN VALUES (x10^9/L)	TIMEPOINTS		
	Baseline	3 months	6 months
WBC (n.v:4-10)	31 (346-5)	30,5 (211-0,3)	11,1 (129,7-5,2)
Lympho (n.v:0,5-5)	25,9 (345-1)	23,6 (200,4-0,1)	6,2 (124-0,8)
Activated T cells: CD3+HLA-DR+ (n.v:0-0,59)	0,4 (2.8-0)	0,2 (2,2-0)	0,3 (0,9-0)
CD4/CD8 ratio (n.v:1-3,5)	1 (6-0,3)	1,4 (6,2-0,6)	1,20 (3,3-0,4)
CD19+ (n.v:0,1-0,5)	21,5 (341-0,1)	36,2 (196,4-0)	4,6 (121,8-0)
CD3+CD4+ (n.v:0,6-2)	1 (3,1-0,3)	0,9 (6,5-0,3)	0,76 (1,3-0,3)
CD3+ (n.v:0,57-2,8)	1,7 (7,5-0,4)	2,3 (10,2-0,7)	1,55 (2,3-0,4)
LAK cells: CD3+CD16+CD56+	0,2 (1,5-0)	0,02 (0,5-0)	0,08 (0,9-0)
NK cells: CD3-CD16+CD56+ (n.v: 0,2-0,4)	0,5 (1,3-0)	0,38 (1-0)	0,02 (0,1-0)

P032

FREQUENCY OF CLL # SUBSETS IN CHRONIC LYMPHATIC LEUKEMIA (CLL): CORRELATION BETWEEN NOTCH1 AND SUBSET IN SOMATIC MUTATION ANALYSIS OF SARDINIAN PEOPLE

F. Culurgioni, R. Murru, S. Lilliu, S. Uda, C. Musiu, E. Desogus, R. Vacca, N. Piras, M. Orrù, G. Caocci, G. La Nasa

S.C. Ematologia e CTMO, Ospedale Oncologico "A. Businco", ARNAS "G, Brotzu" Cagliari, Italy

Introduction: Chronic Lymphocytic Leukemia(CLL) is a chronic B-cell malignancy. Recent studies have revelated recurrent mutations for NOTCH1 and others genes specially in patients with poor prognosis. CLL subsets expressing stereotyped share clinical and biological features, CLL patients associated at subset CLL#1 unmutaded and IGHV1/5/7, subset 2#is associated at variable mutational status, at subset CLL#8 is associated IGHV4-39 and unmutated profile show poor prognosis. These profile are associated ad immune signaling gene expression and variable frequency of del(11q) and high frequency of trisomy 12.

Aim of study: CLL case at starting on Sardinian people, correlation between subset# in IGHV families mutated and unmutated type and NOTCH1 mutations.

Materials and methods: Patients and subsets :We have studied 166 patients at starting of CLL, in S. C. Ematologia of Cancer Hospital of Cagliari, all DNA samples are evaluated from 2016 to 2022. All patients was came from centre and south Sardinia. Detections methods: Polymerase chain reactions amplifications for NOTCH1 and PCR and Sanger sequencing analysis were performed for to evaluate IGHV somatic mutational status. For IGHV analysis we wave followed the indications of ERIC operative protocol of which our molecular laboratory is insert. For subset# analysis Arrest tools were used.

Results: In 166 patients inserted in the study, (10,24%) have display the subset CLL# expression. In summary, the frequency of type of subset# show: the 52,9% were CLL#1 unmuted, 11,76% CLL#6 unmutated, 11,76% CLL#4 mutated, 5,8% CLL#7 unmutated, 5,8% CLL#64b unmutated and 5,8% CLL#8 unmutated. The frequency of all CLL subset was more too in relations at normal frequency by Arrest tools. The analysis of mutations of NOTCH1 were found in 7 patients with subsets. In the two subset CLL # 1 and CLL # 8 was associated one remarkably higher frequency mutations as in 33.3% and 100% of NOTCH1, indicating a role in increased risk and a poor prognosis progression. The analysis, by NGS methodology, on panels with 32 customized genes already in use in our laboratory could reveal further gene associations and involvements within these subset.

P033

EFFICACY OF MOGAMULIZUMAB IN INDOLENT CUTANEOUS T CELL LYMPHOMA

G. Cetani, S. Iaccarino, A. Camera, M. Troiano, G. Farina, G. Monaco, R. Bianco, F. Frigeri

UOC Ematologia AORN Sant'Anna e San Sebastiano, Italy

Mogamulizumab is approved for the treatment of relapsed/refractory Micosis Fungoides (MF) or Sézary Syndrome (SS) following at least one prior systemic therapy. Here we report our experience on treating two patients with cutaneous T cell lymphoma (CTCL) with mogamulizumab.

Case 1. A 70-year-old man presented with a 5-year history of refractory poikiloderma and skin plaques. Consecutive skin biopses showed dermal T lymphocytic infiltrate with aberrant phenotype and epidermotropism with focal Pautrier abscesses. Peripheral blood flow citometry didn't show pathologic T-lymphocytes (TL) with SS phenotype, total body CT scan was negative for lymphoadenopathies. He was diagnosed as stage IIB MF. The patient failed previous therapies with steroid, PUVA and low doses of cyclophosphamide. On December 2021 disease progression occurred with several skin lesions and a big ulcer on the left leg. Due to severe neurologic comorbidities, Mogamulizumab was started in January 2021 with quickly improvement of the skin lesions. No adverse events were observed, therefore patient is still on treatment.

Case 2. In February 2020, a 63-year-old man presented with pruritus and an inguinal lymphoadenopathy. A previous history of Hodgkin Lymphoma diagnosed and treated four years before in another institute was present. Peripheral blood flow cytometry detected 50% of pathological TL CD3- CD5+ CD7+ CD2+ and CD8+ with a clonal TCR rearrangement. A new lymph node biopsy and a histological review of the previous ones were consistent for indolent T lymphoma with the same clonal TCR rearrangement found on peripheral blood TL. In August 2020 pruritus worsened and discoid plaques occurred. Skin biopsy showed a dermal T mature lymphocytic infiltrate. Patient was treated with PUVA and six cycles of gemcitabine, achieving only a partial response. One year later cutaneous progression occurred and mogamulizumab was started. Skin lesions progressively improved and a metabolic response by PET scan was obtained after 6 cycles; treatment is still ongoing. The only side effect observed was a transient increase of transaminase levels during the first cycle without interference on schedule treatment. In our experience mogamulizumab is effective and safe not only in MF/SS but also in unspecified CTCL. It could represent a manageable alternative to chemotherapy, particularly in patients already chemo-exposed or with comorbidities, although further investigations would be desirable.

P034

LONG LASTING SARS-COV2 INFECTION WITH POST-COVID-19 SYNDROME IN TWO PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA: EMERGING THERAPEUTIC ROLE OF CASIRIVIMAB/IMDEVIMAB

L. Ballotta[1,2], O. Simonetti[3], P. D'Agaro[1,4], L. Segat[4], R. Koncan[1,4], P.M. Orellana[5], F. Dattola[5], E. Orsini[5], A. Marcello[5], S. Dal Monego[6], D. Licastro[6], A. Misin[3], S. Mohamed[2], E. Sbisà[2], E. Lucchini[2], G.M. De Sabbata[2], R. Luzzati[1,3], F. Zaja[1,2]

[1]Dipartimento Clinico di Scienze Mediche, Chirurgiche e della Salute, Università degli Studi di Trieste; [2]SC Ematologia, Azienda Sanitaria Universitaria Giuliano Isontina; [3]SC Malattie Infettive, Azienda Sanitaria Universitaria Giuliano Isontina; [4]UCO Igiene e Sanità Pubblica, Azienda Sanitaria Universitaria Integrata Giuliano Isontina; [5]Laboratory of Molecular Virology - International Centre for Genetic Engineering and Biotechnology (ICGEB) - AREA Science Park; [6]AREA Science Park, Italy

Introduction: Although most of patients affected by Coronavirus disease 2019 (COVID-19) fully recover within a few weeks, up-to 76% may develop long COVID. Long COVID includes a post-acute syndrome defined by the presence of non-specific symptoms 4-12 weeks after the onset of the acute phase. Patients with chronic lymphocytic leukemia (CLL) represent a high-risk population for COVID-19 with a risk of death of 31%. Moreover, the response to SARS-CoV-2 vaccination is often absent or inadequate. The introduction of monoclonal antibodies (Mabs) in the treatment landscape of COVID-19 allowed to reduce hospitalization and mortality in mild-moderate SARS-CoV-2 infection, but limited data are available in hematological patients. We here report the effective use of Casirivimab/Imdevimab (CI) in the treatment of two CLL patients with persistent infection and post-COVID-19 syndrome.

Methods: Clinical and biological data from two CLL patients with persistent SARS-CoV-2 positivity after COVID-19 were collected. Full-genome sequencing of viral RNA from nasopharyngeal swabs was performed at the time of COVID-19 diagnosis and before the administration of CI. We also evaluated SARS-CoV-2 antibodies titles before and after the infusion of Mabs (IgG chemiluminescent immunoassay for IgG antibodies anti-trimeric spike glycoprotein and chemiluminescent microparticle immunoassay for IgG antibodies directed against the receptor-binding domain (RBD) of the spike protein).

Results: Both patients experienced persistent SARS-CoV-2 infection with no seroconversion for 8 and 7 months respectively, associated with long COVID symptoms. Patient #1 had a history of untreated CLL with severe hypogammaglobulinemia and was not vaccinated for SARS-CoV-2. Patient #2 had a history of previously treated CLL, he already received 2 doses of SARS-CoV-2 vaccine and at the time of COVID-19 he was on ibrutinib therapy. In both cases after the infusion of CI we observed a rapid negativization of the nasal swabs, the resolution of long COVID and the development of either IgG against trimeric spike protein and RBD. The analysis of viral genome in the period elapsed from the time of COVID-19 diagnosis and the administration of Mabs showed the development of new mutations, especially in the S gene, with a non synonymous/synonymous mutations ratio of 13/6 and 7/3 respectively.

Conclusion: The effects observed in these 2 patients appeared strongly related with passive immunity conferred by CI treatment permitting SARS-CoV-2 clearance and resolution of long-COVID symptoms. The genome variations observed during time suggest a role of persistent SARS-CoV-2 infection as a possible source for the development of viral variants

P035

STARVING IDIOPATHIC MULTICENTRIC CASTLEMAN DISEASE WITH SILTUXIMAB: A CASE REPORT

G. Cetani, S. Iaccarino, A. Camera, G. Farina, G. Monaco, M. Iovine, F. Frigeri

UOC Ematologia AORN Sant'Anna e San Sebastiano, Italy

Human herpes virus-8/human immunodeficiency virus negative idiopathic multicentric Castleman disease (iMCD) is a rare and potentially life-threatening lymphoproliferative disorder nursed by pro-inflammatory cytokines, especially Interleukin-6 (IL-6). Clinical presentation could be insidious, diagnosis and management are challenging. Actually, first line therapy goal is blocking IL-6 pathway.

We diagnosed iMCD in a 76-year-old male who came in our hospital with a previous generic diagnosis of myelodisplastic syndrome made by another institute. A previous treatment with weekly 80 000 UI epoetin and low doses of steroid was uneffective and followed by quick worsening of symptoms. At time of our observation patient presented fatigue, fever, weight loss, skin nodules, lymphoadenopathies, splenomegaly and needed blood transfusions. Laboratory tests showed high levels of erythrocyte sedimentation rate (ESR), ferritin, C-reactive protein (CRP) and polyclonal hypergammaglobulinemia. Active infections were escluded, HIV test was also negative. A whole-body positron emission tomography/computed tomography (PET-TC) confirmed enlarged hypermetabolic lymphadenopathies. An axillary lymph node was sampled and histology was consistent with Castleman disease, plasma cell type, HHV-8 negative. Bone marrow biopsy excluded myelodisplastic syndrome while skin nodule biopsy evidenced a leukocytoclastic vasculitis. In December 2021 siltuximab was started at 11 mg/kg every 3 weeks. Flu-like symptoms promptly solved, ESR and CRP levels slowly recovered while epoietin response was gradually restored and anemia improved, achieving an hemoglobin value of 11,8 gr/dl. After four cycles, patient achieved a clinical improvement with disappearance of lymphoadenopathies and a PET-TC scan has been planned. Notably transient skin nodules are still occurring especially during the third week of each cycle and disappear after siltuximab infusion. The patient is presently receiving siltuximab. In our hands siltuximab is safe and very effective but further efforts should be done in order to improve the diagnosis of iMCD that is a frequent mimic disease with heterogeneous clinical scenarios.

Acute leukemias

P036

VENETOCLAX PLUS AZACITIDINE AS BRIDGE-TO TRANSPLANT STRATEGY FOR *NPM1*-MUTATED ACUTE MYELOID LEUKEMIA IN MOLECULAR FAILURE

C. Sartor[1], L. Brunetti[2], L. Zannoni[1], G. Cristiano[1], J. Nanni[1], E. Ottaviani[3], L. Bandini[1], S. Parisi[3], S. Paolini[3], S. Sciabolacci[4], V. Cardinali[4], C. Papayannidis[3], M. Cavo[1,3], M.P. Martelli[4], A. Curti[3]

[1]Istituto di Ematologia "Seràgnoli", Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale, Università degli Studi di Bologna; [2]Clinica di Ematologia, Azienda Ospedaliero-Universitaria Ospedali Riuniti, Ancona; [3]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli" Bologna; [4]Institute of Hematology, Centro Ricerche Emato-Oncologiche, Ospedale S. Maria della Misericordia, University of Perugia, Italy

In *NPM1*-mutated AML, *NPM1*^{mut} transcript persistence, reoccurrence or progression identifies poor chemotherapy responders to allocate to alloSCT. The proper bridging strategy to alloSCT for patients (pts) in molecular failure after intensive chemotherapy still needs to be defined.

We explored the off-label combination of Venetoclax (VEN) and Azacitidine (AZA) in 7 *NPM1*^{mut} fit AML pts in molecular failure eligible for alloSCT. Six of 7 patients had ELN2017 low-risk AML (1 pt with concomitant *FLT3*-ITD^{low}, 1 with *FLT3*-TKD) and 1 pt had intermediate-risk AML (*FLT3*-ITD^{high}). Median age at diagnosis was 56 years (range 41-66) and 58 years (range 43-68) at VEN-AZA therapy. Pts received in median 4 (range 3-5) cycles of 1st line chemotherapy. Five pts were treated for molecular relapse and 2 for molecular persistence/progression. All pts received full VEN dosage (400 mg/die) and AZA 75 mg/m^2/die s.c. in 5- or 7-day schedule. Pts received a median of 4 cycles (range 2-4). No AZA dose reduction occurred. Median VEN duration during cycle (C)1 was 25 days (range 14-28), 21 days (range 7-28) in C2, 28 days (range 7-28) in C3 and 25.5 days (range 19-28) in C4. VEN dosage reductions were due to neutropenia ≥ G3 in 50% of cases and in 50% for logistic reasons.

Best response to VEN-AZA was CR MRD$_{neg}$ (*NPM1*^{mut} undetectable) in 6/7 (86%) pts, reached after a median of 2 cycles (range 1-4). No pts relapsed ongoing therapy; 1 pt, notably the *FLT3*-ITD^{high} pt, in CR MRD-$_{pos}$ presented molecular progression after C3.

Median time from VEN-AZA start to alloSCT was 4.3 months (range 3.2-8.1). At pre-transplant evaluation 5/7 (71%) pts were in CR MRD$_{neg}$. CR MRD$_{pos}$ pts had *NPM1*^{mut}/*ABL*x100 transcript of 3,0067 and 0,0107. The observed ≥G3 toxicities were neutropenia in 4/7 (57%) and 1 febrile neutropenia, managed out-patient. No TLS was observed. With a median follow-up from alloSCT of 9.3 months (range 8.0-24.0) all patients are alive in CR MRD$_{neg}$. Three pts presented *NPM1*^{mut} positivity after alloSCT: in 2 pts CsA tapering achieved molecular negativity, while the pt in molecular progression pre-alloSCT underwent prophylactic therapy with sorafenib.

In conclusion VEN-AZA demonstrated to be a safe and effective bridging regimen for *NPM1*^{mut} AML pts in molecular failure, allowing to achieve deep responses in the majority of pts with low toxicity. These preliminary encouraging results of VEN-AZA combination will be explored in the GIMEMA AML2521 trial in the same pt subset (NCT04867928).

P037

HEMATOLOGICAL DISORDERS AFTER SALVAGE PARPI TREATMENT FOR OVARIAN CANCER: CYTOGENETIC AND MOLECULAR DEFECTS AND CLINICAL OUTCOMES

E. Todisco[1,2]*, F. Gigli[1], C. Ronchini[3], V. Amato[1], S. Sammassimo[1], R. Pastano[1], G. Parma[4], M.T. Lapresa[4], F. Bertolini[5], C. Corsini[5], G. Gregato[5], C. Poletti[5], P.G. Pelicci[6,7], M. Alcalay[6,7], N. Colombo[4,8], C. Tarella[1,9]

[1]Onco-Hematology Division, IEO, European Institute of Oncology IRCCS, Milan, Italy; [2]Ospedale di Busto Arsizio, ASST Valle Olona, Busto Arsizio (VA), Italy; [3]Laboratory of Clinical Genomics, IEO, European Institute of Oncology IRCCS, Milan, Italy; [4]Department of Gynecology, IEO, European Institute of Oncology IRCCS, Milan, Italy; [5]Laboratory of Hematology-Oncology, IEO, European Institute of Oncology IRCCS, Milan, Italy; [6]Department of Experimental Oncology, European Institute of Oncology IRCCS, Milan, Italy; [7]Department of Oncology and Hemato-Oncology, University of Milan, Milan, Italy; [8]Gynecologic Cancer Program, European Institute of Oncology IRCCS and University of Milan-Bicocca, Milan, Italy; [9]Department of Health Sciences, University of Milan, Milan, Italy

Inhibitors of poly (ADP-ribose) polymerase (PARPi) are increasingly employed as salvage therapy in epithelial ovarian cancer (EOC), but cytotoxic drug exposure along with PARP inhibition may favor the development of hematological disorders. In this study, of 182 women with EOC treated with salvage PARPi, 16 (8.7%) developed therapy-related myeloid neoplasms (t-MNs), with 12 cases of myelodysplasia and 4 of acute myeloid leukemia. All experienced persistent cytopenia after PARPi discontinuation. Seven patients had a del(5q)/-5 and/or del(7q)/-7, nine had a complex karyotype, and TP53 mutations, recently reported as risk factor for t-MNs in EOC post-PARPi, were found in 12 out of 13 tested patients. Four patients had a rapid and fatal outcome, one had stable disease, and 11 underwent induction therapy, followed by allogeneic hematopoietic cell transplantation in seven. Three of these eleven patients experienced refractory disease, and eight had complete remission. During a median observation time of 6.8 months (range 2.3-49), 3 out of 16 patients were alive, with one surviving patient free of both solid and hematological tumors. Ten patients died because of leukemia, two because of transplant-related events, and one from heart failure.

Five more patients experienced persistent cell blood count abnormalities following PARPi discontinuation, without reaching MDS diagnostic criteria. A customized Myelo-panel able to analyze 255 cancer-predisposing, (including MDS/AML susceptibility genes, AML drivers and actionable genes, for which US FDA-approved or clinical trial drug is available) showed clonal hematopoiesis in all five patients (Table 1).

Table 1. Germline and somatic mutations identified in patients with persistent cytopenia and clonal hematopoiesis by analysis with the custom Myelo panel.

	GERMLINE MUTATIONS*					SOMATIC MUTATIONS*					
ID	Gene	Type	VAF (%)	AA substitution	Variant annotation$	Gene	Type	VAF (%)	AA substitution	Variant annotation$	Gene classification&
1	BRCA1	INDEL	51.4	p.Leu1679TyrfsTer2	Pathogenic	IGFN1	SNV	17.9	p.Gly1565Asp	VUS	AML Driver
						NBEAL2	SNV	3.1	p.Leu1093Val	VUS	AML Driver
						TP53	SNV	7.2	p.Cys238Tyr	Pathogenic	AML Driver/Susceptibility
2	BRCA1	INDEL	51.6	p.Asn363IlefsTer11	Pathogenic	EPHA4	SNV	2.5	p.Cys191Arg	VUS	Actionable
						TP53	SNV	4.8	p.Cys176Ser	Pathogenic	AML Driver/Susceptibility
3	NONE					GNA11	SNV	3.2	p.Leu40Phe	Likely pathogenic	Actionable
4	BCR	INDEL	56.8	p.Lys754AsnfsTer34	Pathogenic	EPHB2	SNV	52.9	p.Gln626Arg	Likely pathogenic	Actionable
						NOTCH1	SNV	40.5	p.Thr2090Met	VUS	Actionable
						SLTM	SNV	52.2	p.Gln54Arg	Likely pathogenic	Actionable
						BRCA1	SNV	45.3	p.Arg1495Met	Pathogenic	Susceptibility/Actionable
5	NONE					NOTCH1	SNV	3.2	p.Asn104Thr	VUS	Actionable

$Annotation of variants for pathogenicity by ClinVar, Varsome, RENOVO. &Gene classification based on our gene lists in the customized Myelo panel; for definitions, see Methods section: Hematological and molecular investigations. *Next generation sequencing analysis using custom Myelo panel and the Ion Torrent S5 technology (ThermoFisher) VAF: variant allele frequency; INDEL: insertion/deletion; AA: aminoacidic; SNV: single nucleotide variant; VUS: variant of uncertain significance; AML: acute myeloid leukemia.

In this view, a prospective biological study is ongoing among the gynecological, hematological, and molecular research units at our center, aimed at identifying possible genetic abnormalities, associated with an increased risk for t-MNs after PARPi treatment, including mutations analysis in genes involved in CHIP.

In summary, our study confirms the actual risk of t-MN in EOC patients treated with chemotherapy and subsequently exposed to prolonged PARPi therapy. The management of these patients is quite complex, and the outcome is extremely poor. In this context, a preventive approach based on the identification of gene mutations that may raise risk for t-MNs and "actionable" gene mutations is warranted and could be crucial for protecting these women from a second devastating and often incurable neoplasm. Interesting preliminary data of the ongoing biological study may be available for SIE meeting.

P038

VENETOCLAX PLUS DECITABINE IN NEWLY DIAGNOSIS AND RELAPSED/REFRACTORY ACUTE MYELOID LEUKEMIA: A REAL LIFE EXPERIENCE OF APULIAN HEMATOLOGICAL NETWORK

V. Federico[1], R. Matera[1], A.M. Carella[2], D. Pastore[3], P. Musto[4], A. Guarini[5], G. Tarantino[6], L. Melillo[7], P. Mazza[8], V. Pavone[9], C. Daniela[1], C. Vergine[1], M. Dargenio[1], A. Messa[1], M. Abbenante[2], M. Urbano[3], M. Delia[4], C. Pasciolla[5], C. De Fazio[5], C. Buchicchio[6], L. Ciuffreda[7], A.M. Mazzone[8], E. Preite[9], G. Greco[9], D. Seripa[1], N. Di Renzo[1]

[1]Haematology "Vito Fazzi" Hospital; [2]Haematology "Casa Sollievo della sofferenza" Hospital; [3]Haematology "A. Perrino" Hospital; [4]Haematology "Policlinico" Hospital; [5]Haematology "IRCCS Oncologico" Hospital; [6]Haematology "Mons. Dimiccoli" Hospital; [7]Haematology "Riuniti" Hospital; [8]Haematology "Moscati" Hospital; [9]Haematology "Cardinale Panico" Hospital, Italy

Background: Venetoclax-Hypomethylating combination represent a significant progress in the treatment of both newly diagnosis (ND) and relapsed/refractory (R/R)-AML. Here we report the outcome of patients (pts) with ND-AML or R/R-AML treated with Venetoclax-Decitabina combination (VEN-DEC) aimed to evaluate efficacy and safety of this combination in a real-life experience of 9 haematological Apulian centers.

Method: From May 2018 to January 2022, 103 patients (Pts), 58 with ND-AML and 45 with R/R AML, median age 70 years (range: 23-84) have been included in this analysis. Twenty-five (56%) and 20 (44%) of R/R pts received VEN-DEC as second or more line of treatment respectively. All but one of pts treated in second line received AML-like regimens as induction therapy while 11 (24%) have been previously undergone to Allo-BMT. After rum-up, all pts received Venetoclax at median dose of 100 mg/daily orally (range: 100-400) combined with decitabine 20 mg/m^2 days 1-5 in 28-day cycle. All pts received a median of 3 cycles (range: 1-20) of VEN-DEC.

Results: Clinical characteristic of patients are shown in Table 1. CR + CRi rate was 62% and 45% for ND- and R/R-AML, respectively. In both groups, the median time to response was 2 months (range: 1-5). Twenty-seven (26%) of pts become eligible for Allo-BMT after VEN-DEC (clinical characteristic in Table 1). After a median follow-up of 14 months (range: 2-38), 45 (44%) pts are alive, 28 out of 58 (48%) ND-AML and 17 out of 45 (38%) R/R-AML pts, including 20 pts (20%) still on therapy and in CR. Fifty-eight pts (56%) are died, 48 of progressive disease and 10 because of sepsis while in CRi. Grade 3/4 hematological toxicity was observed in 68% of pts while 35% experienced non-hematological toxicity (fever in neutropenia 35%, sepsis 26% and clostridium enterocolitis in 2%). Considering the whole population, including transplanted pts, there was no statistically significant difference in estimate median OS between ND-AML *vs* R/R AML (14 months *vs* 9 months; p=0.4) while a significant statistical differences has been observed when were analysed the overall survival of non transplanted patients (9.0 *vs* 4.0 months; p=0.007).

Conclusion: These real life data show how the combination Venetoclax and Decitabine is safe and effective and should be considered as salvage therapy in patients failing AML-like induction therapy as well as induction treatment in those with poor performance status at diagnosis.

	NEWLY DIAGNOSIS-AML	RELAPSE/ REFRACTORY-AML	BRIDGE TO ALLO-TMO
N° patients	58	45	27
Median age (range)	71 (41-81)	68 (23-84)	57 (23-72)
Sex:			
• Male	33 (59%)	31 (73%)	17 (63%)
• Female	25 (41%)	12 (27%)	10 (37%)
AML type:			
• De novo	33 (56%)	32 (73%)	17 (63%)
• Secondary	24 (42%)	11 (27%)	10 (37%)
▪ MDS	16 (28%)	11 (27%)	9 (53%)
▪ SMP	8 (14%)	0 (0%)	1 (4%)
• Therapy related	1 (2%)	0 (0%)	0 (0%)
2017 ELN risk stratification by genetics:			
• Favorable risk	4 (7%)	9 (19%)	2 (7%)
• Intermediate risk	20 (32%)	15 (37%)	11 (40%)
• Poor risk	34 (61%)	19 (44%)	14 (53%)
NMP1 status			
• WT	32 (53%)	22 (49%)	24 (88%)
• Mutated	5 (9%)	3 (7%)	1 (4%)
• Not Evaluated	21 (38%)	18 (44%)	2 (8%)
FLT3 ITD/TKD status			
• WT	32 (53%)	25 (56%)	21 (77%)
• Mutated	11 (20%)	4 (10)	2 (7%)
• Not Evaluated	15 (27%)	14 (34%)	4 (16%)
Venetoclax line:			
• First Line	58 (100%)	-	11 (40%)
• Second Line	-	25 (56%)	13 (48%)
• ≥ Third Line	-	20 (44%)	3 (11%)
Prior allogenic SCT	-	11 (24%)	3 (11%)

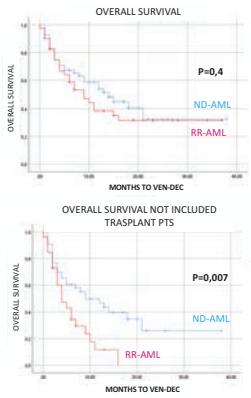


Figure 1. Clinical characteristic of patients.

P039

CPX-351 TREATMENT IN REAL LIFE: RESULTS OF A MULTICENTRE RETROSPECTIVE STUDY

L. Fianchi[1], F. Guolo[2], F. Marchesi[3], M. Bonanni[1], C. Cattaneo[4], M. Gottardi [5], F. Restuccia[6], A. Candoni[7], E. Ortu La Barbera[8], R. Fazzi[9], C. Pasciolla[10], O. Finizio[11], N. Fracchiolla[12], M. Delia[13], F. Lessi[14], M. Dargenio[15], V. Bonuomo[16], M.I. Del Principe[17], P. Zappasodi[18], M. Picardi[19], C. Basilico[20], M. Piedimonte[21], P. Minetto[22], M. Criscuolo[1], G. Dragonetti[1], A. Giordano[1], P. Chiusolo[1], L. Prezioso[23], C. Buquicchio[24], L. Melillo[25] , D. Zama[26], F. Farina[27], V. Mancini[28], I. Terrenato[29], M. Rondoni[30], A. Busca[31], L. Pagano[1]

[1]Dipartimento di Diagnostica per Immagini, Radioterapia Oncologica ed Ematologia, Fondazione Policlinico Universitario A. Gemelli, IRCCS- Università Cattolica del Sacro Cuore; [2]IRCCS Ospedale Policlinico San Martino; [3]IRCCS Istituto Nazionale Tumori Regina Elena; [4]SC Ematologia e Dipartimento di Oncologia Clinica, A.O. Spedali Civili; [5]Ospedale Ca' Foncello; [6]UO Ematologia, Ospedale Civile; [7]Clinica Ematologica, Azienda Sanitaria Universitaria Friuli Centrale, ASUFC; [8]UOC Ematologia con Trapianto Santa Maria Goretti; [9]Hematology Unit - A.O.U.P. Ospedale Santa Chiara; [10]Haematology Unit, IRCCS Istituto Tumori "Giovanni Paolo II"; [11]AORN Cardarelli, Napoli; [12]Fondazione IRCCS Cà Granda-Ospedale Maggiore Policlinico; [13]Azienda Ospedaliero-Universitaria Consorziale Policlinico; [14]Ematologia e Immunologia , Clinica Azienda Ospedaliera; [15]UO Ematologia e Trapianto CSE V. Fazzi; [16]UOC Ematologia, Policlinico Borgo Roma; [17]Dipartimento di Biomedicina e Prevenzione , Università degli studi "Tor Vergata"; [18]Fondazione IRCCS Policlinico San Matteo; [19]Ematologia, AOU Federico II; [20]Azienda Socio Sanitaria Territoriale dei Sette Laghi; [21]Ematologia AOU Sant'Andrea; [22]Ematologia e Trapianto, IRCCS Ospedale Policlinico San Martino; [23]Ematologia e centro trapianti midollo osseo, AOU; [24]Sc ematologia con trapianto, Ospedale Dimiccoli; [25]Ematologia, Ospedale Casa Sollievo della Sofferenza; [26]Policlinico Sant'Orsola Malpighi; [27]U.O. Ematologia e Trapianto Midollo, Dipartimento di Oncologia, Istituto Scientifico San Raffaele; [28]Divisione di Ematologia, Ospedale Niguarda; [29]UOSD Clinical Trial Center e Biostatistica e Bioinformatica, IRCCS Istituto Nazionale Tumori Regina Elena; [30]U.O.C. di Ematologia, Azienda Unità Sanitaria Locale della Romagna; [31]Dipartimento di Oncologia ed Ematologia

SSCVD Trapianto allogenico di Cellule Staminali , A.O. Città della Salute e della Scienza P.O. Molinette, Italy

Background: CPX-351 has been approved for the treatment of adults with newly diagnosed therapy-related AML (t-AML) or AML with myelodysplasia-related changes (AML-MRC)

Aim and methods: To investigate the efficacy and toxicities of CPX-351 in real life, we analysed 199 patients (pts) (M/F 103/96 median age 65 years, range 18-80) treated in 30 Italian hematological centres for t-AML (26.5%), AML-MRC (39%) and secondary AML (sAML,34.5%) after a previous myelodysplastic syndrome. Forty pts (20%) had previously received a median of 8 cycles (range 1-36) of hypomethylating agent (HMA).

Results: All 199 pts received the first induction, 18 pts (9%) received a second CPX induction, whereas 86 pts (43%) proceeded with the first CPX-351 consolidation with 32 (16%) of them receiving also the second consolidation course. The overall response rate (ORR) was 69%: CR/CRi in 122/199 pts (61%), PR in 16/199 (8%), and NR in 49/199 (25%). A significantly lower ORR was observed among pts previously treated with HMA (p 0.011). All pts developed a grade III/IV hematologic toxicity after induction. Febrile events occurred in 176/199 (88%) pts during induction, defined after a diagnostic work-up as febrile neutropenia of unknown origin (FUO) in 60 cases (30%), microbiologically or clinically documented infection in 87 (44%) and 29 cases respectively (15%). Early death occurred in 11% of pts due to infection in 5.5% of cases. Eighty-eight pts (44%) underwent allogeneic hematopoietic cell transplantation (HSCT). The median overall survival (OS) was 17 months 95% CI (14.2-19.8) (Figure 1). Interestingly estimated OS was significantly shorter in patients with s-AML (11 months) *vs* t-AML (21 months) and AML-MRC (23 months) (p 0.004). Worse OS was observed comparing pts previously treated with HMA (10.07 months) *vs* no HMA-pretreated pts (19.07 months) [p 0.0031, 95% CI (0.32-0.9)]. In multivariate analysis, age as a continuous variable (p<0.001), s-AML *vs* t-AML (p-0.025) or AML-MRC diagnosis (p 0.002), no response to CPX-351 treatment (p<0.001) were associated with lower OS. HSCT was instead associated with significantly better outcomes: in pts who underwent HSCT median OS was not reached versus 8.56 months of not-transplanted pts (p<0.0001, 95%CI (2.73-6.05).

Conclusions: These real-world data confirm CPX-351 as an efficient treatment, particularly for t-AML and AML-MRC pts not previously treated with HMA. HSCT after CPX significantly improve prognosis of these high-risk AML pts.

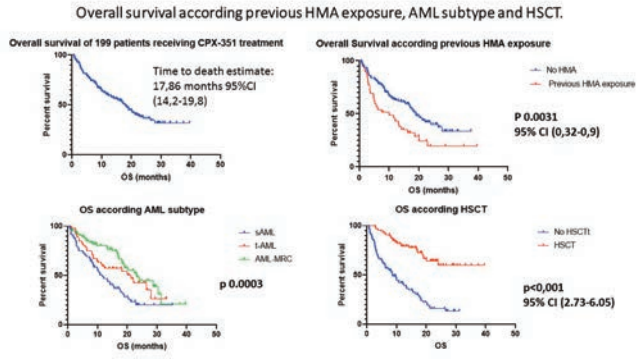


Figure 1.

P040

IDENTIFICATION OF PREDICTIVE FACTORS FOR OVERALL SURVIVAL AND RESPONSE DURING HYPOMETHYLATING TREATMENT IN VERY ELDERLY (≥75 YEARS) ACUTE MYELOID LEUKEMIA PATIENTS: A MULTICENTER REAL-LIFE EXPERIENCE

M. Molica[1], P. Niscola[1], C. Mazzone[1], I. Carmosino[2], A. Di Veroli[3], C. De Gregoris[3], F. Bonanni[4], S. Perrone[5], N. Cenfra[5], L. Fianchi[6], A.L. Piccioni[7], A. Spadea[8], G. Luzi[9], A. Mengarelli[8], L. Cudillo[7], L. Maurillo[4], L. Pagano[6], M. Breccia[2], L. Rigacci[9], P. de Fabritiis[1,4]

[1]Hematology and Stem Cell Transplant Unit, St. Eugenio Hospital; [2]Hematology, Department of Translational and Precision Medicine, Policlinico Umberto I, Sapienza University; [3]Hematology Division, Ospedale Belcolle; [4]Hematology, Department of Biomedicine and Prevention, University Tor Vergata; [5]Hematology, Polo Universitario Pontino, S.M. Goretti Hospital; [6]Institute of Hematology, Fondazione Policlinico Universitario A. Gemelli IRCCS; [7]Hematology and Stem Cell Transplant, San Giovanni Addolorata; [8]Hematology and Stem Cell Transplant Unit, IRCCS Regina Elena National Cancer Institute; [9]Hematology and Stem Cell Transplant, San Camillo Forlanini Hospital, Italy

Azacitidine (AZA) and Decitabine (DAC) have been the standard of care for patients with AML unfit for intensive therapy. We retrospectively analyzed 220 consecutive very elderly AML pts (median age 78.2, range 75-86.2 years) who received AZA (164) or DAC (56) as first-line treatment outside clinical trials at 9 Lazio hematologic centers between Sept 2010 and Dec 2021. Median OS was 8 months (95%CI 5.9-10.2), with 1 and 2-years OS of 39.4% (95%CI 32.7-46) and 17.4% (95%CI 11.7-23.1), respectively.

Table 1.

	< 12 HMAs cycles (n=163)	≥ 12 HMAs cycles (n=57)	*p* value
Median age (years)	78 (76-81)	76 (75-79)	*p*=0.001
Hb (g/dl) at baseline	8.6 (7.8-9.7)	9.5 (8.3-10.9)	*p*<0.001
WBC/µL at baseline	3240 (1320-10350)	3230 (2015-7880)	*p*=0.590
Plts/µL at baseline	50000 (25000-87000)	81000 (55000-118000)	*p*<0.001
Time from diagnosis to the start of HMAs (days)	20 (11-32)	16 (10-35)	*p*=0.851
BMI (Kg/m^2) >25 <25	 78 (48%) 85 (52%)	 19 (33%) 38 (67%)	*p*=0.064
eGFR (ml/min/1.73 mq) >60 <60	 129 (79%) 34 (21%)	 54 (95%) 3 (5%)	*p*=0.007
AML type *de novo* s-AML	 94 (58%) 69 (42%)	 41 (72%) 16 (28%)	*p*=0.060
Infection at baseline Yes No	 43 (26%) 120 (74%)	 6 (11%) 51 (90%)	*p*=0.015
BM blasts (%) >20% >30%<50% >50%	 43 (26%) 58 (36%) 62 (38%)	 35 (61%) 16 (28%) 6 (11%)	*p*<0.001
ELN2017 risk Fav Int Adv Unknown	 7 (4%) 69 (42%) 75 (46%) 12 (7%)	 10 (18%) 31 (54%) 13 (23%) 3 (5%)	*p*=0.001
CCI score <6 ≥6	 75 (46%) 88 (54%)	 37 (65%) 20 (35%)	*p*=0.021
ECOG score 0-1 ≥2	 136 (83%) 26 (16%)	 56 (98%) 1 (2%)	*p*=0.004

No difference in OS was observed according to HMA treatment (AZA

8.3 *vs* DAC 7.8 months, p=0.810); time from diagnosis to the start of therapy (<15 *vs* >15-30 *vs* >30 days) also did not affect OS (7.5 *vs* 11 *vs* 7.7 months; p=0.399). Median OS for pts with CR, PR and SD after 4 cycles was 19.5 (95%CI 12.9-26.2), 15.3 (95%CI 11.6-19.1) and 8.9 months (95%CI 6-11.7) (p=0.008), respectively. Survival was negatively Influenced by age ≥80 years (p=0.001), ECOG≥2 (p<0.001), CCI≥3 (p<0.001), complex karyotype (p=0.003), ELN adverse risk (p<0.001), transfusion dependence (p<0.001) and BM blasts >30% (p=0.03). No differences were found between AZA and DAC in terms of CR rate (21% *vs* 30%; p=0.147) and median time of CR achievement (4.6 *vs* 3.9 months; p=0.112). At univariate analysis, age<80 years (p=0.004), *de novo* AML (p=0.005), baseline eGFR rate ≥60 ml/min/1.73 mq (p=0.005), body mass index <25 (p=0.017), fav-int ELN risk (p=0.005), absence of complex karyotype (p=0.008), ECOG≤2 (p=0.037), CCI<3 (p<0.001) and transfusion independence (p<0.001) were significant predictors of better response. In multivariate analysis, BM blasts ≥50% (p=0.002), s-AML type (p=0.003), ECOG≥2 (p<0.001), CCI≥3 (p<0.001) and transfusion dependence at baseline (p<0.001) significantly predicted poor response. 44 AZA and 13 DAC pts received more than 12 cycles of HMAs (long survivors) with a median OS of 24.3 months (95%CI 20.2-28.3). These pts showed a significant lower blast count (p<0.001), higher eGFR (p=0.007), lower ECOG (p=0.021) and CCI (p=0.004) at baseline and the majority of them were stratified as ELN fav-int risk (p=0.001) compared with the 163 pts who received < 12 cycles. Toxicities (infections, bleeding, others) were similar (p=0.33) with a median time of 60 (IR 24-153) and 65 days (IR 20-189) between the start of treatment and the first complication for AZA and DAC (p=0.868), respectively. Treatment with HMAs was feasible allowing a durable survival in a specific subset of very elderly patients.

P041

SECONDARY ACUTE MYELOID LEUKEMIA EVOLVED FROM MYELODISPLASTYC SYNDROME TREATED WITH AZACITIDINE: A THERAPEUTIC CHALLENGE. A REAL-LIFE MULTICENTRIC EXPERIENCE OF GROM-L GROUP

A.L. Piccioni[1], M. Santopietro[2], A. Di Veroli[3], I. Carmosino[4], L. Fianchi[5], S. Mariani[6], L. Cicconi[7], S. Fenu[1], L. Maurillo[8], R. Palmieri[8], T. Caravita di Toritto[7], L. Rigacci[2], A. Tafuri[6], L. Pagano[5], M. Breccia[4], R. Latagliata[3] on behalf of GROM-L (Gruppo Romano-Laziale MDS)

[1]Haematology and Stem Cell Transplant, St. Giovanni Addolorata Hospital, Rome, Italy; [2]Haematology and Haematopoietic Stem Cells Transplant Unit, AO San Camillo-Forlanini, Rome; Italy; [3]Hematology Division, Belcolle Hospital, Viterbo, Italy; [4]Dpt of Translational and Precision Medicine, Policlinico Umberto I, Sapienza University Rome; Italy; [5]Department of Hematology, Fondazione Policlinico Universitario Agostino Gemelli-IRCCS, Rome; Italy; [6]Hematology, University Hospital St. Andrea, Sapienza, Rome, Italy; [7]UOSD Ematologia, ASL Roma 1, Rome, Italy; [8]Hematology, Policlinico Tor Vergata & Department of Biomedicine and Prevention, Tor Vergata; University Rome, Italy

Background: Azacytidine (AZA) is widely used in the treatment of Myelodysplastic Syndromes (MDS) with improvement of prognosis. When evolution in Acute Myelogeneous Leukemia (AML) occurs in MDS patients during AZA treatment, the survival is dismal and at present no therapy seems to have a role.

Methods: We retrospectively collected data on patients with AML evolved from MDS during AZA treatment followed at eight hematological Centers of the GROM-Lazio Cooperative Group. We analysed age, MDS diagnosis date, comorbidities, biological features prior MDS AZA treatment and after evolution, number of courses received and time to transformation to AML. After evolution, the choice of salvage treatment was at the discretion of the single Center.

Results: A total of 60 patients treated between March 2008 and November 2021 were included. Median age at diagnosis was 71.2 years (range 65.8-74.8) and the male/female rate was 36/24. Baseline characteristics for the MDS patients are reported in the Table 1. Forty-for (73.3%) were stratified as high and very high risk R-IPSS. Cytogenetics abnormalities were in 100 % of the cases with 18.4% complex karyotype. Patients were treated with AZA for a median of 13 courses (range 6-24) and the median time to AML evolution was 15.8 months (range 8.8-29.3). After AML evolution, 23.3% (n=14) received intensive chemotherapy, 11.6% (n=7) venetoclax plus hypomethylating agents (HMA), 10%(n=6) continued AZA or switched to decitabine and 55.1% (n=33) were eligible for supportive care only or hydroxyurea. After a median follow-up of 25.2 months from MDS diagnosis, 51 patients (85%) died, 1 (1.6%) was lost to follow-up and 8 (13.4 %) were alive. Overall survival (OS) was 3.9 months (95%CI 2.8-4.9). Among different variables tested for OS, marrow blasts <30% (p=0.002) and female gender (p=0.041) showed a favourable prognostic significance; no difference was observed between different age groups (<75 *vs* ≥75 years, p=0.359), karyotype risk groups (intermediate *vs* high/very high risk, p=0.919) and different treatment approaches (p= 0.157).

Conclusions: Outside of clinical trials, the treatment choices available for secondary AML evolved from MDS treated with HMA do not appear to give satisfactory results in patients not eligible for allograft. New insights into biological abnormalities could lead to more tailored and effective treatments in this subset of patients with a dismal prognosis up to now, especially in patients unfit for intensive chemotherapy.

Table 1.

Table	
MDS patients clinical features at baseline	
N° of patients	60
M/F, n° (%)	36/24 (60.0/40.0)
Median age at MDS, years (IQR)	71.2 (65.8–74.8)
WHO–MDS classification, n° (%):	
-MDS with multilineage dysplasia	7 (11.7)
-MDS RS with multilineage dysplasia	1 (1.7)
-MDS with excess blasts-1	14 (23.3)
-MDS with excess blasts-2	35 (58.3)
-MDS unclassifiable	3 (5)
R-IPSS classification, n° (%):	
-Intermediate	16 (26.7)
-High	24 (40)
-Very High	20 (33.3)
Karyotype, n° (%):	
-very good	3 (5)
-good	33 (55)
-intermediate	7 (11.6)
-poor	6 (10)
-very poor	11 (18.4)
Median number of AZA cycles, n° (IQR)	13 (6 – 24)
AML patients clinical features at baseline	
Median time to AML evolution, months (IQR)	15.8 (8.8 – 29.3)
Median age at AML, years (IQR)	74.5 (68.0 – 77.9)
Median Hb at AML, g/dl (IQR)	8.4 (7.1 – 10.0)
Median WBC at AML, x 10^9/l (IQR)	3.0 (1.5 – 11.6)
Median PLTS at AML, x 10^9/l (IQR)	33 (14 – 80)
Median marrow blasts, n° (IQR)	32 (25 – 51)

P042

THE ISTH-DIC SCORE PREDICTS 30-DAYS OUTCOME IN NON-M3 ACUTE MYELOID LEUKEMIA PATIENTS

G. Paterno, R. Palmieri, V. Forte, F. Bonanni, L. Guarnera, F. Mallegni, M.R. Pascale, F. Moretti, A. Savi, L. Maurillo, F. Buccisano, A. Venditti, M.I. Del Principe

Hematology, Department of Biomedicine and Prevention, University Tor Vergata, Italy

The International Society of Thrombosis and Haemostasis (ISTH) disseminated intravascular coagulation (DIC) score is widely used to predict mortality in critically ill patients. DIC may lead to potentially fatal clinical manifestations including major bleedings and thromboembolic events. Patients with acute myeloid leukemia (AML) can present with DIC as defined by the evidence of coagulative disorders, in the absence

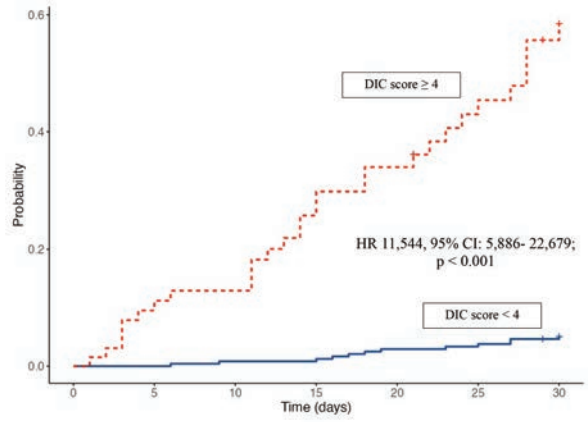
of thrombo-hemorrhagic manifestations. Despite several studies have investigated the association between HM, including AML and DIC in adults, which factors and their contribution to a worse outcome is still a matter of debate. Our aim was to investigate whether the ISTH DIC score can be used to predict the 30-days mortality in patients (pts) with non-M3 AML.

Methods: In this study we included 308 consecutive adult pts (≥18 years of age) who were diagnosed with non-M3 AML between 2010 and 2020. The ISTH DIC score was calculated at AML presentation as follows: platelet count (≥100 x 10^9/L = 0; 50-99 x 10^9/L = 1; <50 x 10^9/L = 2), fibrinogen level (≥100 mg/dL = 0; <100 mg/dL = 1), PT prolongation (<3 sec = 0, 3-6 sec = 1, >6 sec = 2), and D-dimer level (<3 µg/ml = 0, 3-7 µg/ml = 2, >7 µg/ml = 3). A score sum ≥ 4 identified high-risk pts.

Results: Of 308 pts (40% female; median age 64 yrs, range 21-90 years), 183 were treated with intensive chemotherapy, 59 with low intensive therapy and 69 received only supportive care. At AML presentation, 66 pts (21%) had a DIC score ≥ 4. Factors significantly associated with DIC score ≥ 4 were: age >65 yrs (p=0.001), elevated serum LDH (p<0.001), FLT3 and NPM1 mutations (p=0.026 and p=0.018, respectively), and a leukocyte count above 50x10^9/L (p=0.002). The 30-days mortality rate was 13,3% (41/308), with 16 pts dying from hemorrhagic or thrombotic complications. A DIC-score ≥ 4 was associated with a significantly higher 30-days mortality rate (44% *vs* 5%, HR 11,544; p< 0.001) Figure 1. The multivariate analysis confirmed the independent role of DIC score (p=0.001), leukocytosis above 50x10^9/L (p=0.06), and age >65 yrs (p=0.039) in influencing 30-days mortality.

Conclusion: The ISTH-DIC score is easy to assess, and this study suggests that it accurately predicts 30-days mortality risk of AML pts, regardless of age and cytogenetic risk. A potential role of DIC score is to select pts who are at high-risk of fatal bleeding and therefore in need of aggressive transfusion support. Further studies on larger population are needed to confirm the findings, and to incorporate DIC score in prognostic models.

Figure 1. Probability of 30 days mortality in pts with DIC score ≥ 4 vs DIC score <4.



P043

AUTOLOGOUS PERIPHERAL BLOOD STEM CELL MOBILIZATION AND HARVEST IN ADULT PATIENTS WITH FLT3-MUTATED ACUTE MYELOID LEUKEMIA RECEIVING CHEMOTHERAPY COMBINED WITH MIDOSTAURIN: A MONOCENTER RETROSPECTIVE STUDY

S. Cordella[1], A. Parisotto[1], F. Bettelli[1], M. Morselli[1], E. Barbieri[1], S. Pozzi[1], A. Aquilino[1], G. Repaci[1], A. Cuoghi[1], P. Bresciani[1], A. Messerotti[1], C. Colasante[1], A. Gilioli[1], V. Pioli[1], D. Giusti[1], E. Colaci[1], L. Cassanelli[1], G. Ceccherelli[2], M. Bevini[2], R. Malavolti[2], D. Venturelli[2], A. Paolini[1], S. Martinelli[1], R. Maffei[1], G. Riva[3], V. Nasillo[3], T. Trenti[3], P. Comoli[4], E. Tagliafico[5], R. Manfredini[6], P. Barozzi[1], L. Potenza[1], R. Marasca[1], M. Luppi[1], F. Forghieri[1]

[1]Department of Medical and Surgical Sciences, Section of Hematology. University of Modena and Reggio Emilia, Azienda Ospedaliero-Universitaria di Modena; [2]Immuno-Transfusional Medicine Unit. Azienda Ospedaliero-Universitaria di Modena; [3]Department of Laboratory Medicine and Pathology, Unità Sanitaria Locale di Modena; [4]Pediatric Hematology Unit, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Policlinico San Matteo di Pavia; [5]Center for Genome Research. Department of Medical and Surgical Sciences. University of Modena and Reggio Emilia, Azienda Ospedaliero-Universitaria di Modena; [6]Center for Regenerative Medicine "Stefano Ferrari". Department of Life Sciences. University of Modena and Reggio Emilia, Italy

The combination of midostaurin with intensive chemotherapy is considered the standard of care for fit patients (pts) with newly-diagnosed FLT3-mutated AML. However, allogeneic HSCT in first CR is still strongly recommended, at least in eligible intermediate-adverse risk cases. Data on peripheral blood stem cell (PBSC) mobilization, at least for autologous back-up harvest, in FLT3-mutated AML pts in CR receiving midostaurin-based consolidation are not so far available. Among 242 consecutive pts affected with AML (median age 63 years), observed since 2010 to 2021, 42 (17.4%) and 18 (7.4%) were found to harbor FLT3-ITD and TKD mutations, respectively. Fit pts underwent remission induction chemotherapy, without (39 pts) or with (17 pts) addition of midostaurin. Then, pts aged <65 years in CR received consolidation with either intermediate-dose cytarabine/daunorubicin with G-CSF 10 mcg/kg/day since day +20 (cohort A, 19 pts) or high-dose cytarabine and midostaurin with G-CSF 5 mcg/kg/day since day +7 (cohort B, 7 pts), in the attempt of mobilization of autologous PBSC, regardless of planned autologous or allogeneic HSCT. We retrospectively compared variables of PBSC mobilization in the 2 subgroups receiving different treatments. After having received a median of 9 (range 5-22) and 12 (range 12-14) G-CSF doses, PBSC mobilization failed in 5/19 (26.3%) and 0/7 pts from cohorts A and B, respectively (p=0.28). The median peak of circulating CD34+ cells/µl (25, range 7.5-35.5 in cohort A *vs* 75, range 32.5-138.5 in cohort B, p=0.041) occurred on days +22 (range 21-26) and +18 (range 18-19) in each cohort, respectively (p=0.001). Median harvested CD34+ cells x10^6/kg body weight were 3.2 (range 0.4-5.6) and 4.8 (range 4.3-9.4) (p=0.078), with 12/14 (85.7%) and 7/7 (100%) good mobilizers collecting >2 x10^6 CD34+ cells/kg in cohorts A and B, respectively (p=0.24). The median number of aphereses was 1 in both groups. Only 2 pts from cohort A finally underwent autologous HSCT, whereas 12 and 5 cases from cohorts A and B, respectively, received allogeneic HSCT. Although autologous back-up harvest is currently considered unnecessary for well-matched HSCT, the storage of a secondary stem cell source may be useful in cases at higher risk of graft failure. Since FLT3-mutated AML patients are frequently candidate to allogeneic HSCT, we showed that midostaurin-based consolidation approaches may allow adequate results in terms of kinetics and yield of autologous PBSC collection.

P044

ABSOLUTE LYMPHOCYTE COUNT IS AN INDEPENDENT SURVIVAL PREDICTOR IN PATIENTS WITH ACUTE MYELOID LEUKEMIA TREATED WITH INTENSIVE CHEMOTHERAPY

G. Cristiano[1], J. Nanni[1], L. Zannoni[1], C. Sartor[1], S. Parisi[2], S. Paolini[2], C. Papayannidis[2], M. Cavo[1,2], A. Curti[2]

[1]Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna, Bologna, Italy; [2]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli", Bologna, Italy

Background: Absolute lymphocyte count (ALC) is known to be an independent prognostic factor for overall survival (OS) in patients receiv-

ing autologous transplantation for B cell lymphomas and solid cancer. In acute myeloid leukemia (AML) enhanced ALC recovery after intensive chemotherapy (IC) has been associated with superior OS and leukemia-free survival (LFS). However, few if any data correlated ALC recovery with novel therapies as well as with updated molecular prognostic factors.

Aims: Our study aims at evaluating the predictive value of ALC recovery in AML patients treated with IC among different patient subgroups according to therapy response, regimens used and allogeneic stem cell transplantations (HSCT).

Methods: We evaluated 148 newly diagnosed AML patients treated with IC in our center. We defined 4 ALC time-points (TPs), with a 500/mm^3 cut-off: at 15, 21 and 28 days from the start of IC and before consolidation (CC). Apart from any single TP, patients were also grouped in those who obtained ≥500/mm^3 ALC in all 4 TPs and those who had <500/mm^3 in at least one TP. Median follow-up was 51,4 months.

Results: At the single TP evaluation, only ALC-CC recovery showed a statistically significant better outcome. However, significant differences were observed among CR patients (76,3%), considering ALC recovery in all TPs. A trend toward better correlation of ALC with OS was observed in patients who received "3+7-based" regimen (30,8%;) *vs* fludarabine-based" regimen ones (69,1%;). Infact "3+7" patients who had ALC recovery in all TPs and at day 15 had better outcome. Of note, FLT3-ITD positive patients with early ALC-21 recovery had longer OS. Figure 1 shows instead the issue in patients who received HSCT (66,3%) *vs* those who did not (33,6%). In HSCT patients, with expected globally better outcomes, the impact of ALC recovery after IC was minimal. In contrast, patients who had ALC <500/mm^3 ALC in at least one TP and did not undergo HSCT had the worst outcome. Interestingly, patients who were not transplanted but had ≥500/mm^3 in all 4 TPs had a similar outcome as HSCT patients.

Conclusion: In our study ALC recovery is a promising OS predictor in AML. Within the complex interaction between leukemia and the immune system, our study may provide the rationale for an immunological score to be integrated in the current prognostic classification. Larger cohorts studies addressing ALC recovery in correlation with novel agents and minimal residual disease are highly warranted.

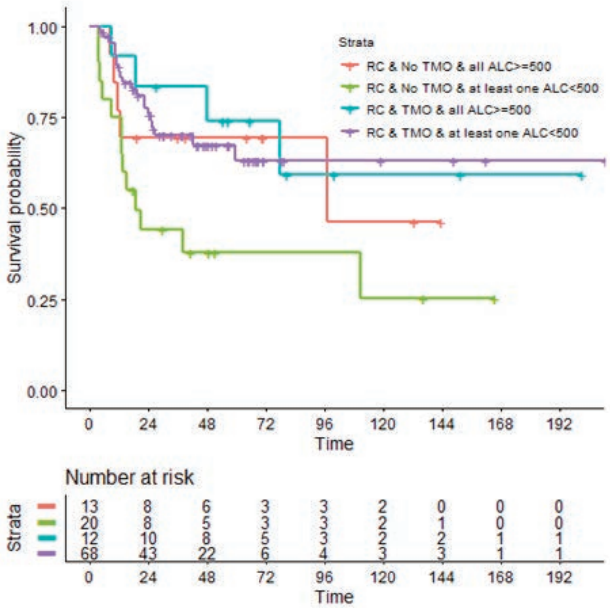


Figure 1.

P045

THE CYTOGENETIC AND MUTATIONAL LANDSCAPE OF NPM1-WILD-TYPE MYELOID MALIGNANCIES DEVELOPING DURING CONTINUOUS COMPLETE REMISSION OF NPM1-MUTATED AML

D. Bertoli[1,2], E. Borlenghi[1], C. Giupponi[1,2], C. Cattaneo[1], T. Zollner[1], A. Passi[1], M. Oberti[1], S. Bagnasco[1], E. Cerqui[1], N. Bianchetti[1], S. Archetti[2], G. Rossi[1], A. Tucci[1]

[1]Hematology, ASST Spedali Civili; [2]Clinical Chemistry Laboratory, Diagnostic Department, ASST Spedali Civili, Italy

Long term remission can be reached in 50-60% of NPM1-mutated AML (NPM1-AML). MRD monitoring of NPM1 mutation is recommended to early identify relapses which occur in 30-40% of cases. The development of secondary myeloid malignancies (sMM) with wild-type NPM1 (NPM1wt) during continuous complete remission (cCR) has been rarely described. Here we present 13 patients (pts) with NPM1-AML who developed sMM with NPM1wt (Table 1). Their cytogenetic and molecular features were studied, including NGS analysis in 8 (Sophia Myeloid Solution kit), and compared to 54 pts who experienced NPM1+ relapse (NPM1rel). From 5/05 to 12/21, CR was obtained in 139/142 consecutive NPM1-AML pts (median age 56) using intensive chemotherapy (iCT) followed by HDARAC consolidation. 13/139 pts (9.5%) (F/M:4/9; median age 62, range 44-69) developed a NPM1wt sMM while in molecular CR (RCMD=6, RAEB-I=3; RAEB-II=1; AML NPM1wt=3). Treatment was iCT (2), HMA (5) or EPO/BSC (6); 4 underwent alloSCT. Median age was higher in sMM than in cCR pts and NMP1rel (64 *vs* 51 *vs* 59 y; p:0.0028). The median time to develop sMM was 62 mo (range 11-175) significantly longer than median time to NPM1m relapse (13 mo; range 3-97) (p<0.0001). Median survival after sMM diagnosis was shorter than expected (24.7 mo in MDS and 2.4 mo in AML). At NPM1-AML diagnosis, 12/13 sMM pts had a normal karyotype (K). At sMM, 9 (70%) acquired new K abnormalities (abn), involving chromosome 7 in 6 (67%). NGS analysis at diagnosis showed additional mutations involving epigenetic/splicing genes and/or IDH1 in 8/8 cases. At least one of such mutations was retained at sMM in 7/8 pts, with similar VAF. Signaling gene mutations were lost in 4/5 pts, while new mutations were acquired in 5/8 pts: FLT3-ITD disappeared in 3/3 NPM1-AML and was acquired in 1 sMM. We next compared genomic characteristics of 18/54 NPM1rel *vs* 8/13 sMM both at diagnosis. sMM had a slightly lower mutational burden (p 0.051) and a lower incidence of KRASm (28% *vs* 0%). Epigenetic/splicing gene mutations and K abn were similar. At sMM development of K abn were significantly more frequent than at NPM1 relapse (9/13 *vs* 7/54, p< 0.0001). NPM1wt sMM develop in about 10% of NPM1-AML in stable CR, are characterized by K abn and have severe prognosis. At diagnosis an epigenetic/splicing mutational landscape is more frequent than expected in NPM1-AML pts evolving to both sMM and NPM1rel. NGS analysis is advisable both at diagnosis and during follow-up, especially in elderly pts.

Table 1.

Pts	AML diagnosis			Secondary Myeloid Malignancies (sMM)					
sex/age	Karyotype	Mutations	Treatment	age	Type	Karyotype	Mutations	Treatment	Survival after s-MM diagnosis (months)
M/67	Normal	NPM1-A, TET2	HD-ARAC	72	AML, NPM1 wt	del(7), t(7;11),-7,-5,-17,-22	TET2, DNMT3A, KRAS, PTPN11, NRAS	i-CT	Dead, (2)
F/44	Normal	NPM1-A, DNMT3A, PTPN11, FLT3-TKD, BRAF	HD-ARAC	47	AML NPM1wt	Normal	DNMT3A, FLT3-ITD, RUNX1, FLT3-TKD	i-CT+ALLOSCT	Dead, (9)
M/68	Normal	NPM1A, FLT3 TKD NGS not done	HD-ARAC	69	AML NPM1 wt	Complex	NGS not done	BSC	Dead, (1)
M/69	Normal	NPM1-A, DNMT3A, IDH1	HD-ARAC	77	CRMD IPSS LR	Normal	DNMT3A, TET2	EPO	Alive, (20)
M/62	Normal	NPM1-B,DNMT3A,NRAS	HD-ARAC	70	RAEBI IPSS HR	+8	IDH1,RUNX1, ASXL1, EZH2	HMA	Alive, (2)
F/66	Normal	NPM1-A, DNMT3A, SF3B1	HD-ARAC	69	RCDM IPSS INT-II	del(4),t(1;4),-7	DNMT3A, SF3B1	HMA+ALLOSCT	Alive, (21)
M/64	Normal	NPM1-A, FLT3-ITD, IDH1	HD-ARAC	66	RCDM IPSS INT-I	add7,del(7q)	IDH1	observation	Alive, (73)
M/62	Normal	NPM1-A, FLT3-ITD NGS not done	HD-ARAC	68	RAEBI IPSS INT-II	del(5q),-7	NGS not done	EPO	Dead, (18)
M/58	del(9q11)	NPM1-A, FLT3-TKD, NRAS, PTPN11, SF3B1	HD-ARAC	75	RAEBI IPSS INT-II	Normal	JAK2, SF3B1	HMA+ALLOSCT	Alive, (16)
F/69	Normal	NPM1-A, FLT3-ITD, TET2	HD-ARAC	77	RCDM IPSS LR	Normal	TET2	EPO	Alive, (9)
F/62	Normal	NPM1-A NGS not done	HD-ARAC	63	CRDM IPSS INT-II	del(7q),-7	NGS not done	HMA	Dead, (24)
M/69	Normal	NPM1-A, FLT3-TKD NGS not done	HD-ARAC	70	RAEBI IPSS INT-II	del(4),t(1;4)	NGS not done	BSC	Dead, (11)
M/52	Normal	NPM1-A, FLT3-TKD NGS not done	HD-ARAC	57	RCDM IPSS INT-I	-Y	NGS not done	HMA+ALLOSCT	Dead, (15)

Abbreviations: Pts: patients; i-CT: intensive chemotherapy; SCT: stem cell transplantation; HMA: hypomethylast agents, BSC: best supportive care, LR: low risk, HR: high risk, int: intermediate, ITD: internal tandem duplication. TKD: tyrosine kinase domain. Genomic abnormalities highlighted in red are those acquired at sMM.

P046

DIAGNOSTIC RELEVANCE OF FLT3/ITD-TKD AND NMP1 GENES IN PATIENTS WITH ACUTE MYELOID LEUKEMIA (AML)

A. Viola[1,2], M. Pisa[1,2], S.M. Muggianu[2], R. Peluso[2], M. Caputo[2], A. Gravetti[1], M. De Simone[1], C. Copia[1], F. Ferrara[1]

[1]U.O.C. Ematologia AO. A. Cardarelli; [2]Laboratorio di Biologia Molecolare- Ematologia e Trapianto CSE AO.A. Cardarelli, Italy

The most frequent acquired molecular abnormalities and important prognostic indicators in patients with Acute Myeloid Leukaemia (AML) are fms-like tyrosine kinase-3 gene (FLT3) and nucleophosmin-1 (NPM1) mutations. Mutations of the FLT3 gene occur in approximately 30% of all AML cases, with the internal tandem duplication (ITD) representing the most common type of FLT3 mutations (FLT3-ITD; approximately 25% of all AML cases). FLT3-ITD is a common driver mutation that presents with a high leukemic burden and confers a poor prognosis in patients with AML. The prognostic value of a FLT3 mutation in the tyrosine kinase domain (FLT3-TKD, approximately 7-10% of all AML cases) is uncertain. NPM1 is a ubiquitously expressed nucleocytoplasmic shuttling protein that plays an active role in ribosomal protein assembly, chromatin remodeling, and DNA repair, replication, and transcription. Mutations in the NPM1 gene are note in ~ 35% of AML cases. The favorable prognosis conferred by NPM1 mutations is associated with higher complete remission (CR) rates and prolonged disease-free (DFS) and overall survival (OS) Although FLT3-ITD mutations in AML confer an adverse prognosis, co-occurrence with a NPM1 mutation partially improves response and survival outcomes. In contrast, simultaneous NPM1 and FLT3-TKD mutations were report to improve response over that of an isolated NPM1 mutation.

Aim of this study was to evaluate the prognostic impact of FLT3 - TKD in the presence of NPM1 mutation in AML patients. We evalueted 133 adults patients (76 males and 57 females), median age was 61 (range 22-83),diagnosed with AML by standard criteria and 39% resulted positive for FLT3 and/or NPM1 mutations; in particular, 42 patients (81%) were FLT3-ITD/NPM1 mutated ,10 patients (19%) were FLT3-TKD/NPM1 mutated. In regards to TKD mutations, all were FLT3-D835 point mutations.

We evaluated the effect of TKD on outcome. The OS was similar in patients with FLT3-TKD /NPM1 mutated (71, 4%) and NPM1 only mutated (72, 4%). Patients with FLT3-TKD/NPM1 mutated show a longer-lasting DFS but similar to patients with only NPM1 mutated 80% and 89%, respectively. These results stress the importance of determining FLT3/TKD status at diagnosis and question about how to consider the prognostic value of NPM1 mutations in the absence of information regarding FLT3/TKD status.

Our preliminary results on FLT3TKD+NPM1+ patients lead us to consider double mutants as a favorable group of patients.

P047

VENETOCLAX COMBINED WITH DECITABINE REPRESENT A GOOD OPTION AS A BRIDGE TO ALLOGENEIC TRANSPLANTATION IN ACUTE MIELOID LEUKEMIA: THE EXPERIENCE OF APULIAN HEMATOLOGICAL NETWORK

V. Federico[1], R. Matera[1], A.M. Carella[2], G. Tarantino[3], V. Pavone[4], L. Melillo[5], D. Carlino[1], C. De Risi[1], G. Campagna[1], C. Vergine[1], M. Dargenio[1], A. Messa[1], F. Colasante[2], T.M. Santeramo[3], M. Leo[3], E. Preite[4], A. Mele[4], L. Ciuffreda[5], D. Seripa[1], N. Di Renzo[1]

[1]Haematology "Vito Fazzi" Hospital; [2]Haematology "Casa Sollievo della sofferenza" Hospital; [3]Haematology "Mons. Dimiccoli" Hospital; [4]Haematology "Cardinale Panico" Hospital; [5]Haematology "Riuniti" Hospital, Italy

Background: The combination of VEN-DEC, represents a practice-changing innovation in the treatment of acute myeloid leukemia (AML). Nowadays VEN and HMA agent are the standard of care for both relapsed/refractory (R/R) AML and for newly diagnosed (ND) AML patients (pts) unfit for intensive chemotherapy. The role of allo-HSCT after this combination is not still fully investigated. We report here the outcome of patients with ND or R/R-AML who underwent to allo-HSCT after VEN-DEC regimen in a real life experience.

Method: From May 2018 to January 2022, a total of 103 pts, 58 with ND-AML and 45 with R/R AML, were treated with VEN-DEC within of Apulian Hematological Network. Twenty-seven pts (26%), 12 ND- and 15 R/R-AML, median age 57 years (range: 23-72) after improvement of their performance status underwent to allo-HSCT while in CR. Allo-HSCT was performed after a median of 3 cycles (range: 2-5) of VEN at median dose of 100 mg/daily (range: 100-400) with DEC 20 mg/m^2 days 1-5 of each 28-day. In all cases graft source was mobilized PBSC; 23 pts (85%) received thiotepa, busulfan and fludarabine as conditioning regimen and 4 pts (15%) fludarabine with treosulfan/busulfan. Eighteen pts (67%) received an haplo-donor and PT-CY 50 mg/Kg day +3 and +5 as GvHD prophylaxis combined with CyA and MMF. Results: The median number of CD34+blood cells infused was 6.4 x 10^6/Kg (range: 4.6-7.8). The median time to neutrophil engraftment > 0.5 x 10^9 /l and platelet > 20 x 10^9/l was 15 days (range: 13-17) and 19 (range: 13-26) respectively. All but one of the patients achieved full engraftment. One patient with ND-AML had primary engraftment failure. The cumulative incidence of aGvHD was 80%, 26% and 13% and cGVHD (evaluated in 18 patients) was 40%, 20% and 13% for grade 0-I, II, III-IV respectively. After a median follow-up of 8 months (range: 4-37), 21 (77%) pts were alive in CR with MRD negativity. Three patients (11%) died of progressive disease at day + 120, + 210 and + 240 respectively. The non relapse mortality was 0% at day 100 and 11% at 1-year. At time to analysis the median EFS and OS it's not achieved and the 1-year estimate PFS and OS was 72% and 74% respectively. No statistically significant difference in estimate median OS was observed when allo-HSCT was performed after VEN-DEC in ND-AML *vs* R/R AML (p=0.75).

Conclusion: Our results albeit obtained in a small series of patients shown how the VEN-DEC combination should be regarded as a good bridge to allo-HSCT both in ND-AML and R/R AML.

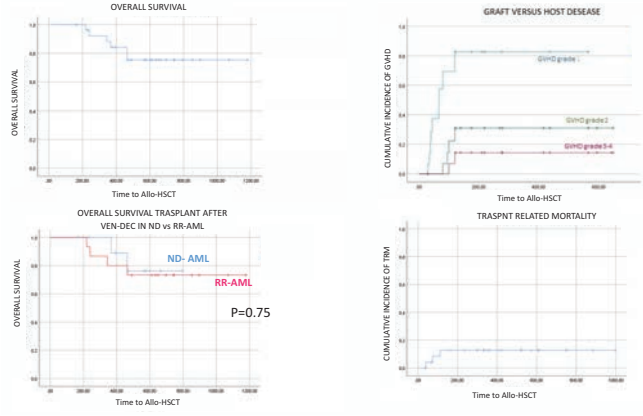


Figure 1.

P048

PROGNOSTIC IMPACT OF TP53 MUTATION IN YOUNGER (<60 YRS) ACUTE MYELOID LEUKEMIA PATIENTS UNDERGOING INTENSIFIED FLUDARABINE/HIGH DOSE CYTARABINE INDUCTION (FLAI)

M. Passannante[1], F. Guolo[1,2], P. Minetto[1,2], M. Cea[1,2], M. Miglino[1,2], E. Carminati[1], C. Nurra[1], F. Puglisi[1], G. Fugazza[1], R. Marcolin[1], M. Frello[1], C. Vernarecci[1], C. Riva[1], B. Ferro[1], E. Maio[1], M. Chies[1], R.M. Lemoli[1,2]

[1]Clinica Ematologica, Dipartimento di Medicina Interna (DiMI), Università degli studi di Genova; [2]IRCCS Ospedale Policlinico San Martino, Italy

Background and aims: Mutations in the tumour suppressor gene TP53 occurs in only 5-10% of *de novo* Acute Myeloid Leukemia (AML) but may be found in up of 30% of therapy-related AML. TP53 mutation is associated with dismal survival outcomes, especially in patients with high risk cytogenetics. Indeed, dysfunctional p53 corelates with a poor prognosis in AML because of resistance to conventional chemotherapy and high rate of relapse. Thus, since TP53 mutations are often associated with high-risk disease, intensified therapeutic strategies are needed. In our experience, we reported the efficacy in term of good overall outcome of a fludarabine, high dose cytarabine and Idarubicin induction regimen (FLAI) as frontline treatment for fit AML patients. The aim of the present study was to evaluate the impact of TP53 mutations on response rates and outcome in a cohort of patients receiving FLAI induction.

Methods: We evaluated mutational status for TP53 in 58 AML patients aged 18-60 (median 50), who received FLAI induction between 2017 and 2021. Sixteen (27%), 26 (49%) and 14 (24%) of them had low, intermediate or high-risk disease according to ELN 2017, respectively. Mutated TP53 was found in 7 patients (12%), 4 of them had concomitant high-risk cytogenetics, mainly complex karyotype.

Results: Fifty-three/58 (91%) patients achieved CR after cycle 1, 2 patients did not respond to induction (3.4%) and 3 patients (5%) died before response evaluation mainly because of severe infections or uncontrolled CNS bleeding. TP53 mutations did not significantly affect CR rate (response rate 6/7, 85% and 47/51, 92%, respectively for mutated and unmutated patients). All 6 TP53 mutated patients underwent allogeneic stem cell transplantation in first CR, 2 of them in a MRD negative status. Unfortunately, 5/6 TP53 mutated patients relapsed after a median of 6 months (range 3-11) after transplantation.

Conclusions: FLAI is an effective therapy for younger AML patients, with a good CR rate also in high risk patients such as TP53 mutated AML patients. However, inclusion of novel agents in FLAI backbone is warranted as relapse is still an issue, even if allogeneic stem cell transplantation consolidation is performed.

P049

ACUTE MYELOID LEUKEMIA AND HIGH-RISK MYELODYSPLASTIC SYNDROMES IN HIV-POSITIVE PATIENTS: HIGH FREQUENCY OF THERAPY-RELATED MYELOID NEOPLASMS

S. Bagnasco[1], C. Cattaneo[1], M. Bernardi[2], V. Mancini[3], C. Pagani[1], P. Zappasodi[4], E. Borlenghi[1], A. Re[1], F. Ciceri[2], M. Oberti[1], L. Masina[1], R. Cairoli[3], G. Rossi[1], A. Tucci[1]

[1]Hematology, ASST-Spedali Civili Brescia; [2]IRCCS San Raffaele Hospital, Hematology and Bone Marrow Transplantation Unit; [3]Hematology, ASST Grande Ospedale Metropolitano Niguarda; [4]Hematology, Foundation IRCCS Policlinico San Matteo, University of Pavia, Italy

Acute Myeloid Leukemia (AML) and High-Risk Myelodysplastic Syndromes (HR-MDS) are relatively uncommon among HIV-positive (HIV-pos) patients (pts) and epidemiologic studies are very limited. To better define the clinical characteristics of AML/HR-MDS HIV-pos pts, we evaluated all HIV-pos AML and HR-MDS pts diagnosed at 4 Hematology Centers belonging to the Rete Ematologica Lombarda (REL). Between 1994 and 2022, 20 pts have been diagnosed: 3 HR-MDS and 17 AML. Median age at AML/MDS diagnosis was 54y (range 28-70), M/F ratio 14/6. Median CD4 count was 388/mcl (range 132-2048). Seven (35%) pts had received previous chemotherapy (cht) for Kaposi sarcoma (1) or non-Hodgkin B-cell lymphoma (6). Eleven (65%) of the 17 evaluable cases showed abnormal cytogenetics, which was adverse in 6 (35%) (4 complex karyotype, 2 del7), intermediate in 4 (20%) (1 trisomy 8, 2 t(7;11) and 1 t(4;12)), favorable in 1 (10%, inv16). Among 9 cases analysed, NPM1 mutation was observed in 2, FLT3 ITD and TKD mutation in 2 and 1, and p53 mutation in 1 case, respectively (Table 1). Two AML pts (10%) did not receive any treatment and rapidly died of progressive disease. Two HR-MDS pts received azacytidine, but they rapidly progressed after 2 courses and died at +7 and +8 months respectively. Sixteen pts were treated with intensive therapy with standard induction cht. Nine out of the 16 evaluable pts (56%) achieved a complete remission (CR) after induction cht; 6 pts received further treatments, including venetoclax+azacytidine, which was successful in 4/6 (66%), the overall CR rate being therefore 87%. Nine pts (8 AML and 1 HR-MDS) underwent stem cell transplantation in first CR: 2 autologous and 7 allogeneic. Overall, 5 of 13 (38%) pts achieving CR relapsed; 2 received salvage treatment and proceeded to alloSCT. Toxicity-related mortality was 3/20 (15%): 1 P. jirovecii pneumonia during induction cht (1/15, 7%), 2 (1 aGVHD and 1 infection) after alloSCT. After a median follow up of 28 months, 7 pts were alive in CR. Median overall survival (OS) of the whole cohort was 10.5 months and 2yOS 32.6%±6.38SEM. AML or HR-MDS of HIV-pos adult pts are characterized by a considerable proportion of therapy-related neoplasms that probably account for the frequent adverse cytogenetics observed. Despite the poor prognostic factors registered, intensive cht and SCT were feasible and effective in HIV-pos AL/HR-MDS pts, with an acceptable toxicity profile and obtained results like the HIV-neg population.

Table 1.

Pts	Age/sex	MN type	Karyotype	Detected mutations	CR achievment	SCT	Follow-up (mo)	Alive /Deceased
1	M/50	t-HR MDS	complex	ne	no	no	7	D
2	M/58	HR MDS	Del 7	ne	no	no	8	D
3	F/41	HR MDS	t(7;11)	ne	yes	allogeneic	17	D
4	M/56	t-AML	46, XY	FLT3 ITD	no	no	13	D
5	M/53	t-AML	inv(16)	ne	yes	no	74,5	A
6	M/47	t-AML	ne	ne	no	no	0,5	D
7	M/55	t-AML	complex	FLT3 TKD	yes	no	8	D
8	F/70	t-AML	Del 7	ne	yes	no	4	A
9	M/45	AML	46, XY	ne	yes	autologous	32	D
10	M/34	AML	+8	ne	yes	autologous	23	D
11	F/28	AML	ne	ne	no	no	2	D
12	M/56	AML	complex	no	yes	allogeneic	8	D
13	M/48	AML	46/XY	ne	no	no	1	D
14	F/46	t-AML	t(7;11)	ne	yes	allogeneic	8	A
15	F/56	AML	complex	p53	no	no	11	D
16	M/57	AML	46, XY	FLT3 ITD	yes	allogeneic	28	A
17	M/64	AML	46, XY	NPM1	yes	no	10	A
18	F/56	AML	46, XX	NPM1	yes	allogeneic	72	A
19	M/49	AML	ne	no	yes	allogeneic	58	A
20	M/67	AML	t(4;12)	no	yes	allogeneic	23	D

P050

CORRELATION BETWEEN IMMUNOPHENOTYPIC PATTERNS AND OUTCOME IN ACUTE PROMYELOCYTIC LEUKEMIA. A POSSIBLE ROLE FOR CD9/CD99 POSITIVITY

P. Musiu, E. Scalzulli, I. Carmosino, C. Ielo, C. Luise, G.M. Assanto, D. Diverio, M.L. Milani, S. Intoppa, A.M. Testi, M. Martelli, A. Guarini, R. Foà, M.S. De Propris, M. Breccia

Hematology, Department of Translational and Precision Medicine, Sapienza University, Italy

The diagnosis of acute promyelocytic leukemia (APL) is traditionally

based on cytomorphology, molecular and cytogenetic analyses. Even though the RT-PCR detection of PML-RARa is nowadays the gold standard for the diagnosis of acute promyelocytic leukemia, flow cytometry could represent a useful, quick and reliable tool in the work-up of APL. Classically, APL cells are characterized by a homogeneous expression of CD33, a heterogenous pattern of expression of CD13, a typical CD34-CD15 pattern in which leukemic cells lose CD34 before they acquire CD15 expression, a negativity for HLA-DR and CD11b. We conducted a retrospective single Center analysis on a total of 69 APL patients studied at diagnosis in order to correlate the immunophenotypic features with the morphological, molecular and clinical characteristics, such as classical or variant APL form, PML-RARa fusion transcript isoforms, relapse risk score at diagnosis, overall survival (OS) and relapse rate. Patients' baseline characteristics are summarized in Table 1. Immunophenotypic findings confirmed the well-known heterogeneous CD13 and homogeneous CD33 patterns of expression of leukemic cells. All cases (100%) were positive for CD9 with a median mean fluorescence intensity (MFI) of 414; 31% of cases were tested for CD9 and CD99, and proved positive with a median MFI of 99.5. No significant association was observed between CD99 MFI levels and the different APL forms (p=0.250). A higher CD34 MFI was associated to variant APL (p=0.035) and to the bcr3 isoform of the PML-RARa fusion transcript (p=0.046), while a higher CD9 MFI was associated with the classical APL form (p=0.049) and the bcr3 transcript (p=0.039). The expression of CD34 in more than 10% of total nucleated cells was correlated with an aberrant CD2 expression in 70% of cases, was more frequently observed in variant APL (p<0.0001) and in high-risk patients (p<0.0001), and was correlated with a shorter OS (p=0.041) and a positive trend for a higher rate of extramedullary relapse (p=0.061). Our results highlight that CD9 and CD99 expression - in addition to the characteristic CD34-CD15 pattern, CD13 heterogeneous and CD33 homogeneous expression, HLA-DR and CD11-b negativity - may represent a valid additional tool in a flow cytometry-based APL diagnostic work-up. Furthermore, we could document the association between the expression of certain tested antigens, morphologic and molecular features, and outcome.

Table 1. Patients' clinical, morphological, molecular and immunophenotypic characteristics.

Median follow-up in months (range)	41.6 (0,0-192,7)
Male - Female (%)	36 - 33 (52.2/47.8)
Median age at diagnosis (range)	53,3 (10.9-84.5)
M3 - M3v (%)	54 - 15 (78.2-21.8)
PML/RARα Bcr1 - Bcr2 - Bcr3 (%)	46 - 0 - 23 (66.7-0-333)
Sanz risk score Low (%) Intermediate (%) High (%)	 20 (28.9) 26 (37.8) 23 (333)
Median blast cells (%) on nucleated cells (range)	85 (27-98)
CD9 expression (%) on nucleated cells (range) Median CD9 MFI (range)	85 (27-98) 414 (112-1254)
CD99 expression (%) on nucleated cells (range) Number of patients tested for CD99 (%) Median CD99 MFI (range)	83.5 (27-94) 22 (33) 99.5 (42-1000)
Heterogenous CD13 expression (%) on nucleated cells (range) Median CD13 MFI (range)	85 (27-98) 284.5 (25-1022)
Homogenous CD33 expression (%) on nucleated cells (range) Median CD33 MFI (range)	85 (27-98) 280 (38-2641)
HLA-DR+ patients (%) Median HLA-DR MFI (range)	7 (10,6%) 30 (14-70)
Patients with >10% of nucleated cells CD34+ (%) Median CD34 MFI in patients with >10% of CD34+ nucleated cells (Range)	10 (14) 38 (17-315)
Patients with >10% of nucleated cells CD2+ (%) Median CD2 MFI in patients with >10% of CD2+ nucleated cells (Range)	9 (13%) 41 (14-426)
CD56+ patients (%) Median CD56 MFI in patients with >10% of CD56+ nucleated cells (Range)	5 (7) 90 (77-200)
CD4+ patients (%) Number of patients tested for CD4 (%) Median CD4 MFI in CD4+ patients (Range)	3 (4,3%) 57 (82,6%) 50 (23-62)
CD11b+ patients (%)	0 (0)

P051

CONSOLIDATION WITH CPX351 IN THE OUTPATIENT SETTING: FEASIBILITY, WITH NO INCREASE IN INTENSIVE CARE UNIT READMISSIONS, IN A MULTI-CENTER REAL LIFE EXPERIENCE

D. Capelli[1], D. Menotti[1], S. Sciabolacci[2], M.P. Martelli[2], A. Fiorentini[1], L. Falini[2], L. Brunetti[2], A. D'Arpino[3], C. Romani[4], B. Falini[2], A. Olivieri[1]

[1]Clinica di Ematologia, Azienda Ospedaliero Universitaria Ospedali Riuniti di Ancona; [2]Ematologia e Immunologia Clinica, Dipartimento di Medicina e Chirurgia, Università degli Studi di Perugia; [3]Direttore S.C. Farmacia, Azienda Ospedaliera di Perugia; [4]S.C. Ematologia e CTMO, Ospedale A. Businco, ARNAS G. Brotzu

CPX-351 has indication in the treatment of MRC, secondary and therapy related AML having shown better overall survival, extrahematological tolerance and reduced mortality compared to 3+7 in phase III study. In our multicenter real life experience, consolidation was therefore administered as an outpatient treatment, to overcome the paucity of beds, caused by the increased admissions rate for infectious complications, during the COVID emergency. Nine patients, 5 male and 4 female, with a median age of 58 years (52-65 years) received CPX-351 as treatment of 2 morphological MRC, 1 therapy-related, 6 secondary AML, between August 2019 and December 2021.

Table 1. Duration, transfusional need, hemopoietic recovery, hematological and extra-hematological toxicities, infusional reactions of Inpatient and outpatient consolidations.

	8 Outpatient consolidation median (range)	3 Inpatient consolidation median (range)
Duration of ambulatorial administration	2	-
Duration of in-hospital administration /non intensive unit readmission	-/0(0-7)*	20 (14-22)/-
Duration of ICU** readmission	0	0
Red blood cells transfusions	0	2
Platelets transfusions	1 (0-3)	1
Duration of neutropenia <500/μl	11 (7-15)	5.5 (2-9)
Duration of neutropenia <1000/μl	13 (11-17)	6.5 (3-10)
Duration of thrombocytopenia < 50,000/μl	11 (10-11)	11.5 (11-12)
Duration of thrombocytopenia <100,000/μl	21 (15-37)	19.5 (18-21)
Duration of iv antibiotic therapy	0 (0-7)	0,5 (0-1)
Duration of iv antifungal therapy	0	0
Chinolonic prophylaxis	11 (7-15)	6 (3-9)
Antifungal prophylaxis	11 (7-15)	3 (3-3)
Infection incidence Febrile neutropenia incidence	0 0	0 1/3
Grade I-II extrahematological toxicity incidence	0	1/3 intestinal mucositis for 2 days
Grade III-IV extrahematological toxicity incidence	0	0
Incidence of infusional reactions: grade I-II grade III-IV	 2/8 (rash) 2/8 (fever, serum sickness disease)	 1/3 (rash and fever) 1/3 (rash, fever and myalgias)

***3 patients had non-intensive readmission: 2 for infusional reactions and one for pre-transplant work-up exames. **ICU: intensive care unit.**

Of the 9 patients, 1 refractory, received reinduction chemotherapy with high-dose cytarabine and idarubicin as a bridge to allogeneic transplantation in CR. Eight responding patients, 5 with negative MRD and 3 with positive MRD, received consolidation, of these one relapsed early and was treated with Decitabine and Venetoclax, achieving a negative MRD response, the remaining patients maintained the response except one who converted positive to negative MRD. Four patients were bridged to allogeneic transplantation, while 3 received a second consolidation followed by allogeneic transplantation. A total of 11 cycles of consolidation were administered: 8 outpatient and 3 inpatient. Of the 8 outpatient patients, 3 were hospitalized for 7 days: 2 for infusion reactions, 1 for pre-transplant work-up examinations who then spent the aplasia at home. None required ICU admission. Hematologic recovery, transfusions, and toxicities did not differ in the 2 groups and are summarized in Table 1. The median duration of hospitalization was 2 days in the outpatients *vs*

20 days (14-22) in the inpatients. Eight of the 9 patients were still alive and in remission, whereas the patient refractory to CPX351, relapsed and died one year after transplant, due to disease progression. The reduction in hospitalization resulted in lower costs due to the different value of DRGs in the outpatient versus the inpatient regimen. A previous review of the phase III registrative study showed that 51% of patients received at least one consolidation with CPX351 in the outpatient regimen *vs* 6% of patients treated with 2+5. Our real life experience confirms the extra-hematological tolerance of CPX351 that allows the outpatient administration of consolidation, with a reduction in costs, bed occupancy and a preserved dose intensity compliance, even in emergency periods.

P052

EFFICACY OF COMBINED HYPOMETHYLATING AGENTS AND VENETOCLAX IN EXTRAMEDULLARY ACUTE MYELOID LEUKEMIA DISEASE

C. Vetro[1], V. Calafiore[2], A. Duminuco[3], C. Maugeri[1], M.S. Parisi[1], E. Mauro[1], P.F. Fiumara[1], B. Garibaldi[3], G.A.M. Palumbo[1,3], S. Leotta[1], F. Di Raimondo[1], C. Patti[2], A. Mulè[2]

[1]Division of Haematology, A.O.U. Policlinico "G. Rodolico" - S.Marco, Catania, Italy; [2]Division of Hematology & Bone Marrow Transplantation, Ospedali Riuniti Villa Sofia-Cervello, Palermo, Italy; [3]Postgraduate School of Hematology, University of Catania, Italy

Background: Venetoclax (VEN) has been used, combined with hypomethylating agents (HMA) (azacytidine -AZA- or decitabine -DEC), for the treatment of unfit adult acute myeloid leukemia (AML). Although widely used, very few data exist on its efficacy in extramedullary AML disease (EMD). The aim of this analysis is to explore, in a real-life setting, the efficacy of HMA-VEN in patients (pts) with EMD.

Methods: From May 2020 to October 2021, we treated 9 pts with AZA-VEN. All but two underwent AZA-VEN as second line therapy (4 refractory to 7+3, 1 refractory to CPX351, 1 relapsed after allogeneic bone marrow transplantation (BMT)), while remaining two pts were treated upfront. Median age was 56 years (range 28-71). Two pts had NPM1 mutation. None had FLT3-ITD or IDHs mutations. One had inv(16), 1 hyperdiploid karyotype and 1 failed cytogenetic, remaining pts had normal karyotype. At time of treatment, 4 pts had EMD without bone marrow (BM) involvement (2 with sole skin, 1 with skin and chest wall and 1 with left arm soft tissue involvement), while 5 pts had concomitant BM involvement (two with skin and 1 with central nervous system involvement and 1 with mediastinal mass).

Results: Pts were treated with AZA-VEN according to Gozzo *et al*., Front Pharmacol. 2021. Most frequent complication was febrile neutropenia (3/9, 33%). 6 pts (66%) experienced a disappearance of EMD (4 had also medullary disease, who responded to treatment), 1 pts(11%) showed a partial remission of EMD (had no BM involvement) and two pts (22%) were refractory (both at first line). 5 responding pts underwent allogeneic BMT. After a median follow-up of 11 months (mo), 4 out of 9 (44%) pts are alive and 4 pts out of the 6 who reached EMD resolution (67%) relapsed. Median progression-free survival (PFS) was 5.7 mo. Pts without BM involvement at time of treatment begin showed a higher PFS compared to pts with concomitant BM involvement (5.7 mo *vs* 3.8 mo, p=0.046). Median overall survival (OS) was 10.5 mo. Pts with concomitant BM involvement had a trend to inferior OS compared to pts with sole EMD (4.5 mo *vs* not reached median, p=0.054). Gender, age, line of therapy, cytogenetic and molecular biology and BMT did not relate with OS and PFS, also because the limited sample size.

Conclusions: AZA-VEN combination therapy seems to be effective in inducing remission in EMD and its efficacy over time would be dependent on concomitant BM involvement. Larger sample size is needed to confirm these findings.

P053

THE "IRON WALL" AGAINST HYPOMETYLATING AGENTS: CHRONIC HYPERFERRITINEMIA WORSEN HEMATOLOGIC RESPONSE AND TRANSFUSION BURDEN IN TRANSPLANT-INELEGIBLE PATIENTS WITH ACUTE MYELOID LEUKEMIA AND INTERMEDIATE / HIGH RISK IPSS / R-IPSS MYELODISPLASTIC SYNDROME

A. Roppolo, C. Spoto, R. Tomasello, A. Rizzuto, A. Pirrera, E. Gigliotta, C. Vullo, G. Camarda, C. Rotolo, M. Napolitano, M. Santoro, S. Mancuso, C. Botta, S. Siragusa

Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties (ProMISE), University of Palermo, Italy

Hypometylating agents (HMAs) Azacitidine (AZA) and Decitabine (DEC) represent a safe and effective therapeutic option for transplant-ineligible acute myeloid leukemia (AML) and intermediate (IR)/high (HR) risk myelodysplastic syndrome (MDS). Given the frailty of these patients, the demand for supportive therapies, such as blood transfusions, is generally moderate/high, thus leading to the risk of iron overload. (IO). Several works on small sample sizes suggest that IO could impair the physiological maturation of myeloid precursors (*e.g.* erythroblasts) as well as patients outcome. Additionally, ineffective erythropoiesis contributes to IO by down-regulating hepcidin, thus increasing intestinal iron absorption. Here, we performed a retrospective analysis on a small population of 11 patients (Figure 1A) with a median age of 73yo (range: 51 to 82yo), M:F ratio of 1.2:1, with a new diagnosis of AML (5/11) or IR/HR MDS (5/11) transplant-ineligibles, treated with AZA (9/11) or DEC (2/11) who were consecutively admitted to our outpatients service in the last 2 years. According to ferritin levels (measured after 4-6 months from the beginning of therapy), patients were divided into a group of "high ferritin" patients (HFPs, >1000ng/ml, 5/11 patients) and a group of "low ferritin" patients (LFPs, <1000ng/ml, 6/11). HFPs showed a reduced peripheral blood cellularity recover, as demonstrated by the non-significant increase in Hb levels (baseline *vs* post: 7.7 *vs* 8.8 g/dl, p:0.13) as compared to LFPs (baseline *vs* post: 8.1 *vs* 11.2 g/dl, p:0.01) (Figure 1B). To further support the hypothesis of a HMAs-related effect, we evaluated the increase of Hb after 4 months from start of treatment in a control group of 11 consecutive AML patients treated with HDC, observing that the increase of Hb was achieved regardless of baseline ferritin values (Figure 1C). Interestingly, we observed a significant post treatment ferritin increase in the control group (Figure 1D).

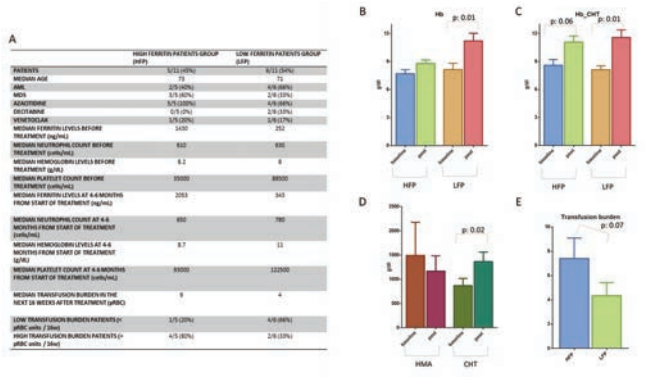


Figure 1.

In HMA patients, a strong difference in transfusion burdens (calculated on packed RBC units (pRBC) per 16 weeks, starting from the beginning of the treatment) was observed between HFPs and LFPs (mean 7.4 *vs* 4.33; p: 0.07). These data provide preliminary evidence that maintaining

ferritin levels below the 1000 ng/ml threshold may improve patients' response to HMAs: this finding support the investigation of iron-chelating agents efficacy in this setting. However, larger multi-center studies are required to validate these findings.

P054

CAN WE INTENSIVELY AND SAFELY TREAT OLDER PATIENTS (>55YEARS) WITH ACUTE LYMPHOBLASTIC LEUKEMIA? A SINGLE CENTRE REAL LIFE EXPERIENCE FROM 2001 TO 2021

T. Zollner[1,2], E. Borlenghi[1], C. Cattaneo[1], M. Malagola[2], C. Pagani[1], M. Oberti[1], E. Cerqui[1], N. Bianchetti[1], A. Passi[1], A. Sottini[4], S. Bagnasco[1], C. Bottelli[1], D. Bertoli[3], L. Imberti[4], S. Archetti[3], G. Rossi[1], A. Tucci[1]

[1]UOC Ematologia , ASST Spedali Civili; [2]Cattedra di Ematologia, Università degli Studi di Brescia; USD Trapianto Midollo Adulti e Programma Terapie Cellulari e Ricerca, ASST Spedali Civili; [3]Dipartimento di Diagnostica, Laboratorio di Chimica Clinica, ASST Spedali Civili; [4]Dipartimento di Diagnostica, Laboratorio CREA (ALL Center for Hemato-Oncologic Research), ASST Spedali Civili, Italy

Acute Lymphoblastic Leukemia (ALL) in the elderly (≥55y old) is potentially curable but its treatment is challenging due to their multiple comorbidities and poor tolerance to intensive therapy (iT).

We have retrospectively analysed the outcome of 81 older ALL patients (pts)(median age 70, range 55-88), consecutively diagnosed between 2001 and 2021. They represent 36% of ALL pts diagnosed at our Unit. Phenotype was B in 65 (80%), T in 15 (19%), mixed in 1, BCR/ABL was detected in 27 pts (33%). B mature ALL were excluded.

iT, defined as dose-adjusted chemotherapy (CT) (NILG protocols) with curative intent, was given to 57 pts (70%), + TKI in 20 Ph+. By clinical judgement based on comorbidities and PS, 7 Ph+ pts received TKI alone and 17 pts non-iT (steroid or low-dose CT). Stem cell transplantation (SCT) was performed in 29 pts: autologous in 14 MRD-neg (17%) (4 Ph+), allogeneic in 15 (19%) (6 Ph+). In 8 pts (4 Ph+) blinatumomab or inotuzumab were given as salvage. At a median follow up of 39 months (m) (range 1-155), the median OS was 15.9 m with significant age-related differences: <65y: 47m; 65-70y: 18,2m; >70y: 8.2 m, p=0.008. OS was 36 +/-5% at 3y and 26+/-5% at 5y. Among Ph- pts (median age 70), 37 (68%) received iT. Their OS was 45+/-9% at 3y and 33+/-9% at 5y. It did not differ significantly from that of 20 Ph+ pts (median age 67) receiving iT+TKI (54+/-11% at 3y and 37+/-11% at 5y). (Figure 1a) Pts undergoing autologous or allogeneic SCT had similar survival (median 44 *vs* 47 m).

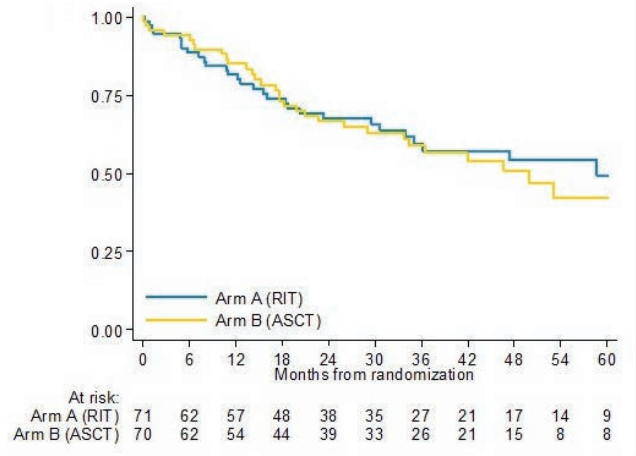


Figure 1.

Survival of pts aged >70 (10 Ph- and 5 Ph+) treated with iT+/-TKI did not differ significantly compared to pts <70. (Figure 1b). Among pts receiving iT, 7 deaths (12%) were therapy-related, including 3 post-alloSCT; pts age was <70y in all of them. Disease progression accounted for 52% of deaths.

Among pts not treated with iT median OS was 9.5m in Ph+ pts given TKI only and 2.4m in Ph- pts. (Figure 1a). Age, non-iT, PS, ALL risk and sex significantly affected OS but only non-iT retained independent adverse prognostic significance at multivariate analysis.

In our series older pts represented over 1/3 of adults with ALL. Using iT with curative intent in 70% of them achieved 33-37% long-term OS, irrespective of Ph status. While age remained an adverse prognostic factor, receiving iT rather than calendar age proved to independently affect survival. Avoiding treatment-related deaths by better selection of pts and using more tailored treatment modalities will further improve results.

Lymphomas I

P055

ABSTRACT NOT PUBLISHABLE

P056

A PHASE 1 STUDY WITH THE NOVEL B-CELL LYMPHOMA 2 (BCL2) INHIBITOR BGB-11417 AS MONOTHERAPY OR IN COMBINATION WITH ZANUBRUTINIB (ZANU) IN PATIENTS (PTS) WITH B-CELL MALIGNANCIES: PRELIMINARY DATA

P. Ghia[1], S. Opat[2,3], C. Cheah[4,5,6], M. Lasica[7], E. Verner[8,9], P. Browett[10], H. Chan[11], J. Soumerai[12], E. González Barca[13], J. Hilger[14], Y. Fang[14], D. Simpson[14], C. Tam[15,16,17]

[1]Università Vita-Salute San Raffaele and IRCCS Ospedale San Raffaele; [2]Monash Health; [3]Monash University; [4]Sir Charles Gairdner Hospital and Pathwest Laboratory Medicine; [5]Medical School, University of Western Australia; [6]Linear Clinical Research; [7]St Vincent's Hospital Melbourne; [8]Concord Repatriation General Hospital; [9]University of Sydney; [10]Auckland City Hospital; [11]North Shore Hospital Auckland; [12]Massachusetts General Hospital Cancer Center, Harvard Medical School; [13]Institut Català d'Oncologia-Hospitalet, IDIBELL, Universitat de-Barcelona; [14]BeiGene (Beijing) Co., Ltd., BeiGene USA, Inc; [15]Peter MacCallum Cancer Centre; [16]University of Melbourne; [17]Royal Melbourne Hospital

BCL2 is aberrantly expressed in many hematologic malignancies and promotes tumorigenesis. The BCL2 inhibitor, venetoclax, is associated with mild gastrointestinal toxicities, neutropenia, and development of BCL2 mutations leading to resistance. BGB-11417-101 (NCT04277637) is an ongoing first-in-human phase 1/1b dose-escalation and expansion study to evaluate safety, tolerability, maximum tolerated dose (MTD), and recommended phase 2 dose of oral BGB-11417 alone or combined with the BTK inhibitor zanu, in pts with relapsed/refractory (R/R) B-cell malignancies. Pts in separate monotherapy and combination therapy cohorts received escalating BGB-11417 doses (40, 80, 160, 320, or 640 mg once daily [QD]) with weekly or daily ramp-up to the target dose; combination cohorts received zanu (320 mg QD or 160 mg twice daily) 8-12 wks before BGB-11417. Dose-limiting toxicity for each dose cohort was evaluated by a Bayesian logistic regression model. Adverse events (AEs) were reported per CTCAE v5.0. As of 17Dec2021, 58 pts received BGB-11417 (32 monotherapy; 26 combination). Of pts receiving BGB-11417 monotherapy, 26 with non-Hodgkin lymphoma (NHL) received doses ≤640 mg and 6 with CLL/SLL received ≤160 mg. Of pts receiving combination treatment, 19 with R/R CLL/SLL received BGB-11417 ≤160 mg and 7 with R/R MCL received ≤80 mg. MTD has not yet been reached. Median follow-up was 3.9 mo (range, 0.1-20.4). AEs are listed in the Table 1. Only 2 grade ≥3 AEs (1 neutropenia, 1 autoimmune hemolytic anemia) were reported in combination cohorts. 20 pts discontinued treatment (17 disease progression; 1 AE; 2 other reasons). One high-risk pt with CLL on monotherapy had laboratory tumor lysis syndrome (TLS) that resolved with no intervention (laboratory TLS <2%). Early efficacy data show that most pts had reduction in sum of product of perpendicular diameters; 2 pts with NHL (monotherapy) had responses (1 complete response). Pts with CLL/SLL had notable reductions in absolute lymphocyte count at doses as low as 1 mg; 2 responses (≥partial response) were seen with monotherapy and 12 responses with combination (≥partial response with lymphocytosis). These preliminary findings suggest that BGB-11417 has promising efficacy and is tolerable at doses ≤640 mg as monotherapy and ≤160 mg in combination with zanu. Dose escalation continues as an MTD has not yet been reached. Enrollment is ongoing, data for Waldenström macroglobulinemia and treatment-naïve CLL/SLL cohorts are forthcoming.

Table 1. Safety Summary.

BGB-11417 Monotherapy (n=32)		
Any AE in >10% of pts, n (%)	**Grade ≥3**	**All Grade**
Nausea	0	12 (37.5)
Diarrhea	0	8 (25.0)
Fatigue	0	8 (25.0)
Neutropenia	6 (18.8)	8 (25.0)
Pyrexia	1 (3.1)	6 (18.8)
Constipation	0	5 (15.6)
Dizziness	0	5 (15.6)
Fall	2 (6.3)	5 (15.6)
Headache	0	5 (15.6)
Abdominal Pain	2 (6.3)	4 (12.5)
Oedema peripheral	0	4 (12.5)
Thrombocytopenia	2 (6.3)	4 (12.5)
Urinary tract infection	0	4 (12.5)
BGB-11417 + zanu Combination (n=26)		
Contusion	0	6 (23.1)
Nausea	0	6 (23.1)
Diarrhea	0	5 (19.2)
Fatigue	0	4 (15.4)
Back pain	0	3 (11.5)
Headache	0	3 (11.5)
Petechiae	0	3 (11.5)

AE, adverse event

P057

ASPEN: LONG-TERM FOLLOW-UP RESULTS OF A PHASE 3 RANDOMIZED TRIAL OF ZANUBRUTINIB (ZANU) VS IBRUTINIB (IBR) IN PATIENTS WITH WALDENSTRÖM MACROGLOBULINEMIA (WM)

A. Tedeschi[1], C. Tam[2], R. Garcia-Sanz[3], S. Opat[4], S. D'Sa[5], W. Jurczak[6], H. Lee[7], G. Cull[8], R. Owen[9], P. Marlton[10], B. Wahlin[11], J. Castillo[12], T. Siddiqi[13], C. Buske[14], V. Leblond[15], W. Chan[16], J. Schneider[16], A. Cohen[16], M. Dimopoulos[17]

[1]ASST Grande Ospedale Metropolitano Niguarda; [2]Peter MacCallum Cancer Centre; [3]Hospital Universitario de Salamanca; [4]Monash Health, Monash University; [5]Centre for Waldenström's Macroglobulinemia and Associated Disorders, University College London Hospital Foundation Trust; [6]Maria Sklodowska-Curie National Institute of Oncology; [7]Flinders Medical Centre; [8]Sir Charles Gairdner Hospital, University of Western Australia; [9]St. James University Hospital; [10]Princess Alexandra Hospital, University of Queensland Brisbane; [11]Karolinska Universitetssjukhuset and Karolinska Institutet; [12]Bing Center for Waldenström Macroglobulinemia, Dana-Farber Cancer Institute, Harvard Medical School; [13]City Of Hope National Medical Center; [14]CCC Ulm - Universitätsklinikum Ulm; [15]Sorbonne University, Pitié Salpêtrière Hospital; [16]BeiGene USA, Inc; [17]National and Kapodistrian University of Athens

ASPEN is a randomized, open-label, phase 3 study comparing zanu, a potent and selective Bruton tyrosine kinase inhibitor (BTKi), with the first-generation BTKi, ibr, in patients with WM. Data with a median follow-up of 43 months is presented. Patients with MYD88 mutations were assigned to cohort 1 and randomized 1:1 to receive zanu 160 mg twice daily or ibr 420 mg once daily. Randomization was stratified by CXCR4

mutational status and lines of prior therapy (0 *vs* 1-3 *vs* >3). Patients without MYD88 mutations were assigned to cohort 2 and received zanu 160 mg twice daily. The primary endpoint was the proportion of patients achieving complete response or very good partial response (CR+VGPR). A total of 201 patients (zanu arm, n=102; ibr arm, n=99) were enrolled in cohort 1 and 28 patients were enrolled in cohort 2. A larger proportion of patients in the zanu arm of cohort 1 *vs* ibr had CXCR4 mutations by next-generation sequencing (32% *vs* 20%, or 33 of 98 *vs* 20 of 92 with data available) and were aged >75 years (33% *vs* 22%). Median duration of treatment was 42 months (zanu) and 41 months (ibr), with 67% and 58% remaining on treatment, respectively. The CR+VGPR rate by investigator assessment was 36% with zanu *vs* 22% with ibr (P=0.02) in cohort 1, and 31% in cohort 2. One patient in cohort 2 achieved CR. In patients with wild type or mutant CXCR4 from cohort 1, CR+VGPR rates with zanu *vs* ibr were 45% *vs* 28% (P=0.04) and 21% *vs* 5% (P=0.15), respectively. Median progression-free survival and overall survival were not yet reached. Rates of atrial fibrillation, diarrhea, hypertension, localized infection, hemorrhage, muscle spasms, pneumonia, and adverse events leading to discontinuation or death were lower with zanu *vs* ibr (table). Exposure-adjusted incidence rates of atrial fibrillation/flutter and hypertension were lower with zanu *vs* ibr (0.2 *vs* 0.8 and 0.5 *vs* 1.0 persons per 100 person-months, respectively; P<0.05). Rate of neutropenia was higher and rate of grade ≥3 infection was lower with zanu *vs* ibr. Safety outcomes of zanu were similar between cohorts 1 and 2. ASPEN is the largest phase 3 trial with head-to-head BTKi comparison in WM. At a median follow-up of 43 months, zanu was associated with higher CR+VGPR rate and demonstrated clinically meaningful advantages in long-term safety and tolerability *vs* ibr.

Table 1. Safety Summary.

AE (all grade), % of treated patients	Cohort 1 zanu (n=101)	Cohort 1 ibr (n=98)	Cohort 2 zanu (n=28)
AE, grade ≥3	74.3	72.4	71.4
AE leading to discontinuation	8.9	19.4	14.3
Atrial fibrillation / flutter[a]	7.9	23.5	7.1
Diarrhea	21.8	34.7	32.1
Hemorrhage[a] / major bleeding[b]	55.4 / 7.9	62.2 / 12.2	39.3 / 7.1
Hypertension[a]	14.9	25.5	10.7
Muscle spasm	10.9	28.6	14.3
Neutropenia[a]	33.7	19.4	21.4
Infection[a] (grade ≥3) / pneumonia	78.2 (20.8) / 5.0	79.6 (27.6) / 18.4	82.1 (32.1) / 14.3

[a]Grouped term. [b]Includes grade ≥3 hemorrhage and central nervous system bleeding of any grade. AE, adverse event; ibr, ibrutinib; zanu, zanubrutinib.

P058

GLOFITAMAB IN PATIENTS WITH RELAPSED/REFRACTORY (R/R) DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL) AND ≥2 PRIOR THERAPIES: PIVOTAL PHASE II EXPANSION RESULTS

C. Carlo-Stella[1], M. Hutchings[2], M. Dickinson[3], F. Morschhauser[4], E. Bachy[5], P. Corradini[6], G. Iacoboni[7], C. Khan[8], T. Wróbel[9], F. Offner[10], M. Trněný[11], S.-J. Wu[12], G. Cartron[13], M. Hertzberg[14], A. Sureda[15], D. Perez-Callejo[16], L. Lundberg[16], J. Relf[17], E. Clark[17], K. Humphrey[17]

[1]Humanitas University and IRCCS Humanitas Research Hospital; [2]Rigshospitalet; [3]Peter MacCallum Cancer Centre, Royal Melbourne Hospital and The University of Melbourne; [4]Hôpital Claude Huriez and CHU de Lille; [5]Centre Hospitalier Lyon-Sud; [6]Università degli Studi di Milano and Fondazione Istituti di Ricovero e Cura a Carattere Scientifico (IRCSS) Istituto Nazionale dei Tumori; [7]Vall d'Hebron University Hospital; [8]Allegheny Health Network; [9]Uniwersytet Medyczny we Wrocławiu; [10]Universitair Ziekenhuis Gent; [11]Charles University Hospital; [12]National Taiwan University Hospital; [13]CHU de Montpellier; [14]Prince of Wales Hospital and University of New South Wales; [15]Institut Català d'Oncologia Hospitalet; [16]F. Hoffmann-La Roche Ltd; [17]Roche Products Ltd.

Introduction: Glofitamab is a T-cell-engaging bispecific antibody (Ab) with a novel 2:1 configuration that confers bivalency for CD20 (B-cells) and monovalency for CD3 (T-cells). In a Phase I/II study (NCT03075696), escalating glofitamab doses were highly active and well tolerated in pts with R/R B-cell lymphomas, with obinutuzumab pretreatment (Gpt) and Cycle (C) 1 step-up dosing providing effective cytokine release syndrome (CRS) mitigation. We present first Phase II expansion results in pts with R/R DLBCL and ≥2 prior therapies.

Methods: Prior regimens of DLBCL (DLBCL NOS, HGBCL, PMBCL or trFL) pts included ≥1 anti-(a) CD20 Ab and ≥1 anthracycline. IV Gpt (1000mg) was given 7 days before the first IV glofitamab dose (step-up doses of glofitamab on Day [D] 1 [2.5mg] and D8 [10mg] of C1 and at target dose [30mg] on D1 of C2–12 [21-day cycles]). Primary endpoint was CR rate (best response) assessed by Independent Review Committee (Lugano 2014 criteria).

Results: As of Sep 14, 2021, 107 pts had received ≥1 dose of study treatment (median age: 66 yrs [21–90]; Ann Arbor stage III–IV disease: 74%; IPI score ≥3: 54%; DLBCL NOS: 74%). Median number of prior therapies was 3 (2–7); 59% had ≥3 prior therapies and 35% had received prior CAR T-cells (CAR-Ts). Most pts were refractory to a prior aCD20 Ab-containing regimen (85%) and to their most recent regimen (85%). Many were refractory to their initial therapy (59%) and to prior CAR-Ts (32%). After a median follow-up of 9 months (0.1–16), ORR and CR rates were 50.0% and 35.2%, respectively. CR rates were consistent in pts with and without prior CAR-Ts (32% *vs* 37%). Median time to CR was 42 days (95% CI 41–48). At data cut, the majority of CRs (33/38; 87%) were ongoing, the projected 12-month OS rate was 48%, and 92% of complete responders were alive. CRS occurred in 68% of pts, was primarily associated with initial doses, and mostly Gr 1 (51%) or Gr 2 (12%). All but 2 CRS events were resolved at data cut. Glofitamab-related neurologic AEs potentially consistent with ICANS occurred in 3 pts (all Gr 1–2). No fatal glofitamab-related AEs occurred. Glofitamab-related AEs leading to discontinuation were uncommon (3 pts, 3%).

Conclusions: Fixed-duration glofitamab induces durable complete remissions and has favorable safety in pts with R/R DLBCL and ≥2 prior therapies, including those with prior exposure to CAR-Ts. Glofitamab is a promising new therapy for pts with heavily pretreated and/or highly refractory DLBCL.

P059

GLOFITAMAB STEP-UP DOSING INDUCES HIGH RESPONSE RATES IN PATIENTS (PTS) WITH RELAPSED OR REFRACTORY (R/R) MANTLE CELL LYMPHOMA (MCL), MOST OF WHOM HAD FAILED PRIOR BRUTON'S TYROSINE KINASE INHIBITOR (BTKI) THERAPY

C. Carlo-Stella[1], M. Dreyling[2], T. Phillips[3], M. Dickinson[4], F. Morschhauser[5], E. Bachy[6], M. Crump[7], M, Trněný[8], N. Bartlett[9], J. Zaucha[10], K. Humphrey[11], D. Perez-Callejo[12], L. Lundberg[12], J. Relf[11], A.F. de L'Etang[12], D. Carlile[11], E. Clark[11]

[1]Humanitas University and Humanitas Research Hospital; [2]Medizinische Klinik und Poliklinik III, Ludwig-Maximilians-Universität München; [3]University of Michigan Medical School; [4]Peter MacCallum Cancer Centre, Royal Melbourne Hospital and The University of Melbourne; [5]CHU Lille, Service des Maladies du Sang, Lille; [6]Hospices Civils de Lyon and Université Claude Bernard; [7]Princess Margaret Hospital, Toronto; [8]1st Fac Medicine, Charles University, General Hospital; [9]Washington University, Siteman Cancer Center St. Louis; [10]Medical University of Gdańsk; [11]Roche Products Ltd; [12]F. Hoffmann-La Roche Ltd.

Background: Glofitamab is a T-cell-engaging CD20xCD3 bispecific antibody with a novel 2:1 molecular configuration that confers bivalency for CD20 (B-cells) and monovalency for CD3 (T-cells). Glofitamab with obinutuzumab pretreatment (Gpt) has shown promising efficacy and manageable tolerability in non-Hodgkin lymphoma (NHL). Pts with MCL have a 2-fold higher clearance of obinutuzumab *vs* other NHL histologies (Gibiansky *et al.* 2014). A higher dose of Gpt prior to glofitamab step-up dosing (SUD) may reduce the risk of cytokine release syndrome (CRS) in MCL. We report preliminary data in pts with R/R MCL.

Methods: All pts received Gpt 7 days prior to glofitamab. Intravenous glofitamab SUD was given on days 1 and 8 of Cycle (C)1, then at the target dose from C2 day (D)1 (from C3D1 for SUD starting at 0.5mg), every 3 weeks for up to 12 cycles (0.5/2.5/10/30, 2.5/10/16 or 2.5/10/30mg after 1000mg Gpt, or 2.5/10/30mg after 2000mg Gpt). Pts on fixed dosing received glofitamab (0.6, 16 or 25mg) after 1000mg Gpt from C1 for up to 12 cycles. Response rates (RR) are based on the Lugano criteria.

Results: As of May 18, 2021, 29 pts had received glofitamab: fixed dosing after 1000mg Gpt (n=3); SUD after 1000mg Gpt (n=7) or 2000mg Gpt (n=19). Median age was 69 years (69% male), 83% had Ann Arbor Stage III–IV disease, 62.1% had MCL international prognostic index score ≥6. Median prior therapy lines were 3, 69% had prior BTKi and 14% prior lenalidomide therapy. Many pts were refractory to their first (52%) and/or last prior therapy (69%) (median time since last therapy was 1.7 months). In efficacy-evaluable pts (n=21), the overall RR was 81.0% and complete metabolic RR 66.7%. Similar RRs were observed in pts with or without prior BTKi therapy. At data cut-off, 85.7% with a CR remained in remission. In safety-evaluable pts (n=29), the most common adverse events (AEs) were CRS (58.6%) and infusion-related reactions (24.1%). CRS events were Grade (Gr) 1–2, except for 1 Gr4 CRS in the 1000mg Gpt + SUD cohort (pt died due to rapid PD). All CRS events were manageable. Neurologic AEs occurred in 6 pts (all Gr1–2). Immune effector cell-associated neurotoxicity syndrome (ICANS)-like AEs occurred in 1 pt (2 Gr1–2 events). Tumor flare events occurred in 3 pts (all Gr1–2). No pts discontinued treatment due to AEs. Three treatment-unrelated deaths were reported.

Conclusions: Glofitamab SUD after Gpt induced high RRs in pts with MCL. CRS rates were manageable and mostly low grade.

P060

SUBCUTANEOUS EPCORITAMAB WITH RITUXUMAB + LENALIDOMIDE IN PATIENTS WITH RELAPSED OR REFRACTORY FOLLICULAR LYMPHOMA: PHASE 1/2 UPDATE

L. Falchi[1], S. Leppä[2], B.E. Wahlin[3], M. Nijland[4], J.H. Christensen[5], S. de Vos[6], H. Holte[7], K.M. Linton[8], A. Abbas[9], L. Wang[9], M. Dinh[10], B. Elliott[9], D. Belada[11]

[1]Lymphoma Service, Memorial Sloan Kettering Cancer Center; [2]Helsinki University Hospital Comprehensive Cancer Center and University of Helsinki; [3]Karolinska Institutet; [4]University Medical Center Groningen and University of Groningen; [5]Odense University Hospital; [6]Ronald Reagan University of California Los Angeles Medical Center; [7]Oslo University Hospital and KG Jebsen Center for B-cell Malignancies; [8]The Christie NHS Foundation Trust and Manchester Cancer Research Centre; [9]Genmab; [10]AbbVie; [11]4th Department of Internal Medicine – Hematology, University Hospital and Faculty of Medicine

Relapsed or refractory (R/R) follicular lymphoma (FL) has a poor prognosis, with less frequent, shorter responses following each line of treatment. Rituximab + lenalidomide (R^2) is an effective regimen with acceptable safety in R/R FL, but the disease remains incurable. Epcoritamab (epco) is an investigational bispecific antibody binding to CD3 on T cells and CD20 on malignant B cells. We present updated data for arm 2 of the phase 1/2 EPCORE NHL-2 trial (NCT04663347), which is evaluating subcutaneous epco + R^2 in adult patients (pts) with R/R FL. Epco and R^2 were administered for 12 cycles (C) of 28 d followed by epco monotherapy, using corticosteroids and epco step-up dosing in C1 to mitigate CRS. The regimen for epco dosing was: QW, C1–3; Q2W, C4–9; and Q4W, C≥10 up to 2 y. Response was assessed using PET-CT. By the data cutoff on December 1, 2021, 30 pts had received epco (24 mg, n=3; 48 mg, n=27) + R^2. The median age was 68 y, 70% had stage IV disease, and 67% had a FLIPI score of 3–5. The median number of prior lines of treatment was 1 (range, 1–5), 30% had primary refractory disease, and 40% had experienced disease progression within 24 mo after starting first-line treatment (20% within 24 mo after starting immunochemotherapy). With a median follow-up of 5.1 mo (range, 0.8–12.3), 25 pts (83%) remained on treatment. Five pts discontinued therapy due to disease progression (n=2), AEs (n=2), or withdrawal of consent (n=1). Infections (57%), injection-site reactions (50%), constipation (37%), fatigue (37%), and neutropenia (37%) were common treatment-emergent AEs (TEAEs) of any grade (G). CRS was seen in 50% of pts (G1/2 43%, G3 7%), mostly occurring in C1. All CRS events resolved with standard management, with median time to resolution of 3 d; 3 pts were treated with tocilizumab, and 1 pt discontinued treatment due to CRS. One pt had G2 ICANS, which resolved. There were no fatal TEAEs. Of 27 efficacy-evaluable pts, 93% (25/27) had a complete metabolic response (CMR) and 7% (2/27) had a partial metabolic response for an overall response rate of 100%. As of the data cut, the longest duration of response was 7.0 mo and ongoing. Subcutaneous epco + R^2 showed promising efficacy with a high CMR rate in pts with R/R FL. The safety profile was consistent with previous reports, and CRS events were mostly of low grade and in C1. Updated data with approximately 30 additional pts will be presented.

This study was funded by Genmab A/S and AbbVie.

P061

OUTCOME OF FOLLICULAR LYMPHOMA PATIENTS IN MAINTENANCE TREATMENT WITH ANTICD20 MONOCLONAL ANTIBODIES IN THE SARS-COV2 ERA: RESULTS FROM A MULTICENTER, RETROSPECTIVE AND PROSPECTIVE ITALIAN STUDY

A. Castellino[1], C. Castellino[1], C. Boccomini[2], M. Clerico[3], P. Nicoli[4], A. Vanazzi[5], F. Fanelli[6], T. Perrone[7], F. Marchesi[8], F. Cocito[9], M. Merli[10], S. Bigliardi[11], B. Mecacci[12], V. Bozzoli[13], G. Margiotta Casaluci[14], E. Meli[15], A. Anastasia[16], L. Farina[17], O. Annibali[18], D. Gottardi[19], M. Zanni[20], A. Conconi[21], C. Ciochetto[22], N. Cenfra[23], F. Rotondo[24], R. Sara[25], A. Cuneo[26], C. Selleri[27], S. Galimberti[28], M. Massaia[1]

[1]Hematology Unit, Santa Croce e Carle Hospital; [2]Hematology Unit, Città della Salute e della Scienza Hospital; [3]Hematology Unit, Città della Salute e della Scienza University; [4]Hematology Unit, San Luigi Gonzaga Hospital and University; [5]Hematology Unit, Istituto Europeo di Oncologia; [6]Hematology Unit, San Camillo Hospital; [7]Hematology Unit, Policlinico Hospital; [8]Hematology Unit, IRCCS Regina Elena National Cancer Institute; [9]Hematology Unit, San Gerardo Hospital; [10]Hematolgy Unit, Ospedale di Circolo ASST Sette Laghi; [11]Hematology Unit, Ospedale Civile; [12]University of Siena; [13]Hematology Unit, Vito Fazzi Hospital; [14]Divisions of Hematology, Department of Translation Medicine, AOU Maggiore della Carità; [15]Department of Hematology, ASST Grande Ospedale Metropolitano Niguarda. 16Hematology Unit, Ospedali Civili; [17]Hematology Unit, Istituto Nazionale Tumori; [18]Hematology and Bone Marrow Transplant Unit, Università Campus Bio-Medico; [19]Hematology Unit, Mauriziano Hospital; [20]Hematology Unit, SS Arrigo e Biagio Hospital; [21]Hematology Unit, Ospedale degli Infermi; [22]Hematology Unit, ASL TO4; [23]Department of Hematology, Ospedale Santa Maria Goretti; [24]Divisions of Hematology, Ospedale Papardo; [25]Hematology Unit, IRCCS Fondazione San Matteo; [26]Hematology Unit, Sant'Anna Hospital; [27]Hematology Unit, AOU S. Giovanni di Dio e Ruggi D'Aragona; [28]Hematology Unit, Santa Chiara Hospital and University, Italy

Background: Maintenance in FL patients (pts) improves progression free survival (PFS). SARS-Cov2 pandemic posed unique challenges for immunocompromised pts.

Methods: This is an observational, multicenter, retrospective and prospective study, aimed to evaluate outcome of FL pts in maintenance with antiCD20-MoAb during SARS-Cov2 pandemic and how suspension of therapy affected lymphoma outcome and the risk, morbidity and mortality of SARS-Cov2 infection.

Results: 420 pts from 18 Italian Centers were included. Main clinical characteristics were: histological grade 1-2 *vs* 3A in 288 (69%) *vs* 109 (26%), respectively; advanced stage in 361 (86%), high FLIPI score in 192 (46%) pts. All 420 pts were in antiCD20-MoAb maintenance at the time of SARS-Cov2 pandemic onset (March 2020): 333 (79%) were receiving maintenance after a first line, 87 (21%) after a second line. 342 (81%) pts were receiving Rituximab, 75 (18%) Obinutuzumab, 3 pts did not start the planned maintenance. Status of disease after induction was complete remission (CR) in 374 (89%), partial response (PR) in 41 (10%), progressive disease (PD) in 1, not evaluated in 4 patients, respectively. At the end of maintenance was CR in 265 (63%), PR in 19 (4%), stable disease (SD) in one and PD in 14 (3%) pts, maintenance is ongoing in 121 (29%) pts. Because of SARS-Cov2 pandemic maintenance treatment was temporary suspended in 122 (29%), definitively interrupted in123 (29%), not changed in 175 (42%). Median number of maintenance treatment administered at March 2020 was 2, in pts who modified treatment median number of performed *vs* lost courses was 7 (range 0-11) *vs* 2 (range 1-12). Patients were divided into two groups according to the approach to maintenance during pandemic: pts who interrupted maintenance: group A (245 (58%)) *vs* pts who did not modified maintenance: group B (175 (42%)). No differences in clinical characteristics, therapy and response were observed between the two groups. 29(7%) relapses were observed: 16 (7%) *vs* 13 (7%) in group A *vs* B. 70 (17%) pts experienced SARS-Cov2 positivity: 47 (19%) *vs* 23 (13%) in group A *vs* B. 53 (76%) pts had symptomatic COVID and 43 (61%) were hospitalized, with no differences between the two groups. Anti-SARS-Cov2 vaccine was administered in 349 patients, serology assessment was done in 46%, showing 21 (13%) reactive *vs* 138 (87%) not reactive pts, with no differences between the two groups. 21 (30%) pts died because of COVID: 9 (19%) *vs* 12 (52%) in groups A *vs* B.

Conclusions: Suspension of maintenance during SARS-Cov2 pandemic did not show a protection in terms of SARS-Cov2 positivity and morbidity. No differences in terms of relapse rate were observed, but longer follow up is needed.

P062

TREATMENT STRATIFICATION ACCORDING TO BIOLOGICAL PROFILE IMPROVES OUTCOME AND LIMITS THE CNS RELAPSE RISK OF NEWLY DIAGNOSED PATIENTS AFFECTED BY DIFFUSE LARGE B-CELL LYMPHOMA: A REAL-LIFE EXPERIENCE

A. Guidetti[1,2], R. Pasquale[1], A. Dodero[1], A. Chiappella[1], L. Devizzi[1], G. Levati[1], V. Marasco[1], L. Farina[1], M. Di Chio[1], C. Rusconi[1], M. Pennisi[1], P. Corradini[1,2]

[1]Divisione di Ematologia e Trapianto di Midollo, Fondazione IRCCS Istituto Nazionale dei Tumori; [2]Dipartimento di Fisiopatologia Medico-Chirurgica e dei Trapianti, Università degli Studi di Milano, Italy

Diffuse Large B-Cell Lymphoma (DLBCL) is a heterogeneous disease characterized by biological and clinical aspects conditioning different prognosis with variable risk of Central Nervous System (CNS) relapse. Patients (pts) with double hit (DH)/triple hit (TH), double expressor (DE) DLBCL or high CNS-IPI require more intensive regimens including a CNS prophylaxis.

This study was aimed at evaluating survival outcomes and CNS relapse rate of DLBCL pts treated according to biological risk in the real-life clinical practice at Istituto Nazionale dei Tumori in Milano.

We retrospectively collected data of all newly diagnosed DLBCL pts who received a risk-adapted treatment from January 2013 to August 2021. Non DE/DH/TH pts received 6 cycles of R-CHOP; DE pts 6 cycles of R-DA-EPOCH and DH/TH pts 4-6 cycles of R-CODOX-M/R-IVAC. All pts with either extranodal lesions at high risk for CNS relapse or CNS-IPI>3 or DE or DH/TH received CNS prophylaxis with triple intrathecal therapy (TIT) and/or intravenous (iv) high dose (HD)MTX.

Since 2013, 243 DLBCL pts were consecutively treated: 139 non DE/DH/TH pts with R-CHOP, 80 DE pts with R-DA-EPOCH and 24 high risk patients (DH/TH or DE with CNS IPI of 3-5) with R-CODOX-M/R-IVAC. Median age was 62 years (range, 21-86) and 97 (40%) had an IPI of 3-5. CNS-IPI was high in 35 pts (14%), intermediate in 123 (51%) and low in 83 (34%), not available in 2 pts. One-hundred seventy-seven pts (73%) received CNS prophylaxis, 27% TIT, 39% ivMTX and 34% ivMTX+TIT. At a median follow-up of 42 months (range, 2-106 months), 3-years PFS and OS according to biological entity and treatment group were not significantly different, being 84%, 77% and 66%, (p=ns) and 93%, 85% and 74%, (p=ns) in non DE/DH/TH, DE and high risk patients, respectively. Overall, CNS relapses were 9 out of 243 pts for a 3-years rate of 4.4%. Among 119 (49%) pts with very high clinical or biological CNS risk (DE, DH/TH, CNS-IPI 4-6) 3-years rate was 6.6% whereas in R-CHOP, R-DA-EPOCH and R-CODOX-M/R-IVAC was 3.9%, 4.9% and 4.5%, respectively (Fig 1). Seven out of 9 relapsed pts (78%) received CNS prophylaxis (TIT n=3, ivMTX+TIT n=2, ivMTX n=2), one did not because of low CNS-IPI, the other due to unknown reason. Five out of 9 pts (55%) died due to disease progression.

In conclusion, a risk-adapted treatment based on biological risk improves the outcome of high risk DLBCL pts and decrease the risk of CNS recurrence (4.4%). CNS recurrence remains a fatal event in most pts.

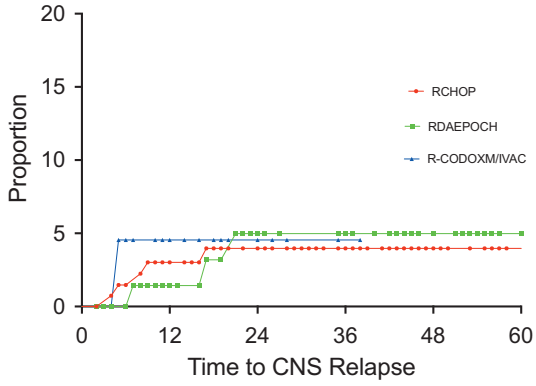


Figure 1.

P063

REAL LIFE ANTI-CD19 CAR-T CELL THERAPY IN LYMPHOMA PATIENTS: IMPACT OF LEUKAPHERESIS T CELL PHENOTYPES ON THE COMPOSITION OF INFUSION PRODUCTS

E. Esposito[1,2], N. Caldarelli[1], M. Magni[1], C. Monfrini[1], C. Vella[1], E. Fardella[1], F. Stella[1,3], P. Corradini[1,3], C. Carniti[1,3]

[1]Hematology and Bone Marrow Transplantation Unit, Fondazione IRCCS Istituto Nazionale Tumori; [2]School of Medicine, Università degli Studi di Milano-Bicocca; [3]School of Medicine, Università degli Studi di Milano, Italy

Background: It has become increasingly evident that the presence of early-memory CAR-T cell populations in infusion products is associated

with superior ability of CAR-T cells to expand *in vivo*. Consistently, we previously reported that infusion of tisagenlecleucel (Tisa-cel) and axicabtagene ciloleucel (Axi-cel) enriched in CD8+CAR-T cells with a central memory phenotype (T_{CM}) mediated improved *in vivo* CAR T-cell expansion and clinical efficacy (Carniti, ASH2021). However, whether pre-manufacturing T cell features of unmanipulated leukapheresis material impact CAR-T cell phenotypes is yet to be consistently defined.

Aim: To investigate the correlation between the T-cell composition of individuals' leukapheresis material and the presence of CD8+ T_{CM} cells in Axi-cel and Tisa-cel infusion products.

Methods: Unmanipulated leukapheresis and CAR-T infusion products of 48 patients receiving either Tisa-cel (20) or Axi-cel (28) were analyzed by flow cytometry. Cells were stained with CD3, CD4, CD8, CD45RO, CD62L, CD197 (CCR7) and CD95. CAR-T cells were detected using the CD19-CAR detection reagent (Miltenyi). Cell acquisition was performed on a BD FACSCanto II (BD Biosciences) and data were analyzed using FlowJo. Statistical analyses were performed using Spearman's rank correlation on GraphPad v9.

Results: Among the analysed T cell populations, a moderate correlation between CD8+ naive T cells (T_N,CCR7+CD45RO-), CD8+CD62L+ T_N cells and CD8+ stem cell memory T cells (T_{SCM}, CCR7+CD45RO- CD62L+CD95+) in the leukapheresis and CAR+ cells with a CD8+ T_{CM} phenotype (CD45RO+CCR7+CD62L+) in infusion products was detected (r=0.43 p=0.0026, r=0.43 p=0.0021, r=0.41 p=0.0040, respectively). Additionally, when dividing patients according to the products they received, in the Tisa-cel cohort, only the presence of CD8+ T_{SCM} cells in the leukapheresis was positively associated with CAR+CD8+ T_{CM} cells in the infusion products (r=0.63 p=0.0026). On the contrary, in the 28 patients receiving Axi-cel, both CD8+ T_N and CD8+CD62L+ T_N cells in the leukapheresis, moderately correlated with CD8+ T_{CM} cells in infusion products (respectively r=0.44 p=0.0193, r=0.47 p=0.0126).

Conclusions: Taken together, these results suggest that less-differentiated T lymphocytes in the leukapheresis positively affect the amount of T cells with central memory phenotype in the infusion product, a relevant population for CAR-T cell *in vivo* expansion and clinical efficacy.

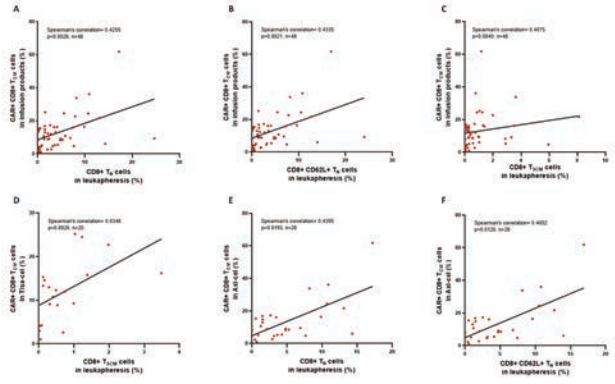


Figure 1. **Correlation between T cell subsets in leukapheresis materials and CAR+CD8+ central memory T cells (CAR+CD8+ T_{CM} cells) in infusion products.** A significant association was found when analysing CD8+ T_N cells, CD8+CD62L+ T_N cells and CD8+T_{SCM} cells present in the leukapheresis and the CAR+CD8+T_{CM} cells in the infusion products in the entire cohort of patients (n=48)(A-C). In patients who received Tisa-cel (n=20), only the CD8+T_{SCM} cells correlated with the CAR+CD8+T_{CM} cells in the infusion products (D), whereas in Axi-cel (N=28), both CD8+ T_N cells and CD8+CD62L+ T_N cells in the leukapheresis correlated with the CAR+CD8+T_{CM} cells in the infusion products (E-F). Spearman's rank correlation was applied to calculate *r* and *p* values.

Figure 1.

P064

HEALTH-RELATED QUALITY OF LIFE EFFECT OF MOGAMULIZUMAB BY PATIENT BLOOD INVOLVEMENT

P.L. Zinzani[1], P. Ortiz-Romero[2], M. Lima[3,4], A.O. Huen[5]

[1]Institute of Hematology "Seràgnoli"; [2]Department of Dermatology, University Complutense, Hospital 12 de Octubre, Medical School, Institute i+12; [3]Unidade Multidisciplinar de Investigação Biomédica, Instituto de Ciências Biomédicas, Universidade do Porto (UMIB/ICBAS/UP); [4]Consulta Multidisciplinar de Linfomas Cutâneos (CMLC) e Unidade de Diagnóstico Hematológico, Serviço de Hematologia Clínica, Centro Hospitalar Universitário do Porto (CHUP); [5]The University of Texas MD Anderson Cancer Center, USA

The most studied subtypes of cutaneous T-cell lymphoma are mycosis fungoides (MF) and Sézary syndrome (SS) and together represent around two-thirds of cases. Leukemic involvement in MF/SS has been found to affect overall survival, disease-specific survival and risk of disease progression, although further research is ongoing. Patient quality of life (QoL) can be seriously affected with disfiguring skin lesions, intractable itching, sleep disturbance, and psychosocial problems. Treatment goals include reducing disease burden, delaying progression, and improving or preserving QoL. This post hoc analysis of MAVORIC trial data sought to determine whether baseline blood tumour burden affected treatment effect on patient QoL, where patients classified as B0 are considered to have no blood involvement and patients classified as B1 and B2 are considered to have blood involvement. The Phase 3 MAVORIC trial (NCT01728805) was an open-label study comparing mogamulizumab to vorinostat. Patient reported outcome (PRO) assessments of QoL were assessed using validated Skindex-29 and FACT-G instruments. Pruritus was assessed using ItchyQoL and Pruritus Likert Scale. All PROs were administered at baseline. Skindex-29 and FACT-G were then administered at every other treatment visit; ItchyQoL and Pruritus Likert Scale were administered every 4 weeks at each cycle. Overall, no statistically significant differences were seen between mogamulizumab and vorinostat for patients with no blood involvement. Statistically significant differences were seen for patients with blood involvement, with mogamulizumab-treated patients seeing statistically significant improvement in Skindex-29 for treatment Cycles 3–11 in all domains (Emotional, Functional, Symptoms); and in the Functional Domain of ItchyQoL at most timepoints. In mogamulizumab-treated patients with blood involvement, the Pruritus Likert Scale Score showed a reduction in itch from Cycle 1 and a trend to reducing levels of itch over 12 cycles. The FACT-G Total Score showed greatest improvement from baseline for mogamulizumab patients with blood involvement compared to those without and all vorinostat patients (Figure 1). Overall, mogamulizumab-treated patients with blood involvement saw greater HRQoL improvement than those without blood involvement. Mogamulizumab offers QoL benefit, assessed across a number of PROs, especially to patients with blood involvement (B1 or B2). Funding Source: Kyowa Kirin.

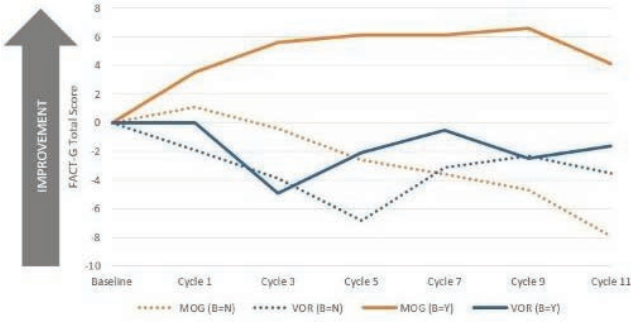


Figure 1. The change from baseline for the FACT-G Total Score by treatment cycle.
B, blood involvement; FACT-G, Functional Assessment of Cancer Therapy-General; MOG, mogamulizumab; N, no blood involvement; VOR, vorinostat; Y, confirmed blood involvement

Figure 1.

P065

A COMBINATION OF DEAUVILLE SCORE AND QUANTITATIVE PET PARAMETERS PREDICTS THE EFFICACY OF ANTI-CD19 CAR T-CELLS

A. Guidetti[1], A. Dodero[1], A. Lorenzoni[2], S. Pizzamiglio[3], G. Argiroffi[2], A. Chiappella[1], F. Bagnoli[1], C. Carniti[1], C. Monfrini[1], M. Pennisi[1], P. Verderio[3], A. Alessi[2], P. Corradini[1]

[1]Dipartimento di Ematologia, Fondazione IRCCS INT Milano; [2]Dipartimento di Medicina Nucleare, Fondazione IRCCS INT Milano; [3]Dipartimento di Statistica, Fondazione IRCCS INT Milano, Italy

Autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy is an effective treatment for about 40% of relapsed/refractory large B-cell lymphomas (LBCL). There is a great interest in understanding the prognostic value of the early disease assessment at day 30 to plan a salvage treatment for patients experiencing transient response or progressive disease. Durable responses were achieved in 40-50% of the patients in CR and in only 10-20% of those in partial remission or stable disease at day 30, respectively. We conducted a single-center prospective study on 47 LBCLs receiving commercial CAR T-cell therapy to evaluate the prognostic value of baseline and after infusion 18-FDG PET-CT parameters. Deauville score, metabolic parameters (SUVmax, SUV mean, SUVpeak), and volume-based parameters (MTV and TLG) were evaluated before lymphodepletion, at day 30 (PET-30) and 90 days (PET-90) post-infusion for a total of 136 examinations. The change of each PET parameter between baseline and PET-30 was a percentage defined as follows: Δ=(baseline-day30)/baseline x 100%. DeltaSUVmean correlated with the clinical response at day 90 [HR 1,49; (95%CI; 1,01-2,2), p=0,04], whereas baseline SUVmax and high ΔSUVmean, ΔTotal Metabolic Tumor Volume (TMTV) and, ΔTotal Lesions Glycolysis (TLG) between baseline and PET-30 were associated with significantly better PFS. Patients with Deauville Score (DS) 4-5 at PET-30 had a higher risk of failure as compared to those with DS 1-3 [HR 2,92, (95%CI; 1,12-7,64), p=0,02]. The combination of DS score and ΔSUVmean identified three groups with different prognoses: the DS1-3 group with 1-year PFS of 60%, the DS4/5 group with a reduction of SUVmean with 1-year PFS of 49%, and the DS4/5 group with increased SUVmean with 1 year PFS of 22%, [p=0.02]. In a multivariable analysis, a higher risk of treatment failure was observed in patients with high LDH [HR 3,2 (95%CI; 1,30-8,1), p=0,01] whereas higher ΔSUVmean was associated to a better outcome [HR 0,6 (95%CI, 0,40-0,92), p=0,01]. In conclusion, DS and variation of SUVmean at PET-30 identify patients at high risk of failure after CAR T. The use of quantitative parameters is of particular interest for patients in PR or stable disease following CAR T-cell infusion and should be confirmed in a larger trial.

P066

THE MOLECULAR PROFILE AND THE CONCOMITANT HEMATOLOGICAL MALIGNANCY ALLOW TO TAILOR THERAPY IN ANTI-MAG ANTIBODY NEUROPATHY WITH IBRUTINIB, VENETOCLAX OR OBINUTUZUMAB

A. Visentin[1], F. Castellani[2], E. Schirinzi[3], S. Pravato[1], C.A. Cavarretta[1], A. Cellini[1], F. Angotzi[1], V. Ruocco[1], M. Campagnolo[2], A. Salvalaggio[2], C. Candiotto[4], R. Bertorelle[4], F. Piazza[1], G. Siciliano[3], C. Briani[1], L. Trentin[1]

[1]Hematology and Clinical Immunology Unit, Department of Medicine, University of Padova; [2]Neurology clinic, Department of Neurosciences, University of Padova; [3]Neurology clinic, Department of Clinical and Experimental Medicine, University of Pisa; [4]Immunology and Molecular Oncology, Veneto Institute of Oncology IOV-IRCCS, Italy

Background: Anti-myelin-associated glycoprotein antibody neuropathy (anti-MAG NP) is a rare demyelinating neuropathy associated with IgM MGUS or Waldenstrom's Macroglobulinemia (WM), marginal zone lymphoma (MZL) or chronic lymphocytic leukemia (CLL). Rituximab is currently used in anti-MAG NP, despite efficacious in almost 50% of cases. Recurrent MYD88^{L265P} mutation has been described in almost 60% of patients anti-MAG NP. While new targeted drugs (anti-CD20 antibody obinutuzumab, BTK inhibitor ibrutinib, BCL2 inhibitor venetoclax) are highly active in chronic B-cell malignancies, their activities in anti-MAG NP have been little investigated.

Aims: To study the molecular profile and the efficacy of novel drugs in patients with anti-MAG NP.

Methods: We included 60 patients with anti-MAG NP, 39 (65%) men, mean age 71.2±9.8 years. Of them, 29 (48.3%) had IgM-MGUS, 27 (45%) WM, 4 (6.6%) CLL or MZL. MYD88^{L265P} and CXCR4^{S338X} were performed using ASO–PCR, from bone marrow mononuclear cells in 45/60 patients and from circulating mononuclear cells in 15/60. All the patients were assessed with MRC sum score, INCAT (Inflammatory Neuropathy Cause and Treatment) Disability and Sensory Sum Score.

Results. Overall 42 (70%) patients harbored the MYD88L265P mutation: 25/27 WM patients (93%), 16/29 (55%) MGUS and 1/4 (25%) CLL/MZL (p=0.001). MYD88^{L265P} was found in 82% and 37% of treatment naive and relapsed patients, respectively (p=0.003). All patients were CXCR4 wt. Thirty-nine patients were treated with rituximab with neurological benefit in 23 (59%). There was no significant difference in neuropathy severity or treatment response between mutated or wt patients. At relapse 6 MYD88^{L265P} WM were treated with ibrutinib; 2 CLL patients (1 with MYD88^{L265P}) were treated with obinutuzumab and another MYD88wt CLL was treated with venetoclax-rituximab. All 8 patients were unresponsive to rituximab, and reported early and progressive improvement, as shown by decrease of INCAT scale, monoclonal protein, IgM level, and anti-MAG antibody titer (p<0.003). Preliminary data seem to show that the cumulative incidence of retreatment was lower with this disease-molecular tailored approach than with rituximab (Figure 1).

Conclusion: We herein confirm the high prevalence of the MYD88^{L265P} in anti-MAG NP, despite it does not seem to be a prognostic factor of neuropathy severity or response to rituximab. In non-responders, new effective tailored targeted therapies should be considered.

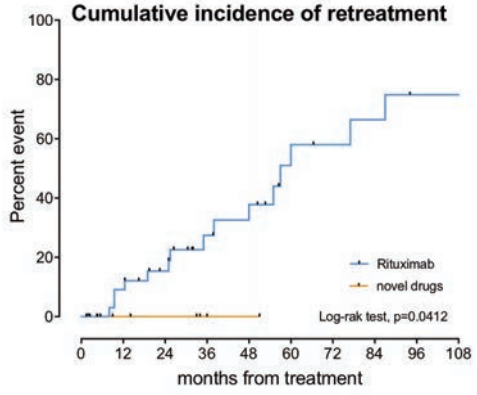


Figure 1.

P067

POLATUZUMAB VEDOTIN PLUS RITUXIMAB, CYCLOPHOSPHAMIDE, DOXORUBICIN, AND PREDNISONE VERSUS RITUXIMAB, CYCLOPHOSPHAMIDE, DOXORUBICIN, VINCRISTINE AND PREDNISONE THERAPY IN PATIENTS WITH PREVIOUSLY UNTREATED DLBCL: RESULTS FROM THE PHASE III POLARIX STUDY

A. Pinto[1], H. Tilly[2], F. Morschhauser[3], L.H. Sehn[4], J.W. Friedberg[5], M. Trněný[6], J.P. Sharman[7], C. Herbaux[8], J.M. Burke[9], M. Matasar[10], S. Rai[11], K. Izutsu[12], N. Mehta-Shah[13], L. Oberic[14], A. Chauchet[15], W. Jurczak[16], Y. Song[17], R. Greil[18], L. Mykhalska[19], J.M. Bergua Burgués[20], M.C. Cheung[21], H.-J. Shin[22], G. Hapgood[23], E. Munhoz[24], P. Abrisqueta[25], J.-P. Gau[26], J. Hirata[27], Y. Jiang[27], M. Yan[28], C. Lee[27], C. Flowers[29], G. Salles[30]

[1]Hematology-Oncology & Stem Cell Transplantation Unit, Istituto Nazionale Tumori, Fondazione 'G. Pascale', IRCCS; [2]Department of Hematology and U1245, Centre Henri Becquerel and University of Rouen; [3]University of Lille, CHU de Lille, ULR 7365-GRITA-Group de Recherche sur les formes Injectables et les Technologies Associées; [4]BC Cancer Centre for Lymphoid Cancer and the University of British Columbia; [5]Wilmot Cancer Institute, University of Rochester; [6]First Faculty of Medicine, Charles University, General Hospital; [7]Willamette Valley Cancer Institute/US Oncology; [8]CHU de Montpellier; [9]Rocky Mountain Cancer Centers/US Oncology; [10]Memorial Sloan Kettering Cancer Center; [11]Department of Hematology and Rheumatology, Kindai University, Faculty of Medicine; [12]National Cancer Center Hospital; [13]Washington University in St. Louis; [14]Department of Hematology, Institut Universitaire du Cancer, Toulouse-Oncopole; [15]Department of Hematology, CHRU Besançon; [16]Maria Sklodowska-Curie National Research Institute of Oncology; [17]Peking University Cancer Hospital; [18]3.rd Medical Department, Paracelsus Medical University, Salzburg Cancer Research Institute-CCCIT and Cancer Cluster Salzburg; [19]Clinical Hospital Feofaniya; [20]Hospital San Pedro de Alcántara; [21]Odette Cancer Centre, Sunnybrook Health Sciences Centre, University of Toronto; [22]Division of Hematology-Oncology, Department of Internal Medicine, Medical Research Institute, Pusan National University Hospital, Pusan National University School of Medicine; [23]Princess Alexandra Hospital; [24]Hospital Erasto Gaertner; [25]Department of Hematology, Hospital Vall d'Hebron, Vall d'Hebron Institute of Oncology (VHIO); [26]Taipei Veterans General Hospital; [27]Genentech, Inc; [28]F. Hoffmann-La Roche Ltd; [29]MD Anderson Cancer Center; [30]Memorial Sloan Kettering Cancer Center

R-CHOP is the standard of care for newly diagnosed patients (pts) with diffuse large B-cell lymphoma (DLBCL), yet 40% remain uncured. Polatuzumab vedotin, a CD79b-targeting antibody-drug conjugate, has shown promising activity and safety in a Phase Ib/II study. We report POLARIX (NCT03274492), a double-blind, placebo-controlled, international Phase III study comparing Pola-R-CHP with R-CHOP in treatment-naïve pts with DLBCL and an International Prognostic Index score of 2–5. Pts were randomised (1:1) to receive 6 cycles of Pola-R-CHP or R-CHOP. On day 1 of cycles 1–6, pts received polatuzumab vedotin 1.8 mg/kg or vincristine 1.4 mg/m² + rituximab 375 mg/m², cyclophosphamide 750 mg/m², and doxorubicin 50 mg/m². Patients also received oral prednisone 100 mg on days 1–5 and two further cycles of rituximab. Investigator-assessed progression-free survival (PFS) was the primary endpoint, with secondary endpoints including investigator-assessed event-free survival (EFS), independent review committee-assessed end-of-treatment (EOT) complete response (CR) rate by PET-CT, disease-free survival (DFS), overall survival (OS), and safety. Overall, 879 pts (median age 65 [range 19–80] years) were randomised (Pola-R-CHP: n=440; R-CHOP: n=439). At primary data cut-off (28 June 2021), median follow-up was 28.2 months. PFS was superior with Pola-R-CHP *vs* R-CHOP (HR 0.73; 95% CI: 0.57–0.95; P=0.02); 2-year PFS rate was improved with Pola-R-CHP *vs* R-CHOP (76.7% [95% CI: 72.7–80.8] *vs* 70.2% [95% CI: 65.8–74.6], respectively). EFS favoured Pola-R-CHP *vs* R-CHOP (HR 0.75, 95% CI: 0.58–0.96; P=0.02). While the EOT PET-CT CR rate was not significantly different with Pola-R-CHP (78.0%) *vs* R-CHOP (74.0%), DFS suggested more durable responses with Pola-R-CHP *vs* R-CHOP (HR 0.70, 95% CI: 0.50–0.98). OS was comparable between treatment arms. Similar safety profiles were seen between treatment groups. For Pola-R-CHP *vs* R-CHOP, rates of grade 3–4 adverse events (AEs) were 57.7% *vs* 57.5%, serious AEs were 34.0% *vs* 30.6%, grade 5 AEs were 3.0% *vs* 2.3%, and AEs leading to dose reduction were 9.2% *vs* 13.0%, respectively. Rates of peripheral neuropathy were similar for Pola-R-CHP *vs* R-CHOP. At data cut-off, fewer pts treated with Pola-R-CHP (23%) *vs* R-CHOP (30%) had received ≥1 subsequent anti-lymphoma therapy. As first-line treatment of DLBCL, Pola-R-CHP demonstrated a 27% reduction in the relative risk of disease progression, relapse, or death, along with a similar safety profile, compared with R-CHOP.

P068

FOLLICULAR LYMPHOMA MICROENVIRONMENT SIGNATURES DEFINE PATIENTS SUBSETS OBTAINING LONG TERM CLINICAL BENEFIT AFTER SINGLE-AGENT FIRST-LINE ANTI-CD20 IMMUNOTHERAPY

E. Derenzini, M. Del Corvo, M.C. Quattrocchi, M. Castelli, M.R. Sapienza, S. Mazzara, S. Fiori, A. Vanazzi, S. Ramadan, S. Pileri, C. Tarella

Oncohematology Division, Haematopathology Division, IEO European Institute of Oncology IRCCS, Milan; Department of Health Sciences, University of Milan, Milan, Italy

The role of first-line single agent anti CD20 immunotherapy in follicular lymphoma (FL) is still a matter of debate and most FL pts are exposed to chemotherapy at some point in their disease course. In this study we retrospectively analyzed the outcome of our single center cohort of 81 FL pts treated from 2000 to 2018 with first-line single agent anti-CD20 therapy with (n=53) or without (n=28) maintenance, in the context of several trials exploring the efficacy of upfront single agent anti-CD20 immunotherapy. Median age was 55 years (y), 52% (42) of patients were female, 72% (58) stage III-IV, 76% (62) were Follicular international prognostic index (FLIPI) score 0-2, 26% (21) were bulky, 52% (42) were high tumor burden according to the GELF criteria. After a median follow-up of 9.5 y, the overall survival (OS) and progression-free survival (PFS) rates were 82% and 35% respectively. Paraffin embedded tissue from initial diagnosis was available in 39 pts. Diagnostic biopsies were analyzed with targeted gene expression profiling (T-GEP) on the NanoString platform, using the PanCancer Immune Profiling panel, which includes 730 genes belonging to the most relevant immunologic checkpoints and pathways. A simple 6-gene immune signature (hereafter ImSig) was significantly associated with PFS, with IL22RA2, CCL22, TNFRSF4, IL17RB, CCL19 overexpression and CD209 downregulation being associated with worse outcome. 10-y PFS was 65% for ImSig low pts *vs* 6% for ImSig high pts (p<0.0001). Cibesort deconvolution indicated enrichment in T-Reg infiltration in the ImSig high subset. In multivariate analysis only ImSig and anti CD20 maintenance retained independent prognostic value (p<0.001 and 0.002 respectively), irrespective of GELF criteria and FLIPI. These data were validated in silico in 2 independent publicly available cohorts of 137 pts (Silva *et al*. 2019) and 50 pts (Bararia *et al*. 2020). Notably, the 10-y PFS rates of ImSig low *vs* high patients mirrored the results observed with single-agent immunotherapy in the discovery cohort. These data indicate that pts with a favorable immune signature could derive maximal benefit from a first-line chemo-free treatment approach with single agent anti CD20 immunotherapy, maintaining complete remission in the long term, irrespective of the tumor burden and other clinical variables.

P069

FOUR CYCLES OF RITUXIMAB IN THE UP-FRONT TREATMENT OF EXTRANODAL MARGINAL ZONE LYMPHOMAS: A TWENTY-YEARS MONOCENTRIC EXPERIENCE

L. Nanni[1,2], A. Broccoli[1,2], V. Stefoni[1,2], B. Casadei[1,2], C. Pellegrini[1], A. Morigi[1,2], M. Carella[1,2], G. Lolli[1,2], P.E. Coppola[1,2], G. Gugliotta[1], G. Bagnato[1,2], M. Gentilini[1,2], L. Argnani[2], P.L. Zinzani[1,2]

[1]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli", Bologna, Italy; [2]Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale, Università di Bologna, Bologna, Italy

Rituximab has widely proved to be effective in the treatment of extranodal marginal zone lymphomas (EMZL), both as single agent and in combination with chemotherapy or novel agents. Rituximab (R) monotherapy, in particular, is largely used and it is associated with high response rates and good safety profile. However, the optimal number of administrations, able to allow long progression-free survival (PFS) rates, remains to be determined. Available data in the literature report different treatment schedules; most centres give 4 weekly cycles of R, but some choose a 6- or 8-cycle schedule. We herein present our single-centre experience with 4 cycles of R (4R) in 64 patients with newly diagnosed EMZL between 2002 and 2019. They all had only one site of disease (30 stomach, 11 eye, 8 skin, 5 lung, 5 parotid, 2 genitals, 1 liver, 1 mouth and 1 intestine). Prior to R, 10 out of 64 patients underwent Helicobacter pylori eradication obtaining the resolution of the infection but not a lymphoma remission. Final responses after 4R were 41 complete responses (CR), 16 partial responses (PR) and 7 stable diseases with an overall response rate of 89.1% and a CR rate of 64.1%. Twenty-six patients relapsed. Median PFS was reached at 6.5 years (Figure 1), median disease survival at 6.4 years and median overall survival was not yet reached (78.4% at 12 years), respectively. Only 2 infusion reactions were registered and only 3 hematological toxicities occurred in 2 patients (a grade 2 thrombocytopenia, a grade 2 anemia and a grade 3 neutropenia). After the first 4 cycles of rituximab, 22 patients received further therapy (16 CR, 6 PR and 1 PD) at a median time to next treatment of 9 months (range 1 month - 7 years). Nineteen patients were re-treated with R as single agent or in combination (15 CR and 4 PR).

Our data suggest that 4R provides durable responses in most patients. Relapses tend to be early and highly responsive to second-line therapy, even to 4R retreatment, so that this subgroup of patients shares the same excellent prognosis of those with longer PFS.

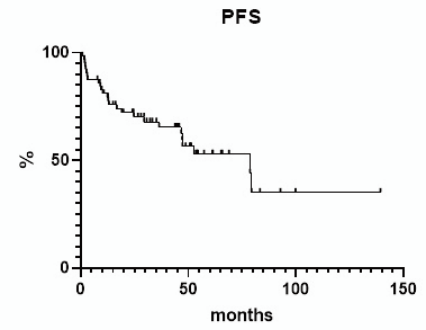


Figure 1.

P070

A LIVING PATIENT-DERIVED BIOREPOSITORY FOSTERING PRECISION MEDICINE IN T-CELL LYMPHOMA

D. Fiore[1,2,3], L.V. Cappelli[3,4], L. Zhaoqi[5], N. Kotlov[6], J. Phillip[7], P. Zumbo[7], L. Yoffe[3], P. Ghione[8], H. Xueshuai[5], V. Fragliasso[9], G. Condorelli[1,2], R. Foà[4], J. Brody[10], D. Betel[7], J. Chan[11], W. Tam[3], D. Weinstock[12], L. Cerchietti[7], R. Rabadan[13], S. Horwitz[8], G. Inghirami[3]

[1]Department of Molecular Medicine and Medical Biotechnology, University of Naples "Federico II"; [2]Institute for Experimental Endocrinology and Oncology, "G.Salvatore" IEOS; [3]Department of Pathology and Laboratory Medicine, Weill Cornell Medicine; [4]Department of Translational and Precision Medicine, Sapienza University of Rome; [5]CAS Key Laboratory of Genomic and Precision Medicine, Beijing Institute of Genomics, Chinese Academy of Sciences; [6]BostonGene Corporation; [7]Department of Medicine, Hematology and Oncology Division, Weill Cornell Medicine; [8]Department of Medicine, Memorial Sloan-Kettering Cancer Center; [9]Laboratory of Translational Research, Azienda USL-IRCCS; [10]Department of Medicine, Hematology and Medical Oncology, Icahn School of Medicine at Mount Sinai; [11]Department of Pathology, City of Hope Medical Center; [12]Department of Medical Oncology, Dana-Farber Cancer Institute and Harvard Medical School; [13]Department of Biomedical Informatics, Center for Computational Biology and Bioinformatics, Columbia University

Background and aims: Despite recent advancements, T-cell lymphoma (TCL) patients still experience poor therapeutic responses and have an unfavorable outcome. Here, we aimed at constructing a large library of TCL patient-derived xenografts (PDX) to foster drug discovery programs and new patient-tailored approaches.

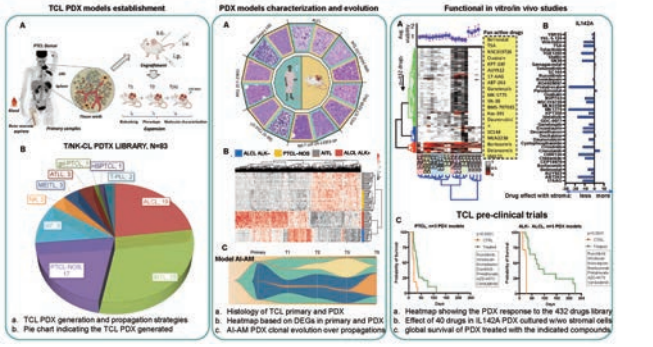


Figure 1.

Results: Three hundred and sixty-two primary TCL samples were implanted to generate 83 PDX and 8 continuous PDX-derived TCL cell lines representative of different TCL subtypes. Serially propagated PDX showed distinct immunophenotypic profiles and TCR gene rearrangements, closely reflecting the corresponding primary samples. WES and RNA-Seq yielded a rich landscape of canonical and novel mutations shared by primary and PDX derivatives, and identified classifiers stratifying different TCL entities. Interestingly, a detailed clonal evolution analysis reported an overall stability of TCL PDX models, with dominant clones preserved over propagations. As fusions distinguish specific TCL, we annotated known and previously undescribed putative tumorigenic chimeric transcripts, and as proof of concept we validated the tumorigenic potential of the MAZ-NF1 fusion in an ALK-ALCL model. Next, we challenged TCL cells with a broad drug library (n=433), demonstrating that responses differed according to the subtype and could be dictated by transcriptomic signatures. Interestingly, the co-culture of TCL cells with stromal elements rescued selected drug treatments. In parallel, we successfully stratified primary and PDX TCL samples using microenvironment-based signatures and correlated the 4 individuated subgroups

with different outcomes. Ultimately, we implemented *in vivo* pre-clinical strategies, testing both current and novel approaches. We proved that PDX recapitulated matched patient responses, as well as the effectiveness of selected combinations (irinotecan plus brentuximab, romidepsin plus ruxolitinib/pralatrexate/duvelisib, cerdulatinib plus AZD-4573) in improving PFS or eradicating lymphoma.

Conclusions: These data demonstrate that TCL PDX: (a) recapitulate the biological features of matched donors; (b) allow the recognition of genetic defects and suitable dependencies; (c) underline tumor-host dependencies and bilateral interactions; (d) provide a reliable platform to design effective therapeutic strategies. We anticipate that this repository will foster scientific discoveries and the implementation of personalized therapeutic approaches for TCL patients.

P071

MOLECULAR REMISSION IS AN INDEPENDENT PREDICTOR OF PROGRESSION-FREE SURVIVAL IN PATIENTS WITH WALDENSTRÖM MACROGLOBULINEMIA TREATED WITH CHEMO-IMMUNOTHERAPY

N. Fabbri[1], S. Zibellini[2], M. Merli[3] , D. Drandi[4], D. Furlan[3], V.V. Ferretti[5], I. Dogliotti[4], M. Ferrante[4], C. Varraso[2], E. Cappello[1], C. Cavalloni[2], B. Bianchi[3], G.V. Facchetti[1], S. Ferrero[4], L. Arcaini[1], M. Varettoni[2]

[1]Department of Molecular Medicine, University of Pavia; [2]Division of Hematology, Fondazione IRCCS Policlinico San Matteo; [3]Department of Hematology, University Hospital "Ospedale di Circolo e Fondazione Macchi - ASST Sette Laghi"; [4]Unit of Hematology, Department of Molecular Biotechnology and Health Sciences, University of Torino; [5]UOS Clinical Epidemiology and Biostatistic, Fondazione IRCCS Policlinico San Matteo, Italy

Background: Waldenström macroglobulinemia (WM) is an incurable mature B-cell neoplasm. The MYD88 (L265P) somatic mutation is the molecular hallmark of WM making it a suitable marker for the assessment of minimal residual disease (MRD). While MRD has a well-established prognostic role in other mature B-cell neoplasms such as follicular lymphoma or mantle cell lymphoma, its role in WM is currently unknown. In this study we evaluated the rate and prognostic impact of molecular responses after chemo-immunotherapy (CIT) in WM patients carrying the MYD88 (L265P) mutation.

Methods: Fifty-four patients were included in the analysis. Patients' characteristics are reported in Table 1. The allelic frequency of MYD88 (L265P) mutation was assessed in CD19+ bone marrow mononuclear cells by real-time quantitative polymerase chain reaction (qPCR). Molecular remission was defined as undetectable MRD (uMRD) after treatment.

Results: The overall response rate was 92.6%. Twenty-one patients (38.9%) had uMRD after therapy and 66.7% of them were in complete response or very good partial response, with fair agreement (68.5%) between clinical and molecular response (Cohen's Kappa: 0.35 95%CI: 0.10-0.61). The rate of molecular responses was not significantly different following nucleoside analogs-based therapy, i.e. FCR or R-Bendamustine (41.9%) or alkylating-based regimens (34.8%) (P=0.778). The 5-year overall survival was 75.3% (95%CI: 58.3.86.2%). The median progression-free survival (PFS) was 32.2 months, and was significantly longer for patients with uMRD as compared with patients with detectable MRD at the end of therapy (median PFS 79.5 months versus 28.6 months respectively, P=0.030). After adjusting for type and line of therapy in a predefined multivariable model, uMRD still retained its association with PFS, with a worse prognosis for patients not achieving molecular response (HR=2.77, P=0.034).

Conclusions: To the best of our knowledge, this is the first study exploring the prognostic impact of MRD in WM. We found that standard CIT is able to induce a molecular remission in nearly 40% of patients and that uMRD is associated with longer PFS. We aim at validating these preliminary results using both qPCR and digital PCR in the ongoing BIOWM trial (NCT03521596), a multicenter retrospective and prospective observational study of the Fondazione Italiana Linfomi including 300 patients with either WM or IgM monoclonal gammopathy of undetermined significance.

Table 1. Patients' baseline characteristics.

Characteristic	
Age (years), median (IQR)	65 (55-70)
Gender, n. of patients (%)	
female	18 (33%)
male	36 (67%)
International Staging System (ISSWM), n. of patients (%)	
Low	11 (27.5%)
Intermediate	14 (35%)
High	15 (37.5%)
Line of therapy, n. of patients (%)	
1	47 (87%)
2	4 (7%)
≥3	3 (6%)
Chemoimmunotherapy, n. of patients (%)	
Rituximab-Bendamustine	28 (52%)
Fludarabine-Cyclophosphamide-Rituximab (FCR)	3 (6%)
Dexamethasone-Rituximab-Cyclophosphamide (DRC)	18 (33%)
Rituximab-Cyclophosphamide-Vincristine-Prednisone (R-CVP)	3 (6%)
Rituximab-Cyclophosphamide-Doxorubicine-Vincristine-Prednisone R-CHOP	2 (4%)
Response, n. of patients (%)	
Complete Remission (CR)	5 (9.3%)
Very Good Partial Response (VGPR)	19 (35.2%)
Partial Response (PR)	25 (46.3%)
Minimal response (MR)	1 (1.8%)
Stable Disease (SD)	4 (7.4%)

FCR: Fludarabine-Cyclophosphamide-Rituximab; DRC: Dexamethasone-Rituximab-Cyclophosphamide; R-CVP: Rituximab-Cyclophosphamide-Vincristine-Prednisone; R-CHOP: Rituximab-Cyclophosphamide-Doxorubicin-Vincristine-Prednisone

P072

ABSTRACT NOT PUBLISHABLE

P073

DIFFUSE LARGE B-CELL LYMPHOMA DURING THE COVID-19 PANDEMIC IN TWO TERTIARY CENTERS - THE ISRAELI/ ITALIAN STUDY

G. Bagnato[1,2], M. Gentilini[1,2], O. Giladi[3,4], S. Shimony[3,4,5], O. Pasvolsky[3,4,6], T. Berger[3,4], G. Itchaki[3,4], P. Raanani[3,4], R. Gurion[3,4], A. Broccoli[1,2], V. Stefoni[1,2], G. Lolli[1,2], L. Argnani[2], P.L. Zinzani[1,2]

[1]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli", Bologna, Italy; [2]Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale, Università di Bologna, Bologna, Italy; [3]Institute of Hematology, Davidoff Cancer Center, Rabin Medical Center, Beilinson Hospital, Petach Tikva, Israel; [4]Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel; [5]Medical oncology, Dana Farber Cancer Institute, Boston, MA, USA; [6]Department of Stem Cell Transplantation and Cellular Therapy, University of Texas M.D. Anderson Cancer Center, Houston, TX, United States

The COVID-19 pandemic posed a major challenge in cancer care worldwide which might have an impact on the management of hematologic malignancies such as diffuse large B-Cell lymphoma (DLBCL). A retrospective study comparing DLBCL patients diagnosed from 1/3/20 to 28/2/21 and those diagnosed between 1/3/19 and 28/2/20 in two tertiary centers in Italy and Israel was conducted to assess eventual difference in characteristics, management and outcomes due to the COVID-19 pandemic. Demographics, disease related, treatment and outcome measures were extracted. One hundred and eighty-two patients were diagnosed with DLBCL during the study period in both centers. More

patients were diagnosed during the pandemic in both centers compared to the year before (60 *vs* 29 and 54 *vs* 39 in Italy and in Israel, respectively). In the Italian cohort (but not in the Israeli one), there was a trend towards older age at diagnosis during the pandemic (68 *vs* 61 years; p=0.13, Table 1). The interval between the initiation of symptoms and diagnosis was longer during the pandemic for both cohorts. Five and 4 patients were diagnosed with COVID-19 during treatment in Italy and in Israel, respectively. For both cohorts, there was no difference in dose density and intensity, before and during the pandemic. The median follow-up during and before the pandemic was 12 and 23 months, respectively. While in the Italian cohort there was a trend towards lower estimated 1-year progression free survival (PFS) (73.7% *vs* 89.7%; p=0.06) during the pandemic compared to the year before, there was no such difference in the Israeli cohort. In a univariate analysis for PFS in the Italian cohort, diagnosis during the pandemic was associated with a 2.6-fold increased risk for progression (95% CI 0.9-7.2; p=0.07). Older age was the only parameter significantly related to progression (hazard ratio 1.08, 95% CI 1.0-1.1; p<0.001). In multivariate analysis age remained the only independent prognostic factor.

Overall, in both cohorts, patients' characteristics were comparable between the periods. Yet, in both centers, more patients were diagnosed with DLBCL during the pandemic and the interval between symptoms and diagnosis was longer, compared to the year before. Still, there was no change in treatment in terms of dose density and intensity. The trend towards a shorter PFS during the outbreak in the Italian cohort can be explained by an older age of the patients treated during this period.

Table 1.

	Italian Cohort		Israeli Cohort	
	Pre-Covid19 period (n=29)	Covid19 period (n=60)	Pre-Covid19 period (n=39)	Covid19 period (n=54)
Characteristics				
Age, years median (range)	61 (20-82)	67 (18-86)	70 (18-90)	71 (40-90)
Male sex, n (%)	15 (52)	38 (63)	26 (67) *	23 (43) *
ECOG 2-4, n (%)	2 (7)	5 (8)	16 (41)	15 (30)
Symptoms to diagnosis interval, days, median (range)	41 (7-339)	64 (9-304)	73 (6-380)	81 (2-691)
Diagnosis to treatment interval, days median (range)	35 (1-229)	35 (3-83)	18 (0-55)	14 (0-92)
Elevated LDH, n (%)	16 (55)	29 (48)	25 (64)	34 (63)
Stage III-IV, n (%)	24 (83)	52 (87)	22 (56) *	55 (83) *
IPI 3-5, n (%)	15 (52)	29 (48)	21 (54)	31 (57)
Transformation, n (%)	5 (17)	7 (12)	5 (13) *	16 (25) *
Average interval between cycles, days median (range)	22.6 (21.0-29.8)	22.0 (18.6-42.0)	21.6 (20.0-34.4)	21.2 (20.5-29.6)
Treatment period, days median (range)	105 (49-108)	105 (42-250)	109 (100-172)	107 (103-148)
Dose reduction, n (%)	5 (17)	12 (20)	17 (44)	20 (37)
Hospitalizations, n (%)	7 (25)	21 (35)	20 (51)	17 (32)
Neutropenic fever, n (%)	3 (10)	6 (10)	12 (31)	10 (18)
Outcomes				
E-PET-CT – CR, n (%)	25 (86)	43 (72)	29 (74)	38 (70)
1-year-PFS (%)	89.7	73.7	74.4	75.3
1-year-OS (%)	93.0	83.1	84.6	81.1

Abbreviations: CR – complete remission; E-PET-CT – end of treatment positron emission computed tomography; ECOG – Eastern Cooperative Oncology Group performance status; IPI – international prognostic index; LDH – lactate dehydrogenase; OS – overall survival; PFS – progression free survival

* – statistically significant (p<0.05)

P074

THE BERLIN-FRANKFURT-MÜNSTER PROTOCOL FOR THE UPFRONT TREATMENT OF BURKITT LYMPHOMAS: THE BOLOGNA EXPERIENCE

M. Gentilini[1,2], A. Broccoli[1,2], L. Argnani[1,2], L. Nanni[1,2], G. Bagnato[1,2], M. Carella[1,2], B. Casadei[1,2], P.E. Coppola[1,2], G. Gugliotta[1,2], G. Lolli[1,2], A. Morigi[1,2], C. Pellegrini[1,2], V. Stefoni[1,2], P.L. Zinzani[1,2]

[1]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli"; [2]Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale, Università di Bologna, Italy

Burkitt lymphoma (BL) is highly curable, and prompt therapy is critical to achieving optimal outcomes. Although current approaches are very effective in disease eradication, treatment-related toxicity makes optimal delivery of curative therapy a challenge, especially in older and immunocompromised individuals and, thus, a univocal standard of care still does not exist. From 2004 to 2021, 50 patients affected by BL (4 HIV-positive) received an intensive treatment according to the Berlin-Frankfurt-Münster (BFM) protocol at our Institute. Treatment plan consisted of initial cytoreduction followed by 3 blocks, A (ifosfamide, vincristine, methotrexate, etoposide, cytarabine), B (vincristine, cyclophosphamide, methotrexate, doxorubicin), C (vindesine, methotrexate, etoposide, cytarabine), each repeated twice, every 28 days, with rituximab at day 1 each block. All patients received central nervous system (CNS) prophylaxis with intrathecal methotrexate. Autologous stem cells harvest was done after 4 cycles, with reinfusion (ASCT) at the end of the 6-blocks after BEAM (carmustine, etoposide, cytarabine, melphalan) conditioning. For patients aged 60 years or older (10, 20%) and age-adjusted protocol was adopted. Twelve patients were females, and median age at onset was 38 years. Forty-one patients (82%) had stage III-IV disease; bulky disease occurred in 38 patients and extranodal involvement in 35, mainly at the gastrointestinal tract (72%). CNS involvement was rare (4%). All but 2 patients received rituximab during treatment. Stem cell harvest was performed in 35 patients (70%) who all received a subsequent ASCT. Treatment withdrawal occurred mainly due to progression, renal toxicities and early patient death in 2 cases. Severe cytopenias, all transient and easily manageable, were documented in those who received ASCT. Forty-three patients were restaged: a complete response rate of 70% with an overall response rate of 74 was registered. At a median follow up of 5 years, median progression-free, disease-free (DFS) and overall survivals were not reached. DFS was 80.3% at 10 years (Figure 1). Intensive treatment according to BFM protocol, with rituximab with/without ASCT, appears feasible, safe and highly effective in adult patients with BL, as demonstrated by long-term survival rates of patients in continuous CR.

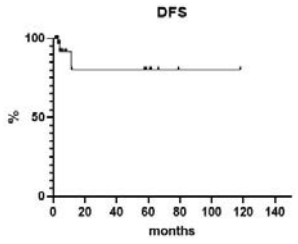


Figure 1.

P075

MONOCYTE-TO-PLATELETS RATIO IS ASSOCIATED WITH INFERIOR OUTCOME IN PATIENTS MANTLE CELL LYMPHOMA: A MULTI-CENTRE REAL-LIFE SURVEY

A. Romano[1,2], I. Ferrarini[3], G. Santuccio[1], L. Gallo[1], A. Chiarenza[1], A. Figuera[1], L. Caruso[1], G. Motta[1], C. Malinverni[3], F. Di Raimondo[1,2], C. Visco[3]

[1]Dipartimento di Chirurgia e Specialità Medico Chirurgiche, Università degli Studi di Catania, Catania, Italy; [2]UOC Ematologia, AOU Policlinico Rodolico San Marco, Catania, Italy; [3]Dipartimento di Medicina, Sezione di Ematologia - AOUI Verona, Italy

Mantle cell lymphoma (MCL) pathogenesis is strongly related to the role of the tumour immune microenvironment (TIME). We aimed to as-

sess the impact of monocyte-to-platelet ratio (MPR), calculated at diagnosis, before any cytotoxic treatment, on progression-free survival (PFS) and overall survival (OS) of consecutive patients with MCL diagnosed and treated in two Italian referral centres. To this end, we reviewed the clinical files of 228 MCL patients who accessed our centres (AOU Policlinico Rodolico San Marco, Catania and Department of Medicine, Section of Hematology, Verona) between 06/2006 and 11/2020. To validate our findings and reduce bias selection given by the retrospective nature of the series, patients were further divided in training (N=85) and validation (N=129) sets.

Results: In whole, we evaluated 214 consecutive patients, whose median age was 69 years (range 53-70). 151 (71%) patients were males, 137 (64%) had high-MIPI score, 62 (29%) had high ki-67%; 127 (58%) patients had extra-nodal involvement (Table 1). Median follow-up for survivors was 65.9 (range 12.3-112.3) months. Overall, 124 (58%) patients were considered not eligible to autologous stem cell transplantation (ASCT), and received standard chemoimmunotherapy, with median (m) PFS of 54.8 months (95% CI 43.9-72.1) and mOS of 65.3 months (95% CI 38.7-76.2). Remaining 90 (42%) patients were treated upfront with consolidative ASCT, and their mPFS was 88.6 months (95% CI 71.4-154.6), and mOS was 95.4 months (95% CI 82.1-126.8). Variables significantly associated to shorter PFS were high MIPI (p=0.002), age >65 (p=0.0003), high Ki67 (p=0.001). NLR and NPR were not associated to clinical outcome. On the contrary, based on ROC analysis, MPR= 7.5 resulted in 55% (C.I. 95% 44-66) sensitivity and 76% (C.I. 95% 68-84) specificity in predicting PFS at 60 months follow-up (Area under the ROC curve, AUC=071, p=<0.0001). Both in the training and the validation set, in univariate analysis MPR ≥7.5 was associated to inferior OS (p<0.0001, and p=0.0002, Figure 1). Multivariate analysis confirmed MPR>7.5, together with elevated MIPI, as significant independent variables in predicting OS (hazard ratio, HR=2.0, 95% CI 1.2-3.5, p=0.01 and HR=2.4, 95% CI 1.4-3.9, p=0.001, respectively). Thus, between the immune dysregulation markers analysed, MPR≥7.5 seems the most promising prognostic factor in patients with MCL, independently of ASCT consolidation, age, MIPI score and ki-67%.

Table 1.

Patients' characteristics	All patients (N=214)	ASCT yes (N=55)	ASCT no (N=159)	p-value
Age at diagnosis, median (range)	69 (53-70)	57 (53- 60)	72 (70-73)	0.002
Sex				
Male, n (%)	151 (71)	38 (69)	113 (71)	0.92
Female, n (%)	63 (29)	17 (31)	46 (29)	
Ki67 percentage				
Low (0) (%)	120 (56)	30 (54)	90 (57)	
High (1) (%)	62 (29)	17 (31)	45 (28)	0.93
NA (%)	32 (15)	8 (15)	24 (15)	
MIPI score				
low (%)	23 (11)	10 (18)	13 (8)	0.06
high (%)	137 (64)	25 (45)	112 (70)	
Bone marrow involvement, n (%)	127 (58)	38 (69)	89 (56)	0.09
Extra nodal involvement, n (%)	186 (87)	50 (91)	136 (85)	0.91
ASCT, n (%)	55 (26%)	55 (100%)	159 (100%)	NA
ARA-C based treatment in first line, n (%)	88 (41%)	51 (93%)	37(23%)	0.02
ANC, median (range), 10^3/µL	4.6 (4.3- 5.1)	5.1 (4.1- 6.1)	4.5 (4.1-5.0)	0.31
ALC, median (range), 10^3/µL	11.1 (6.2- 16.0)	9.3 (4.2-14.4)	11.7 (5.4-18.0)	0.66
AMC, median (range), 10^3/µL	1.2 (0.7-1.6)	0.7 (0.3-1.2)	1.3 (0.7-1.9)	0.29
Platelets, median (range), 10^3/µL	181 (8-420)	168 (35-412)	186 (8-420)	0.86
NLR, median (range)	1.7 (1.4- 2.2)	2.0 (1.2-2.6)	1.6 (1.3- 2.2)	0.18
NPR, median (range)	22.5 (20.9-24.6)	21.6 (20.2-26.2)	22.7 (20.7-25.7)	0.19
MPR, median (range)	2.8 (2.6- 3.2)	2.3 (1.9- 3.3)	2.9 (2.6-3.3)	0.79

P076

HOW I DIAGNOSE SPLEEN INVASION BY LYMPHOMA WITH A MINI-INVASIVE APPROACH: A MONOCENTRIC EXPERIENCE ON 50 PATIENTS

C. Giordano, M. Picardi, N. Pugliese, M. Esposito, D. Abagnale, M. Giannattasio, M. Fatigati, A. Vincenzi, F. Pane

[1]*Department of Clinical Medicine and Surgery, Federico II University Medical School, Naples, Italy*

Mini-invasive approaches with new generation ultrasonography (US) and biopsy needle devices using advanced laboratory tests for accurate immunophenotyping of neoplastic cells, provide the opportunity to develop effective diagnostic strategy for suspected lymphoma in the spleen. The aim of this retrospective study is to test the diagnostic accuracy of spleen core-needle biopsy (CNB) including the impact of immunohistochemistry (IHC) and/or flow cytometry (FC). All patients receiving a diagnosis of lymphoma on lymphnode specimens from 1 January 2009 to 31 December 2019, if eligible for treatment, were screened for enrolment.

Table 1. General characteristics and ultrasonographic aspects in a cohort of 50 percutaneous splenic core needle biopsies of patients included in the study according to the combined routine hematoxylin and eosin plus immunohistochemistry staining, and reference standard results*.

CHARACTERISTICS	ALL PATIENTS	H&E + IHC: TRUE-POSITIVE	H&E + IHC: FALSE-NEGATIVE (FC POSITIVE)
N. OF PATIENTS	50	44	6
MEDIAN AGE (RANGE), YEARS	60 (45-70)	60 (45-70)	60 (60-70)
SEX: MALE/FEMALE	29/21	27/17	2/4
SPLEEN LONG AXIS			
MEDIAN (RANGE) CM	15 (13-20)	15 (13-20)	14 (13-16)
FOCAL LESION LONG AXIS			
MEDIAN (RANGE) CM	3,5 (1,5-7,5)	3,5 (1,5-7,5)	2,5 (1,5-3,5)
PLATELET COUNT X 10^9/L			
MEAN (RANGE)	160 (80-650)	160 (80-650)	100 (90-120)
PT %			
MEAN (RANGE)	80 (70-120)	80 (70-120)	80 (70-110)
BIOPSY PROCEDURE			
US GUIDANCE**	100	100	100
NEEDLE			
MODIFIED-MENGHINI, 18 GAUGE***	100	100	100
SITE OF BIOPSED SPLEEN (NUMBER OF CASES)			
FOCAL LESION	34	32	3
DIFFUSE SPLENOMEGALY	16	12	3
TIME FOR CNB			
MEDIAN (RANGE) MINUTES	40 (30-50)	35 (30-50)	40 (30-50)
CORE-NEEDLE PASSES			
MEDIAN (RANGE)	1 (1-2)	1 (1-2)	2 (1-2)
CORE-NEEDLE SPECIMEN			
MEDIAN LENGTH (RANGE), MM	30 (15-40)	35 (15-40)	20 (15-30)
MEDIAN ESTIMATED VOLUME (RANGE), MM^3	85 (60-130)	90 (82-130)	60 (60-80)
HISTOLOGICAL FINDINGS			
DIFFUSE LARGE B-CELL LYMPHOMA	23	23	-
FOLLICULAR LYMPHOMA	8	8	-
MANTLE CELL LYMPHOMA	4	4	-
SMALL LYMPHOCYTIC LYMPHOMA	2	2	-
MARGINAL ZONE LYMPHOMA	2	2	-
HODGKIN LYMPHOMA	2	2	-
PERIPHERAL T-CELL LYMPHOMA	1	1	-
SARCOIDOSIS	2	2	-
REACTIVE CHANGES****	**6**	-	**6**
MOST COMMON CNB-RELATED ADVERSE EVENTS			
PAIN ON BIOPSY SITE	30	26	4
SUPERFICIAL HEMATOMA	4	2	2

Values are n (%) unless otherwise noted.

H&E= hematoxylin and eosin; IHC= immunohistochemistry; US=ultrasound.

FC= flow cytometry; a basic panel of fluoresceine antibodies with CD3, CD4/CD8, CD2/CD7/CD3, CD5/CD10/CD19/CD20, CD19/κ/λ, FMC7/CD23/CD19, CD38/CD56/CD19, CD43, BCL-2 and/or BCL-6 was used.

*Reference standard included imaging follow-up after anti-lymphoma treatment for 44 patients (true-positive H&E and IHC staining) with FDG PET-CT, contrast-enhanced CT or MRI showing decreased size and/or decreased FDG uptake (regarding splenomegaly or focal lesions, respectively) after anti-lymphoma therapy whereas it included splenectomy (n= 1 case), para-aortic lymph node biopsy (n= 3 cases) and bone marrow aspiration/trephine biopsy (n= 2 cases) for the 6 patients with false-negative H&E and IHC staining.

**Procedure performed as previously described by our group[1].

*** Modified Menghini needle 150 mm in length with automatic aspiration; Biomol® HS-Hospital Rome.

**** The 6 patients with (false-negative) reactive changes (in bold) based on standard H&E and IHC staining (white or red pulp benign hyperplasia) were found to have an immunophenotyping at flow cytometric assessment on CNB samples consisting of B-cell follicular lymphoma (2 cases), small lymphocytic lymphoma (2 cases) and splenic marginal zone lymphoma (1 case), and peripheral T-cell lymphoma (1 case).

[1] Picardi M, Soricelli A, Pane F, et al. Contrast-enhanced Harmonic Compound US of the Spleen to Increase Staging Accuracy in Patients with Hodgkin Lymphoma: A Prospective Study. Radiology 2009; 251: 574-582.

Inclusion criteria were: i) suspected splenic nodules (≥ 1 cm) and/or splenomegaly (≥ 13 cm), investigated by US; ii) availability of spleen tissues obtained by US-guided 18-G CNB; iii) CNB samples fixed in formalin and embedded in paraffin, and histologic sections routinely stained with hematoxylin and eosin (H&E), and IHC; iv) flushing of core needle hub with 5 mL of isotonic saline solution for FC immunophenotyping; v) accepted diagnostic reference standard (see Table 1). We enrolled 50 cases who fulfilled all the inclusion criteria (Table 1). All patients underwent splenic CNB in DH regimen under local anesthesia and nobody suffered

from biopsy procedure-related complications of grade ≥2 according to the CTCAE. Splenic abnormalities of 44 patients were classified in the same way by reference standard as they were by H&E and IHC staining (i.e., as DLBC lymphoma, 23; follicular lymphoma, 8; mantle cell lymphoma, 4; Hodgkin lymphoma, 2; small lymphocytic lymphoma, 2; splenic marginal zone lymphoma, 2; peripheral T cell lymphoma, 1, sarcoidosis, 2). The remaining 6 patients with reactive changes at H&E and IHC staining (false-negative rate, 12%) had a clear pathologic FC immunophenotyping consisting of follicular lymphoma (2 cases), small lymphocytic lymphoma (2 cases), marginal zone lymphoma (1 case) and peripheral T-cell lymphoma (1 case). The rate of failure with CNB by adding FC to the routine evaluation of H&E and IHC was zero, with an excellent diagnostic yield of 100%. The FC was extremely helpful in the diagnosis of spleen invasion by small size malignant B- or T-lymphocytes, whose clonality was essential for differential diagnosis with a reactive process (white or red pulp benign hyperplasia). In our series, a uniform and adequate program of diagnostic tests (E&H, IHC, and FC) on spleen samples harvested by US-guided 18-G CNB enabled effective, fast, and safe tissue characterization for spleen abnormalities in patients with suspected lymphomas, avoiding in most cases the psychological and physical pain of an unnecessary splenectomy.

P077

THE PROGNOSTIC IMPACT OF BULKY MASS IN DIFFUSE LARGE B CELL LYMPHOMA, A SINGLE CENTER RETROSPECTIVE ANALYSIS IN PATIENTS TREATED WITH OR WITHOUT CONSOLIDATIVE RADIOTHERAPY

F. Vassallo[1], B. Botto[2], F. Cavallo[3], M. Clerico[3], V. Peri[3], I. Dogliotti[3], M. Levis[4], S. Ferrero[3], L. Orsucci[2], C. Boccomini[2], G. De Luca[3], M. Coscia[3], R. Freilone[2], U. Ricardi[4]

[1]Ospedale degli infermi di Biella; [2]Divisione di Ematologia, A.O.U. Città della Salute e della Scienza, presidio Molinette, Torino; [3]Divisione di Ematologia Universitaria, Dipartimento di Biotecnologie Molecolari e Scienze per la Salute, Università di Torino, Torino; [4]Department of Oncology, University of Torino, Torino, Italy

Background: Bulky mass is an established risk factor for relapse in diffuse large B-cell lymphoma (DLBCL) in the pre-rituximab era, but this was not univocally confirmed in recent years. Radiotherapy (RT) is used at the end of treatment (EOT) to reduce the risk of relapse in PET-negative patients, but real evidence is poor. We aimed to evaluate if RT may improve the outcome of patients with bulky DLBCL patients PET negative at EOT.

Methods: We performed a single center retrospective analysis on 398 DLBCL patients treated from 2013 to 2019 at the University Hospital Città della Salute e della Scienza, Turin, Italy. All patient performed PET scan at EOT. Bulky disease was considered both formass greater than 7,5 cm and 6 cm.

Findings: A bulky mass greater than 6cm was detected in 145/398 patients, 18% stage I-II, 82% stage III-IV. The most frequent regimen was R-CHOP (90%). A PET-negative scan at EOT was reported in 98 patients (70%) and 38 (27%) of them received consolidative RT to the bulky site. After a median follow up of 49 months, relapse occurred in 55 (38%), with a lower rate of relapse and a better local control among those receiving consolidative RT versus no RT (6 *vs* 49 relapse; 3 *vs* 33 local relapse). The 36 month progression free survival (PFS) was lower for lesions ≥7,5 (68% no *vs* 50% yes; p<0,019). Overall survival (OS) at 36 months was also inferior (bulky≥7,5cm 75% no *vs* 62% yes, p<0,046) Among bulky ≥7,5cm those who received RT after R-CHOP, regardless of disease stage, had a significant improvement on PFS (87% *vs* 65%, p=0,019) and a solid trend on OS (85% *vs* 68%, p=0,095). The PFS advantage was also confirmed when the analysis was restricted to patient with stage III-IV (85% *vs* 55%, p=0,02). Similar results were reported for mass ≥6cm (at 36 months PFS:71% no RT *vs* 50% RT, p<0,0001; OS: 76% no RT *vs* 62% RT, p<0,017).

Interpretation: Bulky greater than 6 and 7,5cm was confirmed to be an adverse prognostic factor both on PFS and OS suggesting the requirement of exceptional attention when selecting adequate therapy course, that possibly include RT. A significant improvement on PFS and a solid trend on OS was observed among patients who received RT after R-CHOP, even in advanced disease. Subsequent salvage treatments may play a role for the trend observed on OS, but this does not come without a cost in terms of toxicity. Further prospective data are needed to confirm that RT may decrease or eliminate the adverse prognostic effect of bulky.

P078

PIXANTRONE AS BRIDGING THERAPY TO ALLOGENEIC TRANSPLANTATION OR CAR-T CELL THERAPY IN PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA: RETROSPECTIVE MULTICENTER STUDY

G. Lolli[1,2], L. Argnani[2], G. Gini[3], B. Casadei[1,2], C. Pellegrini[1], M. Tani[4], V. Pavone[5], M. Cimminiello[6], F. Bonifazi[7], P.L. Zinzani[1,2]

[1]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli", Bologna, Italy; [2]Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale, Università di Bologna, Bologna, Italy; [3]Clinica di Ematologia AOU Ospedali Riuniti, Ancona, Italy; [4]U.O.C Ematologia Ospedale Santa Maria delle Croci, Ravenna, Italy; [5]Department of Hematology and Bone Marrow Transplant, Hospital Card. G.; Panico, Tricase, Italy; [6]Dipartimento Oncologico, U.O.C. di Ematologia-Centro Trapianti di Cellule Staminali, Azienda Ospedaliera Regionale "San Carlo" di Potenza, Potenza, Italy; [7]IRCCS Azienda-ospedaliero Universitaria di Bologna, Bologna, Italy

Diffuse large B cell lymphoma (DLBCL) is one the most common type of lymphoma. Even if 5-year survival rate, in newly diagnosed patients, is between 60% to 70%, a 50% of them results refractory, or eventually relapse. This population has an extremely poor prognosis. In the relapsed/refractory (R/R) setting, standard of care (SOC) consists of intensive salvage chemotherapy regimen followed by autologous stem cell transplantation. This approach is feasible in about 50% of R/R patients. For subsequent lines of therapy, SOC is absent. The main available options include chimeric antigen receptor T (CAR-T) cell therapy, polatuzumab vedotin, bispecific antibodies, lenalidomide as single agent or in combination with rituximab or tafasitamab, pixantrone and other older agents. Allogeneic transplantation (alloSCT) is an effective modality to consolidate a response in a previous multiple-refractory patient.

In our multicentric study we want to explore the role of pixantrone, a novel aza-anthracenedione with less cardiotoxic potential and different mechanism of action in comparison to anthracyclines, in an extremely difficult cohort of R/R DLBCL patients (Table 1). We selected a population where pixantrone has been used as bridging therapy (BT) to CAR-T cell therapy or to alloSCT. We used the term BT to indicate the therapy performed between leukapheresis and infusion of engineered CAR-T cells in the first cohort of patients, and just before alloSCT in the second.

Thirteen patients underwent a median of 2 cycles (range 1-4) of pixantrone between June 2019 and February 2022 as BT to alloSCT (n=2) and CAR-T (n=11). Pixantrone was administered at a median time from leukapheresis of 8 days (range 5-32 days). All patients were successfully led to subsequent therapy at a median time interval of 28 days, without delays due to BT. At the end of the treatment pathway, 7 patients achieved a CR (53.8%, all with CAR-T) and 3 PR (2 with CAR-T and 1 with alloSCT) with an overall response rate of 76.9%. Ten hematological adverse events (AE) were registered in 8 patients. Particularly, 4 grade 3-4 neutropenia emerged, not complicated by infections. Extra-hematological AEs (all grade 1) were reported in 3 patients: 1 oral mucositis, 1 diarrhea and 1 blue coloration of the skin, no cardiotoxicities occurred.

Pixantrone is a suitable option as BT to CAR-T and alloSCT. Toxicity is negligible and mainly hematological, with good tolerance in older and heavily pre-treated patients.

Monoclonal myeloma and gammopathies I

P079

DARATUMUMAB, BORTEZOMIB AND DEXAMETHASONE (DVD) IN LENALIDOMIDE-REFRACTORY MYELOMA PATIENTS: SUBGROUP ANALYSIS OF THE MULTICENTER RETROSPECTIVE CLINICAL EXPERIENCE BY "RETE EMATOLOGICA PUGLIESE"

G. Mele[1], N. Cascavilla[2], M. Carella[2], N. Di Renzo[3], A. Guarini[4], P. Mazza[5], L. Melillo[6], V. Pavone[7], G. Tarantini[8], P. Curci[9], A.P. Falcone[2], C. Germano[8], A. Mele[7], G. Palazzo[5], G. Palumbo[6], A. Quinto[5], G. Reddiconto[3], B. Rossini[4], N. Sgherza[9], G. Specchia[9], P. Musto[9], D. Pastore[1]

[1]Haematology, Ospedale A. Perrino; [2]Haematology, Ospedale Casa Sollievo della Sofferenza; [3]Haematology, Ospedale V. Fazzi; [4]Haematology, Ospedale Giovanni Paolo II°; [5]Haematology, Ospedale G. Moscati; [6]Haematology, Ospedali Riuniti; [7]Haematology, Ospedale Cardinale Panico; [8]Haematology, Ospedale Monsignor R. Dimiccoli; [9]University of Bari Medical School, Policlinico, Italy

The upfront strategy in transplant-eligible patients with MM now includes lenalidomide maintenance. In the non-transplant setting, lenalidomide is the backbone of several three-drug combinations. Therefore, patients who receive lenalidomide early in their treatment represent a clinically relevant population. We report a multicenter observational-retrospective analysis of 68 consecutive patients (M 59.4%, F 40.6%) with symptomatic refractory/relapsed Multiple Myeloma (RRMM), from January 2018 to December 2020, treated with daratumumab, bortezomib, dexamethasone (DVd) as salvage therapy at 9 haematological centers in Puglia. In this experience 70.6% of patients (48/68) were refractory to lenalidomide. The last treatment received before the DVd regimen was KRd (39.6%), Rd (39.6%), EloRd (14.6%) and IxaRd (6.2%).

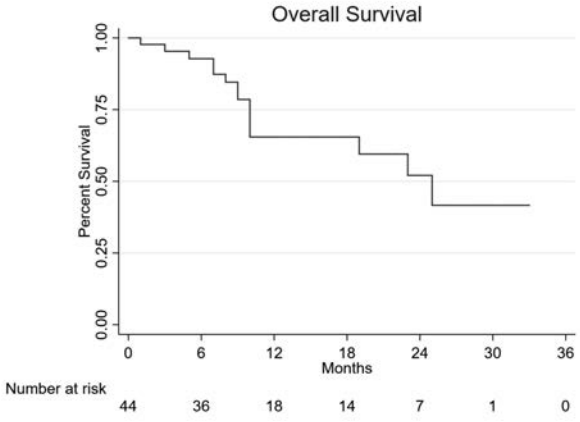


Figure 1. Median OS: 25 months.

The median therapy lines received were 2.5 (range 1-5). Thirty-one patients (64.6%) had previously undergone single or tandem autologous transplant. Forty patients (83.3%) had relapsed MM, while 8 (16.7%) patients had refractory MM. The median age at diagnosis was 62.5 years (range 36-81). The median age at the start of DVd from diagnosis was 68.5 years (range 40-81). The median time to the start of DVd from diagnosis was 5 years (range 0-16). The median number of cycles administered was 8 (range 1-34). The overall response rate was 72.3% (Complete Remission 8.5%, Very Good Partial Response 12.8%, Partial Response 51%). Median time to response was 1.5 months (range 1-5). Best response was achieved at a median number of 4 cycles (range 2-10). 45.8% of patients were shifted to a weekly schedule of bortezomib mainly for haematological toxicities (18.7% thrombocytopenia, 12.5% neutropenia). Median overall survival was 25 months (Figure 1). Median time to progression was 11 months (95% CI: 7-18 months) (Figure 2). 58% of patients discontinued treatment due to relapse. Grade 3/4 thrombocytopenia (20.8%) was the most common haematological toxicity, while grade 3/4 anaemia occurred in 14.6% of patients and grade 3/4 neutropenia in 10.4% of patients. Grade 3/4 infections were the most common non-haematological adverse event (upper respiratory tract infection 6.3%; pneumonia 8.3%). In conclusion, our analysis supports use of DVd regimen as a treatment option in patients with MM refractory to lenalidomide with high ORR and favourable safety profile. Early use of DVd triplet at first relapse could improve outcomes compared with use in later treatment.

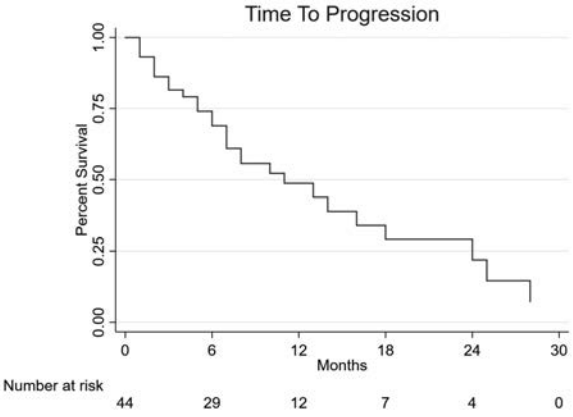


Figure 2. Median TTP: 11 months (95% CI: 7-18 months).

P080

OXIDATIVE STRESS MACHINERY AS NEW THERAPEUTIC VULNERABILITY FOR DIRECT AND IMMUNOMEDIATED TARGETING OF MULTIPLE MYELOMA

C. Botta[1]*, E. Lo Presti[2]*, A.M. Corsale[1], M.S. Azgomi[1], F. Plano[1], C. Perez[3], A. Gullà[4], N.R. Caccamo[5], F. Dieli[5], S. Meraviglia[5], B. Paiva[3], S. Siragusa[1]

*[1]Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties (ProMISE), University of Palermo; [2]National Research Council (CNR)-Institute for Biomedical Research and Innovation (IRIB); [3]Centro de Investigacion Medica Aplicada, Instituto de Investigacion Sanitaria de Navarra Hematology Unit, Clinica Universidad de Navarra, Centro de Investigación Biomédica en Red, Cancér Hematology Unit; [4]Dana-Farber Cancer Institute, Harvard Medical School; [5]Department of Biomedicine, Neurosciences and Advanced Diagnosis, University of Palermo; *equally contributed*

Genomic instability is a key feature of multiple myeloma (MM). It is conceivable, that at the bases of this phenomenon there is intense replicative/oxidative stress with the potential to impair anti-MM immune response and patients' outcome. We performed bulk and single cell (sc) evaluation coupled with extensive data validation on external datasets to investigate cell-stress role in MM pathogenesis, evolution and outcome. By analyzing the transcriptome of 41 normal plasma cells (PCs) samples, 6 clonal PCs (cPCs) from premalignant conditions and 32 MM samples, we demonstrated a progressive deregulation of genes belonging to stress response (Figure 1A), associated with increased levels of "antioxidant" genes (such as SOD1), necessary to deal with the risk of genotoxic-induced cell death. Next, we performed scRNAseq on PCs obtained from 3 healthy subjects (HS) and 11 newly diagnosed MM pa-

tients. Interestingly, we identified 3 main transcriptional programs (Fig 1B): a CCND1/SOD1-driven program; a MCL1-driven program which overexpresses SOD2 and a MAF-driven program characterized by the overexpression of selenoproteins (*e.g.* SELLK, VIMP). We overall validated our previous results with the datasets GSE145977 and GSE124310 which included scRNAseq data from matched PCs and immune cells (ICs) from 6 MM patients and 7 HS (Figure 1C). Next, we focused on the relationships between T/NK/monocyte subpopulations and MM stress profiles. Based on the abundance of each specific immune population, we grouped patients into 3 main clusters which we found to be related to stress-specific transcriptional programs in MM cells: *e.g.* cPCs from group A present a significant overexpression of CCL1 which was mirrored by an increase in abundance of Th2 and monocytes; group C was characterized by a strong prevalence of CD4 cells and the expression of CD44, a molecules that we already demonstrated being associated with myeloma dissemination and cellular/oxidative stress. Interestingly, the increase in stress signals (*e.g.* group C) was mirrored by the increase of activated NKs (GZMB+PFR1+). Lastly, we used the MMRF-CoMMpass dataset to investigate if the presence of specific stress-associated patterns (as identified in sc analysis) correlated with survival (Fig 1D). Interestingly, we found that patients with a SOD1 or SOD2 associate signature presented the shortest overall survival, supporting the targeting of these specific molecules as a novel therapeutic approach for this malignancy.

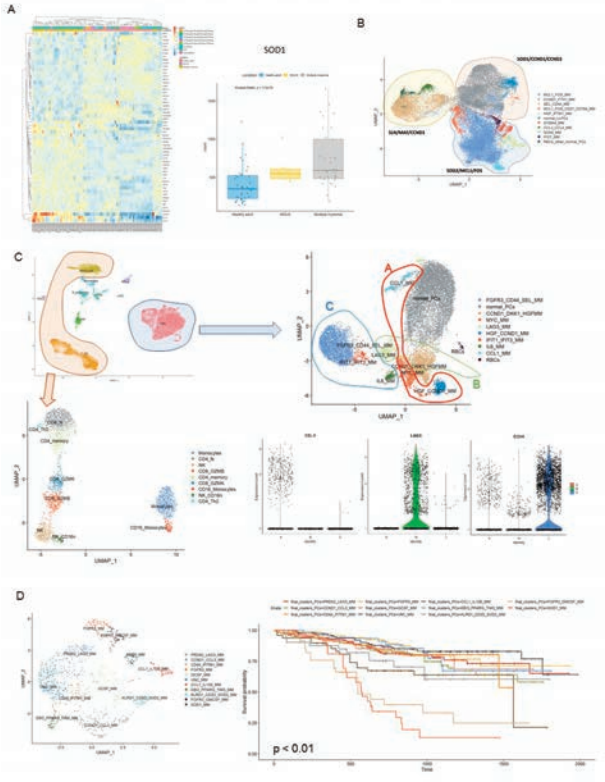


Figure 1.

P081

SINGLE-CELL RNA-SEQ OF BONE MARROW INFILTRATING T CELLS ALONG MULTIPLE MYELOMA EVOLUTION REVEALS AN EARLY ACQUIRED EXHAUSTED PHENOTYPE

A.M. Corsale[1]*, M.S. Azgomi[1]*, F. Plano[1]*, M. Di Simone[2], C. Perez[3], C. Picone[2], E. Gigliotta[1], C. Vullo[1], G. Camarda[1], C. Rotolo[1], M. Santoro[1], N.R. Caccamo[2], F. Dieli[2], J. San Miguel[3], B. Paiva[3], S. Meraviglia[2], S. Siragusa[1], C. Botta[1]

*[1]Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties (ProMISE), University of Palermo; [2]Department of Biomedicine, Neurosciences and Advanced Diagnosis, University of Palermo; [3]Centro de Investigacion Medica Aplicada, Instituto de Investigacion Sanitaria de Navarra Hematology Unit, Clinica Universidad de Navarra, Centro de Investigación Biomédica en Red, Cancér Hematology Unit; *equally contributed*

The immune microenvironment plays a major role in multiple myeloma (MM) pathogenesis. The understanding of the interactions between MM cells and bone marrow (BM) cells is quickly improving patients' characterization, shading light on mechanisms responsible for evolution from premalignant conditions (MGUS/smoldering MM (SMM)).

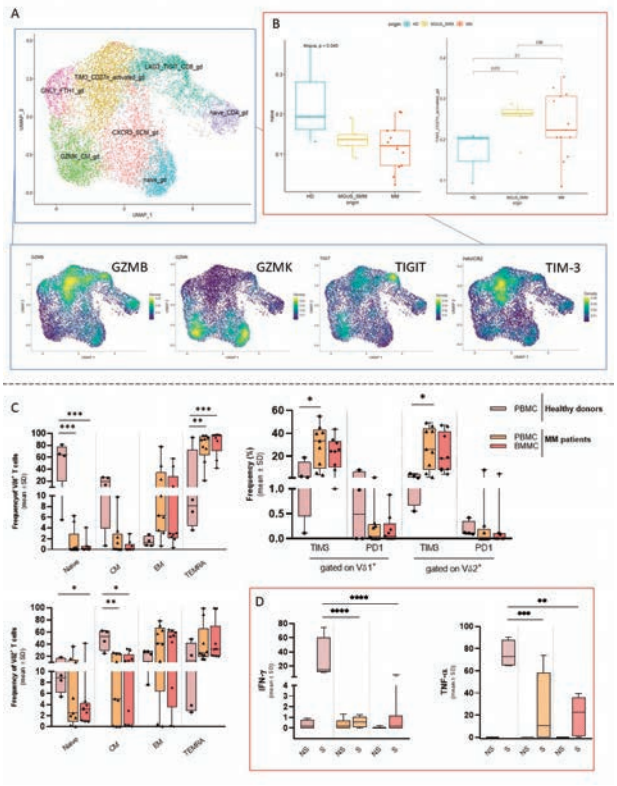


Figure 1.

Among the BM-infiltrating cells, γδ T cells (Tgd) act as bridge between innate and adaptive immune responses and are reported to interact at different levels with various types of cancer. However, their role in MM evolution still needs to be elucidated. To this aim, we investigated the involvement of Tgd in MM and its precursor phases, providing the first single-cell (sc) atlas of this subpopulation in this disease.

Accordingly, CD3+ cells from the BM of 3 healthy donors (HD), 5 MGUS/SMM and 9 active MM patients were sorted and seeded into single drop by Chromium instrument (10X genomics) for scRNAseq analysis. Overall, 12527 Tgd were analysed. Bioinformatics workflow enabled us to identify 7 Tgd clusters: 2 naïve subpopulations (CD4-

/CD8- and CD4+ Tgd), 3 GZMB effector/terminally differentiated subpopulations (CD8+/TIGIT+/LAG3+, TIM3+/CD27- and GNLY+/FTH1+ Tgd) and 2 GZMK memory subpopulations (GZMK+ and CXCR3+ Tgd). Interestingly, we found a reduction in the frequency of naïve, coupled with a trend to increase of TIM3+ Tgd along MM evolution. Next, peripheral blood mononuclear cells (PBMC) and BM cells from additional 4 HD (PBMCs only), 2 SMM and 7 MM patients were collected to validate our results. We had the chance to refine Tgd analysis by investigating separately both Vδ1+ and Vδ2+. Intriguingly, MM patients showed a prevalence of Vδ1+ as compared HD, with an increase in Vδ1+/ Vδ2+ ratio (data not shown). We confirmed by flow cytometry, the accumulation of effector/terminally differentiated Tgd in MM patients as compared to HD, wherein naïve and central memory populations prevailed (Figure 1C). Accordingly, the evaluation of exhaustion markers confirmed the increase of TIM3+ (but not PD1+) Tgd cell subsets in MM. Lastly, we functionally confirmed that the acquisition of an exhausted phenotype translated into a reduction of TNF-α and IFN-γ in both Vδ1+ and Vδ2+ T cells after *in vitro* stimulation (Figure 1D). These data suggest the acquisition of a dysfunctional Tgd phenotype early in premalignant conditions of MM which deserves further mechanistic investigations. In this light, TIM-3 represents a potential new target for MM patients.

P082

COMPARISON BETWEEN DRD VS KRD AS SALVAGE THERAPY FOR MULTIPLE MYELOMA PATIENTS IN FIRST RELAPSE: THE REAL LIFE EXPERIENCE OF RETE EMATOLOGICA PUGLIESE (REP)

A. Mele[1], E. Prete[1], G. Mele[2], S. Citiso[1], D. Pastore[2], N. Sgherza[3], P. Curci[3], P. Musto[3], A.P. Falcone[4], N. Cascavilla[4], C. Germano[5], G. Tarantini[5], G. Reddiconto[6], N. DiRenzo[6] G. Palazzo[7], P. Mazza[7], B. Rossini[8], A. Guarini[8], G. Palumbo[9], L.M.A. Melillo[9], V. Pavone[1]

[1]Department of Hematology and Bone Marrow Transplant, Hospital Card. G. Panico, Tricase; [2]Department of Hematology, Hospital Perrino, Brindisi; [3]Department of Hematology and Bone Marrow Transplant, Policlinico, University of Bari; [4]Department of Hematology and Bone Marrow Transplant, IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo; [5]Department of Hematology, ASL BT, Barletta; [6]Department of Hematology, Hospital Vito Fazzi, Lecce; [7]Department of Hematology and Bone Marrow Transplant, Hospital G.Moscati, Taranto; [8]Department of Hematology, Hospital IRCCS Oncologico, Bari; [9]Department of Hematology, Hospital University Riuniti, Foggia, Italy

Background: Daratumumab (DRD) and Carfilzomib (KRD), in combination with lenalidomide and dexamethasone, performed well in patients with relapsed or relapsed/refractory multiple myeloma (RRMM). The lack of randomized and/or real-life trials comparing the two triplets prompted us to assess their effectiveness and safety in RRMM in first relapse. Aims: To analyzed effectinness and safety of Drd and Krd in first line relapse Multiple Myeloma.

Methods: 176 RRMM patients, including 107 DRD and 69 KRD, entered this non-randomized comparison.

Results: Baseline characteristics and details of the previous therapies are analyzed (Table 1). KRD cohort accounted for a higher incidence of III Durie-Salmon staging (71 *vs* 23%, p 0,001). Instead, a higher number of patients with refractory disease were treated with DRD (29 *vs* 13%, p 0,01). Moreover, median age of patients, elevated LDH, III ISS stage, cytogenetic risk categories, type of previous therapy, were equally distributed between the two therapy arms. Half of them (43%) relapsed after a previous ASCT, without differences in KRD and DRD group of patients. The overall response rate (ORR) was 78% (n=83), with 31% complete response (CR; n= 33) in DRD. In patients treated with KRD, the ORR was 74% (n=51), with 42 % CR (n=29),p 0,31. Median time to best response was shorter in KRD patients (2,8 *vs* 4,3 months, p 0,03). The probability of CR+VGPR response was significantly higher in patients with normal LDH and treated with DRD (41 *vs* 22%, p 0,02). Elevated LDH didn't influenced the probability of response in KRD cohort (45 *vs* 42%, p 0,89). Response was better in late relapse (64 *vs* 21%, p 0.001) and in patients relapsed after a prior autologous transplant (61 *vs* 33%, p 0,02) in KRD arm. After a median follow-up of 18 months, median PFS was NR in DRD and 31 months in KRD, p 0,0001. The 2y-PFS was 72% and 57% in DRD and KRd, respectively. PFS was longer in patients achieving a Very good partial response (VGPR) with median PFS of 28 months and NR, in DRD and KRD, respectively (p 0,001). Better PFS was obtained in patients with normal LDH treated with DRD as KRD. The treatmen discontinuation rate due to adverse events (AEs) was 13% and 22% in DRD and KRD, respectively (p 0,12). No differences in hematologic and non-hematologic AEs were observed between the two triplets

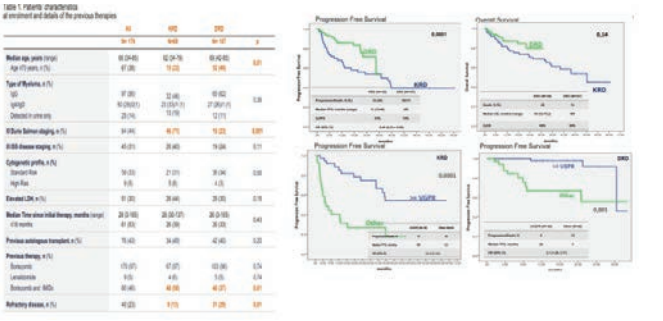


Figure 1.

P083

THE ROLE OF KIDNEY BIOPSY FOR THE MANAGEMENT OF PATIENTS WITH CONCOMITANT MGUS AND RENAL IMPAIRMENT

I. Rizzello[1,2], E. Zamagni[1,2], G. De Cicco[1,2], S. Rocchi[1,2], G. Papalia[2,3], A. Campus[2,3], L. Pantani[1], E. Favero[1,2], F. Bigi[1,2], M. Ursi[1,2], M. Talarico[1,2], B. Fabbrizio[4], O. Baraldi[2,3], M. Cavo[1,2], G. Vischini[2,3], G. La Manna[2,3]

[1]Istituto di Ematologia "Seràgnoli", IRCCS Azienda Ospedaliero-Universitaria di Bologna; [2]Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale, Università di Bologna; [3]Nephrology Dialysis and renal transplantation unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna; [4]SSD Diagnostica istopatologica e molecolare degli organi solidi e del relativo trapianto, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Italy

Background: Patients (pts) frequently show concomitant monoclonal gammopathy (MGUS) and kidney diseases: establish a potential correlation between the 2 entities is crucial for proper management. Kidney biopsy is the gold standard to state the etiology of kidney diseases; monoclonal Ig deposition associated with MGUS defines the so-called monoclonal gammopathy of renal significance (MGRS).

Methods and materials: 1067 kidney biopsies were performed at the Nephrology Unit (IRCCS AOU di Bologna) from 2015 to 2020. In all, MGUS was searched, as presence of monoclonal spike at electrophoresis and positive serum and/or urine immunofixation, and increased levels of kappa/lambda serum free light chain (sFLC). Multiple myeloma pts or with history of kidney transplantation were excluded. Aims of the present study were evaluating the incidence of MGRS among pts carrying MGUS and kidney alteration and identifying MGRS predicting factors.

Results: Out of 1067 biopsies, 48 pts (4.5%) had MGUS (median age

72 years [33-92]). Indications for kidney biopsy in MGUS pts were increased proteinuria (58%), both with impaired (25%) and normal (33%) creatinine levels (median value: 4035 mg/die [374-9537]), rising creatinine level alone (25%) (median value: 3.1 mg/dL [1,32-9,2]), and hematuria (17%). MGUS isotype was IgG in 27 (56%), IgA in 6 (13%), IgM in 6 (13%) pts, while light chain MGUS was seen in 9 pts (19%). Involved light chain was lambda in 27 (56%) and kappa in 21 (44%) pts. sFLC ratio was imbalanced in 22 (42%), normal in 17 (33%) and unavailable in 9 (19%) pts. Kidney biopsy let to diagnose MGRS in 12 pts (25%); Ig-related amyloidosis was the most frequent MGRS subtype (92%), followed by MIDD (8%). The main indications for kidney biopsy in MGRS pts were elevated proteinuria (75%), along with impaired and normal creatinine levels in 42% and 33% of pts, respectively, and rising creatinine level alone (25%). SFLC ratio was imbalanced in 4 (34%) MGRS pts, normal in 7 (58%) and unavailable in 1 (8%).

Conclusion: In our study, the incidence of MGRS among pts carrying MGUS and kidney impairment was 25%. Elevated proteinuria was the most frequent factor associated with MGRS (75%), while imbalanced sFLC ratio was found only in 34% pts. Among MGRS, amyloidosis was the leading cause of kidney damage (92%). Kidney biopsy must be part of the diagnostic work-up of pts with monoclonal gammopathy and renal damage eligible for the procedure, for a correct etiopathogenetic correlation.

P084

ELOTUZUMAB PLUS LENALIDOMIDE AND DEXAMETHASONE IN RELAPSED/REFRACTORY MULTIPLE MYELOMA: EXTENDED 3-YEAR FOLLOW-UP OF AN ITALIAN, MULTICENTER, RETROSPECTIVE CLINICAL EXPERIENCE WITH 319 CASES OUTSIDE OF CONTROLLED CLINICAL TRIALS

A. Bruzzese[1], D. Derudas[2], M. Galli[3], E.A. Martino[1], S. Rocco[4], C. Conticello[5], C. Califano[6], N. Giuliani[7], S. Mangiacavalli[8], G. Farina[9], A. Lombardo[10], M. Brunori[11], E. Rossi[12], E. Antonioli[13], R. Ria[14], R. Zambello[15], N. Di Renzo[16], G. Mele[17], G. Marcacci[18], G. Pietrantuono[19], G. Palumbo[20], N. Cascavilla[21], C. Cerchione[22], A. Belotti[23], C. Criscuolo[24], G. Uccello[25], P. Curci[26], E. Vigna[1], F. Mendicino[1], E. Iaccino[27], S. Mimmi[27], C. Botta[1,28], D. Vincelli[29], N. Sgherza[26], A. Bonalumi[30], L. Cupelli[31], R. Stocchi[32], M. Martino[33], S. Ballanti[34], D. Gangemi[35], A. Gagliardi[36], B. Gamberi[37], A. Pompa[38], G. Tripepi[39], F. Frigeri[11], U. Consoli[27], S. Bringhen[40], E. Zamagni[41], F. Patriarca[32], V. De Stefano[12], F. Di Raimondo[5], S. Palmieri[4], M.T. Petrucci[42], M. Offidani[43], P. Musto[26,44], M. Boccadoro[40], M. Cavo[41], A. Neri[45], F. Morabito[46,47], M. Gentile[1]

[1]Hematology Unit, Azienda Ospedaliera of Cosenza, Cosenza, Italy; [2]Department of Hematology, Businco Hospital, Cagliari, Italy; [3]Hematology and Bone Marrow Transplant Unit, Azienda Socio-Sanitaria Territoriale-Papa Giovanni XXIII, Bergamo, Italy; [4]Hematology Unit, Ospedale Cardarelli, Napoli, Italy; [5]Department of medical and surgical specialties, Hematology Section, University of Catania, Catania, Italy; [6]Onco-hematology Unit, Ospedale Umberto I, Nocera Inferiore, Italy; [7]Hematology Unit, Parma University Hospital, Italy; [8]Hematology Division, Department of Hematology-Oncology, IRCCS Fondazione Policlinico San Matteo, Pavia, Italy; [9]UOC Ematologia a Indirizzo Oncologico, AORN "Sant'Anna e San Sebastiano", Caserta, Italy; [10]Onco-hematology Unit Azienda Ospedaliera Santa Maria of Terni, Italy; [11]Internal Medicine, Ospedale S. Croce, Azienda Ospedaliera Ospedali Riuniti Marche Nord, Presidio of Fano, Italy; [12]Istituto di Ematologia, Università Cattolica, Fondazione Policlinico Gemelli IRCCS, Roma, Italy; [13]Hematology Unit, Careggi Hospital, Florence, Italy; [14]Department of Biomedical Science, University of Bari "Aldo Moro" Medical School, Internal Medicine "G. Baccelli", Policlinico, Bari, Italy; [15]Department of Medicine, Hematology and Clinical Immunology Section, Padua University School of Medicine, Padua, Italy; [16]Hematology Unit, Lecce, Italy; [17]Hematology Unit, Brindisi, Italy; [18]Hematology and Bone Marrow Transplant Unit, Istituto Nazionale Tumori, Fondazione 'G. Pascale', IRCCS, Napoli, Italy; [19]Unit of Hematology and Stem Cell Transplantation, IRCCS-CROB, Referral Cancer Center of Basilicata, Rionero in Vulture (Pz), Italy; [20]Department of Hematology, Hospital University Riuniti, Foggia, Italy; [21]Department of Hematology and Bone Marrow Transplant, IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy; [22]Hematology Unit, IRCCS - Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori, Meldola, Italy; [23]Hematology Unit, A.O. Spedali Civili, Brescia, Italy; [24]Hematology Unit, AO S.G. Moscati, Aversa (CE), Italy; [25]Hematology Department, G. Garibaldi Hospital, Catania, Italy; [26]Unit of Hematology and Stem Cell Transplantation, AOUC Policlinico, Bari, Italy; [27]Department of Experimental and Clinical Medicine, University "Magna Graecia" of Catanzaro, Italy; [28]Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties, University of Palermo, Palermo, Italy; [29]Hematology Unit, Department of Hemato-Oncology and Radiotherapy, Great Metropolitan Hospital "Bianchi-Melacrino-Morelli", Reggio Calabria, Italy; [30]Section of Hematology, Department of Medicine, University of Verona, Verona, Italy; [31]Hematology Unit and Pathology Department, S. Eugenio Hospital Rome, Rome, Italy; [32]Hematology, DISM, University of Udine, Italy; [33]Stem Cell Transplantation Unit, Department of Hemato-Oncology and Radiotherapy, Great Metropolitan Hospital "Bianchi-Melacrino-Morelli", Reggio Calabria, Italy; [34]Institute of Haematology and Stem Cell transplantation, Ospedale Santa Maria della Misericordia, University of Perugia, Perugia, Italy; [35]Hematology Unit, Fabrizio Spaziani Hospital, Frosinone, Italy; [36]Complex Operative Unit of Hematology, S. Maria di Loreto Nuovo Hospital, Napoli, Italy; [37]Hematology Unit, AUSL-IRCCS, Reggio Emilia, Italy; [38]Hematology Unit, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milano, Italy; [39]Nephrology Center of National Research Institute of Biomedicine and Molecular Immunology, Reggio Calabria, Italy; [40]Division of Hematology, University of Torino, AOU Città della Salute e della Scienza di Torino, Italy; [41]Seràgnoli Institute of Hematology and Medical Oncology, University of Bologna, Bologna, Italy; [42]Department of Cellular Biotechnologies and Hematology, Sapienza University of Rome, Italy; [43]Hematology Unit, AOU Ospedali Riuniti di Ancona, Italy; [44]Department of Emergency and Organ Transplantation, "Aldo Moro" University School of Medicine, Bari, Italy; [45]Hematology Unit, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milan, Italy; [46]Hemato-Oncology department, Augusta Victoria Hospital of Jerusalem, Israel; [47]Biotechnology Research Unit, AO di Cosenza, Italy

The combination of elotuzumab, lenalidomide, and dexamethasone (EloRd) enhanced the clinical benefit over Rd with a manageable toxicity profile in the ELOQUENT-2 trial, leading to its approval in relapsed/refractory multiple myeloma (RRMM). The present study is a 3-years follow-up update of a previously published Italian real-life RRMM cohort of patients treated with EloRd. This revised analysis entered 319 RRMM patients accrued in 41 Italian centers. After a median follow-up of 36 months (range 6-55), 236 patients experienced disease progression or died. Median progression-free survival (PFS) and overall survival (OS) were 18.4 and 34 months, respectively. The updated multivariate analyses showed a significant reduction of PFS and OS benefit magnitude only in cases with ISS stage III. Major adverse events included grade 3/4 neutropenia (18.5%), anemia (15.4%), lymphocytopenia (12.5%), and thrombocytopenia (10.7%), while infection rates and pneumonia were 33.9% and 18.9%, respectively. No new safety signals with longer follow-up have been observed. Of 319 patients, 245 (76.7%) reached at least a partial remission. A significantly lower response rate was found in patients previously exposed to lenalidomide. In conclusion, our study confirms that EloRd is a safe and effective regimen for RRMM patients, maintaining benefits across multiple unfavorable subgroups.

P085

FIRST INTERIM ANALYSIS OF A PROSPECTIVE, MULTICENTER, OBSERVATIONAL STUDY ON THE PREVALENCE OF TYPE 1 GAUCHER DISEASE IN PATIENTS WITH MULTIPLE MYELOMA

M. Offidani[1], C. Zizzo[2], S. Rupoli[1], I. Federici[1], A. Bossi[1], S. Morè[1], V.M. Manieri[1], M.T. Petrucci[3], T. Caravita di Toritto[4], M. Brunori[5], A. Gozzetti[6], A. Tordi[4], F. Fazio[3], C. Lisi[3], E. Morsia[1], L. Corvatta[7], A. Olivieri[1], G. Duro[2]

[1]Clinica di Ematologia Azienda Ospedaliero-Universitaria Ospedali Riuniti di Ancona; [2]Istituto per la Ricerca e l'Innovazione Biomedica CNR-Palermo; [3]Azienda Policlinico Umberto I, Sapienza Università di Roma; [4]UOSD Ematologia ASL Roma 1; [5]UOS Ematologia Ospedale Santa Croce; [6]Ematologia, Policlinico Santa Maria alle Scotte; [7]UOC Medicina, Ospedale Profili, Italy

Background: Type I Gaucher disease (GD1) has been associated with increased cancer risk in the International Collaborative Gaucher Group (ICGG) Registry (Rosenbloom et al, 2005). However, due to the retrospective nature of the study and young age distribution of population, cancer risk was likely underestimated. Then, we designed a prospective study to investigate the prevalence of GD1 in a large Multiple Myeloma (MM) patient population.

Aims: Primary end-point of the study is the prevalence of Dried Blood Spots (DBS) test positivity in MM patients. All patients with DBS test positive undergo genetic test to confirm the diagnosis of GD1. If the observed prevalence will be significantly higher than predicted, the identification of potential risk predictors in the selected population will be carried out.

Methods: This is an observational, prospective, cross-sectional, multicentre study. Due to the lack of data on the effective prevalence of GD1 in MM, the sample size has been determined considering clinically relevant a prevalence of the condition > 0.5% for defining as "high risk" the selected population. Considering an alpha error of 5% and a statistical power of 95%, we will enroll approximately 1000 patients in 46 Hematology Centers overall. All patients with a confirmed diagnosis of MM are screened for GD1 by DBS sampling technique. The DBS test is centralized at the Istituto per la Ricerca e l'Innovazione Biomedica CNR-Palermo. This is the first interim analysis planned after the first positive DBS test.

Table 1.

ID	Sex	GBA Enzimatic activity (normal range=0.2-2.5 nMol/h/ml)	Lyso Gb1 (normal range<6.8 ng/ml)	Ivolved GBA gene
KA505	M	2.0	14.6	R170C heterozygous L444P heterozygous
KA492	M	3.9		L444P heterozygous
KA404	M	3.4		N370S heterozygous

Results: So far, 268 patients with a median age of 67 years (range 37-90) have been enrolled, 58% of which were male. No patients were Jews, one was Asian and one was Black, the remaining were Caucasian. Newly diagnosed and relapsed-refractory MM were recognized in 58% and 42% of patients, respectively, whereas SMM and MM in 10% and 90%, respectively. Monoclonal component was IgG in 54%, IgA in 25%, light chain in 11%. Median Ferritin was 322 ng/ml (range 17-1236) and median Alkaline Phosphatase was 81 U/L (range 29-355). Data of DBS test and genetic are reported in the Table 1. DBS test was considered positive in 1 patient so the prevalence was 1/268 (0.4%), so far.

Conclusions: Despite the enrollment of a quarter of the planned patients, preliminary data showed a prevalence of DBS test positivity of 0.4%. In DBS positive patients a pathological genetic test is required to confirm the diagnosis of GD1 and to demonstrate the relationship between GD1 and MM.

P086

BELANTAMAB MAFODOTIN IN PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA: A REGIONAL REAL-LIFE MULTICENTER EXPERIENCE

R. Iula[1], D. De Novellis[2], F. Trastulli[3], R. Della Pepa[1], A. Carobene[2], M. Di Perna[4], A. D'Ambrosio[1], M. Romano[1], A. Leone[1], L. De Fazio[1], A. Fumarella[1], G. Gaeta[1], V. Marafioti[1], S. Palmieri[3], S. Rocco[3], R. Fontana[2], V. Giudice[56], C. Selleri[26], C. Califano[4], F. Pane[1], F. Ferrara[2], L. Catalano[1]

[1]Hematology - Department of Clinical Medicine and Surgery, Federico II University; [2]Hematology and Transplant Unit, University Hospital "San Giovanni di Dio e Ruggi d'Aragona; [3]Division of Hematology and Stem Cell Transplantation Program, AORN Cardarelli Hospital; [4]Onco-Hematology Department, A. Tortora Hospital; [5]Clinical Pharmacology Unit, University Hospital "San Giovanni di Dio e Ruggi d'Aragona; [6]Departement of Medicine, Surgery and Dentistry "Scuola Medica Salernitana" University of Salerno, Italy

Background: Treatment of refractory/relapsed (R/R) multiple myeloma (MM) after proteasome inhibitors, immunomodulatory agents and anti-CD38 antibodies is an unmet clinical need. Belantamab Mafodotin (BM),an immunoconjugate targeting B-cell maturation antigen,showed clinical activity in heavily pre-treated MM patients in phase II DREAMM-2 trial. Here we report a real-life retrospective regional multi-center experience about BM treatment in R/R MM.

Table 1.

Characteristics	WS, N = 27	EP, N = 21
Median age, years (range)	68 (51-83)	67 (51-83)
Gender, n (%)		
Male	16 (59)	13 (62)
Female	11(41)	8 (38)
M-protein type, n (%)		
IgG	16 (59)	11(52)
IgA	5 (19)	4 (20)
Micromolecular	5 (19)	5 (24)
Not secernent	1 (3)	1 (4)
Light chain type, n (%)		
Kappa	16 (59)	13 (62)
Lambda	10(38)	7 (34)
Not secernent	1 (3)	1 (4)
Previous treatment lines, median (range)	6 (3-14)	6 (3-14)
Immunoregulatory drugs, n (%)	27 (100)	21 (100)
Anti-CD 38 monoclonal antibodies		
- Daratumumab, n (%)	27(100)	21 (100)
- Isatuximab, n (%)	0	0
Prior proteasome inhibitor treatment		
-Bortezomib, n (%)	27 (100)	21 (100)
-Carfilzomib , n (%)	23 (85)	18 (86)
Prior autologous stem cell transplantation, n (%)	19 (70)	16 (76)
-Double	3 (10)	3 (12)
M-protein values, g/dL, median (range)	1.2 (0-7)	1.1 (0-6.65)
Osteolytic lesions, n (%)	22 (82)	16 (77)
Thrombocytopenia, n (%)	11 (41)	9 (43)
BM cycles, median (range)	3 (1-21)	4 (2-21)
Years from diagnosis to BM therapy, median (range)	7 (1-19)	7 (1-19)
Steroid and lubricant eye drop premedication, n (%)	27 (100)	21 (100)
Systemic steroid/antihistamine premedication, n (%)	21 (100)	21 (100)
BM response rates		
ORR, n (%)	11 (41)	11 (52)
CR, n (%)	2 (7)	2 (10)
VGPR, n (%)	3 (11)	3 (14)
PR, n (%)	6 (22)	6 (28)
SD, n (%)	3 (11)	3(14)
CBR, n (%)		14 (21)
Median PFS, months (range)	3 (0-20)	5 (1-20)
12-month PFS	32 %	41%
Median OS, months (range)	Not reached (0-20)	Not reached (1-20)
12-month OS	63%	71%
Median DoR, months (range)	NR (1-17)	NR (1-17)
Median time to response (TTR), months (range)	2 (1-5)	2(1-5)

Methods: We included patients who received at least 1 BM dose (whole sample,WS) and those treated with≥2 BM cycles (evaluable pop-

ulation, EP). Patients received intravenous BM 2.5 mg/kg every 3 weeks until progression or unacceptable toxicity.Eye examination was performedat baseline and when clinically indicated. Primary end point was overall response rate (ORR).

Findings: Twenty-seven patients were treated from June 2020 to March 2022 (Table 1). In WS (N=27), ORR was 41% (11/27) [6(22%) partial response (PR), 3(11%) very good partial response (VGPR) and 2(7%) complete response (CR)]. Median progression free survival (PFS) was 3 months (r:0-20). EP (N=21) cohort showed an ORR of 52% (11/21), including 6(28%) PR, 3(14%) VGPR and 2 (10%) CR. Furthermore, 3 (14%) patients had stable disease (SD) with a clinical benefit rate (CBR, ≥SD) of 66% (14/21). Median PFS was 5 months (r:1-20). Median overall survival (OS) was not reached in both cohorts (r:0-20) at 8 months of median follow-up. In patients who achieved CBR, 12-month PFS was 63%. Median time to response (TTR) was 2 months (r:1-5) and median time to best response(TTBR) was 5.5 months (r:1-9). Thrombocytopenia (33%) and keratopathy (43%) were the most frequent adverse effects. Keratopathy was grade 1-2 in 6 (29%) and grade 3 in 3 (14%) patients: in these latter cases treatment was permanently discontinued. No infusion reactions were reported.

Discussion: Our real-life results are consistent with BM outcomes reported in DREAMM-2 trial in highly pretreated MM patients.Toxicity profile was manageable, leading to treatment discontinuation in only 3 cases; if needed, BM toxicity was managed with longer intervals between administrations and dose reductions. We conducted our analysis not only in WS but also in EP cohort because patient clinical conditions could be extremely poor in real-life R/R MM setting, leading to the risk of underestimating BM efficacy. However, short follow-up period is a limit for our analysis. Further validation on larger real-life cohorts is needed.

P087

GROWING NEW DRUGS POTENTIAL REFRACTORINESS STATE COULD JEOPARDIZE SUITABLE TREATMENT OPTIONS IN MULTIPLE MYELOMA: REAL WORLD DATA FROM A TERTIARY CARE HEMATOLOGICAL CENTRE

S. Morè[1], M. Offidani[1], L. Corvatta[2], V.M. Manieri[1], A. Olivieri[1]

[1]Clinica di Ematologia Azienda Ospedaliero-Universitaria Ospedali Riuniti di Ancona; [2]U.O.C. Medicina, Ospedale Profili, Italy

Background: In the last decade novel drugs as IMIDs and monoclonal antibodies (MoAbs) have been licensed for using in the early relapsed/refractory Multiple Myeloma (MM), moving then in the newly diagnosed setting as maintenance or continuous therapy. Therefore, in the near future, patients will become double- or triple-refractory at early relapse. Currently, there are no standard of care for these patients. Moreover, according to regulatory agencies approval, these patients may be orphan of suitable treatment options in many countries.

Methods: We analyzed data of 413 MM patients treated from 2010 to 2021 in our tertiary hematological centre in order to compare the potential refractoriness (PR) status of not-relapsed patients (exposed) with the current refractoriness (CR) status of patients already relapsed, throughout the different lines of therapy (LOT). We defined the refractoriness status according to Mammoth study criteria (Leukemia 2019) considering their past and ongoing therapies.

Results: The analysis included 413 MM patients with a median age of 69 years (range 30-93). Median follow-up was 48.7 months (range 6-140). In patients already relapsed we administered 30, 32, 24 and 17 different treatment regimens in 2nd, 3rd, 4th and 5th LOT, respectively. We pictured comparison between PR and CR in each LOT in the Figure below. Briefly, in frontline, lenalidomide- and anti-CD38-PR were 41% and 17%. Comparing the 2 groups of patients (PR *vs* CR) in 2nd LOT we described the rate of lenalidomide- (70% *vs* 51%), double- (35% *vs* 18%) and anti-CD38-refractoriness (33% *vs* 8.5%). In 3rd LOT, the percentage of triple- and quarter PR was 44% and 8% (*vs* 15% and 3% CR, respectively). In the 4th LOT, we observed a rate of anti-CD38- (40% *vs* 0%), triple- (40% *vs* 11%) and quater-PR *vs* CR (40% *vs* 4.5%). In the 5th LOT, we noticed a 20% penta-PR (*vs* 4% CR) and a 20% anti-BCMA-PR (*vs* 8% CR).

Conclusions: Multiple refractoriness could rapidly increase and be anticipated in currently treated MM patients. Since there is no evidence of cure even with the most modern therapies used in the early lines of therapies, lack of effective regimens in the subsequent lines could result in a loss of all the benefits obtained with these early lines, particularly in patients with high-risk disease. Regulatory agencies should be aware of these issues and adapt the timing and methods of drugs licences according to them to avoid waste of resources.

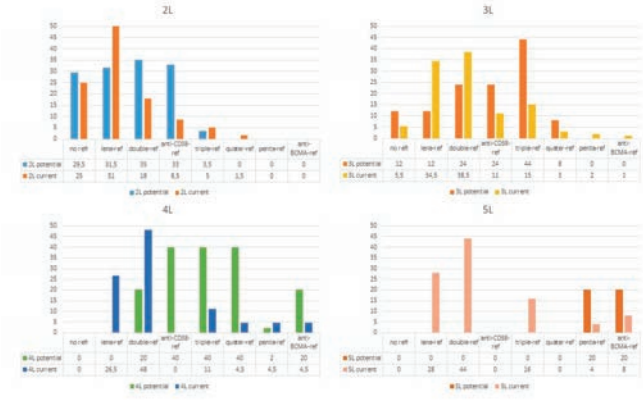


Figure 1.

P088

DARATUMUMAB IN AL AMYLOIDOSIS: A REAL -LIFE EXPERIENCE OF THE "RTM" (REGIONAL TUSCAN MYELOMA NETWORK)

V. Sammartano[1], E. Antonioli[2], G. Buda[3], S. Ciofini[1], V. Candi[4], L. Pengue[2], M.L. Del Giudice[3], I. Attucci[2], F. Bacchiarri[1], U. Occhini[4], M.T. Pirrotta[5], F. Perfetto[6], M. Bocchia[1], A. Gozzetti[1]

[1]Hematology, University of Siena, Azienda Ospedaliera Universitaria Senese; [2]Hematology, Careggi Hospital-University of Florence; [3]Hematology, University of Pisa; Department of Clinical and Experimental Medicine; [4]UOS Ematologia, San Donato Hospital, ASL8 Arezzo; [5]Ematologia Clinica e Oncoematologia, Ospedale San Giuseppe, Empoli; [6]Internal Medicine Division, Careggi Hospital-University of Florence, Italy

AL amyloidosis arise from monoclonal CD38+ plasma cells that produce misfolded immunoglobulin light chains, which form amyloid fibrils that are deposited into different tissue leading to organ damage. Daratumumab is a human IgG/k monoclonal antibody that targets CD38, a glycoprotein uniformly expressed on human plasma cells. Daratumumab has been utilized in latest years with unprecedented responses in multiple myeloma. In patients with relapsed or refractory AL amyloidosis, daratumumab has shown promising efficacy in terms of hematologic responses and improvement in organ function. Here we report real-life treatment with Daratumumab in 33 AL amyloidosis patients treated within the Regional Tuscan Myeloma network at 5 centers. There were no exclusion criteria regarding the presence of concomitant symptomatic MM or other comorbidities of any degree. Median age was 64 years (range, 44-82). 18 (54.5%) patients presented symptomatic multiple myeloma, 11 (33.3%) had smoldering myeloma and only 4 (12.1%) presented MGUS. Overall, 27 (81.8%) patients had cardiac involvement, 13 (39.3%) had renal involvement, and 16 (48.5%) had ≥2 organs involved. 4 (12.2%) patients received Daratumumab as first-line therapy,

while 29 (87.8%) patients were relapsed/refractory to previous treatments. Six (18.1%) patients received daratumumab as monotherapy, while 22 (66.6%) and 5 (15.2%) received daratumumab in combination according to DaraRd and DaraVd scheme, respectively. 22 (66.6%) of 33 patients achieved VGPR or better: 11 patients (33.3%) achieved CR and 11 patients (33.3%) achieved VGPR. 8 (24.3%) additional patients were in PR for an ORR of 90%. 15 of 27 (55.5%) patients with baseline cardiac involvement had a cardiac response. 13 of 8 (61.5%) patients with baseline renal involvement had a renal response. The most common AEs were grade 1/2 infusion reactions after the first dose in 12 (36.4%) patients; no grade 4 or 5 therapy-related AEs were recorded. The median actual follow-up was 17 months (IQR, 1-34). Overall, 6 (18.1%) patients died, 3 of them for disease progression and 3 for SAEs. The median OS was not reached, whereas median PFS estimate was not reached at 34 months (95% CI, 34-34). The achieving of hematological response was the only statistically significant predictive factor for better OS and PFS ($p=0.0002$ and $p<0.0001$, respectively)(Figure 1). In conclusion, Daratumumab showed good efficacy in a real life population of patients with an acceptable toxicity profile.

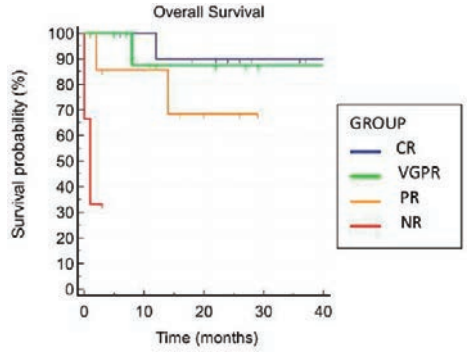


Figure 1.

P089

A DELPHI QUESTIONNAIRE TO REACH EXPERTS' CONSENSUS ON THE DEFINITION AND MANAGEMENT OF HIGH RISK MULTIPLE MYELOMA

C. Marcon[1], V. Simeon[1], P. Deias[1], A. Corso[2], D. Derudas[3], V. Montefusco[4], M. Offidani[5], M.T. Petrucci[6], R. Zambello[7], R. Fanin[1], F. Patriarca[1]

[1]Division of Hematology and Stem Cell Transplantation, University Hospital ASUFC; [2]Division of Hematology, Legnano Hospital; [3]Department of Hematology, Businco Hospital; [4]Hematology Department, Milan IRCCS Foundation Istituto Nazionale dei Tumori; [5]Hematology Clinic, AOU Ospedali Riuniti di Ancona; [6]Department of Cellular Biotechnologies and Hematology, Sapienza University of Rome; [7]Department of Medicine (DIMED), Hematology and Clinical Immunology Section, Padova University School of Medicine, Italy

High risk multiple myeloma (HRMM) at diagnosis is currently recognized according to the Revised International Staging System (R-ISS) which was set up in 2015. Since then, new clinical and biological prognostic factors have been developed, which could implement the definition of HR category. We conducted a survey in order to identify which novel clinical and biological parameters are considered more useful for the clinical practice and to evaluate if the management of MM is changed on the basis of the risk category. A questionnaire, consisting of 8 statements, was submitted to 6 Italian experts, from the European Myeloma Network (EMN) Research Italy, using the Delphi method. The colleagues were asked to answer each question using a scale between 0 and 100. If a statement did not reach at least 60 out of 100 points from all the participants, it was rephrased on the basis of the proposal of the experts and resubmitted in a second or further round of the Delphi questionnaire until a consensus was reached among all. From the first round of the survey a strong consensus was reached regarding the opportunity to revise the R-ISS classification (96.6% agreement) and to include amplification and deletion of chromosome 1 (96.6% agreement), TP53 mutations (91.6% agreement), circulating plasma cells by next generation flow (75% agreement) and multiple extramedullary plasmacytomas (95% agreement). At the first round no consensus was reached for the definition of "double hit" MM and for the application in clinical practice of treatment strategies based on the risk category at diagnosis or on minimal residual disease (MRD) evaluated during the course of the disease.

In the second round of the Delphi questionnaire "double-hit" MM was recognized by the association of at least two high-risk cytogenetic or molecular abnormalities (96.6% agreement). Moreover, the experts agreed to reserve an intensified treatment only to specific conditions such as plasma cell leukemia or patients with multiple extramedullary plasmacytomas (93.3% agreement), while they admitted that there are not sufficient real word data in order to modify treatment on the basis of MRD assessment in clinical practice (93.3% agreement).

This survey suggested that the definition of HRMM could be implemented by novel clinical and biological risk factors; however, we are not yet ready in clinical practice for a treatment strategy stratified according to risk category.

P090

CLINICAL FEATURES AND TREATMENT RESPONSE IN PATIENTS WITH MULTIPLE MYELOMA AND CD20 EXPRESSION

A. Fiorini[1], G. Chavez[2], V. Panichi[3], G. De Angelis[1], G. Topini[3], C. Stefanizzi[1], A. Di Veroli[1], C. Mercanti[1], F. Natalino[1], M. Tarnani[1], L. Bassi[4], M. Poscente[4], R. Isidori[4], G. Trapè[1], A. Silvestri[3], A. Andriani[1], M. Montanaro[1], R. Latagliata[1]

[1]UOC Ematologia - ASL Viterbo – Ospedale Belcolle; [2]Servizio di Medicina Trasfusionale – ASL Viterbo – Ospedale Belcolle; [3]UOC Diagnostica Clinica, Laboratorio di Citofluorimetria – ASL Viterbo – Ospedale Belcolle; [4]UOSD Laboratorio Genetica Medica – ASL Viterbo – Ospedale Belcolle, Italy

Background: Expression of CD20 antigen is generally negative in the immunophenotype pattern of patients (pts) with Multiple Myeloma (MM). However, a small number of MM pts can show various degrees of CD20 expression on neoplastic plasma cells: this CD20 positivity is described in about 15-20% of pts, with some morphological and clinical peculiar features. However, the clinical and prognostic significance of this CD20 expression is still a matter of debat.

Methods: To highlight clinical features and treatment response in this subset, we collected data on 14 pts [7 males and 7 females, median age 64.8 years (range 35-82)] with MM and positive CD20 expression diagnosed and followed at our Centre from 1/2018 to 12/2021.

Result:s Clinical features at diagnosis and response to 1st line therapy are reported in the Table1. CD20 expression was graded as low in 2 pts, intermediate in 4 pts and high in the remaining 8 pts. Karyotype was normal in 4/14 pts (28.5%): among the remaining 10 pts with altered karyotypes, a t(11;14) and/or an involvement of the CCND1 gene (located on the long arm of chromosome 11 – band 11q13) were reported in 7 pts (50% of the entire cohort, 70% of patients with altered karyotype). Two out of 14 pts (14.3%) were asymptomatic without SLIM-CRAB criteria and did not receive any treatment up to now, while the remaining 12 pts (85.7%) were symptomatic and received 1st line treatment with VTD in 6 cases, VMP in 3 cases, DARA-RD in 2 cases and CyBORD in 1 case. One pts was too early: among the 11 pts evaluable up to now, only 3 (27.2%) had a response (1 stringent CR and 2 VGPR), while 7 (63.6%) had a stable disease and 1 a progressive disease. At the last follow-up, 1 pts died from acute myocardial infarction during Covid-19 infection and 13 are still alive.

Conclusions: In this unicentric cohort of patients with MM and CD20 positivity, high rates of t(11-14)/CCND1 gene alterations were reported: in addition, response to treatment seems worse in comparison with MM not expressing CD20, with high rates of stable disease after 1st line therapy. However, larger cohorts of pts are warranted to confirm these results, also to evaluate the role of a possible anti-CD20 tailored treatment.

Table 1. Clinical features, 1st line treatment and response in MM patients with CD20 expression.

Pts	Sex	Age	Type	Stage (IPSS)	Karyotype	CD20 expression	First-line therapy	Response
1	F	35	IgG/K	1	46 XX	+++	No Therapy	NA
2	M	55	IgG/K	1	46 XY	+++	Dara-RD	SD
3	F	57	IgA/K	2	p53 (17p), 1q, 4p, 13q, 16q	+++	VTD	SD
4	M	61	LC-K	3	46 XY	+++	VTD	sCR
5	F	62	IgG/L	3	del13q (79%), ampl **CCND1** (59%)	+	VTD+ AUTO	VGPR
6	F	63,3	LC-L		del13q (22%), **t(11;14)** (14%), tris1q	+++	VTD+ AUTO	NR
7	M	63,9	IgG/K	2	del13q (14%) - IGH/**CCND1** (15,7%)	++	VTD	SD
8	F	65,7	IgG/K	2	del13q (90%), **t(11;14)** (78%)	++	VMP	NV
9	F	68,7	IgG/K	3	del 6q (18%), **CCND1** (7,2%) + cariotipo complesso	+++	VTD	VGPR
10	F	70,5	LC-L	2	46 XX, **t(11;14)**	++	VMP	SD
11	M	71,2	IgG/L	3	del13q (19%)	+	No therapy	NA
12	M	72,6	IgA/L	2	delp53 (49%), ampl 1q (22,5%)	+++	Dara-RD	SD
13	M	73,4	IgA/L	2	46 XY	+++	CyBORD	SD
14	M	81,9	IgA/L	3	45 XY,-15, del13q, **t(11;14)**	++	VMP	SD

P091

TARGETING LIPIDS TRAFFICKING TO INCREASE SENSITIVITY TO BELANTAMAB-MAFODITIN IN MULTIPLE MYELOMA

E. La Spina[1], D. Tibullo[2], C. Giallongo[3], G. Scandura[1], A. Barbato[4], D. Cambria[1], F. Di Raimondo[1], A. Romano[1]

[1]Department of General Surgery and Medical-Surgical Specialties, University of Catania, Catania, Italy; [2]Department of Biotechnological and Biomedical Sciences, University of Catania, Catania, Italy; [3]Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy; [4]Department of Medical, Surgical Sciences and Advanced Technologies G.F. Ingrassia, University of Catania, Catania, Italy

The persistence of multiple myeloma (MM) plasma cells (PCs) depends on specific survival factors including BCMA triggering, induced by its two ligands, BAFF and APRIL. We aimed to address if BCMA is involved in controlling mitochondria integrity in MM-PCs to manage increased energy demand for cell proliferation. Combining *in vitro* assays, immunofluorescence, western blot analysis and RNA-seq we evaluated the response to aBCMA treatment with belantamab mafodotin (BeMa) in three human MM cell lines (NCI-H929, U266, OPM2) and PCs obtained from 20 MM patients.

Results: Metabolomics changes observed after treatment *in vitro* suggested that BeMa could lead to fatty acids (FAs) consumption (with drastic reduction of lipid droplets in sensitive cell lines, like MM1.s), with compensatory upregulation of macrolipophagy, which regulates intracellular lipid storage and induction of free FAs synthases in BeMa-resistant cell lines (*e.g.* OPM2), to preserve cytoplasmatic and mitochondrial membrane dynamics. Pretreatment with palmitic acid (PA) made BeMa resistant H929 and U266 BeMa sensitive cell lines. Co-culture of H5S (an MSC cell line) with primary MM-PCs isolated from RRMM patients showed a peculiar BeMa sensitivity of MSCs, despite BCMA expression on MSCs was 6-folds lower than MM-PCs. In our previous work, we reported that MM-MSCs have decreased reliance on mitochondrial metabolism and increased tendency to transfer mitochondria to MM-PCs (Giallongo, 2022), leading MM-PCs to shift their own metabolism from aerobic glycolysis to utilize more fatty acids FAs and produce more energy by FA oxidation (Tibullo, 2020; Giallongo, 2022). Thus, we evaluated mitochondria integrity in BeMa treated cell lines and we found that U266 showed an overproduction of mitochondrial ROS, suggesting mitochondrial membrane depolarization associated to cell-death induced by BeMa, while OPM2 reported increased mitochondrial mass values without showing mitochondrial ROS production and BeMa refractoriness. RNA-seq analysis of HMCLs treated with BeMa confirmed the metabolic rewiring associated to BeMa sensitivity and lipid metabolism. Ferroptosis key genes GPx4 and SLC7A11 together with intracellular GSH levels were upregulated while pro-ferroptotic ASCL4 was downregulated in OPM2 compared to U266. Taken together, our data suggest lack of efficacy of BeMa in MM-PCs with increased lipid trafficking, opening a new scenario about the molecular pathway underlying BeMa resistance.

P092

ARGININE DEPRIVATION IN MULTIPLE MYELOMA MICROENVIRONMENT INDUCES DYNAMIC CHANGES OF MITOCHONDRIAL FUNCTION, LEADING TO GENOMIC INSTABILITY

G. Scandura[1], D. Tibullo[2], S. Giallongo[1], C. Giallongo [3], E. La Spina[1], A. Barbato[1], D. Cambria, A. Romano[1], F. Di Raimondo[1]

[1]Department of General Surgery and Medical-Surgical Specialties, University of Catania, Catania, Italy; [2]Department of Biotechnological and Biomedical Sciences, University of Catania, Catania, Italy; [3]Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy; [4]Department of Medical, Surgical Sciences and Advanced Technologies G.F. Ingrassia, University of Catania, Catania, Italy

In multiple myeloma (MM), arginine (arg) is a non-essential amino acid which plays an important role in the immune-escape mechanisms and in bortezomib resistance. Thus, we aimed to investigate the metabolic advantages of the adaptive response to arg deprivation to increase cell fitness in MM-plasma cells (PCs). Our *in vitro* studies were carried out on two human myeloma cell lines (HMCLs) U266 and NCI-H929, chosen after a screening of the activation of the integrated stress response (ISR) of 8 HMCLs available in our lab. Cells were cultured in arg-complete (200 µg/mL) or arg-low medium (50 µg/mL, a concentration reached *in vivo* in MM-BM patients) up to 10 days. In U266, induction of endoplasmic reticulum (ER) stress was associated to the activation ISR via phosphorylation of GCN2 (general control nonderepressible 2), while in NCI-H929 ISR was recruited via increased of PERK (protein kinase R-like endoplasmic reticulum kinase). However, within 48 hours from arg deprivation immunoblot analysis of the expression of phosphorylated and total eIF2α, a bona-fide biomarker of ISR activation, confirmed the recovery of ER stress, prompting us to investigate the molecular machinery associated to adaptation to arginine deprivation. Arg deprivation caused mitochondrial distress and transcriptional reprogramming, via increase of ATF-4 dependent asparagine synthetase (ASNS), glutamate dehydrogenase (GLUD) and glutamic oxaloacetic transaminase (GOT), suggesting a modulation of the malate-aspartate shuttle. In U266 cells adaptive response to arg-deprivation was associated to the recruitment of downstream signalling of NRF2/HMOX/TLR4 signalling. Despite maintaining constant the energy charge potential (ECP) up to 10 days of treatment, arg deprivation affected mitochondrial activity, switching from glucose-based metabolism to mitochondrial oxidation of fatty acids, requiring the transfer of fatty acids from lipid droplets to mitochondria, as shown by SeaHorse analysis and immunofluorescence imaging. The low-energy metabolic state induced by the adaptive response to arg-deprivation posed MM cells into a quiescence state, with elevated HMOX to scavenge the excess ROS with subsequent genome instability as shown by increased γHA2X+/ATM+ cells and micronuclei. Thus, identifying cellular tradeoffs tied to the resolution of stress induced by arginine deprivation in MM cells may reveal new therapeutic targets and routes for cancer therapy optimization.

P093

CONTINUOUS INFUSION OF CISPLATIN, DOXORUBICIN, CYCLOPHOSPHAMIDE AND ETOPOSIDE (PACE) IN MULTIPLE MYELOMA (MM) PATIENTS WITH HIGH-RISK CLINICAL AND BIOLOGICAL FEATURES: A SINGLE CENTER RETROSPECTIVE ANALYSIS

E. Favero[1,2], L. Pantani[1], M. Talarico[1,2], V. Solli[1,2], P. Tacchetti[1], K. Mancuso[1,2], S. Rocchi[1,2], I. Rizzello[1,2], G. De Cicco[1,2], G. Marzocchi[2], M. Martello[1], I. Vigliotta[1], M. Ursi[1,2], F. Bigi[1,2], E. Bernetti[1], I. Sacchetti[1,2], B. Taurisano[2], C. Terragna[1], M. Cavo[1,2], E. Zamagni[1,2]

[1]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli"; [2]Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale, Università di Bologna, Italy

Extramedullary disease (EMD), presence of circulating plasma cells (cPC) and/or additional high-risk (HR) characteristics identify a difficult-to-treat subgroup of patients (pts) with MM, for whom there is a lack of standard therapy. We report the outcomes of 75 consecutive HR MM pts with EMD (53%), cPC (27%) or clinically aggressive disease (CAD) non responsive to prior treatments (23%) who received at our center from 2012 to 2021 PACE chemotherapy ± novel agents. Median age was 62 years. 13 pts were newly diagnosed (ND) and 62 relapsed/refractory (RR) after a median of 2 prior lines of therapy (0-8); 30% were triple-refractory. Most frequent sites of EMD were soft tissues (57%) and CNS (38%), 45% had more than one localization. FISH was available for 63 pts; 29 had > 1 cytogenetic alteration (CA). Biochemical high-risk features included high LDH levels in 49% of pts, elevated B2M (median 5.4 mg/l), ISS stage 2/3 (75%) and eGFR<60mL/min (35%). Their frequency was significantly higher in the cPC subgroup compared to EMD and CAD subgroups ($p<0.005$). PACE (median 2 cycles) was more frequently associated with VTD in ND (100%) than in RRMM (13%) pts and more frequently followed by ASCT consolidation (54 *vs* 23%, $p<0.05$). 44 pts subsequently received additional salvage therapies. With a median follow-up of 13 months (mos), overall median PFS, TTP and OS were respectively 3 (IQR 2-5), 4 (3-9) and 8 (5-13) mos, similar in EMD, cPC and CAD. TTNT was 8 mos (5-14). Pts with ND disease experienced significantly better outcomes than the others (best ≥VGPR: 69 *vs* 13%; median PFS: 29 *vs* 2 mos; median OS: NR, with a 1-year estimate of 75%, *vs* 6 mos, $p<0.001$). Achievement of ≥VGPR was associated with prolonged PFS (27 *vs* 3 mos, $p<0.001$) and OS (NR *vs* 8 mos, $p<0.001$). By converse, ISS2/3 and >1 CA correlated with worse OS (5 *vs* 17 and 8 *vs* 29 mos, respectively, $p<0.05$). ASCT consolidation after PACE significantly extended both PFS (14 *vs* 2 mos, $p<0.001$) and OS (48 *vs* 5, $p<0.001$). Regarding safety, all pts presented G4 hematologic toxicity (55% neutropenia, 100% thrombocytopenia), while 64% experienced at least 1 ≥G3 non-hematologic AE, mostly infections, leading to death in 6 RR pts.

In conclusion, our analysis confirms the dismal outcome of HR MM pts. In pts with optimal response, PACE containing regimen proved to be a suitable induction and debulking therapy, often providing a bridge to ASCT or other treatments.

P094

LONG-TERM OUTCOME OF AUTOLOGOUS STEM CELL TRANSPLANTATION IN ELDERLY MULTIPLE MYELOMA PATIENTS

C. Rosignoli[1], G. Petruzzellis[1], T. Berno[2], A. Bonalumi[3], C. Marcon[1], M.L. Battista[1], R. Stocchi[1], R. Zambello[2], R. Fanin[1], F. Patriarca[1]

[1]Division of Hematology and Stem Cell Transplantation, ASUFC, Udine; [2]Department of Medicine (DIMED), Hematology and Clinical Immunology Section, Padua University School of Medicine, Padova, Italy; [3]Hematology Unit, Department of Medicine, Azienda Ospedaliera Universitaria Integrata, Verona, Italy

Background: Autologous stem cell transplant (ASCT) is currently considered the golden standard treatment for newly diagnosed multiple myeloma (MM) patients under the age of 65; however, strong evidence of feasibility and safety of ASCT in elderly population is lacking and its role is still controversial.

Aim: To evaluate retrospectively safety and effectiveness of ASCT in elderly MM patients treated between 2010 and 2019 in the Haematology units of Udine, Verona and Padova.

Patients and Methods: 98 newly diagnosed MM patients were included, 55 males and 43 females with a median age at diagnosis of 67 years (range 63-72). ISS was I in 39%, ISS II in 39%, ISS III 22%. High-risk cytogenetic features [t (14;16), t(4;14), del17p, ampl1q] were found in 11 patients (20%, data available for 55 patients). Myeloma frailty score, ECOG, R-MCI and HCT-CI before ASCT were calculated. Bortezomib-based regimens were adopted before ASCT in most patients; conditioning regimen with Melphalan was administered (100 or 140 or 200 mg/mq, according to clinical evaluation). A second ASCT was performed on the basis of clinical response to the first procedure and cryopreserved PBSC availability. Maintenance with Thalidomide or Lenalidomide was administered in a subset of patients.

Results: Overall response rate (ORR) after induction was 91% (89/98), with 24% (24/98) CR, 38% (37/98) VGPR and 29% (28/98) PR. 29% of patients were conditioned with Melphalan 200 mg/mq, 61% with 140 mg/mq and 10% with 100 mg/mq. 91% of patient underwent a single ASCT and 9% double ASCT. The ORR at day +100 was 96%; in particular, CR increased from 24 to 38% and VGPR from 38% to 47%. At the median follow-up of 47 months (3-140), median PFS and OS were 71 and 82 months, respectively. No patients died because of TRM. In multivariate analysis, the response achieved after induction and after ASCT were the only significant prognostic factors for both PFS and OS. No differences in outcome was observed between conditioning regimen with Melphalan 200 mg/mq and 140-100 mg/mq. Factors related to patient (age, frailty score, HCT-CI or R-MCI, ECOG), disease (ISS, karyotype) and treatment (maintenance) did not impact on PFS and OS in multivariate analysis.

Conclusion: Our data showed long term safety and efficacy of ASCT in the frontline therapy of elderly MM patients, which is significantly related to the response obtained after induction therapy.

Non-oncological hematology and quality of life

P095

CLINICALLY IMPORTANT CHANGE (CIC) IN FUNCTIONAL ASSESSMENT OF CHRONIC ILLNESS THERAPY (FACIT)-FATIGUE SCORE FOR PATIENTS WITH COLD AGGLUTININ DISEASE (CAD): AN ANALYSIS USING THE PHASE 3 CARDINAL AND CADENZA STUDIES

W. Barcellini[1], Q.A. Hill[2], A. Röth[3], B. Jilma[4], C.M. Broome[5], S. Berentsen[6], A.A. Rizio[7], F. Joly[8], P. DasMahapatra[8], X. Jiang[8], F. Shafer[8], M. Iglesias-Rodriguez[8], J. Su[8], M. Kosinski[7], D. Cella[9]

[1]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico; [2]Department of Haematology, St James's University Hospital; [3]Department of Hematology and Stem Cell Transplantation, West German Cancer Center, University Hospital Essen, University of Duisburg-Essen; [4]Department of Clinical Pharmacology, Medical University of Viennaa; [5]Division of Hematology, MedStar Georgetown University Hospital; [6]Department of Research and Innovation, Haugesund Hospital; [7]QualityMetric Incorporated LLC; [8]Sanofi; [9]Department of Medical Social Sciences, Northwestern University, Chicago

Introduction: Sutimlimab is an anti-C1s immunoglobulin G4 antibody whose efficacy in CAD has been assessed in the Phase 3 studies CARDINAL (NCT03347396) and CADENZA (NCT03347422). As fatigue is a leading symptom of CAD, a secondary aim of these studies was examining treatment-related change in fatigue via the FACIT-Fatigue outcome measure. Data from both trials are pooled here to estimate the CIC for FACIT-Fatigue scores in CAD patients (pts), the minimal score change indicating meaningful benefit for individual pts.

Methods: CARDINAL is an open-label, single-arm, multicenter study in CAD pts with recent blood transfusion. CADENZA is a randomized, double-blinded, placebo-controlled study in CAD pts without recent transfusion. This analysis pools data from Part A of both studies. Anchor- and distribution-based analyses estimated the CIC. Anchor-based analyses (mean change and model-based) examined the relationship between change in FACIT-Fatigue scores from baseline (BL) to Week 26 (Wk26) and related anchor variables (ie change in general health [GH01], change in Patient Global Impression of [fatigue] Severity [PGIS], Patient Global Impression of Change [PGIC], and change in hemoglobin [Hb]).

Tables 1 and 2.

Table 1. Polychoric correlation coefficient between FACIT-Fatigue and anchors

Anchors		N	FACIT-Fatigue at baseline	FACIT-Fatigue at Week 26	Change in FACIT-Fatigue
GH01	Baseline	53	0.63	–	–
	Week 26	53	–	0.78	–
	Change	53	–	–	0.64
PGI-S	Baseline	35	0.83	–	–
	Week 26	35	–	0.87	–
	Change	35	–	–	0.80
PGIC	Week 26	53	–	–	0.56
Hemoglobin	Baseline	55	0.20	–	–
	Week 26	55	–	0.41	–
	Change	55	–	–	0.54

Table 2. Results of ROC-based and logistic regression–based analyses

				ROC-based analyses				Logistic regression–based analyses
Anchors	N, total	N, improved	Percentage with improvement	AUC	Sensitivity	Specificity	CIC	CIC
GH01	53	21	39.62	0.79	0.71	0.78	8	8.87
PGI-S	35	15	42.86	0.93	0.87	0.85	5	7.01
PGIC	53	34	64.15	0.74	0.68	0.74	4	4.15
Hemoglobin	55	30	54.55	0.73	0.73	0.68	2	5.66

AUC, area under the receiver operating characteristic curve; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue; GH01, general item of the 12-Item Short Form Health Survey; CIC, clinically important change; PGIC, Patient Global Impression of Change; PGI-S, Patient Global Impression of (fatigue) Severity; ROC, receiver operating characteristic.

Results: Overall, 55 pts were included; 42 (76%) female, age 46–88 years (median 70); CARDINAL (n=17); CADENZA (n=38 [1:1 placebo and sutimlimab]). Mean FACIT-Fatigue was 32.6 at BL and 39.3 at Wk26. Correlations between FACIT-Fatigue and anchors exceeded 0.40, indicating moderately strong associations (Table 1). Anchor-based analyses evaluating mean change in FACIT-Fatigue estimated CIC from 9.20 (PGIC) to 15.69 (PGIS). Model-based anchor approaches (receiver operating characteristic and logistic regression analyses) estimated CIC from 2 (Hb) to 8.87 (GH01) (Table 2). CIC estimates from anchor-based approaches ranged from 2 to 16 (interquartile range [IQR], 5–10). Distribution-based analyses found a CIC of 5.62 based on 0.5 standard deviation of FACIT-Fatigue at BL, and 2.78 based on the standard error of the measure. The empirically determined CIC for CAD pts for FACIT-Fatigue was 5, a median estimate from model-based analysis within the IQR of all anchor-based analyses and convergent with estimates from distribution-based analyses.

Conclusions: The estimated CIC of 5 for FACIT-Fatigue in CAD pts aligns with other disease areas (eg, rheumatoid arthritis, cancer-related anemia), suggesting that FACIT-Fatigue Scale may be a useful measure of fatigue in CAD pts.

P096

MANAGEMENT OF NON-SEVERE APLASTIC ANEMIA: LABORATORY WORKUP AND TREATMENT PATTERNS

G. Cassanello[1], J.A. Giannotta[2], R. Pasquale[2], L. Cro[2], M. Barbieri[2], W. Barcellini[2], B. Fattizzo[1,2]

[1]Department of Oncology and Hemato-Oncology, University of Milan, Milan, Italy; [2]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

Non severe aplastic anemia (NSAA) is a rare and heterogeneous disease characterized by a wide range of cytopenias type and severity. Data on clinical workup and therapeutic strategies adopted are lacking due to the rarity and heterogeneity of the disease.

We evaluated patients diagnosed with NSAA at a single tertiary hematologic center in the last 20 years. We collected baseline hematologic features, bone marrow (BM) histology and flow-cytometry (FCM), and somatic mutations by NGS myeloid panel. Treatment strategies were registered retrospectively and categorized in 1) steroids +/- cyclosporine (CyA), 2) eltrombopag + CyA and 3) watch & wait. Responses were evaluated according to 2009 Marsh criteria.

We included 27 patients, mainly females (59%) and with a median age of 51 years (17-91) (Table 1). The most frequent cytopenia was thrombocytopenia (N=22) and 24% of cases were transfusion dependent. BM samples showed a median cellularity of 10% (range 5-30), with dyserythropoiesis in 44%, dysmyelopoiesis in 18%, and reticulin fibrosis (MF-1) in 15% of patients. BM microenvironment by FCM appeared enriched for lymphocytes, particularly T lymphocytes (median 72%, 58-97).

NGS myeloid panel detected NF1 and U2AF1 mutations (VAF 4.7% and 4.9%) in 1 patient, and a germline SBDS mutation (VAF 48%) in another with familiar history of myeloid neoplasm. During a median follow up of 22 months (1-202), 19 patients received treatment. They had deeper cytopenias and a higher frequency of small PNH clones (p=0.02) as compared to untreated ; seven patients received CyA and 11 patients received eltrombopag+CyA. The overall response rate (CR+PR) in the former group at 3, 6 and 12 months were 71%, 100% and 100%, respectively. In the second one, the corresponding response rates were 80%, 75% and 100%, with no significant differences between treatment groups.

Eight patients (30%) experienced one or more adverse events (AEs), mostly grade 1 or 2 according to CTCAE. Grade 3/4 toxicities were all registered in the eltrombopag+CyAgroup and consisted in retinal thrombosis, gastroenteritis, diarrhea and acute hepatitis. Rise of transaminases and bilirubin was registered led to treatment discontinuation in 3 cases.

In conclusion, NSAA required treatment in about 2/3 of cases with more severe cytopenias. Treatment with CyA+/-eltrombopag led to a significant clinical improvement. Occurrence of G3 liver AEs with combination therapy deserves attention/further studies.

Table 1. Baseline features and outcome in NSAA patients.

	Steroids +/- Cyclosporine N=7	Eltrombopag +/- Cyclosporine and Steroids N= 11	Untreated N=9	All treated patients N=27
Median age, years (range)	40* (20–72)	65* (35–91)	45* (17–63)	51 (17-91)
Male, N(%)	3 (43%)	5 (45%)	3 (33%)	11 (40%)
Female, N(%)	4 (57%)	6 (55%)	6 (66%)	16 (60%)
Transfusion dependence, N (%)	2 (25%)	7 (63%)	0	9 (24%)
Median follow up, days (range)	890 (175–1507)	668 (36–1999)	1037 (342–6055)	942 (36-6055)
Laboratory values, median (range)				
Hb, g/dL	9.8* (7.7-13.9)	8.5 (5.2-11.5)	12.9 (10.1-15)*	10 (5.2-15)
ANC x10^9/L	0.89 (0.46-1.38)	1.16 (0.59-4.99)	1.42 (0.57-5.25)	1.24 (0.46-5.25)
ALC x 10^9/L	1.31 (0.68-2.1)	1.22 (0.37-2.12)	1.17 (1.02-2.84)	1.22 (0.37-2.84)
PLTx10^9/L	45* (18-61)	23 (5-64)	111 (59-216)*	45 (5-216)
Reticulocytes x10^9/L	0.048 (0.039-0.104)	0.052 (0.009-0.108)	0.04 (0.029-0.098)	0.044 (0.009-0.108)
Endogenous EPO U/L	421 (3.9-1052)	129 (85.5-898)	17 (14-40)	129 (3.9-1052)
LDH, U/L	182 (151-243)	208 (140-347)	180 (136-322)	188 (136-347)
Treatment response[1]				
3 months – sample size, N	7	10	8	25
CR, N (%)	1 (14%)	–	1 (12%)	2 (8%)
PR, N (%)	4 (57%)	6 (60%)	1 (12%)	11 (44%)
6 months – sample size (N)	6	8	9	23
CR, N (%)	1 (16%)	1 (12%)	1 (12%)	3 (13%)
PR, N (%)	5 (83%)	3 (37%)	2 (25%)	10 (43%)
12 months – sample size (N)	4	7	9	20
CR, N (%)	–	–	1 (12%)	1 (5%)
PR, N (%)	4 (100%)	7 (100%)	1 (12%)	12 (60%)
Adverse events				
Grade 1 and 2	Gengival Hypertrophy Striae rubrae	CMV reactivation EBV reactivation Diabetes Diarrhea	–	
		Gengival Hypertrophy Irsutism		
Grade 3 and 4		Retinal thrombosis Acute hepatitis Diarrhea Gastroenteritis	–	

*Notes: *P value <0.05 in untreated vs treated patients.*

[1]Response criteria according to "Guidelines for the diagnosis and management of aplastic anemia", Marsh 2009.

P097

HEALTH-RELATED QUALITY OF LIFE IN PATIENTS WITH β-THALASSEMIA UNDERWENT UNRELATED HEMATOPOIETIC STEM CELL TRANSPLANTATION

O. Mulas[1], G. Caocci[1], F. Efficace[2], S. Barella[3], A. Piroddi[4], M.G. Orofino[4], V. Frau[1], C. Targhetta[1], E. Piras[1], A. Vacca[1], G. La Nasa[1]

[1]Ematologia e Centro Trapianti Midollo Osseo, Ospedale Businco, ARNAS G. Brotzu, Dipartimento di Scienze Mediche e Salute Pubblica, Università di Cagliari; [2]Unità Qualità della Vita, Gruppo Italiano per le Malattie Ematologiche Adulte (GIMEMA); [3]SSD Talassemie, Ospedale Regionale Microcitemie, ASL Cagliari; [4]Centro Trapianti Midollo Osseo Pediatrico, Ospedale Regionale Microcitemie, ASL Cagliari, Italy

Introduction: β-Thalassemia major (β-TM) represents one of the most diffuse hemoglobinopathies worldwide. Despite remarkable improvements in supportive therapy, the only curative treatment is represented by hematopoietic stem cell transplantation (HSCT). The ideal donor is represented by a HLA matched sibling, but the probability to find it within the family is only 25%. Matched unrelated HSTC is a feasible and safe approach, but few data are available on long-term Health-Related Quality of Life (HRQoL) in transplanted patients.

Objectives. This study aimed to compare the long-term HRQoL of unrelated and sibling donor HSCT in β-TM patients.

Methods: Fifty-seven HSCT β-TM were evaluated in our institution. Generic HRQoL was assessed by the Medical Outcomes Study 36-Item ShortForm Health Survey (SF-36) and the Functional Assessment of Cancer Therapy–Bone Marrow Transplant (FACT-BMT) scale.

Table 1. Health-Related Quality of Life Profile by the SF-36 of HSCT patients (sibling vs unrelated donors). PCS, physical component scale; MCS, mental component scale; SD, standard deviation

SF-36 scales	Sibling, mean (SD)	Unrelated, mean (SD)	P value
Physical health			
Physical functioning	88.48 (23.08)	87.06 (18.99)	0.3997
Role physical	80.43 (36.89)	74.26 (41.05)	0.5929
Bodily pain	77.48 (27.26)	74.15 (30.56)	0.7285
General health	63.78 (23.12)	59.79 (27.31)	0.6541
PCS	51.98 (8.31)	48.93 (10.63)	0.3413
Mental health			
Vitality	58.26 (23.34)	62.35 (24.10)	0.5957
Social functioning	71.20 (27.81)	77.21 (24.90)	0.4101
Role emotional	68.12 (35.50)	76.47 (36.26)	0.2301
Mental health	63.13 (24.57)	72.24 (17.72)	0.1723
MCS	46.53 (11.72)	51.28 (9.50)	0.1165

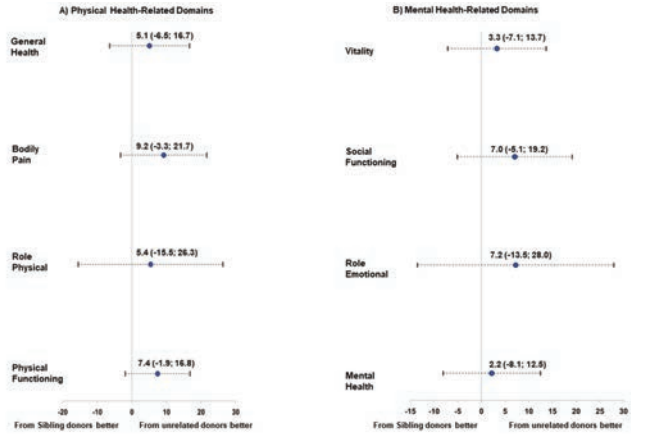


Figure 1. (A) physical and (B) mental health-related scales from the SF-36 questionnaire, adjusted mean differences between transplanted patients from unrelated donors vs transplanted patients from sibling donors

Figure 1.

Results: A total of 23 siblings and 34 unrelated HSCT β-TM patients were collected. The median age at HSCT was 18 (0-36) years and 8 (1-23) years in the unrelated and sibling group, respectively. Median age at questionnaires compilation was 31(17-48) years in the sibling group and 37 (16-54) years in the unrelated cohort (P= 0.012), with a median follow-up since transplantation of 18 years and 22 years, respectively. As expected, the unrelated group reported higher GVHD rates than the sibling group (38% *vs* 17%, p=NS). No significant differences were observed between sibling and unrelated HSCT in physical and mental health domains evaluated by SF36 questionnaires (Table 1). The same scales adjusted by a multivariable regression model, including sex, age, level of education, living arrangements, and ferritin level, showed a better HRQoL profile in matched unrelated transplanted patients, although

no statistically significant results were detected (Figure1). In addition, no differences between sibling and unrelated transplants were found in psychological, social, emotional, and functional well-being domains when specific FACT-BMT, adjusted for possible confounders, was analysed.

Conclusions: Matched unrelated HSCT represents a viable option in β-TM patients without a sibling donor. Our results suggest that β-TM patients that underwent unrelated HSCT do not experience a worse quality of life than those who have a sibling donor. The availability of novel data on HRQoL should provide both physicians and patients with a better comprehension of the advantages and potential risks of unrelated HSCT and assist them in the treatment decision-making process.

P098

IRON CHELATION THERAPY IN CONGENITAL HEMOLYTIC ANEMIAS: AN ITALIAN SINGLE CENTRE STUDY

A. Bosi[1,2], B. Fattizzo[1,3], J.A. Giannotta[1], I. Papetti[2], W. Barcellini[1]

[1]Hematology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [2]University of Milan, Milan, Italy; [3]Department of Oncology and Oncohematology, University of Milan, Milan, Italy

Congenital hemolytic anemias (CHAs) can be associated with iron overload due to chronic hemolysis, ineffective erythropoiesis, and red blood cell transfusions. Because of their rarity, the appropriate management of iron chelation is mainly based on thalassemia experience. Here we aimed at evaluating frequency, duration, efficacy and tolerability of iron chelation in CHAs patients followed at a tertiary center. Clinical and laboratory data at the time of diagnosis, at chelation start, and at subsequent timepoints were retrospectively collected until February 1st 2022. Overall, 206 patients were retrospectively reviewed (151 membrane defects, 31 enzymatic defects and 24 congenital dyserythropoietic anemias – CDAs, Table 1).

Table 1.

Iron chelation in patients with congenital hemolytic anemias

Patients under iron chelation	**26/206 (13%)**
Congenital Dyserythropoetic Anemias	9/24 (38%)
Enzymatic Defects	11/31 (35%)
Membrane Defects	6/151 (4%)
Transfusional Status	
No transfusions	8/26 (31%)
Occasional	10/26 (38%)
History of Transfusional Dependence	8/26 (31%)
Chelator	
DFA	3/26 (12%)
DFX	12/26 (46%)
DFA and DFX	11/26 (42%)
Median daily dose (mg)	
DFA	573 (143; 2500)
DFX	584 (264; 1000)
Type of dosing	
Continuous dosing	15/26 (58%)
Intermittent dosing	11/26 (42%)
Median duration of treatment, months (range)	91 (3; 372)
Efficacy*	
Median ferritin before chelation, ng/mL (range)	1147 (526; 3305)
Median ferritin after chelation, ng/mL (range)	387 (28; 1093)
Patients who reduced ferritin < 500 ng/mL	14/22 (64%)
Median % ferritin variation from baseline (range)	-51 (– 94; +6.2)
Toxicity	**5/22 (23%)**
Renal	2/5 (40%)
Gastrointestinal	2/5 (40%)
Allergic	1/5 (20%)

*Efficacy was evaluated in patients with available data after start of chelation (n = 22/26)

Twenty-six patients (13%) received iron chelation, mostly those with enzymatic defects (35%) or CDAs (38%); at variance, only 4% of patients with membrane defects required chelation ($p < 0.0001$). Transfusion status showed that 31% of chelating patients had history of transfusion-dependence (TD) (5 Pyruvate kynase deficiency and 3 CDAs), 38% had received occasional transfusions, and 31% had never received transfusions. Iron chelator was parenteral deferoxamine (DFA) or oral deferasirox (DFX), with a median daily dose of 573 mg for DFA and 584 mg for DFX. Median duration of treatment was 91 months with a wide range (3 – 372), including patients who received intermittent dosing (42%) and those on continuous chelation (58%). Concerning efficacy, median variation of serum ferritin from baseline was -51%, ranging from -94% to +6% (the latter in a patient who received a suboptimal dose). Overall, 63% of evaluable patients reduced ferritin below 500 ng/mL. Notably, a 33 year-old woman affected by CDA type II with history of transfusion dependence since birth to splenectomy at 9 years, developed cardiac iron overload with a cardiogenic shock. After a 4-year course of DFA, laboratory and imaging tests for iron overload markedly improved and her cardiac function recovered. Regarding toxicity, 5 out of 22 (23%) patients reported reversible renal (n = 2) and gastrointestinal events (n = 2); one patient developed a non-fatal anaphylactic shock, leading to switch to a different chelator (from DFA to DFX). In summary, Iron chelation was required in 13% of patients, mostly CDAs and enzyme defects, independently from transfusion requirements. It allowed a reduction of iron parameters in about 2/3 of cases with good tolerability.

P099

ERYTHROCYTOSIS AND FAMILIARITY: COEXISTENCE OF MULTIPLE MUTATIONS

A. Benetti[1], G. Biagetti[1], F. Polese[2], E. Cosi[1], I. Bertozzi[1], G. Ceolotto[3], M.L. Randi[1]

[1]First Medical Clinic, Department of Medicine – DIMED, University of Padua; [2]Transfusion Medicine, Ospedale dell'Angelo; [3]Emergency Medicine, Department of Medicine – DIMED, University of Padua, Italy

Introduction: Idiopathic Erythrocytosis (IE) and rare Hereditary Erythrocytosis (HE), characterized by haemoglobin (Hb) and hematocrit (HT) above the normal range, are purely studied. The recent availability of NGS offers new opportunities in the study of erythrocytosis and we report here an interesting venetian family in which patients have various mutations in erythrocytosis-associated genes.

Methods: Our NGS gene panel comprehends the following genes: *JAK2*, *EGLN1*, *EPOR*, *FTL*, *FTH*, *ASXL1*, *HFE*, *HFE2*, *TFR2*, *HAMP*, *SLC40A1*, *SLC11A2*, *VHL*, *BPMG*, *EPAS1*. We used bioinformatics tools to analyse data and Sanger Sequencing to validate the germline mutations. The proband (IV.2) is a 24 years old man with Hb 173 g/L and HT 50% observed 6 months after the end of his treatment for acute lymphocytic leukemia (ALL). His 61 years old father suffers for PV (Hb 187 g/L, HT 55%, GB $12x10^9$/L, plts 488 x 10^9/L). We re-evaluated with NGS these 2 patients and we studied 14 of their relatives belonging to 3 different generations (Figure 1).

Results: The proband inherited his mother *JAK2*L393V germinal mutation and his father *EGNL1*C127S (Tibetan mutation); his sister has the same bio-molecular pattern but not erythrocytosis. The patient carries also *ASXL1* R1068* somatic mutation. We found *EGNL1*C127S mutation in 7 relatives, in 2 showing polyglobulic face and border line Hb and HT. Interestingly, in 2 subjects with normal cells counts, *EGNL1*C127S was associated with *EPAS1*T766P mutation. We found also a normal subject with *EPOR*G46E mutation.

Conclusions: In our family different mutations in erythrocytosis-associated genes were found as well as rare germinal *JAK2* mutations and somatic *ASXL1* mutation responsible for epigenetic modifications. The Tibetan mutation is present in 9 out of the 16 evaluated subjects. It appears to be benign, but we surmise that it can play a role in the genesis of ery-

throcytosis at least when associated with other biomolecular alterations. In fact, in the proband it is associated with *JAK2* germinal mutation and in 2 other subjects, with signs of erythrocytosis, with *EPAS1* mutations known to be responsible for hereditary erythrocytosis. The *JAK2*L393V germline mutation, may precede the acquisition of the *JAK2*V617F, and the *ASXL1* R1068* is possibly related to patient's previous leukemia. In conclusion, this study suggests that multiple genes erythrocytosis may explain some erythrocytosis even in the same family.

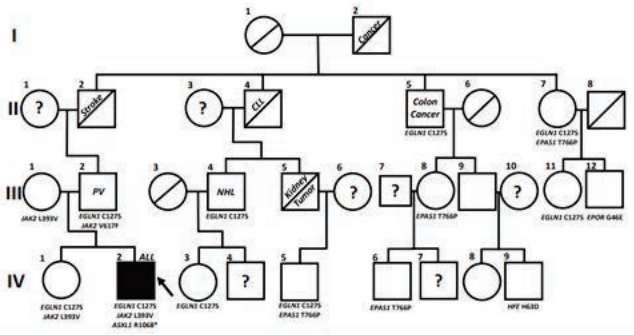


Figure 1.

P100

BROAD SPECTRUM OF ITP CLINICAL SEVERITY IN PREGNANCY: TWELVE YEARS EXPERIENCE IN A TERTIARY CARE ITALIAN HOSPITAL

M. Carpenedo[1], S. Cozzolino[2], A. Zappaterra[1], M.B. Ferrari[1], M. Incerti[2], A. Scian[2], N. Roncaglia[2], P. Vergani[2]

[1]U.O Ematologia e Trapianto ASST Ospedale San Gerardo di Monza; [2]Fondazione Monza e Brianza per il Bambino e la sua Mamma (MBBM)-Ospedale San Gerardo di Monza, Italy

Introduction: Immune thrombocytopenia (ITP) occurs in 1-10/10000 pregnancy (preg). Treatment (tx) involves steroids (P) and IVIg, while immunosuppressive drugs (ID) and splenectomy (splen) are rarely needed. Several cases of TPO-RA use has been published especially at later gestational week (gw)

Aim: 41 preg in a cohort of 37 ITP were retrospectively analyzed for maternal plt count, need and type of tx, preg outcome

Results: Of 37 pts (mean age 31), 70% (26) had ITP diagnosed before preg. 49% (18) were primigravidae (prim); of the 19 multipara (mult) 10 had ITP also in their previous preg. At presentation (mean 21 gw) mean (m) PLT count was 60.7x10 ^{9}/L. We identified 4 groups of pts:

Group A: 24% (10) received only P. Treatment was started at a m of 22,7 gw, with m PLT 39.4x10 ^{9}/L. 6 had a previously known ITP and 5 were prim

Group B: 16% (6) were administered P + IVIG. Group C: 16% (6) were plurirefractory and received a combination of drugs: 4 had previously known ITP. They were given ID (3 CyA 2 azathioprine) with prednisone and IVIg. 1 had undergone splen at 17 gw due to severe bleeding and refractoriness to P, IVIG and azathioprine. 2 received also romiplostim (Rom) started at 33 gw. Group D: 41% (18) did not require any treatment, having m PLT 87.3x10^{9}/L; 11 had been previously diagnosed with ITP and 7 were prim. Median plt count at delivery (del) was 79 x10^{9}/L (47-363) in Group A, 84x10^{9}/L (15-154) in Group B, 107x10^{9}/L (53-406) in Group C, 101 (76-130) in Group D. (Table 1).

Only 1 ITP presented late (37 gw) with 50x10^{9}/L PLT and received only IVIg in preparation of del.

7/38 del occurred with cesarean section (1 twin preg, 3 other obstetrical reasons, 3 for thrombocytopenia –T-) at a m plt 82 x 10^{9}/L (53-363). Overall 2 pts received plt transfusion at vaginal del for plt < 20x10 ^{9}/L but no relevant bleeding was recorded.

Out of 38 newborns (1 late-term abortion, 2 preg still ongoing), 13% (5) had transitory T with m PLT 19x10^{9}/L (4-95), all received IVIG, 4 received also plt transfusion and all recovered a normal plt count within 4 weeks. 2 babies had a previous sibling born with T also included in this report (Table 2)

Conclusions: Despite different severity in plt count and response to tx, most del occurred with a safe plt count, even if some pts need multiple tx. T in babies is not unfrequent, has a complete recovery and might occur also in non multirefractory mothers. Rom help to achieve a safe plt count at del without AE.

Tables 1 and 2.

Table 1
MATERNAL OUTCOMES

	Group A	Group B	Group C	Group D
Treatment	Steroid only	Steroid + IVIG	steroid + IVIG + other*	no treatment
n #	10	6	6	18
median plt x 10*9/L at tx start	36 (4-88)	12 (3-36)	10 (6-36)	87**(54-108)
mean gw at tx start	22	12	14	no tx
median plt x 10*9/L at Del	79 (47-363)	84 (15-154)	107 (53-406)	101(76-130)

** at presentation, no tx required
* other: 2 Cya, 2 azathioprine, 2 Romiplostim, 1 splenectomy
# 1 pt not included, ITP onset in late preg, received only IVIG near delivery

Table 2
NEONATAL OUTCOMES IN THROMBOCYTOPENIC NEWBORNS

n	sex	gw at Del	type of Del	plt at birth	plt at 5 days	plt at 4 weeks	mother tx at Del	newborn tx	previous T sibling
#1	F	37	CS	7000	12000	143000	P +IVIG	IVIG+ plt transf	no (sibling of *)
#2	F	37	CS	4000	10000	132000	P + IVIG	IVIG+ plt transf	yes (sibling of *)
#3	F	35	V	95000	37000	145000	P+IVIG	IVIG	no (sibling of **)
#4	M	38	V	22000	13000	137000	P+IVIG+ CyA + Rom	IVIG+ plt transf	no
#5	F	38	V	19000	90000	144000	P+IVIG+Rom	IVIG+ plt transf	yes (sibling of **)

gw: gestational week
CS: cesarean section
V: vaginal delivery
T: thrombocytopenia
Rom: romiplostim

P101

SEQUENTIAL USE OF EFGARTIGIMOD AND ROMIPLOSTIM RESTORED PLATELET RESPONSE IN MULTIREFRACTORY THROMBOCYTOPENIC PATIENTS WITH PREVIOUS FAILURE OF THROMBOPOIETIN RECEPTOR AGONISTS

M. Carpenedo, B. Ferrari, A. Zappaterra, B. Valeri

U.O Ematologia e Trapianto, ASST Ospedale San Gerardo di Monza; University of Milan Bicocca, Italy

Introduction: Multirefractory patients (pts) with chronic Immune thrombocytopenia (ITP) and low platelet (plt) count have high risk of bleeding and poor QoL related to fatigue, multiple hospital visits, blood tests, drug side effects. In these pts an important goal is to restore a durable safe n of plt. Literature data showed that combination or sequential use of different drugs might be useful. Aim and Method: We reported for the first time the efficacy of sequential use of efgartigimod (EFG) and romiplostim (ROM) after previous failure of thrombopoietin receptor agonists (TPO-RA) in 2 multirefractory pts. EFG is a novel human IgG1 Ab fragment that binds to FcRn, thus preventing IgG recycling, FDA approved for myasthenia and with ongoing phase II/III studies in ITP.

Results: Pt#1 male, previous CABG at 56 yrs, PCI at 68 yrs. ITP diagnosed at 80 yrs, unresponsive to steroid + IVIG, 2nd line treatment with CyA complicated with NSTEMI. 3rd line treatment with azathioprine without response. Eltrombopag (ELT) alone gave no response, with a mild response when associated with prednison. Next lines of therapy were ROM alone and + danazole, Vincristine +PDN, and again ELT + pdn without response. We started EFG associated to ELT and low dose Pdn without results. ROM introduced at the end of EFG treatment (stop

ELT) gave a sudden and complete response, still ongoing after 12 weeks, without any AE (Figure 1).

Pt #2 female, no comorbidities. ITP was diagnosed at 16 yrs, with a brief response to steroid. We started ELT at 19 yrs, with a partial and brief response, heavy recurrent menstrual bleeding requiring rescue treatment with dexamethasone (Dexa). We switched to ROM with a limited response, and need of repeated steroid rescues for bleeding. We started EFG associated with ELT without response apart from Dexa rescue. After the suspension of EFG, we restart ROM alone with a sudden and complete response, lasting now 24 weeks and no AE (Figure 1). Conclusion: EFG seems to restore plt response to ROM in pts previously unresponsive to 1)both TPO-RA alone and 2)with EFG + ELT. It has been demonstrated that 8 weeks following the last administration of EFG in healthy volunteers , IgG levels returned to baseline so a response inside this timeframe is not unexpected, but giving the longer ongoing response in these 2 pts might reveal a potential unknown immune modulatory response following the sequential use of EFG and ROM. Further studies with EFG alone or a sequential use are warranted in ITP patients.

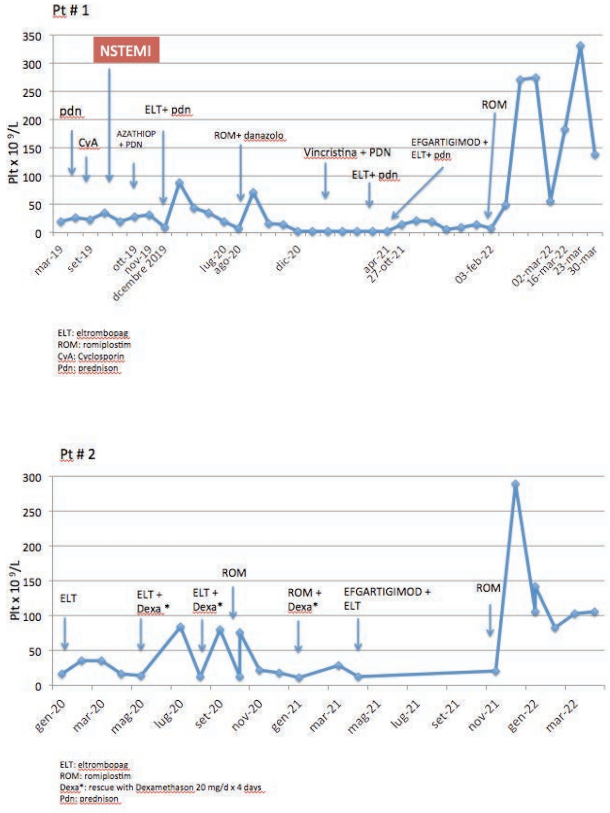


Figure 1.

P102

EFFICACY OF THROMBOPOIETIN RECEPTOR AGONISTS IN THE TREATMENT OF IMMUNE THROMBOCYTOPENIA WITH MYELODYSPLASTIC FEATURES OF MEGAKARYOCYTES

R. Tomasello[1], F. Romano[1], M. Mattana[1], C. Cammarata[1], A. Lucchesi[2], G. Giordano[3], C. Botta[1], M. Santoro[1], S. Mancuso[1], S. Siragusa[1], M. Napolitano[1]

[1]Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties (ProMISE), University of Palermo, Palermo, Italy; [2]IRCCS Istituto Romagnolo per lo studio dei tumori (IRST) "Dino Amadori", Meldola, Italy; [3]Division of Internal Medicine, Hematology Service, Regional Hospital "A. Cardarelli", Campobasso, Italy

Immune Thrombocytopenia (ITP) is a diagnosis of exclusion that may require bone marrow (BM) examination to rule out a unilinear myelodysplastic syndrome (MDS). BM histopathology of patients with ITP usually shows megakaryocyte (MK) hyperplasia with tendency to form diffuse clusters, sometimes associated to mature lymphoid cells infiltration. In a few cases, BM examination shows isolated signs of MK dysplasia with no other criteria compatible with a diagnosis of MDS. There is currently no difference between the treatment of patients with BM compatible with ITP and those with isolated MK abnormalities. We performed a retrospective analysis that included all patients diagnosed with ITP from 2014 to 2021, who started treatment with thrombopoietin receptor agonists (TPO-RAs) as 2nd (or further) line treatment, from 2016 to 2021, whose BM examination (performed before TPO-RA administration) showed signs of MK dysplasia. Patients with a prior diagnosis of MDS, HCV-related liver disease and autoimmune diseases were excluded. All patients that were not treated with TPO-RAs on first relapse developed resistance or intolerance to corticosteroids (CS), some of them were also unresponsive to Rituximab. We evaluated response to TPO-RAs at 2 weeks, 3 months, 6 months and 1 year from start of treatment. We evaluated 16 patients of age at diagnosis ranging from 20 to 83yo (median age 58.5yo), M:F ratio of 1.3:1, who became unresponsive to CS and were ultimately treated with either Eltrombopag (9/16) or Romiplostim (7/16). In all patients, a BM examination showed signs of MK dysplasia. All patients were treated with CS with or without high dose intravenous immunoglobulins (IVIGs) on first line. Four patients started TPO-RAs in 2nd line. Twelve patients started TPO-RAs in 3rd or further lines due to a loss of response to previous immunosuppressive treatments. Two patients treated with Eltrombopag experienced sustained response (PLT >100000/mmc for >3 months off-therapy). Limited to the small number of patients, this study suggests that the overall response to immunosuppressive treatments such as Rituximab or CS appears to be short-lived and hard to maintain in patients with dysplastic features of MKs observed at diagnosis. This suggests a role of MK maturation disorders in the mechanism of thrombocytopenia beside autoimmunity. TPO-RAs may be the optimal 2nd line treatment for these patients, enhancing thrombopoiesis while also inducing a degree of immunotolerance.

Table 1.

GENDER (N)	AGE AT DIAGNOSIS	COMORBIDITIES (N)	2nd LINE THERAPIES (N) (excluding TPO-RAs)	3rd LINE THERAPIES (N) (excluding TPO-RAs)	START OF TPO-RA (N)
Male (9) Female (7)	20-83 y.o. Median 58.5	High blood pressure (7) History of cancer (2) Ischemic cardiopathy (2) Diabetes mellitus type 2 (2) Hypotyroidism (2) Epathic cirrhosis (1)	Steroids +/- IVIG (7), Rituximab (5)	Steroids +/- IVIG (2), Rituximab (2)	2nd line (4) 3rd line (8) 4th line (4)
PATIENT GROUP (N)	**MEDIAN PLATELET COUNT AT 2W (PLT/MMC)**	**MEDIAN PLATELET COUNT AT 3M (PLT/MMC)**	**MEDIAN PLATELET COUNT AT 6M (PLT/MMC)**	**MEDIAN PLATELET COUNT AT 1Y (PLT/MMC)**	**SUSTAINED RESPONSE**
Eltrombopag + Romiplostim (16)	66500 (patients n=16/16)	93000 (patients n=13/16)	140000 (patients n=11/16)	203000 (patients n=7/16)	2/16
Eltrombopag (9)	108500 (patients n=9/9)	93000 (patients n=7/9)	180000 (patients n=5/9)	203000 (patients n=3/9)	2/16
Romiplostim (7)	48500 (patients n=7/7)	77500 (patients n=6/7)	128000 (patients n=6/7)	110000 (patients n=4/7)	0/16

P103

COVID-19 VACCINATION IN PATIENTS WITH IMMUNE THROMBOCYTOPENIA IN TREATMENT WITH TPO-RAS: A MONOCENTRIC EXPERIENCE

E. Rinaldi, G. Guaragna, M.L. Di Noi, G. Mele, F. Merchionne, G. Quintana, C. Schifone, M. Urbano, A. Spina, M.P. Solfrizzi, A.M. Pasanisi, D. Pastore

Haematology A. Perrino Hospital, Italy

COVID-19 vaccination has been described as risk factor for *de novo* immune thrombocytopenia (ITP) but also for exacerbation of thrombocytopenia in patients with pre-existing ITP. We aimed to investigate the safety of COVID-19 vaccination in patients with ITP on treatment with TPO-RAs, in order to identify risk factors for ITP exacerbation in this patients setting. We included 34 ITP patients (one patient with persistent ITP and 33 with chronic ITP). The median age was 60 years [35-89], 74% were female, there was a median of 98 [6-396] months since diagnosis of ITP, and patients had received a median of 2 [1-6] prior medical treatments. Five patients had previously been treated with rituximab. No patients had undergone previous splenectomy. At time of vaccination 19 patients were on therapy with eltrombopag, 9 with romiplostim, 3 with eltrombopag and corticosteroids, 3 with romiplostim and corticosteroids. Thirtythree patients received a mRNA vaccine and one patient a viral vector vaccine.

Table 1. Pre- and post-vaccine platelet counts in ITP patients following dose 1, dose 2 and dose 3 of a SARS-CoV-2 vaccine.

	First dose vaccination	Second dose vaccination	Third dose vaccination
patients evaluated (N)	34	33	27
Platelet count pre-vaccine (x10^9/L)*	157,5 (47-440)	170 (61-353)	143 (53-401)
Patients with >50% decline in platelets count compared to baseline	5 (14,7%)	3 (10%)	2 (7,4%)
Platelets nadir < 30x10^9/L	2 (5,8%)	2 (6%)	0
Timing of platelet nadir (day)#	22 (11-39)	36 (21-46)	11,5 (4-19)
Use of rescue medication	4 (11,7 %)	3 (9%)	1 (3,7%)
Intensification treatment	3 (8,8%)	2 (6%)	1 (3,7%)
Addition extra Medication§	1 (2,9%)	0	0
Intensification treatment + Addition extra medication	0	1 (3%)	0
Bleeding	0	1 (3%)	0
Non haematological adverse events	0	0	0

*platelet count available in the 4 weeks before vaccination

§corticosteroid

Data relating to patients with >50% decline in platelets count compared to baseline platelets nadir < 30x10^9/L

Among 34 ITP patients treated with TPO-RA who received a covid-19 vaccine, 8 (24%) experienced an ITP exacerbation (any of: ≥50% decline in platelet count, nadir platelet count <30 x 10^9/L and/or use of rescue therapy). All patients had received a mRNA vaccine. Five patients were treated with eltrombopag and three patients with romiplostim. Median timing of platelet nadir was 22 days (4-46).Median of duration of ITP was 189 months (16-265). Median of duration of TPO-RA therapy was 30 months (5-118). Median of previous treatments was 3. Two patients had previously been treated with rituximab. Three patients who experienced ITP exacerbation had other autoimmune diseases including systemic lupus erythematosus, Hashimoto's thyroiditis and sero-negative arthritis. No patient experienced major bleeding and non-haematological adverse events such as thrombosis. Two patients presented ITP exacerbation after 2 dose of vaccination. These patients were treated with eltrombopag. All patients responded to rescue therapies and returned to pre-vaccination dose treatment. Details on platelet counts pre and post each vaccine dose and the need for rescue therapy are summarized in Table 1. Our experience confirms the safety of vaccination in ITP patients on treatment with TPO-RAs, but this setting of patients needs to be closely monitored after vaccination because longer duration of ITP, presence of current treatment for ITP and more prior lines of therapy are risk factors for exacerbation.

P104

TIME TO BEST RESPONSE TO TPO-RA TREATMENT IN ELDERLY ITP PATIENTS

S. D'Angelo[1], F. Morelli[1], C. Giubbilei[1], V. Paradiso[1], A.M. Vannucchi[2], V. Carrai[3]

[1]Hematology Unit, University of Florence; [2]Center for Innovation and Research in Myeloproliferative Neoplasms, Hematology Unit, Azienda Ospedaliera Universitaria Careggi, University of Florence; [3]Hematology, Department of Oncology, Azienda Ospedaliera Universitaria Careggi, Italy

Background: The introduction of thrombopoietin receptor agonists (TPO-RAs) in the management of idiopathic thrombocytopenic purpura (ITP) has changed this disease's history. According to the current guidelines, the use of TPO-RAs represents the second line of treatment after steroids in case of steroid-resistance or -dependence. The mechanism of action consists in acting on thrombopoietin receptor and stimulating platelet production without any impact on the cardiovascular or metabolic system, avoiding steroid-related side effects. Nevertheless, indications concerning the inefficacy of treatment are not well defined and also there isn't a consensus about the timeline for TPO-RAs tapering.

Aims: We evaluated the median time after the TPO-RAs start to reach a stable platelet count >50000/μL and how long the starting dose of TPO-RAs is maintained in this cohort of elderly patients without increasing.

Materials and methods: We retrospectively collected data about a monocentric cohort of 32 ITP patients (15 women, 17 men) with a median age of 74 years (67-91) at the time of TPO-RAs start. Eltrombopag was the TPO-RAs for 15 patients, while the other 17 received romiplostim. The platelet values at the beginning were: 25 patients ≤ 30000/μL, 7 with a range of 31000-50000/μL.

Results: The median time required to achieve platelet values > 50000/μL was 14 days (2-47) and the initial drug dose has been stably maintained for a median time of 28 days (7-1764). The median treatment duration was 100 months (4-338), and has been suspended in 15 patients (47%) for different reasons: 3 loss of response, 10 maintenance of response, 2 adverse events. Three of these patients (20%) needed to be re-treated, 2 with the same TPO-RAs previously stopped and one with corticosteroids. Currently, 17 patients (53%) are still under TPO-RAs treatment, 1 (3%) is under corticosteroid treatment, while 8 (25%) are off-treatment. 6 (19%) died from medical conditions not related to ITP or to TPO-RAs treatment.

Conclusions: With these preliminary data, we observed that our patients reach a platelet count >50000/μL in a median time of two weeks. Despite the age of our cohort, this count is reached with the minimum dose of TPO-RAs.

P105

SINGLE CENTRE EXPERIENCE OF SARS-COV-2 VACCINATION IN IMMUNE-MEDIATED THROMBOTIC THROMBOCYTOPENIC PURPURA

E. Rinaldi, G. Guaragna, M.L. Di Noi, G. Mele, F. Merchionne, G. Quintana, C. Schifone, M. Urbano, A. Spina, M.P. Solfrizzi, A.M. Pasanisi, P. D'Errico, M.R. Coppi, D. Pastore

Haematology A. Perrino Hospital, Italy

Immune-mediated thrombotic thrombocytopenic purpura (iTTP) is a rare disease characterized by microangiopathic, hemolytic anemia, thrombocytopenia and microvascular thrombosis caused by ADAMTS13 deficiency. Vaccines are known risk factors for triggering *de novo* iTTP but also for iTTP relapse. It is also known that iTTP patient in clinical remission, but who have not achieved complete ADAMTS-13 remission, have an increased risk of relapse. Various cases of *de novo* and relapsed iTTP following SARS-CoV-2 vaccination have been described. Therefore we prospectively evaluated 10 iTTP patients (8 female and 2 men) who underwent SARS-CoV-2 vaccination to investigate the safety of SARS-CoV-2 vaccination and to check for possible risk factors for relapse. The median age was 50 years [31-58]. iTTP had been present for a median of 90 months [9-249]. At the time of SARS-CoV-2 vaccination five patients did not relapse after the first episode of acute TTP. Instead five patients had experienced relapses of TTP and had previously been treated with rituximab. Before vaccination eight patients had ADAMTS13 activity > 20% [33-112], one patient an ADAMTS13 activity of 14% and one patient an undetectable ADAMTS13 activity (<3%) without ADAMTS13 antibodies. All patients received mRNA vaccine (BNT162b2). Seven patients received 2 doses of the vaccine, while 3 patients received 3 doses. Patients were monitored with whole blood counts before and weekly for six weeks after each vaccination dose. ADAMTS13 activity and anti-ADAMTS13 antibodies have been evaluated before, after 2 dose of vaccine and, in three patients, after the third dose. After a median follow-up of 20 weeks [3-36] after 2 doses of vaccine and 12 weeks after 3 doses [6-14], no patients had relapse of iTTP. After vaccination ADAMTS13 activity did not significantly decrease except in one case in which it halved but remaining > 20%. Despite the potential risk of relapse from any vaccination, our experience confirms that SARS-CoV-2 vaccination is still recommended in patients with iTTP but with close clinical and laboratory monitoring in particular with serially assessment of ADAMTS-13 activity.

P106

CARDIOVASCULAR AND THROMBOEMBOLIC RISK ASSESSMENT IN ITP PATIENTS UNDERGOING LONG TERM TPO-RA TREATMENT: A MONOCENTRIC REAL-LIFE EXPERIENCE

C. Giubbilei[1], F. Morelli[1], S. D'Angelo[1], V. Paradiso[1], A.M. Vannucchi[2], V. Carrai[3]

[1]Hematology Unit, University of Florence; [2]Center for Innovation and Research in Myeloproliferative Neoplasms, Hematology Unit, Azienda Ospedaliera Universitaria Careggi, University of Florence; [3]Hematology, Department of Oncology, AOU Careggi, Italy

Background: Thrombopoietin receptor agonists(TPOra) treatment made an important contribution to the chronic management of idiopathic thrombocytopenic purpura(ITP).However, TPOra are not free from side effects, especially thromboembolic(TE) and cardiovascular(CV).In elderly patients(pts) these risks are amplified by age-related comorbidities.For this reason, we conducted a retrospective analysis to compare the occurrence of CV/TE events in patients with and without CV/TE comorbidity at TPOra start.

Aims: Evaluating any differences in the occurrence of CV/TE events in elderly,TPOra-treated pts and comparing to the general population.

Materials and methods: A monocentric group of 45 ITP elderly pts(22 male, 23 female) was enrolled, with a median age of 69 y(65-91) at TPOra start. According to the Cumulative Illness rating scale,23 pts were considered fit and 22 unfit.Pts with no records of CV/TE comorbidity were assigned to GROUP 1 (16 pts,36%), pts with previous CV/TE events to GROUP 2 (29 pts, 64%). The number of event recurred in GROUP 2 are reported in Table 1. Data were collected from 2009 to 2021.The median duration of TPOra treatment was 140 months(4-158).

Results: In GROUP 1 two events occurred: one episode of atrial fibrillation(AF) and one of deep vein thrombosis(DVT);GROUP 2 registered two episodes of AF and one of DVT. These adverse events occurred after a median time of 123 months from TPOra start(7-134).Comparing our data to the general population, we noticed a higher prevalence of AF(6,7% *vs* 3%) and of DVT(4,4% *vs* 2.5%).No statistically significant difference was found between fit(17%)and unfit(5%)pts in the occurrence of CV/TE events(p=0.15).Neither a previous cardiovascular history has an impact on the occurrence of CV/TE events (p=0.52).Moreover, no significant difference was found between our subgroups in occurrence of CV/TE events (GROUP 1 *vs* GROUP 2, 12.5% *vs* 10% respectively,p=0.07).All events registered weren't life-threatening and no pts discontinued the TPOra due to CV/TE events. Not further CV/TE events occurred.

Conclusion: Our little data shows an increased risk in our pts compared to the general population. In ITP pts a medical history for CV/TE events seems not having an impact on occurrence of new episodes in TPOra-treated ones. This evidence leads us to remember the importance of risk assessment before starting treatment. Hovewer these limited data should be confirmed by expanding the case series.

Table 1.

CV/TE comorbidities	N. of events (%)
Arterial hypertension	21 (47%)
Peripheral artery disease	4 (8%)
Atrial fibrillation	2 (4%)
Deep venous thrombosis	3 (7%)
Acute coronary syndromes	7 (15%)
Hypercholesterolemia	4 (9%)
Heart failure	1 (2%)
Cerebrovascular attack	2 (4%)
Thrombophilia (FV Leiden)	1 (2%)
Valvular disease	1 (2%)

P107

EFGARTIGIMOD: A NOVEL FCRN ANTAGONIST IN THE TREATMENT OF AUTOIMMUNE DISEASES

H. de Haard, W. Parys, P. Ulrichts, A. Guglietta, F. Rocca

argenx, Ghent, Belgium

Introduction: Immunoglobulin G (IgG) autoantibodies play a key role in the pathogenesis of immune thrombocytopenia (ITP) and other au-

toimmune diseases, such as myasthenia gravis (MG), chronic inflammatory demyelinating polyneuropathy (CIDP), pemphigus vulgaris (PV) and foliaceus (PF), bullous pemphigoid (BP), and myositis. The neonatal Fc receptor (FcRn) is the central regulator of IgG homeostasis, rescuing IgG (including pathogenic autoantibodies) and albumin from lysosomal degradation and is responsible for the long half-life of IgGs.

Aims: Therapeutic blocking of FcRn has been shown to lead to reduction of all IgG subtypes without reducing other immunoglobulin types, making it a rational target for treatment of autoimmune disorders while maintaining normal immunological responses.

Methods: Efgartigimod, an FcRn antagonist, is a human IgG1-derived Fc-fragment that outcompetes endogenous IgG binding, reduces IgG recycling, and increases IgG degradation. In healthy volunteers, efgartigimod reduced IgG by 50–75%.

Results: In a Phase 3 study in MG (ADAPT), efgartigimod induced mean maximum reductions of 57.6% in acetylcholine receptor (AChR) antibodies and 61.3% in IgG, in AChR antibody-positive patients. IgG reductions occurred rapidly without impacting IgM, IgA, or albumin levels while participants recorded statistically significant functional improvements. In a Phase 2 trial in ITP, efgartigimod dosed at 5 and 10 mg/kg weekly for 4 weeks reduced IgG by 63.7%, leading to clinically relevant increases in platelet counts (46% of efgartigimod patients *vs* 25% on placebo achieved a platelet count of $\geq 50 \times 10^9$/L on ≥2 occasions). Phase 2/3 studies in CIDP (ADHERE), PV/PF (ADDRESS), BP (BALLAD), and myositis (ALKIVIA) are ongoing. In all studies to date, efgartigimod was well tolerated, and adverse events were mainly mild to moderate. Efgartigimod is approved in the US and Japan for treatment of generalized MG in adult patients. Phase 3 studies in ITP (ADVANCE and ADVANCE SC) are ongoing.

Conclusion: FcRn inhibition by efgartigimod is a promising potential therapeutic option for several autoimmune diseases mediated by pathogenic IgG autoantibodies.

P108

CASE REPORT OF ESSENTIAL THROMBOCYTHEMIA JAK2 V617 MUTATED FOLLOWING THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP) IN UNDIFFERENTIATED CONNECTIVE TISSUE DISORDERS (UCTD) AND A REVIEW IN LITERATURE OF AUTOIMMUNE SECONDARY PTT IN UCTD PATIENTS AND THEIR IMMUNOLOGICAL RISK FACTORS

C. Buquicchio, T.M. Santeramo, M.Leo, V. Carluccio, C. Germano, G. Lerario, S. Mallano, R. Miccolis, G. Desantis, V. Castagnaro, D. Loconte, G. Tarantini

SC Ematologia con Trapianto, Ospedale Dimiccoli, Italy

Background: Thrombotic thrombocytopenic purpura (TTP) is a life threatening syndrome characterized by thrombocytopenia and microangiopathic haemolitic anemia caused by deficiency (congenital or acquired) of ADAMTS 13, a proteinase that cleaves Von Willebrand Factor (VWF) in little multimers.The presence of large VWF multimers brings microvascular platelets clumbing in capillaries and arterioles of multiple organs.TTP is classified in "congenital"or "acquired"and " idiophatic" and "secondary" to neoplasias, infections, rheumatologic autoimmune disease, more frequently systemic lupus erythematosus or Sjogren syndrome, rarely with undifferentited connective tissue disorders (UCTD).

Aims: The coexistence of UCTD and TTP has been reported only in few cases in literature (14 in total); in 2012 was reported a sequential occurence of TTP, ET and ITP diagnosis but only with empirical dates, without the confirm JAK2 molecular test and deficiency of ADAMTS 13.

Methods: We analized in this retrospective study all patients with TTP admitted to our department in Dimiccoli Hospital of Barletta, from 2011 to 2021.The cases observed in these period were 8: 4 "idiophatic" (3 males and 1 female) and 4 "secondary" to collagenosis (4 females). The median age was 25 years (range 20–30) in "idiophatic group" and 37 years(range 30−45) in rheumatologic disease (1 systemic lupus erythematosus, 1 Sjogren's Syndrome in overlap with systemic lupus erythematosus, 2 UCTD). In particular, we describe the case of a 29 years old women admitted in our ward in april 2019 with normochromic normocytic anemia (9 g⁄dl), severe thrombocytopenia ($10x10^3$⁄μL), increased reticolocytes (10%). On physical examination she presented fever, headache, arthralgies, gradual disorientation, paraestesias, arthralgies. Biochemical analysis revealed normal epatorenal tests, but decreased plasma fibrinogen level (100), Coombs tests negative and we observed several schistocytes in peripheral blood smear. Besides was documented the deficiency of ADAMTS 13 activity (<1%) and the presence of autoantibodies against ADAMTS13(2UB⁄μL)that leaded to a diagnosis of TTP. Angio magnetic resonance imaging not presented specific brain abnormalities. We started immediately daily plasmapheresis, fresh frozen plasma infusion and metilprednisolone (1mg⁄kg body weight). After 10 days of treatment she showed a moderate improvement of anemia e thrombocytophenia, then the autoimmunity test were positive for ANA(1÷1280), reduction C3 (complement factor) level.Thus the diagnosis was of UCTD associated to TTP.After 20 days of treatment we observed a decrease of platelet count ($10x10^3$ μ L) so the patient received 4 doses of rituximab (375 mg⁄m^2⁄week).Four weeks later the blood count become normal such as the level of ADAMTS 13 (83%); the autoantibodies against ADAMTS 13 were absent and we have not observed anymore schistocytes in peripheral blood smear. She was discharged with rheumatological therapy azatioprine 50mg⁄d and aspirine. After 2 years of follow up,she presented persistent thrombocytosis ($600x10^3$⁄μL),she resulted driven Jak2 V617F mutation and the diagnosis of essential thrombocythemia was made on the basis of bone marrow histopathological examination and WHO criteria.

Results: Thrombocytopenia in "secondary TTP" by connective tissue disease has an immune pathophysiology associated with autoimmune disorders and the presence of rheumatological autoantibodies mediates platelets destructions. Activation of complement has been proven to be involved in systemic autoimmune diseases (C3 consumption), besides there is an important role of endothelial damage by endothelial inflammation and by antibodies (ANA) and depressed plasma fibrinolytic action could explain their potential role in the pathogenesis of vasculitis, thrombocytopenia and thrombosis in "autoimmune TTP".

Summary/Conclusion: In conclusion in connective tissue disease the release of proinflammatory cytokines could contribute to stimulate ROS related to precursors of JAK2 mutation, the onset of Clonal Hematopoiesis of Indeterminate Potential (CHIP) and, finally,may have favorite the instability of the haematological diseases and the evolution in ET pathways

P109

ACQUIRED TYPE 2 WILLEBRAND'S DISEASE IN A PATIENT WITH ESSENTIAL THROMBOCYTHEMIA

D. Dragonetti[1], R. Nuccorini[2], S. Pascale[2], A. Calabrese[1], A. Picerno[1], A. Matturro[2], M. Cimminiello[2], A. Amendola[2], N. Filardi[2], D. Vertone[2], R. Chitarrelli[2], K. Iula[2], M. Ferrara[2], D. Caputo[2], M. Cardillo[1], S. Coluzzi[2], M. Pizzuti[2]

[1]UOC di Patologia Clinica e Microbiologia; [2]Dipartimento di Ematologia, Azienda Ospedaliera Regionale San Carlo, Italy

Introduction: Essential thrombocythemia (TE), due to the consistent increase in platelets, can directly develop thrombotic events. Sometimes, however, a very high number of platelets can lead to their malfunction, resulting in a paradoxically increased risk of bleeding. In a study of 809 patients, 65% experienced thrombosis, 15% both thrombosis and bleeding, and 1.4% only bleeding. One of the causes of hemorrhage, often gastrointestinal or muco-cutaneous, is a reduction in Willebrand factor (vWF-RCo) activity due to a decrease in high molecular weight multimers, with normal antigenic concentration and reduced vWF-RCo/vWF-

Ag ratio. Desmopressin (DDAVP) can induce a dose-dependent increase in high molecular weight multimers of vWF with improvement in vWF:Ag/vWF:RCo. After few hours, there is clearance of multimers, whose rapidity is correlated with platelet count.

Case report: We report the case of a patient, suffering from JAK2 negative TE, with type 2 mutation in the Calreticulin gene, who needed laparoscopic multiple myomectomy surgery. At preoperative screening tests, a reduction of vWF-RCo was present; therefore, we performed a test with DDAVP 0.3 μg/kg. The results obtained from the laboratory tests (Table 1), showed an approximately twofold increase in vWF-Ag concentrations, and a fivefold increase in its activity and in Factor VIII concentrations. The patient underwent surgery after administration of DDAVP every 12 hours for 3 days, without hemorrhagic complications.

Conclusions: We confirm the evidence in published literature on the possibility of hemostatic alterations in patients with TE due to the reduction of vWF-RCo and underline that the administration of DDAVP can re-establish a proper, although transient, balance between vWF-RCo/vWF-Ag and optimize hemostatic mechanisms also thanks to the release of Factor VIII, in a way not yet known, but perhaps Willebrand independent. Thanks to the supplementation of DDAVP, the patient can safely undergo surgery and more effectively manage any hemorrhagic manifestations. Finally, we suggest evaluating the vWF-RCo/vWF-Ag ratio in all patients with TE, to limit the risks of anti-thrombotic prophylaxis with aspirin as much as possible.

Table 1.

Test	Time 0	90 min	180 min
Prothrombin Time	96%	94%	85%
Activated Partial Thromboplastin Time	29.9 sec	21.8 sec	25.1 sec
Von Willebrand Antigen vWF-Ag	80.9 %	195.1 %	193 %
Von Willebrand Activity vWF-RCo	26 %	135 %	132 %
vWF-Ag/ vWF-RCo	0.32	0.69	0.68
PFA (Epinephrine)	196 sec	62 sec	111sec
PFA (ADP)	>200 sec	63 sec	68 sec
Factor VIII	89 %	426 %	293 %
Platelet count at diagnosis	$1.071*10^3$		

P110

DOMICILIARY NURSING MANAGEMENT FOR PATIENTS AFFECTED BY MULTIPLE MYELOMA DURING COVID-19 PANDEMIA IN THE VITERBO HOME CARE UNIT: DATA ANALYSIS FROM MARCH 2020 TO MARCH 2022

E. Emanueli Cippitelli[1], V. Innocenti[1], G. De Angelis[1], S. Bertelli[1], R. Talucci[1], V. Panichi[2], G. Topini[2], A. Fiorini[1], A. Di Veroli[1], C. Mercanti[1], F. Natalino[1], M. Tarnani[1], M. Morucci[1], C. Mastino[1], G. Trapè[1], M. Montanaro[1], R. Latagliata[1], S. Ciambella[1]

[1]UOC Ematologia - ASL Viterbo – Ospedale Belcolle; [2]UOC Diagnostica Clinica, Laboratorio di Citofluorimetria – ASL Viterbo – Ospedale Belcolle, Italy

Background: Covid-19 pandemia constituted in the last two years a challenge in the management of frail patients (pts) with Multiple Myeloma (MM). The availability in the Viterbo province of a Domiciliary Hematologic Care Unit (DHCU) allowed a correct clinical assistance of our pts with MM during Covid-19 pandemia.

Methods: To evaluate the impact and efficacy of nursing management for frail MM pts followed by DHCU during Covid-19 pandemia, all nursing activities from 3/2020 to 3/2022 were analysed. Chemotherapies (CHT) allowed for nurse parenteral administration in MM pts were bortezomib and, more recently, daratumumab for subcutaneous injection.

Results: In the study period, 58 pts in 35 different municipalities of Viterbo province were followed by 4 nurses specifically dedicated to DHCU. Main features of the pts at DHCU admission are reported in the Table: at DHCU admission, 30 pts (51.8%) aged > 75 years. At beginning of the study period (08/03/2020), 17 pts (29.3%) were already followed by DHCU, while 41 pts (70.7%) entered DHCU assistance during the study period. Median distance from DHCU central site in Viterbo to pts house was 28 Km [Interquartile range (IQR) 20 – 38]: in particular, distance from DHCU was < 20 Km in 11 cases (19.0%), ≥ 20 < 40 Km in 33 (56.9%) and ≥ 40 Km in 14 (24.1%). A total number of 1637 nursing accesses was done in the whole period. According to the type of different procedures, 722 blood samples were performed, with a median number of 9 (IQR 4 – 15): in addition, there were 617 accesses for CHT administration (152 bortezomib-based cycles in 37 pts, 6 daratumumab-based cycles in 3 pts) and 298 accesses for other procedures (132 PICC medications, 114 therapies other than CHT, 29 assistances for transfusions, 17 assistances for marrow aspirates and 6 antigenic tests). In the study period, 5 pts (8.6%) developed Covid-19 infection. At the last follow-up (31/03/2022), 35 pts (60.3%) were alive and still in DHCU, 11 pts (19.0%) were alive and returned to Day-Hospital (DH) setting due to clinical improvement and 12 pts (20.7%) died while in domiciliary assistance.

Conclusions: Domiciliary nurse assistance during Covid-19 pandemia allowed to follow in a safer way compared to standard DH setting an important number of frail pts with MM, two/thirds of them in 1st active line of therapy. This peculiar type of nursing management should represent the best type of assistance for elderly and/or frail pts even beyond Covid-19 period of pandemia.

Table 1. Patient clinical features at baseline of domiciliary nursing management.

N° of patients	58
M/F, n° (%)	33/25 (56.9/43.1)
Median age, years (IQR)	76.0 (67.4 – 80.3)
Phase of disease, n° (%):	
1st line treatment	37 (63.7)
Resistant to 1st line treatment	1 (1.7)
1st relapse	10 (17.3)
2nd or following relapse	10 (17.3)
Reason for domiciliary management, n° (%):	
Age only	17 (29.3)
Symptoms burden	6 (10.3)
Performance status ≥ 2 (ECOG)	4 (6.9)
Motility impairment	17 (29.3)
Social/familiar disability	6 (10.3)
Prevention of Covid-19 infection	8 (13.9)

P111

PSYCHOLOGICAL HEALTH IN PATIENTS WITH HAEMATOLOGICAL MALIGNANCIES: IMPLICATIONS DURING COVID-19 PANDEMIC

A. Salemme, C. Giordano, D. Lisi, M. Lamagna, L. De Fazio, R. Reina, F. Pane, L. Luciano

Hematology Unit, Department Clinical Medicine and Surgery, University Federico II, Italy

COVID-19 pandemic has profoundly changed clinical practice, altering the experiences of patients suffering from hematological diseases and influencing their mental state and psychological condition. Mental health problems in general population have increased during the COVID-19 pandemic; however, data regarding their incidence in hematological patients are scarce. The aim of our prospective study was to evaluate whether COVID-19 pandemic had an impact on mental state and psychological conditions, particularly stress, anxiety and depression in patients with hematological diseases referring to our Unit. The Depression, Anxiety and Stress Scale (DASS-21) was administered by our psychon-

cologist to adult patients diagnosed with chronic myeloid leukemia (CML), myeloproliferative (MPD) or lymphoproliferative diseases (in follow up after chemotherapy) between October 2020 and February 2021 focusing on their feelings related to COVID-19 pandemics. One-hundred patients were enrolled (Table1). Patients with psychiatric comorbidities were excluded. Among patients with CML (n=62) and MPD (n=21), 89% and 67%, respectively, were receiving chronic oral treatment, while all patients with lymphoproliferative syndromes (n=17) were in follow up after chemotherapy treatment. In our cohort, according to the DASS-21 questionnaire, patients with CML reported the highest scores for stress, anxiety and depression but no differences were found in terms of age, sex, time of diagnosis (Table1). CML and MPD patients under oral treatment showed higher stress (p=0.013) compared with patients who were off therapy, on the other hand, no differences in depression and anxiety were found. In conclusion, our study shows high levels of stress in patients receiving oral treatments during the COVID-19 pandemics, probably related to the intrinsic stress of the chronic hematologic diagnosis. COVID-19 represented a further source of stress affecting patients on a psychological and emotional level. The possibility of an additional infectious disease, with an unpredictable course, tends to worsen psychological health in the chronic disease group.

Table 1.

	Cohort	Stress/yes	Stress/no	p-value	Anxiety/yes	Anxiety/no	p-value	Depression/yes	Depression/no	p-value
	TOT=100	TOT=85	TOT=15		TOT=60	TOT=40		TOT=71	TOT=29	
Age, y median (range)	59 (7-89)	43 (19-89)	59 (33-77)	0.66	59 (19-89)	59 (7-77)	0.16	59 (19-89)	59 (28-77)	0.18
Male sex	53 (53%)	43 (50%)	10 (60%)	0.25	28 (46%)	25 (62%)	0.12	35 (49%)	18 (62%)	0.25
Female sex	47 (47%)	42 (50%)	5 (40%)		32 (54%)	15 (38%)		36 (51%)	11 (38%)	
Time for diagnosis, y median (range)	7 (3-12)	7 (0-34)	6 (0-23)	0.30	7 (0-34)	7 (0-30)	0.53	7 (1-30)	7 (0-21)	0.28
Type of diagnosis				0.94			0.50			0.99
CML	N (62)	N (54)	N (8)		N (43)	N (19)		N (37)	N (19)	
	62%	64%	53%		72%	48%		52%	66%	
MPD	N (21)	N (20)	N (1)		N (22)	N (10)		N (11)	N (2)	
	21%	24%	7%		37%	25%		15%	7%	
Lymphoproliferative syndromes	N (17)	N (11)	N (6)		N (6)	N (11)		N (6)	N (8)	
	17%	13%	4%		1%	28%		8%	27%	

Values are expressed as n (%) if not specified otherwise.

Monoclonal myeloma and gammopathies II

P112

NOVEL AGENTS-BASED SALVAGE THERAPY AS BRIDGE TO AUTOLOGOUS TRANSPLANT FOR RELAPSED/REFRACTORY MULTIPLE MYELOMA

I. Attucci[1], L. Pengue[1], A. Buzzichelli[1], M. Messeri[1], A.M. Vannucchi[1-2], E. Antonioli[2]

[1] Department of Experimental and Clinical Medicine, University of Florence, Italy; [2]Haematology Department, Careggi Hospital, Florence, Italy

Aims: The role of a salvage transplant in relapsed/refractory multiple myeloma patients still eligible for high dose chemotherapy is not yet well defined. Furthermore, there are no guidelines on which reinduction therapy should be preferred, especially after the availability of several novel agents. Against this background, we retrospectively evaluated the impact on OS and PFS of lenalidomide-based triplets with novel agents, followed by an ASCT in a cohort of real-life patients.

Methods: We evaluated patients who started a salvage therapy from February 2017 to May 2021. All patients received DaraRd or KRd treatment according to POLLUX and ASPIRE schedule, respectively, and ASCT conditioning with melphalan 200mg/msq or 140mg/msq.

Results: Our observational retrospective study included 29 RRMM patients, M/F=16/13, median age 56, high-risk cytogenetic in 14%. All patients had previously been treated with a single line of therapy (bortezomib-based). None of them had ever been exposed to lenalidomide before. A first group of 16 patients had already undergone an ASCT. They relapsed after a median of 30 months after the first ASCT. They started a second line of therapy with Rd-based triplet regimen: 9 patients received DaraRd treatment and 7 KRd schedule. After a median of 8 cycles (7-10) all of them underwent a second ASCT. At day 100 post-ASCT the overall response rate was 100%, with MRD negativity achieved in 11 patients (68%). The median overall survival rate was not reached, whereas the median progression-free survival rate was 39 months (IC 95%: 30-47). In MRD negative patients the median PFS was NR *vs* 31 months in MRD positive patients. A second group includes 13 patients who were refractory to first line (62%) or had achieved less than a partial response after the first treatment (38%). They started a salvage therapy with DaraRd schedule (2 patients) or KRd (11 patients, 85%), as bridge to first ASCT. After a median of 4 cycles (3-10) all of them obtained at least a PR, and a VGPR or better was achieved in 8 patients (85%). They underwent an autologous transplant, and 85% of them achieved MRD negativity after ASCT. By univariate analysis, the achievement of at least a VGPR and MRD negativity were associated with increased PFS (31 months *vs* 18 months, p=0,01). The median PFS was 30,5 months and OS after 70 months was 60%.

Conclusions: Reinduction therapy with novel agents and a subsequent ASCT is an efficacy and safe option for salvage therapy in RRMM.

P113

THE IMPACT OF OMICRON VARIANT ON THE HUMORAL AND CELLULAR RESPONSE TO SARS-COV-2 MRNA VACCINATION AND BOOSTER DOSE IN PAZIENTS WITH MULTIPLE MYELOMA

P. Storti[1], R. Vescovini[1], V. Marchica[1], V. Franceschi[2], V. Raimondi[1], B. Dalla Palma[3], L. Notarfranchi[1,3], M.T. Giamo, D. Toscani[1], J. Burroughs Garcia[1], N. Iannozzi[1], G. Donofrio[2], N. Giuliani[1,3]

[1]Dipartimento di Medicina e Chirurgia, Università di Parma; [2]Dipartimento di Scienze Medico Veterinarie, Università di Parma; [3]Ematologia e CTMO, Azienda Ospedaliero-Universitaria di Parma, Italy

Patients with multiple myeloma (MM) share several immunological defects and they may have a reduced response to vaccination including the one anti-SARS-CoV-2. Actually, the humoral and cellular response to SARS-CoV-2 mRNA booster immunization as well as the impact of spike variants, including Omicron, are still unclear and have been investigated in this study. We enrolled a cohort of 38 COVID-naïve patients with monoclonal gammopathies: 6 with monoclonal gammopathies of undetermined significance (MGUS), 10 smoldering myeloma (SMM), 9 newly diagnosed MM (NDMM) and 13 relapsed MM (MMR). Peripheral blood (PB) samples were collected 14±2 days after the second dose of the mRNA BNT162b2 vaccine. In a subset of 16 patients with MM, PB samples were also collected after 14±2 days of a heterologous booster dose with mRNA-1273 vaccine. SARS-CoV-2 spike IgG antibodies (Abs) were measured by the ELISA test. The fraction of neutralizing Abs (NAbs) against spike of Wuhan-Hu-1 strain and five variants (alpha, beta, gamma, delta and omicron) was assessed by a SARS-CoV-2 pseudovirus neutralization assay. The collected PB-mononuclear cells were stimulated, with overlapping peptides pools spanning SARS-CoV-2 spike protein and CD4+ and CD8+ T cells were identified by intracellular cytokine staining for IFN-γ, IL-2, TNF-α, and CD107a+ using flow cytometry assay. We found that MMR patients had significantly lower SARS-CoV-2 spike IgG Abs and NAbs compared with MGUS, SMM and NDMM patients after full vaccination and the booster dose. All the analyzed variants, remarkably Omicron, had a significant negative impact on the NAbs ability in SMM and MMR patients, on the other hand, after the booster dose, MMD patients recover this negative impact. We also observed a variable spike-specific CD4+ and CD8+ T cell responses, with a decrease of spike-specific IL-2+CD4+ T cell responses in SMM and NDMM patients compared to MGUS patients. The booster dose increased spike-specific T cells in both MMD and MMR reaching the 100% of responder patients with an increased percentage of IL-2+CD4+ T cells. In conclusion, our study indicates that Omicron show a negative impact on the neutralizing ability of the vaccine-induced Abs in MM patients. Booster immunization improved spike humoral and cellular responses in MMD patients and in most, but not all, MMR patients, suggesting these patients need to be considered still at risk of Omicron SARS-CoV-2 infection with a clinically relevant disease.

P114

BELANTAMAB MAFODOTIN IN RELAPSED-REFRACTORY MULTIPLE MYELOMA PATIENTS: EFFICACY DATA AND OCULAR TOXICITY IN A REAL LIFE SINGLE CENTER EXPERIENCE

R. Ribolla[1], A. Belotti[1], C. Crippa[1], L. Pasquini[2], N. Zanini[1], G. Rossi[1], A. Tucci[1]

[1]Division of Hematology, ASST Spedali Civili di Brescia; [2]Division of Ophthalmology, ASST Spedali Civili di Brescia, Italy

Introduction: Belantamab mafodotin represents a new treatment option for patients (pts) with relapsed-refractory multiple myeloma. Overall response rate (ORR) reported in DREAMM-2 single agent trial was 32% (Lonial S et al, Cancer 2021), with several ocular toxicities reported: focusing on these adverse events, we present our preliminary experience in clinical practice.

Methods: Eighteen pts were treated with belantamab at the starting dose of 2,5 mg/kg Q3W from May 2020 to April 2022: their median age was 64 yrs, 12 of them (67%) had high risk cytogenetics and median number of prior therapies was 4 (4-8). Patients' characteristics are listed in table 1. Keratopathy and visual activity scale (KVA) was applied by Ophthalmologists in order to document ocular toxicity.

Table 1.

Patients' Characteristics (n=18)	
Sex M/F, n (%)	9/9 (50/50)
Median age, years (range)	64 (48-76)
ISS stage 3, n (%)	7 (39)
High Risk cytogenetics, n (%)	12 (67)
Extramedullary disease, n (%)	4 (22)
Prior ASCT, n (%)	17 (94)

Results: After a median follow up of 18,1 mo, response rates were: MR 22%, PR 5,5%, VGPR 11,1% and CR 16,7 % (ORR 33,3%). Median PFS was 2,3 mo (1-year PFS: 25%); median OS was 12,2 mo (1-year OS: 46%). In patients with ≥ PR, median PFS and OS were not reached (NR) (1-year PFS and 1-year OS 80%). Grade ≥2 ocular toxicity occurred in 8/18 pts (44%) with 59 days (39-386) as median time to the onset of the first G≥2 event. All these pts required dose reduction and at least one dose delay. As of this analysis and where data were available, 5/8 pts (62.5%) recovered to G1 or better according to the KVA scale, with a median time to recovery of 28 days (21-56). Among the other 3 pts, one was still in follow up at the time of this analysis and 2 did not complete Ophthalmologist's follow up due to death related to progressive disease (PD). After recovery from the first event, all 5 pts experienced subsequent reappearance of G≥2 ocular toxicity requiring further dose delay. With the intent to maintain these pts on belantamab therapy, subsequent infusions have been planned every 4 to 6 weeks with better tolerance and easily management of the toxicity. Despite the delayed infusion schedule, 3 of them deepened response category, 2 of them maintained the same response category, 1 of them developed PD. After a median follow up of 21 months, median PFS of this subgroup was NR (67% rate at 18 months).

Conclusion: We confirm efficacy and safety of belantamab mafodotin in our real life experience. In pts with recurrent G≥2 ocular toxicity, 4-6 weeks infusion schedule could be a reasonable compromise between safety and efficacy even in heavily pre-treated pts in order to avoid permanent treatment discontinuation.

P115

CHEMOTHERAPY OR CHEMO-FREE REGIMENS IN HEAVILY PRETREATED MULTIPLE MYELOMA? ROLE OF BENDAMUSTINE-BORTEZOMIB-DEXAMETHASONE (BVD) IN NOVEL AGENTS' ERA

C. Cerchione[1], L. Catalano[2], D. Nappi[3], S. Rocco[4], S. Palmieri[4], A.E. Pareto[2], G. Musuraca[1], S. Ronconi[1], M. Ceccolini[1], D. Cangini[1], M. Marchesini[1], F. Pane[2], F. Ferrara[4], G. Martinelli[1]

[1]Hematology Unit, Istituto Scientifico Romagnolo per lo Studio e la Cura

dei Tumori (IRST) IRCCS; [2]Hematology, AOU Federico II; [3]Department of Hematology & CBMT, Ospedale di Bolzano; [4]Hematology, A.O.R.N. Cardarelli, Italy

The treatment of heavily pretreated Multiple Myeloma (MM) continues to be considered unmet clinical need. Bendamustine is an old bifunctional alkylating agent proved to be effective in relapsed, refractory and in new diagnosed MM. Thus, aiming to provide further insights in this field, also in novel agents'era, we present here a retrospective, real-life analysis of patients with relapsed/refractory MM (rrMM), who had received salvage therapy with bendamustine in combination with bortezomib and dexamethasone (BVD)

81 patients (44 M/37 F), with rrMM, median age at diagnosis 59.4 years (r. 36-82), median age at start of treatment 63.6 years (r.37-86) treated with several lines of treatments (median 6, r. 2-11), every refractory to all the drugs previously received (also Bortezomib), received BVD (B 90 mg/sqm days 1,2; V 1.3 mg/sqm days 1,4,8,11, D 20 mg days 1,2,4,5,8,9,11,12, Pegfilgrastim day +4) every 28 days, until progression. All patients had previously received bortezomib-based and IMIDs-based treatments, and 32% (26/81) had also received radiotherapy. 69% (56/81) had undergone single or double autologous and three (2%) allogeneic stem cell transplant. All patients were relapsed and refractory to last therapies received before BVD.

Bendamustine was well tolerated, with grade 3-4 transfusion-dependent anemia in 56% (46/81) of patients, and 43% (35/81) grade 3-4 neutropenia (no ospedalization was required, no septic shocks were observed). No severe extrahematologic toxicity was observed, only grade 1 gastrointestinal side effect (nausea), treated by common antiemetic drugs. According to IMWG, ORR was 63% (51/81: 7 CR, 18 VGPR, 15 PR, 11 MR) with 11 PD and 19 patients in SD, which can be considered as an impressive result in this subset of rrMM patients. In particular, for 11 patients, BVD was, after having achieved at least a PR, a bridge to second auSCT, and for two patients a bridge to alloSCT. Eight patients have surprisingly achieved a notable PR after failure of novel agents (i.e. Carfilzomib, Daratumumab and Pomalidomide).

Median time to response was 1.3 months (r.1-3), median OS from diagnosis was 67.3 months (r.6-151), median OS from start of Bendamustine was 9.6 months (r.2-36).

The triplet Bendamustine-Bortezomib-Dexamethasone has shown significant efficacy in a particularly severe setting of patients, relapsed and refractory to all available therapeutic resources, and, in particular cases, it could be considered as a bridge to a second autologous or allogenic SCT, also after failure of novel agents.

P116

CLINICAL DATA AT DIAGNOSIS OF LYMPHOMA AND MYELOMA PATIENTS AT HOSPITAL ADMISSION DURING THE COVID-19 OUTBREAK. EXPERIENCE OF THE HEMATOLOGY UNIT OF AZIENDA OSPEDALIERA S. GIOVANNI-ADDOLORATA, ROMA

B. Anaclerico, V. Bongarzoni, P. Anticoli Borza, E. Finolezzi, E. Ceresoli, M. Cedrone, S. Fenu, S. Leonetti Crescenzi, A.L. Piccioni, A. Tamburini, L. Cudillo

U.O.C. Ematologia. Azienda Ospedaliera San Giovanni-Addolorata, Italy

The COVID-19 outbreak influenced a delay to hospital admission of patients (PTS) due to contagion fear, as previously observed. Here we report clinical data at diagnosis of Lymphoma (NHL and HL) and Multiple Myeloma (MM) PTS observed at our Hematology Unit, S. Giovanni-Addolorata hospital, in years 2019, 2020 and 2021, thus before and during COVID-19 outbreak. We also evaluated how many PTS have been previously admitted to Emergency Department (ED) of our hospital and how many PTS were outpatient before admittance to hematology unit at disease diagnosis. In 2019 46 NHL and HL and 27 MM PTS were diagnosed, median age was 66 yrs (range 24-86) and 72 yrs (range 37-87), respectively. Stages were III-IV in 24 Lymphoma (52%) with PS (WHO) > 2 in 5; stages were IIIA/IIIB in14 MM (51%) ISS were 2 in 2 and 3 in 10 PTS, with PS > 2 in 15. 3 Lymphoma and 8 MM PTS were admitted to ED. In 2020 35 NHL and HL and 23 MM PTS were diagnosed, median age was 69 yrs (range 22-84) and 70 yrs (range 44-88), respectively. Stages were III-IV in 26 Lymphoma (74%), PS (WHO) > 2 in 10; stages were IIIA/IIIB in 15 MM (65%) ISS was 2 in7 and 3 in 9 PTS, with PS (WHO) > 2 in 14 . 5 Lymphoma and 14 MM were admitted to ED. In 2021 34 NHL and HL and 20 MM were diagnosed median age was 68 yrs (range24-85) and 68 yrs (range 56-87), respectively. Stages were III-IV in 25 Lymphoma (73%) with PS (WHO) > 2 in 9; stages were IIIA/IIIB in 16 MM (80%), ISS was 2 in 2 and 3 in 8 PTS, with PS(WHO) > 2 in 14. 5 Lymphoma and 9 MM were admitted to ED. During outbreak years a negative impact was observed on early disease diagnosis. Our data showed PTS diagnosed with a more advanced disease and with worse PS, suggesting a delay in attending hospital and hematology unit. We observed an increase of admittances to hospital emergency department, this was probably due to advanced symptomatic disease, requiring an urgent and prompt hospitalization. A longer follow up is needed to better understand how these consequences of COVID-19 outbreak could affect the prognosis of such diseases.

P117

SAFETY OF SUBCUTANEOUS DARATUMUMAB IN PLASMA CELL DYSCRASIAS: A RETROSPECTIVE MULTI-CENTER REAL LIFE EXPERIENCE

D. De Novellis[1], R. Fontana[1], A. Carobene[1], L. Mettivier[1], F. Trastulli[2], S. Rocco[2], S. Palmieri[2], M. Di Perna[3], A. Pagano[3], R. Della Pepa[4], M. Calabrò[4], G. Cerciello[4], R. Bianco[5], G. Cetani[5], V. Giudice[1-6], F. Frigeri[5], C. Califano[3], F. Pane[4], F. Ferrara[2], C. Selleri[1-6]

[1]Hematology and Transplant Unit, University Hospital "San Giovanni di Dio e Ruggi d'Aragona"; [2]Division of Hematology, Cardarelli Hospital; [3]Division of Hematology, Andrea Tortora Hospital; [4]Hematology – Department of Clinical Medicine and Surgery, Azienda Ospedaliera Universitaria Federico II; [5]UOC Ematologia , AORN Sant'Anna e San Sebastiano; [6]Department of Medicine, Surgery and Dentistry "Scuola Medica Salernitana", Italy

Introduction: Daratumumab, an anti-CD38 monoclonal antibody approved for plasma cell disorder treatment, is administered intravenously (IV) at a dosage of 16 mg/kg with high rates of infusion-related reactions (IRR; 45-56%), especially during the first cycle. Subcutaneous (SC) formulation has similar efficacy with lower IRR risk and shorter administration time (3-5 minutes) compared to IV daratumumab. Moreover, SC daratumumab has a fixed dosage of 1800 mg, regardless renal function or body weight. In this retrospective multi-center real word experience study, we investigated safety of SC daratumumab in plasma cell disorder treatment.

Material and Methods: A total of 45 patients diagnosed with multiple myeloma or light chain amyloidosis from December 2021 were included in this retrospective study. Enrolled subjects were daratumumab-naïve and were directly treated with at least one dose of SC formulation in association with any other drug (Table 1). Primary end point was SC daratumumab safety, especially for IRR incidence and severity.

Results: All patients received dexamethasone-paracetamol-antihistamine premedication; montelukast was used in 39 (87%) cases. Median number of SC administrations was 7 (range 1-13) and administration time ranged from 3 to 5 minutes. One patient (2%) experienced grade III IRR in 2 consecutive administrations. Grade I hematological and gastroenteric toxicities were observed in 6 (13%; 2 thrombocytopenia, 1 neutropenia and 3 lymphopenia) and 1 (diarrhea; 2%) case, respectively. Two (4%) subjects experienced CMV reactivation.

Discussion: In our multicenter retrospective experience, SC daratumumab showed high safety with a very low (2%) IRR rate compared to that reported in the PAVO and PLEIADES trials, regardless renal function, body weight and montelukast premedication. The only patient with grade III IRR was 65 kg, had normal renal function and did not receive montelukast premedication. This subject was switched to IV daratumumab without further IRR suggesting an SC formulation excipient-relatedintolerance rather than daratumumab-induced reaction.

In conclusions, our real-life findings showed that SC daratumumab is very manageable with an excellent safety profile and very short administration time. Further validation on larger and prospective clinical studies are needed.

Table 1.

Patients' characteristics before first SC daratumumab administration

Characteristics	N = 45
Median age, years (range)	66 (36-85)
Gender, n (%)	
Male	25 (56)
Female	20 (44)
Diagnosis, n (%)	
Multiple Myeloma	39 (87)
Light chain amyloidosis	6 (13)
M-protein type, n (%)	
IgG	30 (67)
IgA	10 (22)
IgD	1 (2)
Micromolecular	4 (9)
Light chain type, n (%)	
Kappa	28 (62)
Lambda	17 (38)
Body weight, n (%)	
≤ 65 kg	16 (36)
> 65 kg	29 (64)
Median glomerular filtration rate, ml/min (range)	78 (7-125)
Glomerular filtration rate ≥ 40 ml/min, n (%)	
Yes	34 (76)
Not	11 (24)
Montelukast premedication, n (%)	
Yes	39 (87)
Not	6 (13)
Association regimens, n (%)	
Daratumumab-Bortezomib-Thalidomide-Dexamethasone	21 (47)
Daratumumab-Lenalidomide-Dexamethasone	11 (24)
Daratumumab-Melphalan-Prednisone	4 (9)
Daratumumab-Bortezomib- Dexamethasone	2 (4)
Daratumumab as single agent	7 (16)
First line (%)	34 (76)
1 prior therapy (%)	9 (20)
≥ 2 prior therapies (%)	2 (4)
SC Daratumumab administrations, median for single patient, (range)	7 (1-13)
SC Daratumumab administrations, total	311
IRR rate for patient, n (%)	
Yes	1 (2)
Not	44 (98)
IRR rates for total SC administrations, n (%)	
Yes	2 (0.6)
Not	309 (99.4)

Abbreviations. Ig, immunoglobulin; IRR, infusion-related reaction; SC, subcutaneous.

P118

ELOTUZUMAB, POMALIDOMIDE, AND DEXAMETHASONE (ELOPD) AS SALVAGE THERAPY FOR PATIENTS WITH MULTIPLE MYELOMA: MULTICENTER, RETROSPECTIVE CLINICAL EXPERIENCE WITH 107 CASES OUTSIDE OF CONTROLLED CLINICAL TRIALS

M. Gentile[1], S. Palmieri[2], D. Derudas[3], M. Galli[4], R. Mina[5], E. Zamagni[6,7], C. Califano[8], C. Conticello[9], M. Musso[10], R. Rizzi[11], G. Margiotta Casaluci[12], R. Zambello[13], R. della Pepa[14], M. Offidani[15], G. Tarantini[16], N. Di Renzo[17], A. Pompa[18], E.A. Martino[1], A. Bruzzese[1], E. Vigna[1], A. Neri[19], F. Morabito[20,21], F. Di Raimondo[8], P. Musto[18]

[1]Hematology Unit, Azienda Ospedaliera of Cosenza, Cosenza, Italy; [2]Hematology Unit, Ospedale Cardarelli, Napoli, Italy; [3]Department of Hematology, Businco Hospital, Cagliari, Italy; [4]Hematology and Bone Marrow Transplant Unit, Azienda Ospedaliera Papa Giovanni XXIII, Bergamo, Italy; [5]SSD Clinical Trial in Oncoematologia e Mieloma Multiplo, Division of Hematology, University of Torino, Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino, Torino, Italy; [6]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli", Bologna, Italy; [7]Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale, Università di Bologna, Bologna, Italy; [8]Onco-hematology Unit, Ospedale Umberto I, Nocera Inferiore, Italy; [9]Department of medical and surgical specialties, Hematology Section, University of Catania, Catania, Italy; [10]UOC di Oncoematologia e TMO Dipartimento Oncologico "La Maddalena" Palermo, Palermo, Italy; [11]Department of Emergency and Organ Transplantation, "Aldo Moro" University School of Medicine and Unit of Hematology and Stem Cell Transplantation, AOUC Policlinico, Bari, Italy; [12]Division of Hematology, Department of Translational Medicine, Amedeo Avogadro University of Eastern Piedmont, Novara; [13]Department of Medicine (DIMED), Hematology and Clinical Immunology Branch, Padova University School of Medicine, Padova, Italy; [14]Unità di Ematologia, Università Federico II, Naples; [15]Clinica di Ematologia, Azienda Ospedaliero-Universitaria Ospedali Riuniti di Ancona,Torrette, Italy; [16]Hematology Unit, Dimiccoli Hospital, Barletta, Italy; [17]Hematology and Stem Cell Transplant Unit, "Vito Fazzi" Hospital, 73100 Lecce, Italy; [18]Hematology Unit, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milano, Italy; [19]Scientific Directorate, Azienda USL-IRCCS of Reggio Emilia, Reggio Emilia, Italy; [20]Biotechnology Research Unit, AO of Cosenza, Cosenza, Italy; [21]Hematology and Bone Marrow Transplant Unit, Hemato-Oncology Department, Augusta Victoria Hospital, East Jerusalem, Israel

Here we report preliminary data of a real-life experience on Elotuzumab (Elo), in combination with pomalidomide (P) and dexamethasone (d) (EloPd) as salvage therapy for relapsed/refractory multiple myeloma (RRMM) patients treated according to marketing approval outside of controlled clinical trials.

Table 1 Characteristics of the 107 patients at baseline.

	No. of patients (%)
Age (years)	
<70	54 (50.5)
≥70	53 (49.5)
Sex	
Male	59 (55.1)
Female	48 (44.9)
Paraproteins (isotype)	
Immunoglobulin G	71 (66.4)
Immunoglobulin A	22 (20.6)
Immunoglobulin D	12 (11.2)
Immunoglobulin M	1 (0.9)
Light chain only	1 (0.9)
Creatinine clearance (mL/min)	
≥60	72 (67.3)
<60	35 (32.7)
Stage ISS	
I	36 (33.6)
II	41 (38.3)
III	30 (28)
Number of previous lines	
2	48 (44.9)
3	38 (35.5)
≥4	21(19.6)
Previous ASCT	
No	48 (44.9)
Yes	59 (55.1)
Previous exposure to Daratumumab	
No	35 (32.7)
Yes	72 (67.3)
Status of the disease	
Biochemical relapse	15 (14)
Symptomatic relapse	42 (39.3)
Refractory to last treatment	50 (46.7)

The cohort included 107 RRMM patients from 17 Italian centers who received at least one cycle of EloPd as salvage treatment between January 2021 and April 2022. Responsive patients had to reach at least a partial remission (PR). Baseline characteristics are shown in Table 1. The median age was 70 years (range 38–83 years); 55.1% were males.

The median number of previous therapy regimens was 3 (range 2–9); 58 patients (54.2%) received a previous autologous stem cell transplantation (ASCT); 50 patients (46.7%) were refractory to the last therapy. At last data collection, 100 cases were evaluable for response.

The median number of courses administered so far was 4 (range 1–18). The overall response rate (ORR) was 55%, with 5 complete remissions (CRs) (6%), 16 very good partial remissions (VGPRs) (16%) and 34 PR (34%). A significant higher ORR was observed in patients who had received only 2 previous lines of therapy than those who had received >2 lines (68% *vs* 43%; p=0.032) and in those with ISS stage I or II than those with stage III (64% *vs* 63% *vs* 34%; p=0.031). Age, sex, previous ASCT, previous exposure to daratumumab, status of the disease at EloPd start (biochemical *vs* symptomatic relapse *vs* refractory to last therapy) and creatinine clearance did not significantly impact the probability of achieving a response. The median time response was 2 months. After a median follow-up of 5 months (range 1-14 months), 36 patients stopped treatment due to disease progression, 4 due to toxicity, and 2 due to death from causes unrelated to therapy. Twelve-two patients died (17 from progressive disease, 3 from infection, and 2 for reasons unrelated to treatment). Follow-up data regarding PFS and OS are not sufficiently mature to be analyzed. Common grade 3-4 adverse events were neutropenia (39.3%), fatigue (29%), lymphocytopenia (26.2%), anemia (17.8%), infection (17.8%). Infusion reactions occurred in 1 patient (0.9%) and were of grade 2. The infusion reaction resolved, and the patient continued treatment. Our real-world preliminary data confirm that EloPd is an effective and safe regimen for RRMM patients, resembling results obtained in controlled clinical trials.

P119

ROLE OF VEGF AND IL-6 IN PATIENTS WITH IGM–MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE AND WALDENSTROM MACROGLOBULINEMIA: A MONOCENTRIC EXPERIENCE

A. Tomasso[1*], I. Innocenti[2*], G. Benintende[1], F. Autore[2], A. Fresa[1], F. Vuono[1], L. Stirparo[1], A. Mosca[1], C. Giannotta[3], M. Luigetti[4,5], S. Baroni[6], L. Laurenti[1,2] Contributed equally to this study.

[1]Sezione di Ematologia, Dipartimento di Scienze Radiologiche ed Ematologiche, Università Cattolica del Sacro Cuore; [2]Dipartimento di Diagnostica per Immagini, Radioterapia Oncologica ed Ematologia, Fondazione Policlinico Universitario A. Gemelli IRCCS; [3]Department of Medical Biotechnology and Translational Medicine, Milan University, Neuromuscular and Neuroimmunology Service, Humanitas Clinical and Research Center; [4]UOC Neurologia, Fondazione Policlinico Universitario A. Gemelli IRCCS; [5]Dipartimento di Neuroscienze, Università Cattolica del Sacro Cuore; [6]Dipartimento di Chimica Clinica, Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Italy

Background: Angiogenesis plays an important role in the development and the maintenance of hematolymphoid malignancies. Serum levels of angiogenic cytokines, such as vascular endothelial growth factor (VEGF) and interleukin 6 (IL-6), are known to be increased in patients (pts) with Waldenstrom Macroglobulinemia (WM) and IgM monoclonal gammopathy of undetermined significance (MGUS). Even if the role of IL-6 and VEGF as markers of disease status and severity has been recognized, there is no proof about any correlation between their serum levels in MW and IgM-MGUS pts.

Aims: This study aims to find a correlation of serum levels of VEGF and IL-6 with the burden of disease in our pts with IgM-MGUS and MW and to evaluate a possible relationship between the two angiogenic cytokines.

Methods: We enrolled 18 pts (ten with WM and eight with IgM-MGUS) with a median age of 73 years (range: 52-90), whose 66% were male. Pts with MW were at different stages of disease (four were naive, four in remission, two relapsed/refractory). A total of 18 controls with a similar age and gender distribution were also tested. In all pts and controls, we evaluated serum levels of VEGF and IL-6 using Immunoassay panels (i.e., anti-IL-6 and anti-VEGF ELISA kit). In order to find a relationship of those cytokines with a laboratory parameter, IgM levels dosage have been performed for each patient.

Results: All pts showed elevated values of angiogenic cytokines when compared with controls (P value < 0.05). Both VEGF (median value: 623,5 pg/mL, range: 113,4-1981 pg/mL) and IL-6 (median value: 4,5 pg/mL, range: 0,3-21,9 pg/mL) serum levels showed a positive correlation with IgM serum levels (median value: 2055 mg/dL, range: 300-6123 pg/mL) (Figure 1a and 1b). Furthermore, the relationship between IL-6 and VEGF was statistically significant and could be explained by a linear model (P value = 0,007) (Figure 1c). No statistically significant differences were observed between the different phases of WM.

Conclusions: Evidence from our sample shows that serum levels of angiogenic cytokines as VEGF and IL-6 have a comparable pattern with IgM levels. Therefore, it seems reasonable to suggest that they could be used in clinical practice as marker of severity of disease and response to treatment. Moreover, since the cytokines profiles are comparable, IL-6 can be used interchangeably with VEGF, allowing the monitoring of the disease with easily availability and unexpensive techniques.

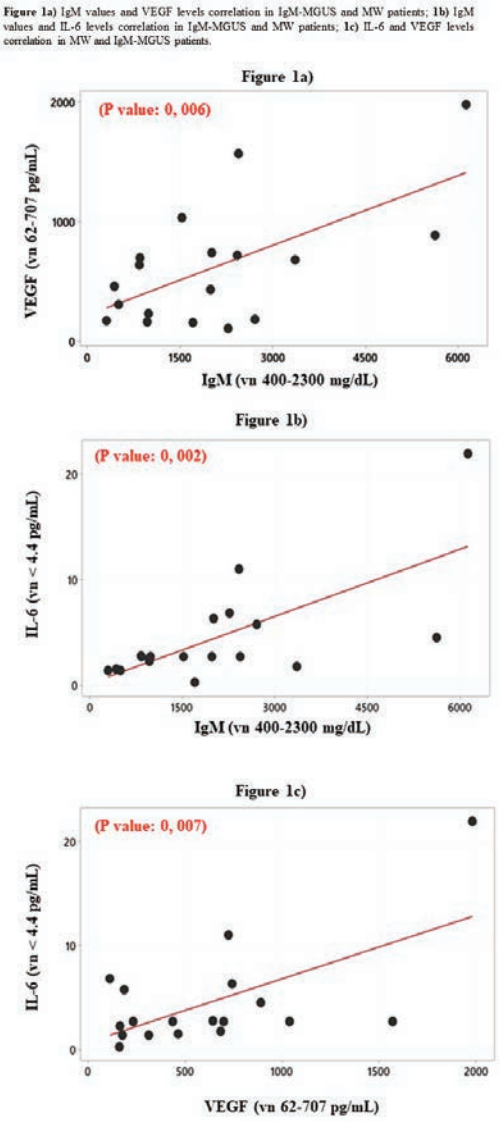


Figure 1.

P120

BORTEZOMIB-LENALIDOMIDE-DEXAMETHASONE (VRD) FOR NEWLY DIAGNOSED MULTIPLE MYELOMA PATIENTS: REAL-LIFE MONOCENTRIC EXPERIENCE

D. De Novellis[1], R. Fontana[1], A. Carobene[1], B. Serio[1], R. Guariglia[1], V. Giudice[1-2], C. Selleri[1-2]

[1]Hematology and Transplant Unit, University Hospital "San Giovanni di Dio e Ruggi d'Aragona"; [2]Department of Medicine, Surgery and Dentistry "Scuola Medica Salernitana", Italy

Introduction: Association of bortezomib-lenalidomide-dexamethasone (VRD) was documented as highly effective in first-line multiple myeloma (MM) treatment, and consolidation with autologous stem cell transplantation (ASCT) is still considered the standard of care in eligible patients in Europe. In this real-life single-center retrospective experience, we compared the efficacy of VRD induction followed by ASCT versus VRD without ASCT as upfront MM therapy.

Methids: A total of 56 patients with newly diagnosed MM treated with VRD at the Hematology and Transplant Center, University Hospital "San Giovanni di Dio e Ruggi d'Aragona" of Salerno from 2015 to March 2022 were included in this retrospective study. Eighteen of them received VRD followed by ASCT (C1 cohort), while 38 VRD without ASCT (C2 cohort). Clinical characteristics are shown in Table 1. Primary end points were progression free survival (PFS) and overall survival (OS).

Results: Patients in the C1 cohort were younger (median age, 55 *vs* 72 years; p<0.005) and more frequently with normal renal function (median glomerular filtration rate, GFR, 96 *vs* 50 mL/min, p<0.005; GFR≤40 mL/min, 11% *vs* 39%, p=0.03) compared to the C2 cohort. Median number of VRD cycles was similar between the two cohorts and lenalidomide maintenance was performed in 61% *vs* 55% cases, respectively. Median PFS and OS were not reached for both cohorts, as 5-year PFS was 51% *vs* 73% and 5-year OS was 67% *vs* 86% for C1 *vs* C2, respectively (p>0.05).

Discussion: Our real-life experience suggested that VRD might be effective in MM treatment regardless consolidation with ASCT, while personalized therapeutic strategies based on VRD plus lenalidomide maintenance without ASCT might be a treatment option, especially when associated to sustained minimal residual disease (MRD) negativity. Further validation on larger prospective trials is needed

Table 1.

Patients' characteristics at baseline.

Characteristics	ASCT, N=18	No ASCT, N=38	P value
Median age, years (range)	55 (38-68)	72 (41-84)	<0.005
Gender, n (%)			
Male	12 (67)	25 (66)	NS*
Female	6 (33)	13 (34)	
M-protein type, n (%)			
IgG	12 (55)	25(66)	
IgA	3 (17)	4 (10)	NS
Micromolecular	3 (17)	9 (24)	
Not secernent	2 (11)	0	
Light chain type, n (%)			
Kappa	13 (72)	22 (58)	NS
Lambda	5 (28)	16 (42)	
Median Serum M-protein, g/dL, (range)	1.7 (0-5.9)	2 (0-7)	NS
Median FLC ratio (involved/uninvolved chain), (range)	36 (1.3-1000)	20.5 (0.6-1160)	NS
Median β9+-2 microglobulin, mg/dL (range)	3 (1.6-11)	3.6(1.7-32)	NS
Median albumin, g/dL (range)	3.9 (2.4-5)	3.3 (1.6-4)	NS
High-risk cytogenetic abnormalities, n (%)	6 (33)	5 (13)	NS
Osteolytic lesions ≥ 3, n (%)			
Yes	12 (67)	30 (79)	NS
Median glomerular filtration rate, ml/min (range)	96 (12-123)	59 (9-125)	<0.005
Glomerular filtration rate ≤ 40 mL/min	2 (11)	15 (40)	0.03
International Staging System, n (%)			
I	4 (22)	2 (5)	
II	8 (44)	12 (50)	NS
III	6 (33)	17 (45)	
VRD cycles, median (range)	5 (2-7)	6 (1-12)	NS
Median VRD cycles to better response, (range)	4 (1-6)	3 (1-8)	NS
Lenalidomide maintenance, n (%)			
Yes	11 (61)	21 (55)	NS
Progression free survival, median (range)	Not reached (9-50)	Not reached (2-52)	NS
5 year- progression free survival	51%	73%	
Overall survival, median (range)	Not reached (9-50)	Not reached (2-52)	NS
5 year- overall survival	67%	86%	

*Not significant

P121

PEGFILGRASTIM VERSUS FILGRASTIM IN THE SUPPORTIVE CARE OF HEAVILY PRETREATED MULTIPLE MYELOMA IN TREATMENT WITH POMALIDOMIDE-DEXAMETHASONE

C. Cerchione[1], L. Catalano[2], D. Nappi[3], A.E. Pareto[2], G. Musuraca[1], S. Ronconi[1], M. Ceccolini[1], D. Cangini[1], M.B. Giannini[1], M. Marchesini[1], F. Pane[2], G. Martinelli[1]

[1]Hematology Unit, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS; [2]Hematology, AOU Federico II; [3]Department of Hematology & CBMT, Ospedale di Bolzano, Italy

Pegfilgrastim is a pegylated long-acting recombinant form of G-CSF that extends the half-life and allows for once-per-cycle dosing, requiring less frequent dosing than nonpegylated G-CSF. The objective of this study was to compare the efficacy and safety of pegfilgrastim in patients affected by heavily pretreated MM, treated with pomalidomide-dexamethasone, in order to determine whether a single subcutaneous injection of pegfilgrastim is as effective as daily injections of standard filgrastim, in terms of haematological toxicity, febrile neutropenic episodes, antibiotic usage and hospedalization duration. 57 patients (31 M and 26 F) were enrolled, median age at diagnosis 69 years (r. 52-84), and median age at start of treatment 76 years (r.56-90) treated with several lines of treatments (median 7, r. 2-12), every refractory to all the drugs previously received, received Pomalidomide-Dexamethasone (P 4 mg for 21 days, D 40 mg days 1,8,15,22, pegfilgrastim day +8) every 28 days, until progression. Since first course, received in domestic setting, with a very good compliance, patients performed blood counts once weekly and received, from day +8 to day +19, prophylactic oral chinolonic antibiotics and anti-fungal drugs. During neutropenia after first cycle, Filgrastim (5 μgr/kg/day for 3 days) was given if neutrophils count was <1500 x 10^9 cells/L. Median number of filgrastim administrations was 4.6 (r. 3-6); nadir neutropenia was registered after a median of 10.4 days (r. 7-14); median of nadir neutrophil count was 1.13 x 10^9 cells/L (r.0.3 – 1.5), with maximum duration of 14 days. From the second course, all patients switched to prophylaxis with pegfilgrastim (6 mg), injected subcutaneously with a single administration on day +3 independently from the neutrophil count at that time. During pegfilgrastim, neutropenia was never longer than 8 days, with a consequent reduction of neutropenia-related infections. Median nadir neutrophil count, evaluated for every patients for at least three courses of therapy (r. 3-6) registered at day +11, was 1.28 (r.0.9-2.2). Only 4 patients needed a supplement of 3 administrations of filgrastim. Pegfilgrastim was well tolerated in all patients: main side effects in our patients were mild fever and bone pain (21.2%).

In patients affected by heavily pretreated MM treated with pomalidomide-dexamethasone, pegfilgrastim seems to reduce the incidence of severe neutropenia and infections and may increase the possibility to maintain the scheduled time of treatment.

P122

IDENTIFICATION OF CHROMOSOME 1 REARRANGEMENTS IN MULTIPLE MYELOMA PATIENTS WITH FLUORESCENT IN SITU HYBRIDIZATION: MONOCENTRIC EXPERIENCE

I. Caliendo, C. Fabbricatore, M. Langella, M. Lucignano, A. Pagano, A. Di Feo, G. Malferà, A. Cuomo, T. Romano, I. Viscardi, C. Califano

U.O.C. di Ematologia ed Autotrapianto di Cellule Staminali Emopoietiche, Italy

Multiple Myeloma (MM) is the second most common hematologic malignancy, characterized by an accumulation of malignant plasma cells (PCs) in the bone marrow (BM). Primary immunglobuline translocations involving immunoglobulin heavy chain (IGH) at the 14q32 region in-

cluding t(4;14), t(14;16), t(14;20), and the hyperdiploid including trisomies of chromosomes, occur as initiating events during tumor pathogenesis. Secondary chromosomal abnormalities occur later during disease progression. Additional copies of chromosome 1q (+1q) is one of the most common secondary cytogenetic abnormalities in patients with MM, but the sensitivity and precision of karyotyping to identify large chromosomal aberrations remains suboptimal due to the lower proliferation rate of plasma cells. Fluorescent in Situ Hybridization (FISH) overcame many of these barriers in MM and showed the presence of chromosomal alterations and extra copies that have highly prognostic significance. With FISH, + 1q is identified in approximately 40% of newly diagnosed MM cases. Among patients with +1q, describes patients with only one additional copy of 1q (3 total copies), whereas amp (1q) identifies patients who have amplification of 1q (≥4 copies). Here, we report the FISH analysis results performed on bone marrow of 20 patients with MM in the year 2021. The FISH probes used are: LSI TP53/CEP 17 FISH Probe Kit, IGH/FGFR3 DF FISH Probe Kit, LSI IGH/CCND1 DF FISH Probe Kit, LSI IGH/MAF DF FISH Probe Kit, LSI D13s319/13q34 FISH Probe Kit, 1q21 CKS1B Spectrum Orange/1p32 CDKN2C Spectrum Green FISH Probe Kit (Vysis). The FISH analysis showed the presence of abnormal chromosome 1q21 in six patients (30%); four patients showed gain (+1q), while amp (1q) was found in two patients. Abnormalities of chromosome 1 are always associated with other cytogenetic abnormalities found in FISH. In five patients the deletion or monosomy of chromosome 13 is associated, and in two of these there is the IGH/FGFR3 and in one the IGH/MAF rearrangements. Our results confirm the data reported in the studies. Patients with +1q and amp (1q) are at increased risk of drug resistance, disease progression, and death. Several genes on chromosome 1q are associated with aggressive MM cell phenotypes, including ILF2, CKS1B, PSMD4, ANP32E, and MCL-1. However, much remains to be learned about the biology of these genes for the development of new targeted therapeutic approaches to treat these patients for whom effective therapies are currently lacking.

P123

ADDITION OF CARFILZOMIB AS A THIRD AGENT IN LENALIDOMIDE-REFRACTORY MULTIPLE MYELOMA: SWITCHING FROM DOUBLET TO TRIPLET

C. Cerchione[1], L. Catalano[2], D. Nappi[3], S. Ronconi[1], M. Ceccolini[1], D. Cangini[1], G. Musuraca[1], M. Marchesini[1], F. Pane[2], G. Martinelli[1]

[1]Hematology Unit, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola, Italy; [2]Hematology, AOU Federico II; [3]Department of Hematology & CBMT, Ospedale di Bolzano, Italy

Carfilzomib is an epoxyketone proteasome inhibitor of second generation, proved to be effective and safe in relapsed and refractory Multiple Myeloma (rrMM), in combination with dexamethasone or lenalidomide and dexamethasone. In this retrospective observational trial, it has been evaluated efficacy and safety of carfilzomib, in combination with lenalidomide-dexamethasone (KRD) as salvage regimen in patients with rrMM, refractory to lenalidomide, where lenalidomide-based regimens have no proven efficacy. 41 patients (23 M/18 F), with rrMM, median age at diagnosis 63.7 years (r. 43-82), median age at start of treatment 67 years (r. 48-84) previously treated with several lines of treatments (median 3, r. 2-11), underwent to KRD regimen (ASPIRE trial schedule) for a median treatment cycles of 8 (r 2-18). ISS was equally distributed, and all patients had previously been treated with bortezomib and IMIDs, and were refractory to this agents. 61% (19/31) of them had undergone at least to a single ASCT. According to IMWG criteria, after a median follow-up of 9 months (r. 2-18), ORR was 68,2% (28/41: 9 CR, 12 VGPR, 7 PR) with 5 progressive diseases (PD) and 8 patients in stable disease (SD): this can be considered as an impressive result in this subset of rrMM patients, refractory to lenalidomide. In particular, for 11 patients, KRD was, after having achieved at least a PR, a bridge to second/third autologous SCT. Median time to response was 1.3 months (r.1-4), median OS from diagnosis was 62 months (r. 9-170), median OS from start of Carfilzomib was 11 months (r. 2-18). Carfilzomib was well tolerated, with grade 2 anemia in 39%(16/41) of patients, successfully managed by ESAs, without necessity of blood transfusions; 29% (12/41) grade 3-4 neutropenia (pegfilgrastim in primary prophylaxis was given, no ospedalization was required, no septic shocks were observed); 34% (14/41) grade 2, 21% (9/41) grade 3 and 12% (5/41) grade 4 thrombocytopenia, without hemorrhagic events and transfusion-dependency. Moreover, it was observed pneumonia in 39% (16/41) of patients, treated by common antibiotic drugs and always solved. A cardiac monitoring was performed for all patients: hypertension (grade 2-3) in 34% (14/41) of patients; fatigue in 39% (16/31) of patients. Carfilzomib-Lenalidomide-Dexamethasone has shown significant efficacy in a particularly severe setting of patients, relapsed and refractory to all available therapeutic resources, also lenalidomide, and it could be considered as a bridge to a second autologous or allogenic SCT.

P124

CYBORD ADMINISTRATION IN A PATIENT WITH LEFT VENTRICULAR ASSISTED DEVICE AS BRIDGE TO HEART TRANSPLANT IN AL AMYLOIDOSIS: CASE REPORT

A. Vincenzi, C. Giordano, G. Cerciello, A. D'Ambrosio, A. Fiumarella, G. Scairati, F. Pane

Department of Hematology, Federico II University, Italy

AL is caused by the amyloid deposition of a misfolded protein responsible for organ damage. In 75% of cases, AL amyloid is derived from the λ light chain. In systemic AL, the heart is frequently the predominant organ involved and symptoms of cardiac involvement are generally consistent with infiltrative cardiomyopathy. This is a first case report of a patient with AL amyloidosis with heart involvement receiving chemotherapy treatment with Left Ventricular Assisted Device (LVAD) implanted. In september 2020, a previously healthy 38 yo woman received a diagnosis of systemic AL amyloidosis, L type, on the endomyocardial biopsy with stage IV according to the Revised Mayo clinic 2012 criteria. The bone marrow biopsy revealed a plasma cells count of 26% CD138+, CD38++, CD56-, CD19-, CD45- with monosomy of chromosome 13 and t(11;14)(q13:q32) MYEOV/IGH (42,3%). For this reason, she started treatment with CyBorD (Cyclophosphamide, Bortezomib, Dexamethasone) with reduced dose of Bortezomib (0,7 mg/m^2) according to guidelines, due the severe cardiac involvement. The first cycle was overall well tolerated but on after the 2nd cycle, the patient presented symptoms of abdominal tension, weight gain, nausea, hypotension, ascites. TnI concentration was higher: 4200 pg/ml (>30% in two weeks) therefore chemotherapy was delayed and an incremented dose of diuretic was employed (Furosemide 175 mg/die). After few days, ECG was performed showing BBdx and abnormalities of repolarization but considering the high risk of postponing chemotherapy, with patient's informed consent, the second cycle of CyBorD was started at same dose. After 72h from the administration, the patient's clinical condition worsened (estimated ECOG 3) with dyspnea at rest and increase of the ascites. Therefore, chemotherapy is ultimately suspended, standing by for a comprehensive cardiological evaluation that resulted in a diagnosis of progressive biventricular failure and for this reason, the patient underwent to implantation of LVAD as bridging therapy to cardiac orthotopic transplant (BTT- Bridge to Transplant) at AORN Monaldi of Naples. The aim was to make the patient stable and improve her ECOG in order to continue the planned chemotherapy hoping to obtain a complete hematologic response (necessary condition for the heart transplant). After post-surgical recovery, the patient resumed chemotherapy with the CyBorD scheme. Through the implantation of VAD it has been possible the continuation of the chemotherapy, thereby achieving hematological com-

plete response, evaluated 6 weeks after the end of chemotherapy (December 2021). The patient was candidated to receive heart tranplantation, postponed for SARS-CoV-2 infection (january 2022). On february 27 heart transplantation was performed, however the patient died few days later for surgical complications

P125

DOMESTIC OPPORTUNITY IN HEAVILY PRETREATED MULTIPLE MYELOMA NOT ELIGIBLE TO HOSPITAL-BASED TREATMENT: ROLE OF POMALIDOMIDE-DEXAMETHASONE

C. Cerchione[1], L. Catalano[2], D. Nappi[3], A.E. Pareto[2], G. Musuraca[1], A. Lucchesi[1], S. Ronconi[1], M. Ceccolini[1], D. Cangini[1], M.B. Giannini[1], M. Marchesini[1], F. Pane[2], G. Martinelli[1]

[1]Hematology Unit, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS; [2]Hematology, AOU Federico II; [3]Department of Hematology & CBMT, Ospedale di Bolzano, Italy

Many patients affected by heavily pre-treated Multiple Myeloma could be not eligible to hospital-based treatment: in this context domestic opportunities should be considered. Pomalidomide is a new generation IMID, with a very good compliance, thanks to oral administration, which can be used also in heavily pretreated patients, in a domestic setting. In this retrospective observational trial, It has been evaluated efficacy and tolerance of pomalidomide plus dexamethasone (PD) as salvage regimen in heavily pretreated patients with relapsed and refractory MM (rrMM), whose prognosis is particularly severe. 57 patients (31 M/26 F), with rrMM, median age at diagnosis 69 years (r. 52-86), and median age at start of treatment 76 years (r.56-90) treated with several lines of treatments (median 7, r. 2-11), every refractory to all the drugs previously received (also Bortezomib, Thalidomide and Lenalidomide), received Pomalidomide-Dexamethasone (Pomalidomide 4 mg for 21 days, Dexamethasone 40 mg days 1,8,15,22, pegfilgrastim day +8) every 28 days, until progression. ISS was equally distributed, and cytogenetic at relapse was evaluable in 14 patients. All the patients had previously been treated with schedule containing bortezomib and IMIDs. 63% (36/57) had undergone at least to a single ASCT. All patients were relapsed and refractory to last therapies received before PD. Pomalidomide was well tolerated, with grade 3-4 transfusion-dependent anemia in 58% (33/57) of patients, 44% (23/57) grade 3-4 neutropenia (pegfilgrastim in primary prophylaxis was given, no hospitalization was required, no septic shocks were observed), 40% (23/57) grade 3-4 thrombocytopenia without hemorrhagic events and transfusion-dependence. No severe extra-hematologic toxicity was observed. According to IMWG, ORR1 (≥PR) was 47.3% (27/57: 5 CR, 11 VGPR, 7 PR, 4 MR), but, considering that we are evaluating a cohort of heavily pretreated patients, with poor prognosis, another parameter should be considered, ORR2 (≥SD), considering stable disease as a successful result in progressive MM. ORR2 was 77.1% (17 SD). These can be considered as impressive result in this subset of patients. Oral treatment gives a really good compliance, in frail and unfit patients, and response, when present, is always really fast (median time to response: 2 months (r.1-6)), median OS from diagnosis was 94 months (range 21-234), median OS from start of pomalidomide was 9 months (range 1-25). Nine patients have surprisingly achieved a notable response (3 VGPR, 4 PR, 2 MR) after failure of novel agents (i.e. Carfilzomib, Daratumumab and Pomalidomide). Pomalidomide-dexamethasone has shown significant efficacy and a very good compliance, thanks to oral administration, in a particularly severe setting of heavily pretreated patients, relapsed and refractory to all available therapeutic resources, also after failure of novel agents.

P126

UNEXPECTED PARVOVIRUS B19 INFECTION IN A MYELOMA PATIENT TREATED WITH DARATUMUMAB

M. Palazzo[1], G. Ciolli[1], S. Pilerci[1], I. Attucci[1], L. Pengue[1], A.M. Vannucchi[1,2], E. Antonioli[2]

[1]Department of Experimental and Clinical Medicine, University of Florence; [2]Haematology Department, Careggi Hospital, Florence, Italy

Introduction: Infections are a significant cause of morbidity and a leading cause of death in multiple myeloma (MM) patients. A changing spectrum of infections has been recently described, possibly due to the novel MM treatment approaches. Daratumumab is known to impair immune homeostasis leading to an increased risk of infections, especially viral, as demonstrated both in clinical trials and in real-life settings. Herpes Zoster and CMV reactivation are reported as the most common infections during daratumumab treatment. Any Parvovirus B19 infection has been reported, to date. Here we present the case of a 52-year-old man affected by IgG lambda RRMM complicated by cardiac and renal amyloidosis, currently in second-line treatment with daratumumab-lenalidomide-dexamethasone (DRd) association since 2019. In November 2021, while in sCR, the patient developed pancytopenia, first attributed to lenalidomide, which was discontinued and then reintroduced to haematological recovery. However, a few months later, in February 2022, the patient presented with fever and asthenia; blood tests revealed Hb 7.6g/dL, ANC $0.17x10^9$/L, PLT $67x10^9$/L. Treatment was stopped and the diagnostic work-up for acute pancytopenia was performed: the peripheral blood smear showed no morphological abnormalities; no vitamin deficiency was found; the haemolytic indices were negative. Chest x-ray and blood cultures excluded pulmonary or systemic infections. We looked for viral infections and found high levels of Parvovirus B19-DNA in the blood by quantitative polymerase chain reaction (PCR) analysis (1,500,000 copies/ml). The patient required red blood cells transfusion support. He was treated with intravenous immunoglobulin (IGIV) 0.4g/kg for 5 days, the subsequent PCR showed unchanged the copies of Parvo-B19, but the Hb values remained stable (10 g/dl) and an improvement in the ANC and PLT count was observed. The treatment with IVIG was repeated for another 5 days, obtaining a reduction of viral copies (600.000/ml). In consideration of the clinical and haematological recovery, DRd was resumed; the patient also performs anti-infective prophylaxis with subcutaneous IG in association.

Conclusion: Routine monitoring for Parvovirus-B19 is not recommended. With the ever-changing therapeutic landscape and the introduction of immunotherapy even in the early stages of the disease, the optimal approach to prophylaxis and treatment of emerging infections represents an unmet clinical need.

Lymphomas II

P127

THE LEARNING CURVE IN THE REFERRAL OF PATIENTS ELIGIBLE FOR CAR-T CELL TREATMENT

A. Chiappella[1], A. Guidetti[12], A. Dodero[1], L. Arcaini[3], B. Botto[4], R. Bruna[5], I. Casaroli[6], C. Ciochetto[7], C. Fozza[8], M. Krampera[9], S. D'Agostino[10], M. Massaia[11], P. Musto[1213], J. Olivieri[14], M. Picardi[15], B. Puccini[16], F.G. Rossi[17], G. Spizzo[18], A. Tucci[19], E. Lucchini[20], M. Merli[21], M. Pennisi[1], F. Stella[1], P. Corradini[12]

[1]Division of Hematology and Stem Cell Transplantation, Fondazione IRCCS Istituto Nazionale dei Tumori; [2]Chair of Hematology, University of Milano; [3]Department of Hematology Oncology, Fondazione IRCCS Policlinico San Matteo; [4]Hematology, Città della Salute e della Scienza Hospital and University; [5]Division of Hematology Department of Translational Medicine, University of Eastern Piedmont; [6]Department of Hematology San Gerardo Hospital; [7]SSD Hematology, ASLTO4 Presidio Ospedaliero di Ivrea; [8]Department of Medical, Surgical and Experimental Sciences, University of Sassari; [9]Unit of Hematology and Stem Cell Transplantation, AOUI Policlinico G.B. Rossi; [10]Division of Hematology, IRCCS- CROB; [11]Division of Hematology, AO S. Croce e Carle; [12]Department of Emergency and Organ Transplantation, "Aldo Moro" University School of Medicine; [13]Unit of Hematology and Stem Cell Transplantation, AOUC Policlinico; [14]Division of Hematology and Stem Cell Transplantation and Cellular Therapy "Carlo Melzi" Azienda Sanitaria Universitaria Friuli Centrale; [15]Division of Hematology and Stem Cell Transplantation, AOU Federico II; [16]SOD Hematology, AOU Careggi; [17]Division of Hematology, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico di Milano; [18]Department of Internal Medicine, Oncologic Day Hospital, Hospital of Bressanone (SABES-ASDAA); [19]Unit of Hematology, ASST Spedali Civili; [20]Unit of Hematology, Azienda Ospedaliera Universitaria Giuliano Isontina; [21]Unit of Hematology, ASST Sette Laghi, Ospedale di Circolo e Fondazione Macchi

The introduction of anti-CD19 chimeric antigen receptor T cells (CAR-T) in the treatment of relapsed/refractory large B-cell lymphoma, showed impressive results. From 2019, tisagenlecleucel (tisa-cel) and axicabtagene ciloleucel (axi-cel) are registered and reimbursed in Italy by Agenzia Italiana del Farmaco (AIFA) for the treatment of relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) and primary mediastinal B-cell lymphoma (PMBCL) patients after at least 2 lines, with an ECOG 0-1, and an age lower than 71 years. The identification of the patient eligible to CAR-T treatment and the timing of the referral is a crucial step. The aim of this analysis was to evaluate the improvement of the referral over the years for the patients candidate to CAR-T cells reported to Hematology, Fondazione IRCCS, Istituto Nazionale dei Tumori in Milano.

In our experience, a pre-evaluation based on charts was conducted by phone or by email, then patients that fulfilled the AIFA approved indications were admitted for a visit by a haematologist of the CAR-T team.

Since October 2018 to end of 2021, 173 pre-evaluation forms were evaluated, 89 until December 2019, 47 in 2020 and 37 in 2021, and 94/175 (54%) performed a face to face visit. By years, 24/89 (27%) referred patients were eligible to CAR-T treatment in 2019, 36/47 (77%) in 2020 and 36/37 (97%) in 2021; 79 (46%) were not eligible due to: unconfirmed histology in 2, active central nervous system involvement in 4, severe comorbidities in 40, rapidly progressive disease in 30, complete remission (CR), in 3. Of the 94 patients that performed the face to face visit, 90 (96%) were considered eligible to CAR-T treatment according to AIFA indications and were leukapheresed; 85/90 (94%) were infused; 5 were not due to fatal severe infection during bridging therapy in one, death due to rapidly progressive disease in 2, complete remission confirmed by lymph-node biopsy on false positive residual uptake at PET scan in one, and acute autoimmune vasculitis in one.

The clinical characteristics of infused patients are reported in table 1. Response at day +30 after infusion was: 42 (49%) CR, 19 (22%) partial response/stable disease, 24 (28%) progressive disease. At a median follow-up of 12 months, 1 year progression free survival was 47% and 1 year overall survival was 85%.

In our experience, the learning curve in the referral is improving, ensuring a better chance of cure to the patients eligible to CAR-T treatment.

Table 1.

Clinical characteristics, N = 85	
Median age, N (range)	54 (21-70)
Male, N (%)	53 (62%)
Lines of prior therapies, N (range)	3 (2-7)
Stage III/IV, N (%)	58 (68%)
Histology, N (%)	
DLBCL	41 (49%)
HGBCL	13 (15%)
tFL	8 (9%)
PMBCL	19 (22%)
MCL	4 (5%)

P128

OUTCOME DEI LINFOMI B AGGRESSIVI ASSOCIATI A LINFOMA INDOLENTE CONCOMITANTE O PRECEDENTE E ALTERAZIONI DI MYC

C. Pagani[1], R. Daffini[1], A. Re[1], A. Anastasia[1], L. Gandolfi[1], M. Motta[1], A. Passi[1], G. Campostrini[1], C. Cattaneo[1], L. Lorenzi[2], G. Rossi[1], A. Tucci[1]

[1]U.O.C. Ematologia, ASST Spedali Civili di Brescia; [2]U.O.C. Anatomia Patologica, University of Brescia, ASST Spedali Civili di Brescia, Italy

Introduction: Aggressive B-cell lymphoma (AL) transformed from indolent lymphoma (IL) has been traditionally associated with poor response to treatment and outcome, but recent studies have shown no significant difference in survival between *de novo* AL and transformed AL (tAL) without prior treatment exposure. Moreover many studies have shown a negative prognostic impact of double expression of MYC and BCL2 ("double expressor lymphomas" (DEL)) with or without concomitant translocation involving MYC gene (including single hit lymphomas (SHL) and double or triple hit lymphomas (DHL/THL)). There are very few data on the impact of these abnormalities (abn) in tAL.

Aims and methods: This is a single center retrospective study, designed to evaluate the outcome of patients (pts) with tAL [diffuse large B cell lymphoma (DLBCL) or high grade B cell lymphoma (HGBCL)] and MYC+/- BCL-2+/-BCL-6 abn detected by FISH or by immunohystochemistry (double expression of MYC and BCL2). The tAL were classified according to their time of onset.

Results: From March 2010 to June 2021, we identified 91 pts with tAL and MYC abn: 32 pts had a concomitant onset of IL and AL (group 1), 32 pts a previously untreated IL (group 2), 31 pts a previously treated IL (group 3); in 13 tAL developed during IL treatment (group 4). Table 1 shows clinical, histological and treatment characteristics of each group: IPI≥3, age<60 years and HGBCL were significantly more frequent in group 4, DEL in group 1. All but one pts in group 4 received intensified therapy. With a median follow up of 40 months (ms) (range 7-92 ms), 2-years overall (OS) and progression free survival (PFS) were 77% and 74% in group 1, 59% and 40% in group 2, 53% and 41% in group 3 and 15% and 8% in group 4. The differences in OS and PFS between group 1 and 4 were highly significant (both p<0,0001), even excluding DEL.

Conclusions: This study confirms that the prognosis of transformed lymphoma with MYC abn markedly differs according to their time of onset. Lymphoma transformation during treatment of IL occurred in younger pts but carried a particularly poor prognosis, despite the shift to

an intensive immunochemotherapeutic treatment. This group of patients may likely benefit from an early switch to newer therapeutic approaches like CAR-T or bispecific antibodies.

P129

CIRCULATING LIVER-RELEASED MIR-122-5P PROMOTES PEDIATRIC ALCL DISEASE AGGRESSIVENESS

C. Damanti[1,2], L. Ferrone[1,2], E. Gaffo[3], A. Garbin[1,2], I. Gallingani[1,2], A. Tosato[1,2], G. Contarini[1,2], R. Angioni[2,4], B. Molon[2,4], E. Carraro[5], M. Pillon[5], S. Bortoluzzi[3,6], F. Lovisa[2], L. Mussolin[1,2]

[1]Maternal and Child Health Department, Padova University; [2]Istituto di Ricerca Pediatrica Città della Speranza; [3]Department of Molecular Medicine, Padova University; [4]Department of Biomedical Sciences, Padova University; [5]Pediatric Hematology, Oncology and Stem Cell Transplant Division, Padova University Hospital; [6]Interdepartmental Research Center for Innovative Biotechnologies (CRIBI)

Background: Anaplastic large cell lymphoma (ALCL) represents approximately 20% of pediatric non-Hodgkin's lymphomas. Modern therapeutic strategies lead to cure >70% of patients, whereas refractory/relapse diseases convey a dismal prognosis. Liquid biopsy has the potential to help clinicians screen for disease, stratify patients to the best treatment and monitor therapy response. In this field, evidences are accumulating on the role of plasma small extracellular vesicles (S-EVs) as cancer biomarkers and inter-cellular messengers actively contributing to the disease process.

Objectives: To analyze the role of plasma S-EVs on pediatric ALCL tumorigenesis and disease progression.

Patients and Methods: Plasma S-EVs were obtained from plasma samples at diagnosis of 20 ALCL patients and 5 healthy donors (HD). S-EVs RNA was extracted and processed for small RNA-seq on an Illumina platform. Data were analyzed by using the software miR&moRe and DESeq2. Selected miRNAs expression was validated in an extended cohort of 66 ALCL patients and 19 HD by qRT-PCR. MiR-122-5p targets were analyzed by qRT-PCR and Western blotting in MEF-1 cells. Functional assays were performed on ALCL cells treated with conditioned media from MEF-1 cells overexpressing miR-122-5p or a negative control. Finally, S-EVs enriched in miR-122-5p or negative control were administrated to mice before tumor cells injection and ALCL cells dissemination was evaluated by qRT-PCR, immunohistochemistry and flow cytometry.

Results: RNA-seq data analysis revealed different miRNA expression profiles between S-EVs from ALCL patients and HD. In particular, the liver-specific miR-122-5p was found more abundant in patients' plasma S-EVs compared to HD. Elevated levels of miR-122-5p correlated with advanced stage disease and impaired hepatic function in ALCL patients. Moreover, miR-122-5p was able to inhibit glucose consumption in MEF-1 cells and the resulting increased glucose availability enhanced ALCL cells aggressiveness *in vitro*, as well as tumor dissemination *in vivo*.

Conclusions: In this study, we demonstrated that elevated levels of the liver-released miR-122-5p in plasma S-EVs of ALCL patients play an active role in promoting ALCL cells growth, aggressiveness and dissemination both *in vitro* and *in vivo*. Our findings pave the way for investigating the clinical use of miR-122-5p antagonists in ALCL patients with high levels of S-EVs-delivered miR-122-5p.

P130

TIMELY LYMPHOCYTE-APHERESIS AND TYPE OF DISEASE MAY INFLUENCE T CELL FITNESS FOR CAR-T MANUFACTURING

M. Farina[1], M. Chiarini[2], C. Almici[3], E. Accorsi Buttini[1], A. Galvagni[2], A. Leoni[1], F. Colnaghi[1], V. Radici[1], E. Ferrari[3], A. Bianchetti[3], I. Volonghi[4], L. Poli[4], D. Moratto[2], F. Re[1,5], K. Bosio[1,5], S. Bernardi[1,5], N. Polverelli[1], A. Turra[1], E. Morello[1], C. Cattaneo[6], M. Malagola[1], D. Brugnoni[2], A. Re[6], D. Russo[1]

[1]Unit of Blood Diseases and Bone Marrow Transplantation, Cell Therapies and Hematology Research Program, Department of Clinical and Experimental Sciences, University of Brescia, ASST Spedali Civili di Brescia; [2]Clinical Chemistry Laboratory, Flow Cytometry Section, Diagnostics Department, ASST Spedali Civili di Brescia; [3]Laboratory for Stem Cells Manipulation and Cryopreservation, Department of Transfusion Medicine, ASST Spedali Civili di Brescia; [4]U.O.C. Neurology Center for Neuromuscular Diseases, Department of Clinical and Experimental Sciences, University of Brescia, ASST Spedali Civili di Brescia; [5]Research Center Ail (CREA), Chair of Hematology-Department of Clinical and Experimental Sciences, Unit of Blood Diseases and Stem Cell Transplantation, University of Brescia, ASST Spedali Civili di Brescia; [6]U.O.C. Hematology, Department of Clinical Oncology, ASST Spedali Civili di Brescia, Italy

Background: Chimeric antigen receptor T (CAR-T) cells are effective therapy in Diffuse large B-cell Lymphoma (DLBCL), Primary Mediastinal B-cell Lymphoma (PMBCL) and Acute Lymphoblastic Leukemia (ALL). CAR-T cells from T-lymphocytes (T-Ly) enriched for early lineage T-cells have shown higher replicative potential and better response. In the BioCART BS study, we assessed the T-cell repertoire at Ly-apheresis for evaluating the impact of previous treatments and type of disease.

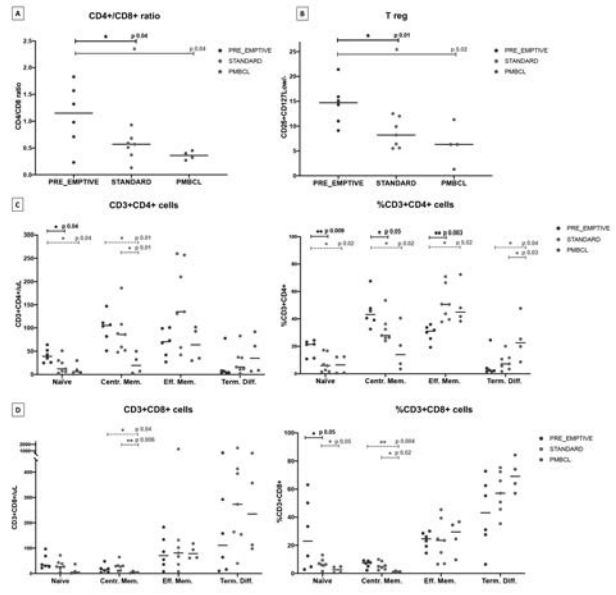


Figure 1.

Methods: Between April 2021 and March 2022, 18 patients (pts) underwent Ly-apheresis (13 DLBCL, 4 PMBCL and 1 ALL). 6 out of the 13 DLBCL pts with poor prognostic risk factor (refractory to I line of treatment; PET positivity before ASCT; first complete response less than

12 months) were enrolled in an early/pre-emptive Tisa-cel Ly-apheresis program, scheduling leukapheresis as soon as possible, before ASCT. Combinations of monoclonal antibodies were used by Flow Cytometry to evaluate the CD4+/CD8+ T-ly subsets: T-naïve (CD45RA+CCR7+); central memory (CM, CD45RA-CCR7+); effector memory (EM, CD45RA-CCR7-); terminally differentiated (TD; CD45RA+CCR7-), and T-reg (CD4+CD25+CD127low/-).

Results: 6 out of the 13 (45%) DLBCL pts (median age: 60 ys) underwent Tisa-cel pre-emptive Ly-apheresis before ASCT, while the other 7 underwent Ly-apheresis following standard indications (3 Tisa-cel; 4 Axi-cel). At the time of Ly-apheresis, no differences were observed between pts who previously underwent ASCT and those who did not, except for age. ASCT induced a more "exhausted" T-cells profile (Figure 1). Pts who underwent ASCT had lower CD4+/CD8+ ratio as well as lower levels of CD4+ Naïve and CM T-Ly, and lower CD8+ Naïve T-Ly. They also had higher prevalence of CD4+ EM T-Ly. In addition, pts in the pre-emptive group had higher levels of T-reg Ly. The 4 PMBCL pts (median age: 38 ys) showed a Ly-profile more similar to the DLBCL-standard group pts, having an even more exhausted T-Ly profile (Fig 1) characterized by lower levels of CD8+ Naïve and CD4+/CD8+ CM T-Ly, as well as higher CD4+ TD T-Ly compared to the DLBCL-standard group pts. Notably, 4 out of 6 (67%) pre-emptive DLBCL pts had already activated a CAR-T cells program.

Conclusion: ASCT before Ly-apheresis may result in a more "exhausted" T-Ly repertoire. In high-risk DLBCL pts, timely pre-ASCT Ly-apheresis would be considered. In addition, type of disease may also influence Ly-repertoire. Indeed, PMBCL pts had lower levels of "Fit" Ly compared to DLBCL pts.

P131

HELICOBACTER PYLORI ERADICATION THERAPY IN THE FIRST LINE TREATMENT OF GASTRIC MARGINAL ZONE LYMPHOMAS

G. Gugliotta[1], L. Nanni[1,2], V. Stefoni[1,2], B. Casadei[1,2], A. Broccoli[1,2], C. Pellegrini[1], A. Morigi[1,2], M. Carella[1,2], G. Lolli[1,2], P.E. Coppola[1,2], G. Bagnato[1,2], M. Gentilini[1,2], L. Argnani[2], P.L. Zinzani[1,2]

[1]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli", Bologna, Italy; [2]Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale, Università di Bologna, Bologna, Italy

Chronic Helicobacter Pylori (HP) gastritis is a predisposing factor for gastric extranodal marginal zone B-cell lymphomas (MZLs). The association among infections, autoimmune conditions, and MZLs has clinical consequences. Gastric MZL has good prognosis due to clinical response to treatment and favorable overall survival, but HP should be eradicated in all patients with gastric MZL and HP infection, irrespective of the stage. In this study, clinical characteristics and treatment of patients of HP positive gastric MZL were retrospectively analyzed. Forty-two patients were diagnosed with HP positive gastric MZL at our institute between 2002 and 2018 and received timely HP eradication (five patients underwent a second eradication). All but 4 had only one site of disease, i.e. 38/42 (90.5%) presented with stage IE. After eradications, all patients resulted as HP negative and 13/42 (30.9%) had lymphoma complete disease remission (CR). Median progression free survival was reached at 3.1 months, median disease free survival at 5.7 years and median overall survival (OS) at 15.5 years, respectively. Five out of 13 responder patients were still in continuous complete response at the latest available follow up with a median of response duration of 5 years (range 2 – 5).

Patients in whom HP eradication therapy was not effective, alternative treatments options including chemo-immunotherapy (15), immunotherapy (9), chemotherapy (3), radioimmunotherapy (1) and surgery (1), were given with a median time to next treatment of 4.4 months and a CR rate of 93% (27/29). In no case was radiotherapy resorted to.

HP eradication therapy demonstrated a low CR rate, but long CR maintenance, and a good OS for patients with localized gastric MZL in this retrospective, practice-based, monocentric study.

P132

IBRUTINIB IN RELAPSED/REFRACTORY PATIENTS WITH WALDENSTRÖM MACROGLOBULINEMIA: A REAL-LIFE, RETROSPECTIVE, STUDY ON BEHALF OF THE "RTL" (REGIONAL TUSCAN LYMPHOMA NETWORK)

E. Cencini[1], I. Romano[2], F. Ghio[3], C. Camerini[4], I. Bertaggia[5], R. Giachetti[6], L. Mannelli[7], M.T. Pirrotta[8], D. Breccia[1], G. Lucco[1], M. Ciceri[2], G. Cervetti[3], E. Sant'Antonio[4], F. Simonetti[5], S. Birtolo[6], B. Puccini[2], M. Bocchia[1], A. Fabbri[1]

[1]Unit of Hematology, Azienda Ospedaliero-Universitaria Senese and University of Siena; [2]Lymphoma Unit, Azienda Ospedaliero-Universitaria Careggi and University of Florence; [3]Unit of Hematology, Azienda Ospedaliero-Universitaria Pisana and University of Pisa; [4]UOC Ematologia Aziendale, Azienda USL Toscana Nordovest, Ospedale S. Luca; [5]UOC Ematologia Aziendale, Ospedale Versilia; [6]SOS Oncoematologia; [7]SOS Oncoematologia, Ospedale S. Stefano; [8]UOS Oncoematologia Ospedale San Giuseppe, Italy

Introduction: Ibrutinib is an inhibitor of Bruton kinase and represents the first approved treatment for patients with Waldenström macroglobulinemia (WM). Several clinical trials showed long-lasting efficacy with manageable toxicity for ibrutinib in previously treated WM. However, there are very few published experiences in a non-trial setting. In this study, we investigated treatment response, survival and safety of ibrutinib in daily clinical practice.

Methods: We retrospectively analyzed 49 consecutive R/R WM patients managed in 8 Tuscan onco-hematological centers receiving ibrutinib since its approval. The treatment regimen consisted of oral, single-agent ibrutinib, maximum dosage of 420 mg once per day, until disease progression or unacceptable toxicity.

Results: Median age was 65 years (range 32-86) and the median number of previous regimens was 2 (range 1-5). Overall and major response rate were 91.8% and 87.7%, respectively. Median time to first response was 2 months. At best response, median IgM level declined from 3,094 to 831 mg/dl and Hb level increased from 10.4 to 12.7 g/dl. Disease response was not influenced by MYD88 status (assessed in 22/49 cases). Median duration of treatment was 15 cycles (range 1-60). In an intention-to-treat analysis, 36/49 patients (73.5%) were still receiving treatment, while 13/49 (26.5%) had discontinued therapy, due to progressive disease (PD) (4/49 cases, 8.2%), second malignancies (1 prostate cancer), patient decision (1 case), treatment toxicity (7/49 cases, 14.3%). Six out of 49 cases (12.2%) relapsed after an initial response and 13/49 (26.5%) had a dose reduction. Median PFS was not reached, estimated 2-year PFS was 76.7%, median DOR was not reached (estimated 2-y DoR 88.7%), median OS was not reached (estimated 2-year OS was 84.1%). After a median follow-up of 18.3 months (range 1-62), 43/49 patients (87.8%) were alive and 6/49 patients (12.2%) died. Hematological toxicity occurred in only 2 cases. The most frequent nonhematologic AE included atrial fibrillation or flutter (6/49 cases, 12.2%), bleeding (6/49 cases, 12.2%), arthralgya/myalgia (5/49 cases, 10.2%).

Conclusions: In this study we suggest ibrutinib is highly effective and could represent a suitable therapeutic option for R/R WM patients in clinical daily practice. PFS and OS were durable and DoR was very prolonged for responsive patients. Treatment toxicity is not negligible, but manageable in most cases without treatment discontinuation.

P133

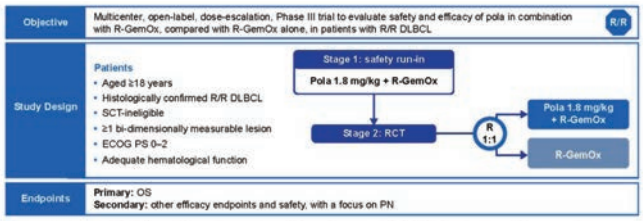
POLARGO: RANDOMIZED PHASE III STUDY OF POLATUZUMAB VEDOTIN (POLA) PLUS RITUXIMAB (R), GEMCITABINE (GEM), AND OXALIPLATIN (OX) IN RELAPSED/REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA (R/R DLBCL)

S. Santini[1], M. Matasar[2], C. Haioun[3], J.-M. Sancho[4], A. Viardot[5], J. Hirata[6], T. Perretti[7], L. Musick[6], A.K. McMillan[8]

[1]ASL Toscana Centro - SOC Oncoematologia; [2]Memorial Sloan Kettering Cancer Center; [3]Lymphoid Malignancies Unit, Groupe Hospitalier Henri Mondor; [4]ICO-HU Germans Trias i Pujol, Barcelona; [5]Department of Internal Medicine III, University Hospital of Ulm; [6]Genentech, Inc; [7]F. Hoffmann-La Roche Ltd; [8]. Centre for Clinical Haematology, Nottingham University Hospitals NHS Trust

Introduction: Pola is an antibody-drug conjugate targeting CD79b on malignant B-cells. Pola + bendamustine and rituximab (Pola-BR) improved complete response (CR) rate and overall survival (OS) *vs* BR alone in patients (pts) with R/R DLBCL. Several treatment options exist for R/R DLBCL, including Ox + R and Gem (R-GemOx). Adding Pola to R-GemOx (Pola-R-GemOx) may improve clinical efficacy, but the safety must be considered as platinum-based therapies and Pola are associated with neuropathy. The ongoing POLARGO study is assessing the safety and efficacy of Pola-R-GemOx *vs* R-GemOx alone in pts with R/R DLBCL who are ineligible for stem cell transplant (SCT).

Methods: POLARGO (NCT04182204) is a multicenter, open-label, phase III study, comprising a safety run-in stage (Pola-R-GemOx; n=10), and a randomized controlled trial (RCT) stage (Pola-R-GemOx *vs* R-GemOx; n=206; Figure 1) recruiting from 80-90 sites. Pts must be aged ≥18 years with R/R DLBCL, have received ≥1 line of prior systemic therapy, and for the RCT stage, have availability of tumor tissue. Pts are also required to have an ECOG PS of 0-2, and adequate hematologic function. Exclusion criteria include prior allogeneic SCT, planned autologous/allogeneic SCT, and baseline peripheral neuropathy (PN) greater than grade 1.



Abbreviations: DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; OS, overall survival; PN, peripheral neuropathy; pola, polatuzumab vedotin; R, randomization; RCT, randomized controlled trial; R-GemOx, rituximab + gemcitabine + oxaliplatin; R/R, relapsed/refractory; SCT, stem-cell transplant.

Figure 1.

Results: The primary endpoint of the safety run-in stage is the safety (incidence, nature, and severity of adverse events with a focus on PN) and tolerability (dose interruptions, reductions, and intensity) of Pola (1.8 mg/kg) + R-GemOx (R, 375 mg/m^2; Gem, 1000 mg/m^2; Ox, 100 mg/m^2) administered in 21-day cycles. G-CSF primary prophylaxis is required in each cycle of therapy. In the RCT stage, pts will be stratified by the number of previous lines of therapy, outcome of last therapy (relapsed *vs* refractory), and age (≤70 *vs* >70 years). Pts will be randomized (1:1) to receive up to eight 21-day cycles of Pola-R-GemOx or R-GemOx. The primary efficacy endpoint of the RCT stage is OS. Key secondary endpoints include CR and objective response (OR) rate (assessed by independent review committee), and progression-free survival, duration of OR, and event-free survival (assessed by investigator), according to Lugano 2014 criteria. Treatment impact on quality of life will also be assessed, and pts will be followed for up to 2 years.

Conclusions: As of July 7, 2021, the safety run-in stage has completed enrollment with a total of 13 pts, and the RCT stage was opened in November 2021.

P134

FEASIBILITY OF OUTPATIENT HIGH-DOSE INTRAVENOUS METHOTREXATE (HD-MTX) AS CENTRAL NERVOUS SYSTEM (CNS) PROPHYLAXIS FOR AGGRESSIVE LYMPHOMAS: A RETROSPECTIVE MONOCENTRIC EXPERIENCE

A. Soravia, G. Petruzzellis, S. Volpetti, P. Lauzzana, M. Girgenti, C. Filì, A. Candoni, R. Fanin, J. Olivieri

Hematology and SCT Unit, Azienda Sanitaria-Universitaria Friuli Centrale, Italy

CNS involvement in aggressive lymphomas is an infrequent event but portending a very poor prognosis. Prophylaxis with high-dose MTX combined with intrathecal chemotherapy is still considered the standard treatment to prevent CNS disease dissemination. HD-MTX administration is generally performed inpatient owing to the need of continuous hydration to avoid renal failure which can lead to catastrophic consequences; however, hospitalization cannot be implemented for all patients requiring CNS prophylaxis. Since 2016 in our center we started to apply an outpatient protocol for HD-MTX administration at different doses tailored to patient renal function and other comorbidities. We therefore aimed to evaluate the feasibility of outpatient HD-MTX administration by comparing the toxicity associated with cycles delivered as outpatient or inpatient. Twenty-six patients underwent HD-MTX for CNS prophylaxis: 19 were DLBCL-NOS, 2 double-hit lymphomas, 3 primary testicular lymphomas, 1 transfomed follicular lymphoma, 1 PMBCL; 15 were males and 11 females; median age was 66 years (range 40 – 78); the R-IPI was poor (3 – 5) in 77%; 21 were treated exclusively outpatient, 3 only inpatient and 2 in both regimens.

A total of 57 HD-MTX cycles were administered: 13 at doses of 1 g/mq (all outpatient), 29 cycles at 1.5 g/mq (24 out and 5 in), 15 at ≥3 g/mq (14 out and 1 in). To allow a comparison for the category of ≥3 g/mq, we added to the evaluation 4 patients undergoing HD-MTX ≥3 g/mq for PCNSL for further 13 cycles. HD-MTX ≥3 g/mq was seldom used in patients ≥65 years (1/14) compared with those < 65 years (6/12, p=0.01); doses of HD-MTX did not differ by comorbidity burden measured with CIRS. We evaluated the toxicity of HD-MTX cycles measuring the highest creatinine increase relative to basal value (hCrI): hCrI was 21% for outpatient and 24% for inpatient. We then applied a multivariate linear regression analysis using hCrI as endpoint: age, CIRS, IV hydration (normalized for BSA) and regimen of administration (in *vs* outpatient) were not significant predictors. The only independent significant variable was HD-MTX dose ≥3 g/mq (p=0.048). In fact for HD-MTX doses of ≥3 g/mq, the hCrI was 45% in the 14 out and 23% in the 14 in cycles. Our experience supports the feasibility of outpatient HD-MTX administration for doses up to 1.5 g/mq. However, for doses of HD-MTX ≥3 g/mq, inpatient treatment is preferred to reduce the risk of renal toxicity.

P135

ABSTRACT NOT PUBLISHABLE

P136

PRE-CAR-T MARKERS OF MONOCYTE ACTIVATION: POSSIBLE ASSOCIATION WITH SEVERE INFLAMMATORY COMPLICATIONS

M. Gambella[1], A.M. Raiola[1], C. Ghiggi[1], L. Giannoni[1], R. Varaldo[1], A, Ghiso[1], N. Colombo[2], R. Mangerini[2], E. Tedone[2], S. Luchetti[1], A. Bo[1], E. Angelucci[1]

[1]U.O. Ematologia e terapie cellulari, IRCCS Ospedale Policlinico San Martino; [2]U.O. Anatomia Patologica, IRCCS Ospedale Policlinico San Martino, Italy

The monocyte-macrophage (MoMa) system mediates CAR-T toxicities. In a minority of patients (pts), massive MoMa activation can progress to Hemophagocytic Lymphohistiocytosis/ Macrophage-Activation Syndrome (HLH/MAS). Major treatment approaches are based on MoMa cytokine axis disruption, through IL6/R (siltuximab, tocilizumab) or IL1/R (anakinra) inhibitors. Identification of MoMa activation markers before CAR-T therapy could anticipate rescue strategies, such as prophylactic tocilizumab or steroids employment, and mitigate toxicity. As circulating monocytes counts, IL6 and ferritin levels have been linked to MoMa activation, we aimed to explore their potential association with severe CAR-T toxicities.

Methods: We retrospectively analysed a cohort of 18 pts who received CAR-T cells at our center for Aggressive B-cell Lymphoma (17 DLBCL, 1 PMBCL) from November 2020 to December 2021; 15 received tisagenlecleucel, 3 axicabtagene-ciloleucel. Median age was 62 yrs (28-70), median number of previous lines was 2 (2-4). Six pts had a transformed lymphoma, 3 a bulky (> 10cm) at CAR-T. Peripheral blood circulating monocytes, IL6 and ferritin levels were measured on day 0 (d0) of CAR-T, before infusion. Monocytes were assessed through multiparametric-flow-cytometry as a CD45pos, medium side scatter circulating population.

Results: According to ASTCT score, 5 pts developed Gr. 3-4 toxicities (2 CRS, 1 ICANS, 2 both CRS and ICANS). Median time to Gr. 3-4 CRS was 1 day (0-2), to Gr. 3-4 ICANS was 6 days (2-8). As continuous variables, d0 mean values resulted significantly different in pts who developed Gr. 3-4 CRS, as compared with those who did not: lower circulating monocytes (mean, 95%CI: 48 (12.57 – 109.07) *vs* 121 (60.56 – 181.44); p = 0.04), higher IL6 (22 (15.86 – 29.39) *vs* 5 (3.66 – 6.35); p = 0.002) and ferritin (1168 (163.84 – 2173.16) *vs* 413 (207.64 – 619.22); p = 0.04) levels resulted in Gr. 3-4 CRS. Hence, a 3-points score was designed with < 50 cells/mcl (monocytes), > 20 pg/ml (IL6) and > 1000 mcg/ml (ferritin) as cut-off levels, to classify pts in a standard-risk (SR: 0-1 points) or a high-risk (HR: 2-3) group: none of the 13 SR pts developed Gr. 3-4 CRS, as compared to 4/5 (80%) in the HR group (Chi-square test for association: p = 0.002).

Conclusion: We conclude that d0 severe monocytopenia, high IL6 and ferritin levels are suggestive of MoMa activation and could be gathered in a score, to identify pts at higher risk of severe complications.

P137

LAMIVUDINE 18-MONTH PROPHYLAXIS IS THE BEST CHOICE FOR THE PREVENTION OF OCCULT HEPATITIS B VIRUS REACTIVATION IN HBCAB POSITIVE PATIENTS WITH DLBCL UNDERGOING UPFRONT R-CHOP-21

C. Giordano, M. Picardi, M. Esposito, C. Fatigati, D. Abagnale, M. Gianattasio, N. Pugliese, M. Ciriello, G. Muccioli Casadei, A.F. Salemme, F. Pane

Department of Clinical Medicine and Surgery, Federico II University Medical School, Naples, Italy

Occult hepatitis B virus infection (OBI) refers to HBsAg negative(-)/HBcAb positive(+) individuals with a condition where replication-competent HBV-DNA is present in the liver and absent in the blood. The analysis of liver tissue appears to be the most direct approach for OBI diagnosis; however, liver tissue is not always available. In patients with advanced-stage diffuse large B cell lymphoma (DLBCL) undergoing 6 cycles of R-CHOP-21 plus 2 additional R, OBI reactivation is a frequent and severe complication. There is no consensus among recent guidelines whether a pre-emptive approach or primary antiviral prophylaxis is the best solution in this setting of patients; questions still unresolved are the adequate prophylaxis duration and the type. For this reason, in this case-cohort study, we compared a prospective series (from January 2018 to September 2020) of 31 HBsAg-/HBcAb+ patients with newly diagnosed high-risk DLBCL receiving 100 mg daily lamivudine (LAM) prophylaxis 1 week before R-CHOP-21 (standard schedule) until 18 months after (18-month LAM cohort), versus 96 HBsAg-/HBcAb+ patients (from January 2005 to December 2011) with newly diagnosed DLBCL undergoing a pre-emptive approach (pre-emptive cohort) and versus 60 HBsAg-/HBcAb+ patients from January 2012 to December 2017 with newly diagnosed DLBCL receiving LAM (same schedule as above, except for the suspension at 6 months after the completion of R-CHOP) prophylaxis (6-month LAM cohort). Efficacy analysis focused primarily on OBI reactivation incidence and secondarily on acute hepatitis and R-CHOP disruption. OBI reactivation didn't occur in any of the 31 patients in the 18-month LAM cohort versus 6/60 patients (10%) in the 6-month LAM cohort (P = 0.07, by χ^2 test) or 12/96 (12%) patients in the pre-emptive cohort (absolute risk reduction, 0.89; 95% CI, 0.1-0.91; P = 0.04). None of the patients in the 18-month LAM cohort developed acute hepatitis compared with 3 (with massive HBV replication) in the 6-month LAM cohort and 6 in the pre-emptive cohort. No patient in the 18-month LAM cohort and in the 6-month LAM cohort experienced R-CHOP disruption versus 6 R-CHOP disruptions in the pre-emptive cohort. For patients experiencing OBI reactivation in the 6-month LAM cohort, therapy with tenofovir disoproxil fumarate was promptly started at 245 mg daily, whereas, for those in the pre-emptive cohort, therapy with LAM was promptly started at 100 mg daily. This is the first study collecting data regarding a consistent and homogenous sample of 187 HBsAg-/HBcAb+ patients. In our study, 18-month long prophylaxis with LAM appears to be the most effective approach with a null risk of OBI reactivation, hepatitis flare-up and chemotherapy disruption.

Table 1. Clinical and serological characteristics of OBI reactivation of patients in the pre-emptive cohort and in the 6-month prophylaxis cohort.

Patients no.	Age (y)	Sex	Stage	Cohort	Baseline			At OBI reactivation		Time of diagnosis of OBI reactivation	Time to HBV recovery (weeks)	Antiviral tp duration	Follow up HBsAg status	Status
					HBsAg	HBV-DNA (IU/ml)	ALT (U/L)	HBV-DNA ($x10^3$ UI/ml)	Peak ALT (X N.V)	Mo after R-CHOP start	weeks after antiviral tp	weeks	Pos/Neg	Outcome
1	50	F	IV	Pre-emptive	Neg	Neg	23	3,5	4,5x	10	8	28	Neg	Alive (NHL remission)
2	73	M	IV	Pre-emptive	Neg	Neg	18	4,5	10x	6	4	36	Neg	Alive (NHL relapse)
3	64	F	III	Pre-emptive	Neg	Neg	25	6,5	12x	3	3	22	Neg	Alive (NHL remission)
4	62	M	IV	Pre-emptive	Neg	Neg	34	1,3	4x	13	8	34	Pos	Alive (NHL relapse)
5	50	F	IV	Pre-emptive	Neg	Neg	19	9,1	20x	5	6	44	Neg	Alive (NHL remission)
6	71	M	IV	Pre-emptive	Neg	Neg	31	1,6	11x	6	3	48	Neg	NHL related death
7	66	M	III	Pre-emptive	Neg	Neg	29	1,7	3,7x	5	5	41	Pos	Alive (NHL remission)
8	70	M	III	Pre-emptive	Neg	Neg	34	1,6	5,4x	18	3	38	Pos	Alive (NHL remission)
9	52	F	IV	Pre-emptive	Neg	Neg	22	5,5	6,1x	3,5	3,5	Until death	Neg	NHL related death
10	60	M	IV	Pre-emptive	Neg	Neg	24	3,4	6x	15	5	25	Pos	NHL related death
11	58	F	III	Pre-emptive	Neg	Neg	26	2,2	5x	4,5	4,2	48	Neg	Alive (NHL remission)
12	44	F	IV	Pre-emptive	Neg	Neg	32	3,1	2,8x	8	3,8	34	Pos	Alive (NHL remission)
13	62	M	IV	6-months LAM	Neg	Neg	32	2,1	7x	13	4,5	24	Neg	Alive (NHL relapse)
14	80	M	III	6-months LAM	Neg	Neg	25	8,4	5x	15	6	20	Neg	Alive (NHL remission)
15	72	M	III	6-months LAM	Neg	Neg	30	4,8	3x	14,5	7	24	Pos	Death for other cause
16	67	F	IV	6-months LAM	Neg	Neg	16	5,2	1,7x	18	6,5	22	Pos	Alive (NHL remission)
17	58	M	IV	6-months LAM	Neg	Neg	21	3,9	3,8x	7	3,8	42	Pos	Alive (NHL relapse)
18	47	M	III	6-months LAM	Neg	Neg	29	1,9	4,3x	10	5	38	Neg	Death for other cause

OBI reactivation: defined as HBsAg seroconversion and HBV-DNA detectable in the serum (>2000 IU/mL); Acute hepatitis: ≥3-fold increase in serum AST that exceeded the reference range; R-CHOP disruption: premature termination of immune-chemotherapy or delay ≥ 7 days between immune-chemotherapy cycles or any modification of dose density/intensity. In the 6-month LAM cohort and 18-month LAM cohort HBV monitoring consisted in monthly ALT and HBsAg analysis and 3-monthly HBV-DNA analysis for 12 months after prophylaxis end. In the pre-emptive cohort HBV monitoring consisted in monthly ALT and HBsAg analysis and throughout 16 months after.

P138

VERY LONG RESPONSES IN PATIENTS AFFECTED BY FOLLICULAR LYMPHOMA: ACHIEVING THE CURE?

G.M. Assanto, M. Salvatori, P. Musiu, C. Luise, G. Lapietra, L. Pappalardo, G. Annechini, G.M. D'Elia, M. Martelli, I. Del Giudice, A. Pulsoni

Hematology, Department of Translational and Precision Medicine, Sapienza University of Rome, Italy

Follicular lymphoma (FL), despite prolonged survival and high response rates, is still considered an incurable disease. Nevertheless, a minority of patients achieves very long progression free survival (PFS). We conducted a retrospective single-institution analysis on FL patients with PFS longer than 10 years from the last treatment (very long responders - VLR), trying to identify common strategies and clinical features. We evaluated 99 pts out of about 800 FLs, collected across twenty years (1992-2012), that became VLRs, after first (n= 71) or further lines of treatment (n= 28). Median follow-up was 169 months (range 120-303). No distinctive clinical features characterized this cohort of VLRs (Table 1A). Low-risk FLIPI and FLIPI2 patients were 49.5 % (49/99) and 52.5% (52/99) of the cases, intermediate-risk were 35.4% (35/99) and 37.4% (37/96), high-risk 15.1% (15/99) and 10.1% (10/99), respectively. Of VLR after front-line treatment, 31 (43.7%) received immune-chemotherapy (mostly R-CHOP), 22 (31%) chemotherapy alone, 2 (2.8%) rituximab alone; sixteen (22.5%) with early-stage disease were treated with radiotherapy alone (Table1B). x

Table 1. Clinical and treatment features of Very Long Responders (VLR) patients.

IA

Patients Characteristics		Absolute Number or median value	% or Range
Age at diagnosis(years)		53(32)	20-70
Ki-67%		30(0)	15-70
Sex	Male	51	51.5%
	Female	48	48.5%
Grading	1	31	31.3%
	2	54	54.6%
	3A	14	14.1%
Ann Arbor Stage	I	17	17.2%
	II	11	11.1%
	III	19	19.2%
	IV	52	52.5%
B Symptoms	Yes	2	2.1%
BULKY Disease	Yes	8	8.4% %
Lymphocytosis	Yes	3	3.1%
BM Involvement	Yes	44	45.8%
β2 Microglobulin	Above range	15	27.8%
LDH	Above range	22	21.8%
FLIPI	Low Risk	49	49.5%
	Intermediate	35	35.4%
	Risk		
	High Risk	15	15.1%
FLIPI2	Low Risk	52	52.5%
	Intermediate	37	37.4%
	Risk		
	High Risk	10	10.1%

IB

Patients achieving 10 -year PFS after first line of treatment (n=71)	Response after line	CR	57	80%
		PR	13	18.3%
		SD	2	2.8%
	Maintenance/ consolidation	Radiotherapy	3	4.2%
		Rituximab	8	8%
		Ibrutumomab tiuxetan	3	3.08%
	I Line Therapy	R-Bendamustine	1	1.4%
		R-CVP	3	4.2%
		CHOP	16	22.5%
		R-CHOP	20	28.2%
		Purine Analog	6	8.5%
		R-Purine analog	7	9.9%
		Radiotherapy	16	22.5%
		Rituximab alone	2	2.8%
Patients achieving 10 -year PFS after at least two lines of treatment (n=28)	Response after last treatment line	CR	21	75%
		PR	7	25%
		SD/PD	0	0.0%
	II-further line therapy	Radiotherapy	3	10%
		HD+ASCT	7	26%
		Chemo-Immunotherapy	15	54%
	Allo -SCT after third line		3	10%
	Maintenance/ Consolidation (After I Line)	Rituximab	2	7%
		Other agents	2	7%
		Ibrutumomab tiuxetan	1	3.5%
	I Line Therapy	Radiotherapy	2	7%
		R-CVP	2	7%
		CHOP	7	25%
		R-CHOP	8	28%
		Purine Analog	3	11%
		R-Purine analog	3	11%
		Radiotherapy	4	13.5%
		Rituximab alone	1	3.5%

Legend: IA baseline characteristics of the whole cohort; IB treatment characteristics of patients achieving a very long response either a First Line treatment or after second or subsequent line of therapy. BM, Bone Marrow; LDH, Lactate dehydrogenase; CR, Complete Response; PR, Partial Response; SD, Stable Disease; R, Rituximab; CVP, Vincristine, Cyclophosphamide, Prednisone; CHOP, Vincristine, Adriblastine, Cyclophosphamide, Prednisone; HD+ASCT, High-dose chemotherapy regimen followed by autologous stem cell transplantation; allo-SCT, allogeneic stem cell transplantation

Of VLRs patients after further lines of therapy, 6 received autologous stem cell transplantation; 15 other immune-chemotherapy, 2 radiotherapy, 3 underwent allogeneic stem cell transplantation (after the fourth line), 2 achieved VLR after the fifth line. A higher proportion of FL achieved the "cure" after chemo-immunotherapy received in first-line than in subsequent line of treatment (82% *vs* 57%, p 0.036); similarly, patients obtaining CR exhibit a higher probability to be cured after first-line (77% *vs* 65% p 0.001). In our cohort, due to the historical collection of these cases, the outcome was not strictly treatment-dependent and it was achievable within any stage, histology subtype and FLIPI risk category. In conclusion, a subset of FL patients can achieve a "cure" of their disease. Long-term follow-up of trials combining PET assessment, reliable MRD monitoring and lymphoma-associated mutations could allow to define a better risk stratification for outcome prediction, which could also identify upfront patients candidate to be "cured". We suggest that in a near future, in a subset of young and fit patients with FL, the treatment strategy could move from disease control and treatment of symptomatic disease to a curative approach.

P139

SINGLE CENTER EXPERIENCE OF DA-EPOCH AS FRONTLINE TREATMENT FOR AGGRESSIVE DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL)

G. Francia[1], E. Montanari[1], A. Todiere[2], C. Salvetti[2], F. Guolo[1,2], M. Schirru[1], E. Fioreibello[1], F. Santoro[1], F. Ballerini[2], R.M. Lemoli[1,2]

[1]Clinic of Hematology, Department of Internal Medicine (DiMI), University of Genoa, Genoa, Italy; [2]Department of Oncology and Hematology (DIPOE), IRCCS Ospedale Policlinico San Martino, Genoa, Italy

Background: Diffuse Large B-cell Lymphoma (DLBCL) is the most frequent high-grade lymphoma. Unfortunately, only 60% of DLBCL can be cured with standard therapy. Indeed, DLBCL is a heterogeneous disease, with some characteristics of aggressiveness, such as mutation of c-MYC, BCL2 or BCL6 (identifying double or triple hit lymphoma), elevated proliferation index (i.e. Ki67), ABC type and high IPI score that are associated with poor prognosis. CALGB 503 randomized study did not show a significant survival advantage of R-DA-EPOCH as compared to conventional R-CHOP in DLBCL, but the patients enrolled showed favorable prognostic features. Here, we aimed to identify subgroups of patients with features of aggressiveness that may benefit from a more intensive regimen.

Methods: We have retrospectively analyzed the outcome of 40 patients affected by DLBCL and treated in first line with R-DA EPOCH from 2016 to 2021. The median age was 62 years (from 31 to 74 years) and the median FUP was 21 months. 37% of patients had more than 65 years, while 67,5% had a ki67>80% (32% ki67>90%), 55% were ABC type and 55% had an IPI score > 3. Only 2 patients had triple hit lymphoma.

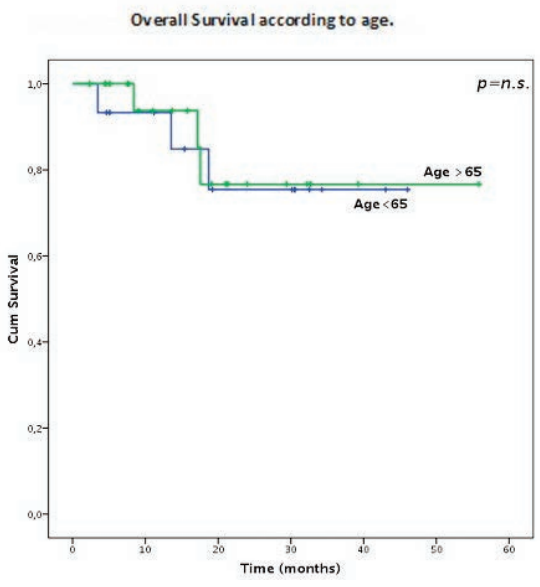


Figure 1.

Results: Therapy was overall very well tolerated without significant adverse events, also among older patients, and most patients were able

to proceed with the scheduled incremental dose. The (CRR) after 6 cycles was 75% and the OS and PFS at 2 years were 76.4% and 71.2%, respectively. No differences in OS were seen according to age (2-year OS of 76.7% *vs* 75.4%, for patients aged more or less than 65 years, respectively, p=0.82, Figure 1), elevated IPI score (2-year OS of 85.7% and 70.9%, for patients with IPI I-II and III-IV, respectively, p=0.281), ABC type DLBCL (2-year OS 80.4% *vs* 64% for ABC and GC cell type, respectively, p= 0.543) and very high ki67 (2 year OS 77% *vs* 66.7% for patients with ki67 higher or lower than 90%, p=0.925).

Discussion and conclusions: Our data showed that R-DA-EPOCH is very well tolerated, also among elderly patients, and results in a favorable CRR, despite the unfavorable characteristics of our cohort. Specifically, in our experience there was no impact on CRR or OS from the classical adverse prognostic features, such as ABC as cell of origin, higher IPI and older age. Thus, R DA EPOCH is a good backbone chemotherapy for patients with aggressive DLBCL, which may be further improved in the future with the inclusion of novel targeted agents.

P140

SYNCHRONOUS TUMORS AND INCIDENTAL LYMPHOMAS

R. Malafronte[1], F. Campana[1], F. Bellisario[1], E. Alma[1], E. Maiolo[1], S. Bellesi[1], S. Hohaus[1,2], F. D'Alò[1,2]

[1]Dipartimento di Diagnostica per Immagini, Radioterapia Oncologica ed Ematologia, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Roma; [2]Dipartimento di Scienza radiologiche ed ematologiche, Università Cattolica del Sacro Cuore, Roma, Italy

It is not uncommon during the staging of a neoplasia to diagnose an associate lymphoma or, vice versa, to discover an associate solid tumor during the staging of lymphoma. The exact incidence of such condition, designed as "synchronous tumor" or "incidental lymphoma" is not well established, but has a great clinical and biological relevance. Two tumors that are diagnosed contemporarily could share common genetic background and environmental risk factors, and could influence each other by conditioning the tumor microenvironment and the local cytokine milieu. To define the exact incidence of such event, we conducted a retrospective monocentric study about 2020 patients newly diagnosed with lymphoma in our Center from January 2014 to December 2021.

We considered synchronous tumors those diagnosed during the staging procedures of lymphoma and those radiologically present at the time of lymphoma diagnosis but biopsied at the end of treatment in sites not responding to lymphoma-directed therapy. Similarly, we defined incidental lymphoma those diagnosed during the primary staging of a solid cancer or at the end of treatment through the biopsy of a tissue not responding to antineoplastic therapy. We identified 80 cases of synchronous tumors/incidental lymphomas (male 38, female 42, median age 69, range 29-92), with an incidence of 3.96% of the study population. Lymphoma histology subtypes were: 28 DLBCL (35%), 18 FL (22.5%), 11 MZL (13.75%), 6 SLL (7.5%), 4 HL (5%), 3 MCL (3.75%), 2 BL (2.5%), 2 PTCL (2.5%), 2 ALCL (2.5%), 4 others (5%). Synchronous cancers were: 17 colon/rectal (21.25%), 15 breast (18.75%), 9 lung (11.25%), 4 prostate (5%) 4 renal cell (5%), 4 urothelial (5%), 4 endometrial (5%), 3 gastric (3.75%), 3 pancreatic (3.75%), 2 hematological (2.5%), 2 GIST (2.5%), 13 others (16.25%). Lymphoma was at early stage (I-II) in 16 patients and in advanced stage (III-IV) in 64 patients. Thirty-two patients had lymphoma and solid cancer involving the same organ, while 23 patients had lymphoma involving nodes proximal to solid cancer. mFourteen patients were treated only for lymphoma, 21 patients only for solid tumor, 43 patients were treated for both. Primary treatment was lymphoma-directed in 36 patients and cancer-directed in 42 patients.

In conclusion, almost 4% of lymphoma patients are carrier of a synchronous tumor at diagnosis. A multidisciplinary approach is needed both in disease staging and in treatment planning for a more personalized medicine.

P141

CAR-T ACTIVITY IN LIGURIA IN 2021. PERFORMANCE AND COMPLIANCE WITH EXPECTED NEEDS

A.M. Raiola[1], C. Ghiggi[1], M. Gambella[1], T. Calzamiglia[2], M. Cavaliere[3], R. Tassara[3], R. Goretti[4], F. Ballerini[5], M. Scudeletti[6], F. Olcese[7], S. Beltramini[8], A. Bo[1], S. Giuffrida[9], E. Angelucci[1]

[1]Ematologia e terapie cellulari, IRCCS Ospedale Policlinico San Martino, ASL3; [2]Ematologia, Stabilimento Ospedaliero di Sanremo, ASL1; [3]Medicina Interna 1, Ospedale San Paolo, ASL2; [4]Medicina Interna 1, Ospedale Santa Corona, ASL2; [5]Clinica Ematologica, IRCCS Ospedale Policlinico San Martino, ASL3; [6]Medicina Interna, Ospedale Sestri Levante, ASL4; [7]Oncologia, Ospedale S. Andrea, ASL5; [8]Farmacia, IRCCS Ospedale Policlinico San Martino, ASL3; [9]. IRCCS Ospedale Policlinico San Martino, ASL3

Background: CAR-T therapy for aggressive B cell lymphomas (a-BCLs) was released in Italy in August 2019 for patients (pts) up to 70-year-old. Despite SARS-CoV-2 pandemic, limited numbers of such procedures performed in Italy raised concern on its affordability in the real-world setting. In Liguria district CAR-T has become available since Sept 1st, 2020 (qualification process completed on Feb 5, 2020) and 1st treatment was performed in October. To verify regional and transplant program performance and effectiveness, we compared treatment numbers provided to Liguria residents to the expected number requiring this approach.

Methods: ISTAT 2020 data has been used for the Italian and Liguria population. Aggressive BCLs incidence has been calculated using most recent epidemiology data in western countries in up 70-yrs-old pts. Number of pts approaching 3rd line of therapy has been calculated from most recent evidence including recent therapeutic approaches.

Results: *Expected*. By ISTAT data Italian population in 2020 was 59,236,213 and in Region Liguria 1,518,495. In 2020, 13,200 and 338 new cases of non-Hodgkin lymphomas were diagnosed in Italy and Liguria, respectively (AIOM-Airtum. I numeri del cancro in Italia 2021). Roughly 25% were aggressive a-BCLs, implying 74 new cases/year. Based on unmodified incidence in the last year and median age (Blood 2010; 116: 3724) we expect 48-49 new cases/year of a-BCL up to 70-yrs-old, in our area. By standard chemo-immunotherapy more than 50% can be cured (N Engl J Med 2021; 384: 842-58). It follows that 20-22 pts/year approach salvage 2nd line treatment, which can potentially cure 25-30% (N Engl J Med 2021; 384; 842-58). Consequently, in Liguria, 15-16 pts/year up to 70-yrs-old can require further therapies.

Evaluated. In 2021, 16 resident pts affected by a-BCLs were evaluated for CAR-T; About regional distribution 3 pts were from the west area, 2 from the middle west, 7 from the central including Genova city, 2 from the middle east, 2 from the east. One presented exclusion criteria and 2 had rapidly progressive lymphoma not permitting further treatment.

Treated. Overall, we infused 13 pts with a-BCL (11 Diffuse Large B-cell lymphoma and 2 primary mediastinal B lymphoma). Up today 8 (63%) are alive and 5 (38%) in continuous complete remission.

Conclusion: Regional health care system and San Martino Transplant program, despite SARS-CoV-2 pandemic, provided CAR-T therapy to nearly all pts requiring this innovative approach.

P142

PROGNOSTIC ROLE OF 18F-FDG PET/CT TEXTURE IN PATIENTS WITH BULKY MEDIASTINAL CLASSICAL HODGKIN LYMPHOMA

M. Palazzo[1,2], E. Abenavoli[3], I. Romano[1,2], M. Ciceri[1,2], L. Nassi[2], F. Mungai[4], V. Berti[5], A.M. Vannucchi[1,2,6], B. Puccini[2]

[1]Department of Experimental and Clinical Medicine, University of Florence; [2]Hematology Department, Azienda Ospedaliero-Universitaria Careggi; [3]Department of Nuclear Medicine, Azienda Ospedaliero-Universitaria Careggi; [4]Department of Emergency Radiology, Azienda Ospedaliero-Universitaria Careggi; [5]Nuclear Medicine Unit, Department of Experimental and Clinical Biomedical Sciences, University of Florence; [6]CRIMM, Centro di Ricerca e Innovazione per le Malattie Mieloproliferative, Azienda Ospedaliero-Universitaria Careggi, Italy

Introduction: The prognostic value of mediastinal bulky disease in classical Hodgkin lymphoma (cHL) is controversial. To date, no clinical characteristics at baseline have been proved as a predictor of chemo-refractoriness (R) to first-line therapy. The aim of this study was to evaluate whether specific 18F-FDG PET/CT radiomic features at baseline may predict R.

Methods: We retrospectively collected data of 69 cHL pts with bulky disease (defined as greater tumor lesion at least 5 cm), treated at our Institution from 2010 to 2021. Lesions were delineated using an automated preselection of FDG-avid structures (SUV≥2.5) and radiomic PET/CT features were measured with LIFEX software. R was defined as a positive interim or end-of-treatment PET/CT or an early relapse within one year from the end of therapy. To identify the prognostic indicators for R, Kaplan Meier univariate and Cox regression multivariate analysis were performed using only continuous variables with AUC greater than 70% at ROC curves.

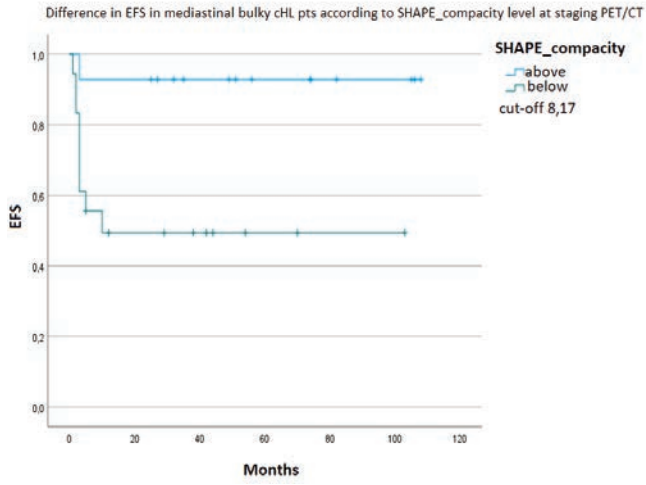


Figure 1.

Results: All the pts underwent PET/CT at staging: 31 were unfavourable early-stage and were treated with 4 ABVD cycles followed by radiotherapy; 38 were advanced-stage and received 6 ABVD cycles. 14 pts (11 advanced and 3 unfavourable early-stage) were refractory to front-line therapy and proceeded to BeGEV escalation. Among radiomic parameters, extracted from staging PET/CT, SUVmean, GLRLM_HGRE, GLRLM_SRHGE, GLRLM_LRHGE, NGLDM_Contrast, SHAPE_compacity and GLRLM_SRHGEct exhibited a significant predictive power in Mann-Whitney test and then at discriminant analysis, therefore were selected for the univariate and multivariate analysis. Kaplan Meier curves showed that NGLDM_Contrast and SHAPE_compacity were significantly correlated with EFS, considered as the time from diagnosis to R; the Cox Regression analysis showed only the SHAPE_compacity as predictive of R (p=0.012; HR:9.19, 95%CI 1.61-52.22). Considering only advanced-stage pts, SHAPE_compacity was confirmed both in univariate and multivariate, as independent predictor (p=0,05) of R and EFS (Figure 1), with a positive predictive value of 90% and a negative predictive value of 95%, 90% sensitivity and 95% specificity.

Conclusion: Our study showed that specific texture indices are associated with a higher risk of R to front-line therapy in advanced-stage bulky cHL pts and may be used to predict chemo-refractoriness at diagnosis. These results are promising but ought to be validated in a larger, multicentric cohort.

P143

LONG-TERM EFFICACY OF PD1 INHIBITOR THERAPY IN HODGKIN LYMPHOMA WITH AND WITHOUT HEMATOPOIETIC STEM CELLS TRANSPLANT. RETROSPECTIVE ANALYSIS OF THE RETE EMATOLOGICA PUGLIESE

F. Gaudio[1], G. Loseto[2], V. Bozzoli[3], P.R. Scalzulli[4], A.M. Mazzone[5], L. Tonialini[6], V. Fesce[7], G. Quintana[8], G. De santis[9], P. Masciopinto[10], E. Arcuti[10], F. Clemente[2], S. Scardino[3], G. Tarantini[9], D. Pastore[8], L. Melillo[7], V. Pavone[6], P. Mazza[5], A.M. Carella[4], N. Cascavilla[4], N. Di Renzo[3], A. Guarini[2], P. Musto[1,10]

[1]Unit of Hematology and Stem Cell Transplantation, AOUC Policlinico, Bari; [2]Hematology Unit, "Giovanni Paolo II" IRCCS Cancer Institute Oncology Hospital, Bari; [3]Hematology and Stem Cell Transplant Unit, "Vito Fazzi" Hospital, Lecce; [4]Hematology Unit, IRCCS "Casa Sollievo della Sofferenza", S. Giovanni Rotondo (FG); [5]Hematology Unit, Department of Hematology-Oncology, "Moscati" Hospital, Taranto; [6]Hematology and Transplant Unit, "Cardinal Panico" Hospital, Tricase (LE); [7]Hematology Unit, Azienda Ospedaliero Universitaria-Ospedali Riuniti, Foggia; [8]Hematology Unit, "Perrino" Hospital, Brindisi; [9]Hematology Unit, "Dimiccoli" Hospital, Barletta (BAT); [10]Department of Emergency and Organ Transplantation, "Aldo Moro" University, Bari, Italy

Checkpoint inhibitors have significantly changed the prognosis of patients with relapsing refractory (R/R) Hodgkin lymphoma (HL), demonstrating exceptional results in heavily pretreated patients. Long-term efficacy of anti-PD1 therapy and the need for a consolidation with autologous/allogenic haematopoietic stem cell transplantation (HSCT) remain unclear in patients with R/R HL.

Materials and Methods: We performed a retrospective, multicenter analysis of 66 patients enrolled by the Rete Ematologica Pugliese (REP) with RR HL who received PD-1 inhibitors in a non-trial, real-life setting. Forty-three patients (65%) were treated with nivolumab and 23 (35%) with pembrolizumab. The median number of treatments attempted prior to PD-1 inhibitor therapy was 4 (range, 3 to 7).

Results: The overall response rate (ORR) to PD-1 inhibitor therapy was 70%: 47% complete remission (CR) and 23% partial remission (PR). Twenty-four immune-related adverse events were documented;Toxicity resolved in all patients and there were no deaths attributed to checkpoint inhibitor therapy. After PD-1 inhibitor treatment, twenty-two patients (33%) relapsed or progressed. The overall survival (OS) and progression free survival (PFS) at five years were 65% and 54%, respectively. Fifteen patients who responded (*i.e.* in CR or PR) to PD-1 inhibitor therapy underwent consolidation with HSCT (4 autologous and 11 allogeneic). Among responding patients, 3-year PFS was 92% (Figure 1) for those who underwent subsequent HSCT, whereas it was 65% for the 31 patients who were not consolidated with HSCT (p=0.04). There was no difference in OS between the two groups (100% *vs* 96%). No relevant transplant-related toxicities were observed. After a median follow-up of

26 months, fifty-four patients (82%) are alive and 12 (18%) died. The cause of death was attributed to disease progression in 9 patients, and sepsis in 3 patients.

Conclusions: In our real life experience, approximately half of patients with RR HL treated with anti-PD1 therapy achieved CR and in a further quarter PR occurred. Patients non achieving CR, however, rapidly progressed. Patients undergoing consolidation with HSCT after anti-PD1 therapy experienced prolonged PFS compared with non-transplanted ones, but this difference did not translate into a benefit in OS. This information should be considered when evaluating the risk/benefit ratio of HSCT after anti-PD1 therapy in RR HL.

P144

ALTERED AMINO ACID HOMEOSTASIS IN PERIPHERAL BLOOD OF HODGKIN LYMPHOMA MAY ELICIT AN ADAPTIVE RESPONSE VIA UPREGULATION OF UFMYLATION

A. Romano[1], G. Scandura[1], D. Tibullo[1], A.M. Amorini, F. Puglisi[1], E. La Spina[1], A. Barbato[1], D. Cambria[1], N.L. Parrinello[1], C. Giallongo[1], A. Chiarenza[1], G. Motta[1], A.L. Caruso[1], V. Simeon[2], C. Tripodo[3], C. Cerchione[5], G. Martinelli[5], G. Simonetti[5], S. Pileri[4], P. Musto[2] F. Di Raimondo[1]

[1]Division of Hematology, AOU "Policlinico - Vittorio Emanuele", University of Catania, Catania, Italy; [2]Laboratory of Pre-clinical and Translational Research IRCCS - CROB Referral Cancer Center of Basilicata Rionero in Vulture (PZ); [3]Tumor Immunology Unit, Department of Health Science, University of Palermo, Palermo, Italy; [4]Unità di Diagnosi Emolinfopatologica, IEO, Milano, Italy

We tested the adaptive response of Hodgkin`s Lymphoma (HL) cells to arginine (arg) and tryptophan (trp) deprivation, as consequence of expansion of high-density neutrophils releasing the respective amino acid degrading enzyme Arg-1 and IDO-1 in 64 newly diagnosed patients.

Three human HL cell lines (L428, L540 and KM-H2) were individually cultured for 48 hours with customized complete media or lacking Trp (W0) or Arg (R0) for global metabolomic analysis, and transcriptome profiling by RNA-seq.

Results: peripheral blood of HL patients showed dysregulated distribution of aminoacids, with significant increase of arginine, tryptophan, kynurenine, glutamate (specular to reduced amounts in the lymph node) and reduction of glutamine, asparagine, histidine, threonine, alanine, valine and methionine (Table 1), confirming *in vivo* the relevance of amino acid deprivation in HL.

In vitro, the effect on the cellular metabolome depended largely on the cell type and which amino acid was removed. Removal of trp and arg from L428 and KMH2 resulted in changes in the specific-amino acid related metabolites, but L540 cells remained largely resistant to those changes. In arg lack, L540 and L428 cells increased levels of long chain saturated fatty acids, suggesting that specific-amino acid deficiency leads to an increase in uptake of free fatty acids from the media to maintain membrane integrity. In arg deprived KMH2 we found increased pyruvate, associated with a metabolic rewiring to maintain mitochondrial integrity in response to increased oxidative stress, while no significant changes were observed in tryptophan deprivation. Gene set enrichment analysis (GSEA) showed deep transcriptome rearrangements in all cell lines tested, with down-regulation of CCNI2, LCROL, MKI67, NCAPG, PEX10 and UFSP2, upon both arg and trp deprivation, suggesting that increased ribosome stalling following amino acid starvation can engage the UFMylation pathway, an adaptive response never investigated before in HL. Taken together, we found that in HL there is a dysregulation in amino acid metabolism as consequence of the complex crosstalk between neoplastic cells and their microenvironment.

Table 1. Aminoacid quantification in peripheral blood of newly-diagnosed HL patients.

Aminoacid	advanced HL (N=64) Mean (ng/mL)	advanced HL (N=64) Standard deviation	healthy subjects (N=240) Mean (ng/mL)	healthy subjects (N=240) Standard deviation	p-value
Arginine	83.3	49.63	31.1	10.5	*<0.0001*
Tryptophan	127.8	53.72	69.7	12.9	*<0.0001*
Kynurenine	2.2	0.75	1.79	0.56	*0.0008*
Glutammate	299.5	237.62	179.9	57.6	*0.0002*
Phenylanine	105.6	71.57	64.4	13.8	*<0.0001*
Serine	130.3	60.07	68.7	23.3	*<0.0001*
Glutamine	216.5	148.76	368.9	77.15	*<0.0001*
Histidine	47.3	27.32	74.46	19.6	*<0.0001*
Asparagine	43.8	29.57	65.6	13.9	*<0.0001*
Threonine	94.8	48.57	129.7	26.9	*<0.0001*
Citrate	14.1	6.93	27.04	7.6	*<0.0001*
Alanine	299.8	124.52	383.7	101.7	*0.0001*
S-adenosylhomocysteine	21.1	9.64	25.6	10.6	*0.01*
Valine	190.8	70.31	274.2	62.3	*<0.0001*
Methionine	18.8	8.59	24.6	5.9	*<0.0001*
Isoleucine	67.4	24.06	73.2	18.4	0.13
Leucine	131.3	48.17	139.1	30.2	0.29
Aspartate	61.1	29.03	53.51	17.6	0.08
Glycine	262.0	117.14	226.9	82.5	0.06
Taurine	103.0	58.54	97.5	23.1	0.49
Tyrosine	30.2	12.20	25.6	21.05	0.13

P145

VALIDATION OF THE PROGNOSTIC VALUE OF LYMPHOCYTE/MONOCYTE RATIO IN CLASSICAL HODGKIN'S LYMPHOMA: A RETROSPECTIVE OVERVIEW IN THE PET-GUIDED ERA

A. Cellini[1], C.A. Cavarretta[1], F. Angotzi[1], S. Pravato[1], M. Pizzi[2], M. Gregianin[3], F. Crimì[4], S. Vio[4], F. Piazza[1], L. Trentin[1], A. Visentin[1]

[1]Hematology and Clinical Immunology Unit, Department of Medicine, University of Padua; [2]Surgical Pathology and Cytopathology Unit, Department of Medicine, University of Padua; [3]Nuclear Medicine Unit, Istituto Oncologico Veneto IOV-IRCCS; [4]Institute of Radiology, Department of Medicine, University of Padua, Italy

Background: Current therapy protocols for Hodgkin's Lymphoma (HL) integrate interim PET-CT scans (iPET) to tailor treatment. iPET positivity, as well as disease refractoriness or relapse, are still however associated with worse outcomes. No baseline characteristics have been identified as reliable predictors for worse outcomes, as classical prognostic scores have lost their significance in the PET-guided era. Low lymphocyte to monocyte ratio (LMR) has already been investigated as a prognostic factor in HL and its usage could help better identify patients that might benefit from monoclonal antibody based frontline therapies.

Aim: The aim of this study was to identify potential predictors of worse overall survival outcomes in patients affected by HL treated with a PET-guided chemotherapeutic approach.

Methods: We included HL patients diagnosed at the University Hospital of Padova between 2004 and 2020. All patients were staged with 18-FDG PET-CT and received PET-guided escalated ABVD therapy. iPET positivity was defined as a Deauville score ≥4 and low LMR as ≤2.1. Event-free survival (EFS) was defined as time from diagnosis to iPET positivity, relapse, or death by any cause.

Results: Of the 261 patients analyzed, 101 (39%) had early-stage and 160 (61%) had advanced-stage (≥IIB) HL. After a median follow up of 59 months the 5-year OS, PFS and EFS for the whole population were

93%, 74%, 66%, respectively. *44* (17%) patients were iPET-positive and their 5-year OS and PFS were 82% and 42%, respectively, and were significantly different from those of the iPET negative patients (96% and 80%; p<0.001). In univariate and multivariate analysis only stage ≥III (HR 1.87; 1.12–3.11) and low LMR (HR 1.85; 1.02–3.35) correlated with a shorter EFS. Considering these variables 53%, 39%, 8% of patients had of 0, 1 or 2 risk factors, respectively. The 5-year OS, PFS and EFS decreased progressively among the 3 groups (OS: 99%, 89%, 79%; PFS: 84%, 66%, 46%; EFS: 77%, 58%, 39%; p<0.01) [Figure 1].

Conclusion: We herein confirmed the reliability of LMR as a prognostic factor and that its incorporation into prognostic scores may help to better identify patients that might benefit from frontline brentuximab or nivolumab-based therapies.

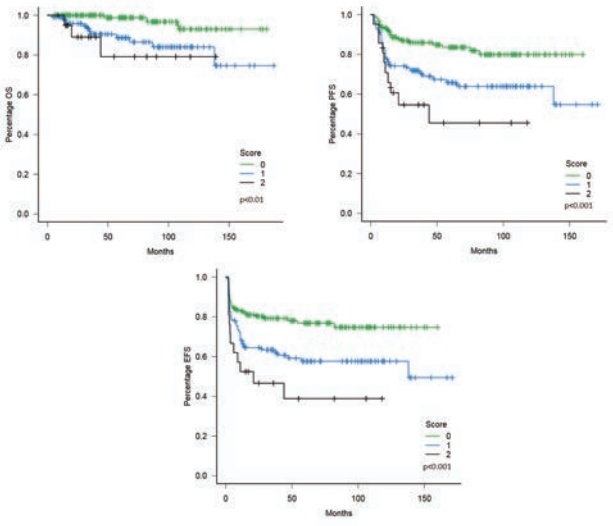


Figure 1.

P146

ANTI-PD1 THERAPY EXPOSURE PRIOR TO HAPLOIDENTICAL ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION LEADS TO HIGHLY FAVOURABLE OUTCOMES IN RELAPSED/REFRACTORY HODGKIN LYMPHOMA: A SINGLE-CENTER EXPERIENCE

A.M.E. Maraglino[1,2], S. Sammassimo[1], V. Amato[1], A. Vanazzi[1], S. Viviani[1], T. Radice[1], A. Agazzi[1], F. Gigli[1], R. Pastano[1], C. Tarella[1], E. Derenzini[1,3]

[1]Divisione di Oncoematologia, IEO Istituto Europeo di Oncologia IRCCS; [2]Sezione di Ematologia, Dipartimento di Scienze Radiologiche ed Ematologiche, Università Cattolica del Sacro Cuore; [3]Dipartimento di Scienze della Salute, Università di Milano, Italy

Background: Allogeneic Hematopoietic Stem Cell Transplantation (allo-SCT) is a potentially curative option in patients (pts) with Relapse/Refractory classical Hodgkin lymphoma (R/R cHL) after autologous stem cell transplant (ASCT). Recent studies suggest that pts undergoing allo-SCT after prior exposure to anti-PD1 directed therapies may experience improved outcomes.

Methods: We investigated the impact of prior therapies on disease status at the time of allo-SCT and subsequent outcome in pts with R/R cHL. We retrospectively reviewed clinical data of 29 consecutive R/R cHL patients undergoing allo-SCT at our Institution between 2003 to 2020.

Results: After a median follow up of 7,5 years (range 2-18), 20 pts (69%) are in continuous complete remission (cCR) while 9 (31%) pts progressed or relapsed after allo-SCT. Median age at allo-SCT was 30 years (range 20-44). 17 pts (60%) were male. Median time from diagnosis to allo-SCT was 3 years (range 1-13), with a median of 5 systemic therapies (range 4-8) prior to allo-SCT, which included ASCT in all pts. Pts were stratified in subgroups, depending on the type of therapies received during disease course prior to allo-SCT: Group 1 [chemotherapy (CHT) only (N=17, 60%)], Group 2 [CHT + Brentuximab Vedotin (N=6, 20%)], Group 3 [any exposure to anti-PD1 directed therapy prior to allo-SCT (N=6, 20%)]. 17 pts (60%) received haploidentical allo-SCT (35% pts in Group 1, 84% in Group 2, 100% in Group 3). 23 pts (80%) received reduced intensity conditioning (RIC). Notably, complete response (CR) prior to allo-SCT was obtained in 24% pts in Group 1 (4/17) *vs* 50% in Group 2 (3/6) *vs* 100% in Group 3 (6/6) (p=0.005). In Group 3, 5 of 6 pts achieved CR after CHT bridging following prior anti PD-1 therapy administration. Among known prognostic variables (including disease status at allo-SCT, haplo, RIC), only prior anti-PD1 therapy exposure was associated with outcome following allo-SCT. Notably, 2-year PFS was 100% in Group 3 *vs* 83% in Group 2 *vs* 29% in Group 1 (p=0.04). 15 pts (52%) showed Graft Versus Host Disease of any grade: 10 pts (59%) in Group 1, 1 (17%) in Group 2 and 4 (65%) in Group 3 (p=ns).

Conclusion: These data confirm that any exposure to anti-PD-1 immunotherapy prior to haploidentical allo-SCT results in a highly favorable outcome, suggesting the sequential use of anti PD1 treatment followed by CHT as optimal bridging therapy to allo-SCT in cHL pts relapsing after ASCT.

P147

LONG TERM RESPONDER HODGKIN LYMPHOMA PATIENTS TREATED WITH CHECKPOINT INHIBITORS

V. Stefoni[1,2], B. Casadei[1,2], A. Broccoli[1,2], C. Pellegrini[1], L. Nanni[1,2], A. Morigi[1,2], M. Carella[1,2], G. Lolli[1,2], P.E. Coppola[1,2], G. Bagnato[1,2], M. Gentilini[1,2], G. Gugliotta[1], L. Argnani[2], P.L. Zinzani[1,2]

[1]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli", Bologna, Italy; [2]Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale, Università di Bologna, Bologna, Italy

In recent years, checkpoint blockade with anti-PD1 antibodies demonstrated remarkable efficacy in patients with relapsed/refractory Hodgkin lymphoma (R/R HL). Studies evaluating anti-PD1 therapy in these patients, which account for more than 450 patients in total, showed an overall response rate of around 70% and complete responses (CR) of up to 20%. These results led to the approval of nivolumab and pembrolizumab for R/R HL by FDA in 2016 and 2017, respectively. Despite remarkable immediate efficacy, many questions remain unanswered regarding the long-term efficacy and optimal management of patients with HL treated with anti-PD1, including the duration of treatment and the need for a consolidation with stem cell transplantation.

R/R HL patients included in our study received pembrolizumab (n=1) and nivolumab (n=5) both in international experimental clinical trials, through the compassionate use program, and through the 5% AIFA fund. The objective of this post-hoc analysis is to evaluate the sub-sample of patients who have obtained a response lasting at least one year, without having received any consolidation (transplantation or other), describing in particular their characteristics and the toxicities occurred even in the long term. All patients received ABVD as first line approach and subsequent autologous transplantation with a median of pred anti-PD1 lines of 6 (range, 5-7). All patients resulted refractory to the last therapy prior to the anti-PD1. Just after the first response assessment patients obtained 4 CR and 2 partial responses. At the final restaging 6 CR were achieved with a median of 47 cycles received (range 18-59). The patient who received 18 cycles discontinued treatment due to pneumonia, but he did not lose the response. Toxicities during treatment were in line with the ones reported in literature. The median duration of response from the

first time of the CR has been ascertained resulted 48.4 months (range 12.5-69.6) (Figure 1). At the latest available follow up all patients were still in CR without any type of consolidation (and only 1 patient deceased due a recurrence of a second malignancy). No long-term toxicities have not yet registered.

We showed that prolonged remissions can be achieved after anti-PD1 discontinuation in patients with CR also without any type of consolidation.

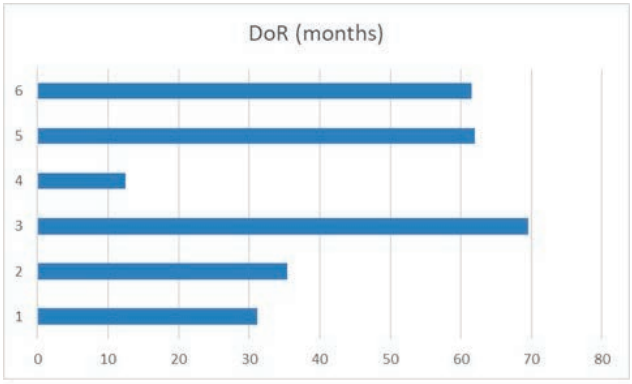


Figure 1.

P148

EARLY DETECTION OF RECURRENCE BY ROUTINE IMAGING SURVEILLANCE IMPROVES THE OUTCOME IN HIGH-RISK HODGKIN LYMPHOMA

N. Pugliese[1], F. Grimaldi[1], M. Picardi[1], R. Della Pepa[1], C. Giordano[1], A. Lucania[2], A. Severino[1], F. Muriano[1], A. D'ambrosio[1], C. Salvatore[3], M. Mascolo[4], A. Rocino[2], F. Pane[1]

[1]Department of Clinical Medicine and Surgery, University of Naples Federico II; [2]Unit of Hematology, Hospital ''Loreto Mare''; [3]Department of Economics, University of Molise; [4]Department of Advanced Biomedical Sciences, Pathology Unit, University of Naples Federico II, Italy

Despite the high complete response (CR) rate to first-line therapy, approximately one-third of patients with advanced stage Hodgkin lymphoma (HL) eventually relapses. In up to 30 -50% of patients, relapses are initially evident only by imaging procedure, however a definitive consensus on the best surveillance approach for high-risk HL patients has not yet been reached. The purpose of this cohort study is to evaluate the long-term outcome, after salvage treatment and autologous stem cell transplantation (ASCT), of high-risk HL patients who relapse under imaging surveillance compared to those who relapse under conventional clinical monitoring. Follow-up procedures within the imaging group involved either FDG-PET/CT or ultrasound plus chest X-Ray. We evaluated a total of 123 high-risk HL patients in first relapse (after remission to first line therapy) discovered either with systematic imaging-based surveillance (Imaging cohort, n= 80) or with standard clinical surveillance (standard cohort, n = 43). The 2-year event free survival (EFS) was significantly longer in the patients of the Imaging cohort with respect to the standard cohort (70% *vs* 37.2%, respectively; p= 0.001) and the rate of complete responses (CR) was higher in the former cohort (CR rate, 68.8% *vs* 41.9%, respectively; p< 0.004). These differences were most likely due to the capability of routine imaging surveillance to identify early onset of clinically silent relapses which show a significantly better EFS at 2 years than the standard follow-up (69.1% *vs* 37.2%, respectively; p< 0.001). Our data indicate that routine imaging follow-up allows a timely administration of salvage therapy to patients with a more limited extension of relapse and, consequently, an EFS improvement.

P149

SERUM TARC CONCENTRATION KINETIC IN CLASSICAL HODGKIN LYMPHOMA DURING FIRST-LINE TREATMENT

I. Romano[1,2], B. Puccini[2], L. Signori[3], M. Palazzo[1,2], M. Ciceri[1,2], M. Zizza[3], G. Coltro[1,2,3], B. Sordi[1,2], F. Pancani[3], E. Galli[1], L. Mannelli[2], A. Bosi[1,2], L. Nassi[2], A.M. Vannucchi[1,2,3]

[1]Department of Experimental and Clinical Medicine, University of Florence; [2]Hematology Department, Azienda Ospedaliero-Universitaria Careggi; [3]CRIMM, Centro di Ricerca e Innovazione per le Malattie Mieloproliferative, Azienda Ospedaliero-Universitaria Careggi, Italy

Introduction: Serum TARC (sTARC) has been proposed as a predictor of response in patients (pts) with classical Hodgkin Lymphoma (HL).In the current study, we analyzed the kinetic of sTARC during first-line treatment, aiming to evaluate its potential predictive value.

Methods: We prospectively collected plasma samples of 43 untreated HL pts from March 2018 and September 2020, stratified according to GHSG risk categories and treated according to a PET-driven strategy. Samples were collected before treatment on day 1 of each ABVD cycle, before radiotherapy in localized stages,on day 1 of each cycle of salvage therapy, including autologous stem cell transplantation, and 1 month after end of treatment (EOT). We excluded 4 stage I pts (because of a low baseline sTARC and a limited sTARC variation during treatment cycles) and 7 pts for missing samples (included 3 PET-2 positive pts); overall evaluable pts were 32. Median age was 32.5 years (17–65),56% pts were male,56% of pts had B-symptoms, and 69% had an advanced stage (IIB, III, IV).Four pts (11%) were refractory, as documented by EOT-PET positivity.

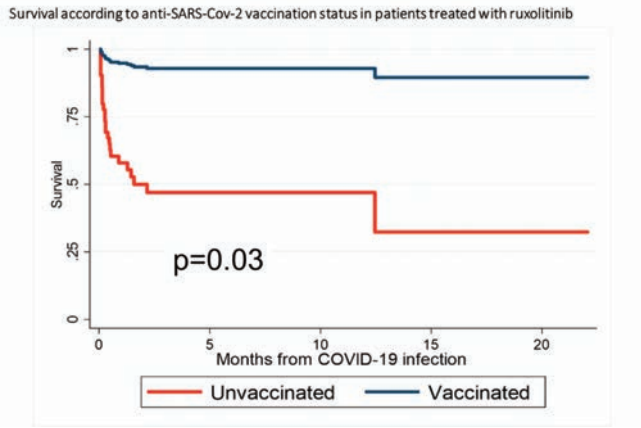


Figure 1.

Results: Median baseline sTARC was 50,605 pg/ml (5,475–183,225). Median sTARC after 2 ABVD cycles (sTARC-2) was 493 pg/ml (97–2,071), with a median logarithmic reduction (logRED) versus baseline of 1.94 (0.73–3.12). A non-statistically significant higher median baseline sTARC level was observed in chemorefractory pts *vs* chemosensitive pts: 95,236 pg/ml (53,502–135,787) and 35,454 (5,475–183,225),respectively (P=.077), while sTARC-2 and the logRED of sTARC-2 were not significantly different between the two groups: 654 pg/ml (97–1,564) *vs* 463 (150–2,071) and 2.1 (1.6–3.1) *vs* 2.0 (-0.7–2.6), respectively. Hence, we evaluated sTARC values after PET-2 and before EOT-PET, and their log variation (logΔ) as compared to sTARC-2: refractory pts showed a remarkable increase of sTARC at the time of relapse, with median sTARC

of 32,202 pg/ml (14,362–71,807) compared to 373 pg/ml (166–1,102) in responding pts at EOT (P=.001).The corresponding logΔ values were -1.5 (-2.9 to -1.1) and 0.1 (-0.3–0.6)(P=.001), respectively (Figure 1).

Conclusion: Our findings show that the kinetic of sTARC variation in stage II-IV HL is correlated with treatment response as assessed by PET. Specifically, an increase of sTARC during treatment after sTARC-2 may predict refractoriness and anticipate the results of EOT-PET. A larger number of pts is mandatory to confirm the role of sTARC monitoring in HL.

Myeloproliferative syndromes

P150

PREDICTORS OF COVID-19 DISEASE AND SURVIVAL TO COVID-19 IN MPN PATIENTS TREATED WITH RUXOLITINIB

F. Palandri[1], D. Bartoletti[1,2], E.M. Elli[3], G. Auteri[1,2], M. Bonifacio[4], G. Benevolo[5], M.M. Trawinska[6], C. Bosi[7], E. Rossi[8,9], M. Tiribelli[10], A. Tieghi[11], A. Iurlo[12], N. Polverelli[13], G. Caocci[14], G. Binotto[15], F. Cavazzini[16], E. Beggiato[17], D. Cilloni[18,19], C. Tatarelli[20], F. Mendicino[21], M. Miglino[22,23], M. Bocchia[24], M. Crugnola[25], C. Mazzoni[1,2], A.D. Romagnoli[1,2], G. Rindone[3], S. Ceglie[9], A. D'Addio[26], B. Garibaldi[27], E. Santoni[4], D. Cattaneo[12], R.M. Lemoli[22,23], M. Krampera[4], A. Cuneo[16], G. Semenzato[15], R. Latagliata[28], E. Abruzzese[6], N. Vianelli[1], M. Cavo[1,2], A. Andriani[29], V. De Stefano[8,9], G.A. Palumbo[30], M. Breccia[31]

[1]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli"; [2]Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale, Università di Bologna; [3]Ospedale San Gerardo, ASST Monza; [4]A.O.U. Integrata Verona; [5]A.O.U. Città della Salute e della Scienza; [6]Ospedale S. Eugenio, Università Tor Vergata; [7]AUSL di Piacenza; [8]Fondazione Policlinico Universitario A. Gemelli IRCCS; [9]Dipartimento di Scienze radiologiche ed ematologiche, Università Cattolica del Sacro Cuore; [10]A.O.U. Integrata di Udine; [11]Azienda USL - IRCCS di Reggio Emilia; [12]Foundation IRCCS Ca' Granda, Ospedale Maggiore Policlinico; [13]ASST Spedali Civili di Brescia; [14]Polo oncologico "A. Businco", Università degli studi di Cagliari; [15]A.O.U. di Padova; [16]A.O.U. Arcispedale S. Anna; [17]Dipartimento di Oncologia, Università di Torino; [18]AOU San Luigi Gonzaga; [19]A.O. Ordine Mauriziano di Torino; [20]A.O.U. Sant'Andrea; [21]Dipartimento di Emato-Oncologia, A.O. Annunziata; [22]IRCCS Policlinico San Martino; [23]Dipartimento di Medicina interna e Specialità mediche, Università di Genova; [24]Policlinico S. Maria alle Scotte, A.O.U. Senese; [25]A.O.U. di Parma; [26]Dipartimento Oncoematologico, AUSL della Romagna; [27]Scuola di Specializzazione in Ematologia, Università degli Studi di Catania; [28]Ospedale Belcolle; [29]Ospedale "Fabrizio Spaziani"; [30]Dipartimento di Scienze Mediche, Chirurgiche e Tecnologie Avanzate "G.F. Ingrassia", Università di Catania; [31]A.O.U. Policlinico Umberto I, Università degli Studi di Roma "La Sapienza", Italy

Ruxolitinib (RUX) use and discontinuation are risk factors for COVID19 infection and COVID19-related death in myelofibrosis (MF) and polycythemia vera (PV) patients (pts). To identify RUX-treated pts at higher risk of COVID19 and assess prognostic factors for overall survival (OS), we used data from the RUX-MF and PV-ARC observational studies including consecutive adult MF (n=815) and PV (n=172) pts, respectively.

At pandemic start, 494 pts (359 MF and 135 PV) were on RUX and were included in this analysis. From Feb20 to Jan22, 66 (13.6%) pts (PV n=11, MF n=55) had a COVID19 infection (asymptomatic, mild, moderate, severe, critical, and fatal in 1.5%, 21.2%, 13.6%, 25.8%, 6.1% and 31.8%, respectively); 42 (63.7%) pts were hospitalized (COVID19-HOSP). Overall, 14, 38 and 14 infections were observed during the 1st (Feb-Jun20), 2nd (Jul20-Jun21) and 3rd (Jul21-Jan22) pandemic wave. Overall, 316/406 evaluable pts (77.8%) received ≥1 dose of Comirnaty vaccine. At COVID19 diagnosis, RUX was reduced in 10 (15.1%) pts and discontinued in 9 (13.6%) pts, comparably in MF and PV. All-grade COVID19 was more frequent in pts with MF (p=0.04), with ≥1 comorbidity (p=0.04) and in unvaccinated pts (p<0.001). COVID19-HOSP pts were more frequently ≥70 yrs (p=0.04) and unvaccinated (p<0.001). Compared to outpatients, COVID19-HOSP pts were more frequently diagnosed during the 1st/2nd wave (64.3%/73.7% *vs* 35.7% in the 3rd wave, p=0.04), had lower median platelet count (p<0.001) and were unvaccinated (p<0.02) at the time of infection. In MF, lack of spleen response (p=0.04), at COVID19 diagnosis was associated to higher risk of

hospitalization. From Feb20, 10 thromboses (8 venous, 2 arterial) were observed, with an IR of 1.8 per 100 pt-yrs. Two venous thromboses were in COVID19 pts (all hospitalized) (IR 10.2 x100 pt-yrs, *vs* 8 in no-COVID19 pts, IR 1.4 x100 pt-yrs, p=0.04). In multivariable analysis, OS to COVID19 was significantly longer in vaccinated pts (HR=0.11, p=0.03) (Figure 1), in non-hospitalized pts (HR=0.19, p=0.03) and in pts <70 yrs (HR=0.39, p=0.03). MF diagnosis and comorbidities emerged as significant predictors for COVID19 infection in RUX-treated pts. Older, unvaccinated pts and MF pts with no spleen response are at higher risk for hospitalization and should be prioritized for antiviral therapy. Vaccine was the most protective factor against COVID-19 disease, hospitalization, and mortality. All RUX-treated pts should be sensitized to adherence to the vaccine program.

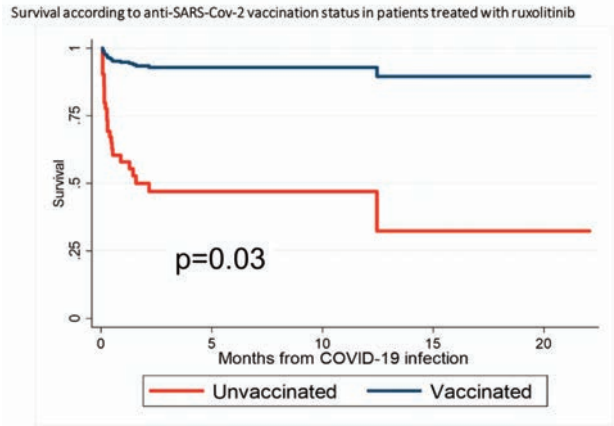


Figure 1.

P151

THE IMPACT OF PACTRINIB ON MYELOFIBROSIS SYMPTOMS IN PATIENTS WITH MODERATE AND SEVERE THROMBOCYTOPENIA: A RETROSPECTIVE ANALYSIS OF PATIENTS IN THE PERSIST-2 STUDY

A. Vannucchi*, J. Palmer, R. Mesa, J-J. Kiladjian, C. Harrison, A. Gerds, P. Bose, S. Oh, R. Rampal, S. Buckley, K. Roman-Torres, A. Craig, J. Mascarenhas, S. Verstovsek

*[1]Center for Research and Innovation of Myeloproliferative Neoplasms – CRIMM, Azienda Ospedaliera Universitaria Careggi, University of Florence; [2]Division of Hematology and Medical Oncology, Mayo Clinic; [3]UT Health San Antonio Cancer Center; [4]Université de Paris, Clinical Investigations Center, Saint-Louis hospital; [5]Guy's and St Thomas' NHS Foundation Trust; [6]Leukemia Program, Department of Hematology and Medical Oncology, Taussig Cancer Institute, Cleveland Clinic Taussig Cancer Institute; [7]Department of Leukemia, MD Anderson Cancer Center; [8]Washington University School of Medicine; [9]Leukemia Service, Department of Medicine, Memorial Sloan Kettering Cancer Institute; [10]CTI BioPharma; [11]Icahn School of Medicine at Mt Sinai;*presenting author*

Objectives: Thrombocytopenia, a hallmark of cytopenic myelofibrosis (MF), is associated with poor survival and reduced quality of life. MF with moderate/severe thrombocytopenia (platelet counts <100x10^9/L, <50x10^9/L) is associated with high symptom burden as measured by the total symptom score (TSS; Mesa R, et al. NCCN 2022). Pacritinib (PAC), a JAK2/IRAK1 inhibitor, was studied in patients with platelet counts ≤100x10^9/L in the PERSIST-2 trial. Unlike registrational studies of other available JAK1/2 inhibitors that used a modified TSS (mTSS) with 'tiredness' excluded, PERSIST-2 included 'tiredness' as part of TSS and reported response rates of 25% for PAC *vs* 14% for best available therapy (BAT), P=0.08. We retrospectively analyzed mTSS in PERSIST-2 and evaluated the impact of PAC and BAT on MF symptoms.

Methods: In PERSIST-2, patients were randomized 1:1:1 to PAC 200mg BID, PAC 400mg QD, or BAT. All patients in the intention-to-treat population randomized ≥22 weeks prior to the end of study were included. The mTSS was calculated as the sum of scores for early satiety, abdominal discomfort, rib pain, night sweats, itching, and bone pain. Response was defined as ≥50% reduction in score at week 24.

Results: Patients receiving PAC 200mg BID (n=74), 400mg QD (n=75), or BAT (n=72) were analyzed. At baseline, 39% had moderate and 46% had severe thrombocytopenia. The TSS response rate with PAC *vs* BAT showed a significant difference using mTSS: 31% *vs* 14%, P=0.008 (Fisher's Exact test). The mTSS response rate was higher for patients treated with PAC 200mg BID *vs* BAT (35% *vs* 14%, P=0.004, Figure 1a). Among patients on BAT, mTSS response rates were modestly higher for patients who did *vs* did not receive ruxolitinib on study prior to week 24 (19% *vs* 10%). Patients receiving PAC 200mg BID experienced greater percentage reductions in individual symptoms at week 24 *vs* BAT (Figure 1b, 1c). For physical function symptoms, severity was reduced more on PAC 200mg BID *vs* BAT (median reduction in tiredness: 30% *vs* 13%, P=0.0261; inactivity: 22% *vs* 7%, P=0.099; Wilcoxon Rank Sum test).

Conclusions: PERSIST-2 demonstrated symptom benefit in patients with moderate / severe thrombocytopenia. The mTSS response (35% reduction from baseline to Week 24) in patients treated with PAC 200mg BID is comparable to that reported for approved JAK1/2 inhibitors in patients with higher platelet counts, suggesting potential for PAC to address symptom burden for patients with cytopenic MF.

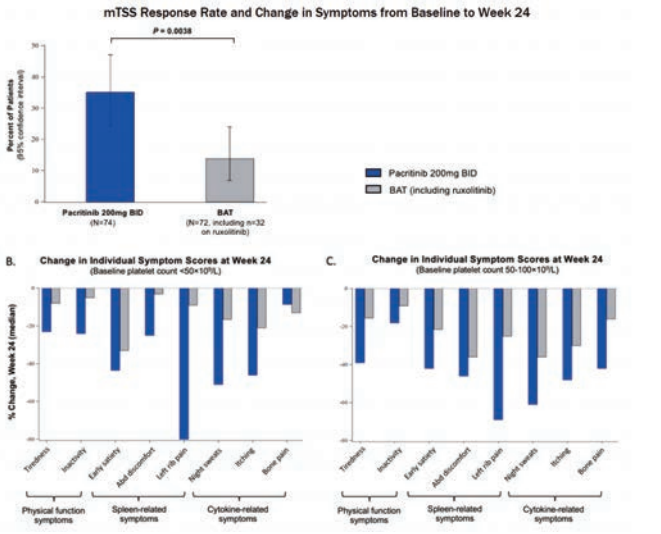


Figure 1 mTSS Response Rate and Change in Symptoms from Baseline to Week 24.png

P152

DISEASE-MODIFYING POTENTIAL OF PELABRESIB DEMONSTRATED BY IMPROVEMENTS IN BONE MARROW FUNCTION AND RESULTING CLINICAL BENEFITS IN PATIENTS WITH MYELOFIBROSIS

A. Vannucchi[1], S. Verstovsek[2], M.E. Salama[3], J. Mascarenhas[4], M. Talpaz[5], R.A. Mesa[6], R.K. Rampal[7], S.T. Oh[8], H. Olteanu[3], A. Chiu[3], D. Chen[3], C.A. Hanson[3], N. Curto-Garcia[9], P. Taverna[10], J. Cui[10], O. Zavidij[10], T.-W. Chang[10], G. Colak[10], C.N. Harrison[9]

[1]Azienda Ospedaliero Universitaria Careggi; [2]University of Texas MD Anderson Cancer Center; [3]Mayo Clinic; [4]Tisch Cancer Institute, Icahn

School of Medicine at Mount Sinai; [5]Rogel Cancer Center, The University of Michigan; [6]Mays Cancer Center, UT Health San Antonio MD Anderson Cancer Center; [7]Memorial Sloan Kettering Cancer Center; [8]Washington University School of Medicine; [9]Guy's and St Thomas' NHS Foundation Trust; [10]Constellation Pharmaceuticals a MorphoSys Company

Myelofibrosis (MF) is characterized by progressive bone marrow (BM) fibrosis (BMF) resulting from aberrant megakaryopoiesis and expression of proinflammatory cytokines. These processes, heavily influenced by BET protein-mediated gene regulation, lead to myeloproliferation and cytopenias. Pelabresib (CPI-0610) is an investigational, selective, oral small-molecule BET inhibitor that can modify the expression of genes involved in NF-κB signaling. Pelabresib is being investigated in MF in the MANIFEST Phase 2 study (NCT02158858).

In Arm 1, pelabresib is given as monotherapy to pts intolerant/refractory to or ineligible for Janus kinase inhibitor (JAKi) treatment; in Arm 2, as 'add-on' to ruxolitinib (RUX) in pts with a suboptimal/lost response; and in Arm 3, combined with RUX in JAKi treatment-naïve pts. To evaluate the effects of pelabresib on BM biology, exploratory analyses were conducted using BM biopsy samples obtained pretreatment and at 24 wks post treatment. Central pathology review of reticulin staining was conducted to evaluate BMF grading. Independent digital images of stained BM slides were evaluated with a semi-quantitative cell-specific detection algorithm for reticulin density, ERY markers (CD71+), MK markers (CD61+) and mean distance between nuclei for CD61+ MK.

In exploratory analyses across the three arms, paired comparison by digital analysis of baseline and 24-wk treatment BM biopsies showed ≥15% reduction in reticulin intersections per field in 44% (28/64) pts. Digital analysis of CD71+ ERY from paired biopsies showed increased ERY progenitors in 51% (20/39) pts at 24 wks, and digital analysis of CD61+ MK showed decreased MK density in 63% (20/32) pts and decreased MK clustering in 55% (16/29) pts. Correlative analysis showed that a 1% increment of MK distance suggests increased probability of reaching ≥35% spleen volume reduction (SVR35) at Wks 24, 36 and 48 by 14.8, 27.9 and 10.4-fold, respectively. At Wk 24, 68% (57/84) of pts in Arm 3 and 20% (16/81) of pts in Arm 2 achieved SVR35, and 56% (46/82) of pts in Arm 3 and 37% (30/91) of pts in Arm 2 achieved a total symptom score reduction of ≥50% (TSS50). The most common (≥20%) hematological TEAEs were thrombocytopenia (52% each in Arms 2 and 3) and anemia (42% in Arm 3, and 27% in Arm 2).

These data of pelabresib treatment for MF either alone or combined with RUX in JAKi treatment-naïve or -experienced MF pts suggest clinical activity for pelabresib to improve BM histology and function.

P153

REAL-WORLD MANAGEMENT OF ADVANCED SYSTEMIC MASTOCYTOSIS TREATED WITH AND WITHOUT MIDOSTAURIN: ANALYSIS OF PATIENT CHARACTERISTICS FROM AN ITALIAN OBSERVATIONAL STUDY (OVIDIO)

C. Papayannidis[1], M. Sciumè[2], F. Mannelli[3], R. Zanotti[4], M. Triggiani[5], M. Rondoni[6], C. Sartor[7], A. Romano[8], F. Giona[9], F. Pane[10], C. Elena[11], F. Crupi[3], V. Federico[12], A. Bernardelli[13], R. Parente[14], A. Ermacora[15], A. Malato[16], E.M. Elli[17], L. Pagano[18], D. Cilloni[19], L. Pochintesta[20], A. Ricco[21], P. Mazza[22], M. Miglino[23], R. Bini[24], D. Valsecchi[24], F.I. Grifoni[2]

[1]IRCCS Azienda Ospedaliero-Universitaria di Bologna; [2]Hematology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico; [3]AOU Careggi, Università degli Studi di Firenze; [4]Azienda Ospedaliera Universitaria Integrata Verona; [5]"Scuola Medica Salernitana", Università di Salerno; [6]Azienda USL della Romagna; [7]Hematology Institute Seràgnoli, Università di Bologna; [8]Università degli Studi di Catania; [9]Sapienza Università di Roma/AOU Policlinico Umberto I; [10]Dipartimento di Medicina Clinica e Chirurgia, Università di Napoli Federico II; [11]Hematology Unit, Fondazione IRCCS Policlinico San Matteo; [12]Polo Ospedaliero "Vito Fazzi"; [13]Università degli Studi di Verona; [14]Azienda Ospedaliera Universitaria San Giovanni di Dio e Ruggi d'Aragona; [15]Azienda sanitaria Friuli Occidentale (AS FO); [16]Ospedali Riuniti Villa Sofia-Cervello; [17]Ospedale San Gerardo; [18]Policlinico Gemelli Roma; [19]Azienda Ospedaliero-Universitaria San Luigi Gonzaga; [20]Ospedale civile Guglielmo da Saliceto; [21]Azienda Ospedaliero Universitaria Consorziale Policlinico; [22]Ospedale San Giuseppe Moscati; [23]Ospedale Policlinico San Martino; [24]Novartis Farma SpA, Italy

Mastocytosis is a rare heterogenous disease resulting from the accumulation of clonal mast cells in ≥1 organ systems. Diagnosis can be challenging and requires multidisciplinary collaboration. OVIDIO (ObserVational study in patients with aDvanced systemic mastocytosis treated in Italy with midOstaurin) is a multicenter, non-interventional study aiming to describe a cohort of adult patients with advanced systemic mastocytosis (AdvSM) treated with and without midostaurin in clinical practice, to fill the knowledge gap between the clinical experience from registration trials and routine patient management in Italy. This study has two cohorts: 1) up to 80 patients with AdvSM treated with midostaurin starting from Jan 2016 (MT); 2) up to 50 patients with AdvSM not treated with midostaurin (diagnosis between Jan 2010–Dec 2015) (MNT). The data collection period is 60 months from the start of midostaurin treatment or from the initial diagnosis of AdvSM for cohorts MT and MNT, respectively.

Table 1.

Characteristic at diagnosis	Midostaurin Treated Cohort (N=62)				Midostaurin Not Treated Cohort (N=16)			
	All Patients	SM-AHN (n=28)	ASM (n=32)	MCL (n=2)	All patients	SM-AHN (n=6)	ASM (n=6)	MCL (n=3)
Median (range) age, years	66.5 (31–91)	69.0 (31–91)	63.5 (33–84)	65.5 (64–67)	66.0 (26–78)	64.0 (36–75)	67.0 (26–70)	67.0 (65–78)
Male, n (%)	40 (64.5)	20 (71.4)	18 (56.2)	2 (100.0)	11 (73.3)	5 (83.3)	4 (66.7)	2 (66.7)
WHO criteria, n (%)								
MC infiltrates in bone marrow/other extracutaneous organs on histologic evaluation	58 (93.5)	24 (85.7)	32 (100.0)	2 (100.0)	12 (80.0)	3 (50.0)	6 (100.0)	3 (100.0)
Aberrant MC morphology[a]	22 (35.5)	10 (35.7)	11 (34.4)	1 (50.0)	8 (53.3)	4 (66.7)	1 (16.7)	3 (100.0)
KIT^{D816V} mutation	43 (69.3)	19 (67.9)	22 (68.7)	2 (100.0)	8 (53.3)	2 (33.3)	5 (83.3)	1 (33.3)
MCs in bone marrow/blood/ extracutaneous organs express CD2 and/or CD25	36 (58.1)	20 (71.4)	15 (46.9)	1 (50.0)	9 (60.0)	5 (83.3)	1 (16.7)	3 (100.0)
Baseline serum tryptase level >20 ng/ml	50 (80.6)	24 (85.7)	24 (75.0)	2 (100.0)	11 (73.3)	3 (50.0)	5 (83.3)	3 (100.0)
C- findings, n (%)[b]	*n=43*	*n=15*	*n=26*	*n=2*	*n=10*	*n=1*	*n=6*	*n=3*
Cytopenia(s)	17 (39.5)	6 (40.0)	9 (34.6)	2 (100.0)	5 (50.0)	1 (100.0)	2 (33.3)	2 (66.7)
Palpable hepatomegaly	14 (32.6)	4 (26.7)	9 (34.6)	1 (50.0)	3 (30.0)	0	2 (33.3)	1 (33.3)
Skeletal involvement	17 (39.5)	4 (26.7)	13 (50.0)	0	1 (10.0)	0	1 (16.7)	0
Palpable splenomegaly	11 (25.6)	3 (20.0)	7 (26.9)	1 (50.0)	5 (50.0)	0	3 (50.0)	2 (66.7)
Malabsorption	10 (23.3)	3 (20.0)	7 (26.9)	0	1 (10.0)	1 (100.0)	0	0
Laboratory, mean (SD)								
Hemoglobin (g/L)	*n=41* 11.3 (2.3)	*n=19* 11.8 (2.5)	*n=20* 10.9 (2.1)	*n=2* 9.8 (3.3)	*n=11* 11.7 (2.5)	*n=4* 13.4 (2.8)	*n=4* 11.4 (2.3)	*n=3* 9.8 (0.5)
Platelet count (10^9/L)	*n=41* 205.9 (127.2)	*n=19* 209.7 (138.6)	*n=20* 209.5 (121.3)	*n=2* 133.5 (103.9)	*n=11* 269.7 (203.6)	*n=4* 388.7 (232.8)	*n=4* 176.2 (120.2)	*n=3* 235.7 (238.2)
White blood cell count (10^9/L)	*n=40* 11.9 (14.9)	*n=19* 16.5 (20.5)	*n=19* 7.2 (3.2)	*n=2* 12.7 (10.2)	*n=11* 7.6 (4.9)	*n=4* 8.9 (6.8)	*n=4* 5.3 (2.2)	*n=3* 9.1 (5.3)
Neutrophils (10^9/L)	*n=37* 7.6 (11.3)	*n=18* 11.3 (15.3)	*n=17* 3.8 (2.3)	*n=2* 7.5 (6.3)	*n=11* 4.8 (3.3)	*n=4* 4.4 (3.9)	*n=4* 3.4 (1.3)	*n=3* 7.2 (3.9)
GGT (U/L)	*n=23* 79.0 (62.4)	*n=10* 65.8 (64.4)	*n=12* 76.7 (44.1)	*n=1* 238.0	*n=5* 138.4 (136.6)	*n=3* 192.3 (162.5)	*n=2* 57.5 (0.7)	-
Alkaline phosphatase (U/L)	*n=21* 174.6 (129.7)	*n=9* 156.4 (144.3)	*n=11* 184.2 (127.5)	*n=1* 233.0	*n=6* 120.0 (42.8)	*n=3* 85.0 (7.9)	*n=2* 155.0 (41.0)	*n=1* 155.0
Albumin (g/L)	*n=18* 71.2 (129.3)	*n=8* 110.7 (192.9)	*n=10* 39.7 (13.2)	-	*n=4* 42.0 (4.7)	*n=1* 47.0	*n=2* 40.0 (5.7)	*n=1* 41.0
Serum tryptase (ng/ml)	*n=37* 147.6 (118.4)	*n=17* 120.6 (86.9)	*n=18* 170.2 (145.4)	*n=2* 173.0 (38.2)	*n=10* 309.8 (613.4)	*n=2* 17.0 (5.6)	*n=5* 110.6 (92.1)	*n=3* 837.0 (1036.5)

[a] >25% of all MCs were atypical cells (type I or II) on bone marrow smears or were spindle shaped in MC infiltrates detected on sections of visceral organs. [b] Percentages were computed on enrolled patients for each cohort with C-findings assessed.
ASM, aggressive systemic mastocytosis; GGT, gamma glutamyl transpeptidase; MC, mast cells; MCL, mast cell leukemia; MNT, midostaurin not treated; MT, midostaurin treated; SD, standard deviation; SM-AHN, systemic mastocytosis with an associated hematological neoplasm.

This first interim analysis evaluated the patient demographics, disease characteristics, medical history, and laboratory data at diagnosis. At data cut-off (Nov 30, 2021), 77 patients were enrolled (MT *vs* MNT, 62 *vs* 15); 5 patients were screened but did not fulfill inclusion/exclusion criteria (MT *vs* MNT, 1 *vs* 4). All patients met the criteria for AdvSM diagnosis according to the WHO 2016 classification. Clinical characteristics at diagnosis are shown in the table. The median age at diagnosis was 66.5 (31–91) and 66.0 (26–78) years (MT *vs* MNT). Diagnosis was confirmed by bone marrow biopsy (87% of cases). Evolution to AdvSM from non-AdvSM was reported in 34% *vs* 13% of cases (MT *vs* MNT). According to WHO 2016 criteria, 45% *vs* 40% had SM-AHN, 52% *vs* 40% had ASM and 3% *vs* 20% had MCL (MT *vs* MNT). The key diagnostic mutation KITD816V was not assessed in 24% *vs* 40% of patients (MT *vs* MNT), whereas C-findings and serum tryptase were not evaluated in 31% *vs* 33% and 40% *vs* 33% of patients, respectively (MT *vs* MNT). In summary, this interim analysis focused on the characteristics

at diagnosis of the first 77 patients enrolled in the OVIDIO study. Preliminary results showed heterogenous diagnostic approaches among Italian sites, in particular lack of C-findings, tryptase and molecular assessments that are needed for proper patient staging and treatment selection; these results require further exploration. Accrual is ongoing and updated results will be presented at the upcoming congress.

P154

IMMUNOSUPPRESSIVE AGENTS INCREASE HOSPITALIZATION RATE FOR SARS-COV2 INFECTION IN PH-NEG CHRONIC MYELOPROLIFERATIVE NEOPLASMS: RESULTS OF EPICOVIDEHA SURVEY

M. Marchetti[1], J. Salmanton-García[2], S. El-Ashwah[3], L. Albertin[1], F. Marchesi[4], Z. Ráčil[5], M. Hanakova[5], G. Zambrotta[2,6], L. Verga[7], F. Passamonti[8], F. Itri[9], J. Van Doesum[10], S. Martín-Pérez[11], A. López-García[12], J. Dávila-Valls[11], R. Cordoba[12], G. Abu-Zeinah[13], G. Dragonetti[14], C. Cattaneo[15], V. Bonuomo[16], L. Prezioso[17], A. Glenthøj[18], F. Farina[19], R. Duarte[20], O. Blennow[21], O.A. Cornely[22], L. Pagano[23]

[1]Azienda Ospedaliera Nazionale SSAntonio e Biagio e Cesare Arrigo, Alessandria, Italy; [2]University of Cologne, Faculty of Medicine and University Hospital Cologne, Department I of Internal Medicine, Excellence Center for Medical Mycology (ECMM), Cologne, Germany; University of Cologne, Faculty of Medicine and University Hospital Cologne, Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), Cologne, Germany; [3]Oncology Center, Mansoura University, Mansoura, Egypt; [4]Hematology and Stem Cell Transplant Unit, IRCCS Regina Elena National Cancer Institute, Rome, Italy; [5]Institute of Hematology and Blood Transfusion, Prague, Czech Republic; Department of Physiology, Faculty of Medicine, Masaryk University, Brno, Czech Republic; [6]Azienda Ospedaliera San Gerardo - Monza, Monza, Italy; Università Milano-Bicocca, Milan, Italy; [7]Azienda Ospedaliera San Gerardo - Monza, Monza, Italy; Università Milano-Bicocca, Milan, Italy; [8]University Insubria Varese, Italy; [9]San Luigi Gonzaga Hospital - Orbassano, Orbassano, Italy; [10]University Medical Center Groningen, Groningen, Netherlands; [11]Hospital Nuestra Señora de Sonsoles, Ávila, Spain; [12]Fundacion Jimenez Diaz University Hospital, Health Research Institute IIS-FJD, Madrid, Spain; [13]Division of Hematology and Oncology, Weill Cornell Medicine, New York, United States; [14]Hematology Unit, Fondazione Policlinico Universitario Agostino Gemelli - IRCCS, Rome, Italy; [15]Hematology Unit, ASST-Spedali Civili, Brescia, Italy; [16]Department of Medicine, Section of Hematology, University of Verona, Verona, Italy; [17]Hospital University of Parma - Hematology and Bone Marrow Unit, Parma, Italy; [18]Department of Hematology, Copenhagen University Hospital - Rigshospitalet, Copenhagen, Denmark; [19]IRCCS Ospedale San Raffaele, Milan, Italy; [20]Hospital Universitario Puerta de Hierro, Majadahonda, Spain; [21]Department of Infectious Diseases, Karolinska University Hospital, Stockholm, Sweden; [22]University of Cologne, Faculty of Medicine and University Hospital Cologne, Department I of Internal Medicine, Excellence Center for Medical Mycology (ECMM), Cologne, Germany; University of Cologne, Faculty of Medicine and University Hospital Cologne, Chair Translational Research, Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), Cologne, Germany; University of Cologne, Faculty of Medicine and University Hospital Cologne, Clinical Trials Centre Cologne (ZKS Köln), Cologne, Germany; University of Cologne, Faculty of Medicine and University Hospital Cologne, Center for Molecular Medicine Cologne (CMMC), Cologne, Germany; German Centre for Infection Research (DZIF), Partner Site Bonn-Cologne, Cologne, Germany; [23]Hematology Unit, Fondazione Policlinico Universitario Agostino Gemelli - IRCCS, Rome, Italy; Hematology Unit, Università Cattolica del Sacro Cuore, Rome, Italy

Objectives: Philadelphia-negative chronic myeloproliferative neoplasms (MPN) typically incur high rates of infections and cytoreductive drugs may modulate such risks. The present analysis aims at assessing the severity and outcomes of MPN facing coronavirus disease 2019 (COVID-19). Hence, we aimed to assess the impact of immunosuppressive agents in COVID-19 outcome.

Methods: The EPICOVIDEHA registry is an online survey (www.clinicalsurveys.net) that has collected since April 2020 several thousand cases of COVID-19 in individuals with baseline haematological malignancies. The survey is promoted by the EHA - Infectious Diseases Working Party (EHA-IDWP) and has been approved centrally by the IRB of Fondazione Policlinico Universitario Gemelli, Rome, Italy.

Results: Overall, 308 MPN patients were observed for a median of 102 days (IQR: 21-223, range 22-97) after COVID-19 diagnosis. Median age at infection was 69 years (IQR: 58-77, range 22-97) and at least one comorbidity was reported from most of the individuals (62.6%, n = 193). Myelofibrosis (MF) (n=140, 45.4%) was the most prevalent baseline malignancy. Overall, 72 patients (23.4%) of the whole cohort (42.8% of MF) received immunosuppressive therapies including steroids, immunomodulatory drugs (IMiDs) or JAK-inhibitors. Hospitalization and consecutive admission to intensive care unit was required for 187 (60.7%) and 45 (24%) patients, respectively. At multivariate logistic regression, hospital admission was predicted by age >70 years (OR 2.809; 95% CI 1.651-4.779), exposure to immunosuppressive therapies (OR 2.802; 95% CI 1.5380-5.103) and comorbidity burden. Overall, 84 patients deceased and the fatality rate (FR) decreased from 40.3% (50 out of 124) in the first two quarters of year 2020 to 15.8% (3 out of 19) in the first two quarters of year 2021 (p<0.05). FR was particularly high (38.6%, HR 2.501; 95% CI 1.384-4.519) in MF patients, in patients with 3 or more comorbidities (61.1%, HR 2.956; 95% CI 1.403-6.227) and in patients receiving immunosuppressive agents (32 out of 86, 37%).

Conclusions: COVID-19 infection led to a particularly dismal outcome in patients exposed to immunosuppressive agents and in those with multiple comorbidities, particularly chronic heart or pulmonary diseases, and diabetes. These data allows to tailor future strategies for preventing severe COVID-19 in MPN patients.

Table 1.

LOGISTIC REGRESSION ANALYSIS OF HOSPITAL ADMISSION

	Univariable analysis				Multivariable analysis			
INDEPENDENT VARIABLES:	p value	OR	Lower limit 95% CI	Upper limit 95% CI	p value	OR	Lower limit 95% CI	Upper limit 95% CI
Age (=70)	<0.001	3.589	2.200	5.855	<0.001	2.809	1.651	4.779
Immunosuppressive therapies	0.001	2.537	1.451	4.435	<0.001	2.802	1.538	5.103
Malignancy								
Essential thrombocythemia	-	-	-	-	-	-	-	-
Myelofibrosis	0.027	1.862	1.073	3.230	0.365	1.362	0.698	2.655
Polycythemia vera	0.419	1.286	0.699	2.367	0.430	1.313	0.668	2.58
Cardiopathy	<0.001	3.132	1.851	5.299	-	-	-	-
Comorbidities:								
No comorbidities	-	-	-	-	-	-	-	-
1 comorbidity	<0.001	2.834	1.622	4.950	0.003	2.429	1.34	4.403
2 comorbidities	<0.001	3.859	1.980	7.520	0.007	2.686	1.314	5.49
3 or more comorbidities	<0.001	8.724	2.850	26.702	0.002	6.268	1.968	19.967

P155

TREATMENT OF BLASTIC PLASMACYTOID DENDRITIC CELL NEOPLASM IN PEDIATRIC PATIENTS WITH TAGRAXOFUSP, A CD123-TARGETED THERAPY

E. Angelucci[1], N. Pemmaraju[2], A. Pawlowska[3], B. Cuglievan[2], J. Lasky[4], A. Kheradpour[5], N. Hijiya[6], A. Stein[3], S. Meshinchi[7], C. Mullen[8], T. Mughal[9,10], L. Vinti[11]

[1]IRCCS Ospedale Policlinico San Martino; [2]The University of Texas MD Anderson Cancer Center; [3]City of Hope National Medical Center; [4]Cure 4 The Kids Foundation; [5]Loma Linda University Children Hospital; [6]Columbia University Irving Medical Center; [7]University of Washington School of Medicine; [8]University of Rochester Golisano Children's Hospital; [9]Tufts University Medical School; [10]Stemline Therapeutics Inc;

[11]*IRCCS Bambino Gesù Children's Hospital*

Background and aims: Blastic plasmacytoid dendritic cell neoplasm (BPDCN), a rare and aggressive hematologic malignancy, derives from plasmacytoid dendritic cells that overexpress CD123. Pediatric cases of BPDCN are uncommon, limiting available robust safety and efficacy data. A first-in-class, CD123-directed therapy, tagraxofusp (TAG, SL-401) is the only treatment approved by the FDA for patients aged ≥2 years with newly diagnosed (1L) and relapsed or refractory (R/R) BPDCN. TAG is also approved by the EMA for 1L treatment of adult patients with BPDCN. Herein, we present safety and efficacy data of TAG therapy in a case series of pediatric patients with BPDCN.

Methods: Pediatric case reports of BPDCN were collected across the US and Europe. TAG was administered according to local institutional guidelines. Analyses included tumor response, survival, and safety.

Results: Eight pediatric patients with BPDCN were treated with TAG (n = 5 1L, n = 3 R/R). Median age was 15.5 years (range 2–21 years), and 7 of the 8 patients were female. All patients received 12 mcg/kg TAG throughout all treatment cycles [1–4 cycles], including a 2-year-old patient who also received 7 mcg/kg at second relapse. Five of eight patients experienced adverse events (AEs): two had decreased albumin, two had increased transaminases, and one experienced capillary leak syndrome (grade 2 in cycle 1). All AEs were manageable and resolved. Three 1L patients achieved a complete response (including 1 patient with extensive disease), one 1L patient showed partial response and one R/R patient had a minor response. One 1L and 1 R/R patient (each) had stable disease and one R/R patient had disease progression. Five patients were bridged to stem cell transplant following TAG treatment.

Conclusions: These cases expand the knowledge base of BPDCN treatment in pediatric patients. TAG was well tolerated in all patients, showing a manageable safety profile and promising efficacy that bridged 63% of our cohort to stem cell transplant.

P156

VALIDATION OF A PROGNOSTIC MODEL TO PREDICT SURVIVAL AFTER 6 MONTHS OF RUXOLITINIB IN MYELOFIBROSIS: A SINGLE CENTER EXPERIENCE

E. Scalzulli, C. Ielo, C. Luise, P. Musiu, I. Carmosino, G.M. Assanto, M. Martelli, M. Breccia

Hematology, Department of Translational and Precision Medicin, Sapienza University, Italy

Myelofibrosis (MF) is a myeloproliferative neoplasm characterized by splenomegaly, cytopenias, bone marrow fibrosis and constitutional symptoms, affecting quality of life and survival. Ruxolitinib, approved for primary and secondary MF patients, reduce spleen volume and disease-related symptoms, with responses usually observed within the first 3-6 months of treatment. Nevertheless, a proportion of patients do not respond adequately to treatment and experienced a progressive disease, albeit there is no consensus definition of ruxolitinib failure.

We applied the Response to Ruxolitinib after 6 months (RR6) prognostic model in a retrospective, single center experience to ruxolitinib treated MF patients, to confirm its predictive ability. RR6 consider ruxolitinib dose at baseline, 3 and 6 months, palpable spleen length reduction from baseline ≤30% at 3 and 6 months and transfusion requirement at month 3 and/or 6 and at all time.

We evaluated 140 MF patients (primary MF 46%, secondary MF 54%), with a median age at diagnosis of 63 years; a slightly female predominance was observed (52.9% *vs* 47.1 %). Before ruxolitinib start, 10.7% of patients were transfusion dependent. Ruxolitinib starting dose was 20 mg BID in 41% of patients, 15 mg BID in 27.5%, 10 mg BID in 19.6% and 5 mg BID in 10.9%. According to RR6, 7.1%, 70.8% and 27.1% of patients were classified as low, intermediate and high-risk. The overall survival (OS) rate was 100%, 82.6% and 71% respectively, with an estimated median OS not reached for low-risk, 80 months for intermediate-risk and 50 months for high-risk (p=0.027) (Figure 1). We further highlighted RR6 prognostic impact according to patients' characteristics and we observed that for intermediate-risk, female patients showed an increased estimated median OS (99 versus 63 months) (p=0.027). High-risk RR6 had a significantly increased risk of mortality in patients with secondary post-PV MF (p=0.002) and in patients with overt MF at diagnosis (p=0.046). High-risk according to RR6 model, showed an estimated median event-free survival (EFS) of 27 months versus 51 months for low/intermediate-risk patients (p=0.009). Multivariate analysis confirmed RR6 stratification role in predicting outcomes in ruxolitinib treated MF patients both in terms of OS (p=0.002) and EFS (p=0.003) for high-risk patients. In conclusion, the RR6 model could be applied for early identification of MF patients with inferior survival and candidate to alternative treatments.

LOGISTIC REGRESSION ANALYSIS OF HOSPITAL ADMISSION

	Univariable analysis				Multivariable analysis			
INDEPENDENT VARIABLES:	p value	OR	Lower limit 95% CI	Upper limit 95% CI	p value	OR	Lower limit 95% CI	Upper limit 95% CI
Age (=70)	<0.001	3.589	2.200	5.855	<0.001	2.809	1.651	4.779
Immunosuppressive therapies	0.001	2.537	1.451	4.435	<0.001	2.802	1.538	5.103
Malignancy								
Essential thrombocythemia	-	-	-	-	-	-	-	-
Myelofibrosis	0.027	1.862	1.073	3.230	0.365	1.362	0.698	2.655
Polycythemia vera	0.419	1.286	0.699	2.367	0.430	1.313	0.668	2.58
Cardiopathy	<0.001	3.132	1.851	5.299	-	-	-	-
Comorbidities:								
No comorbidities	-	-	-	-	-	-	-	-
1 comorbidity	<0.001	2.834	1.622	4.950	0.003	2.429	1.34	4.403
2 comorbidities	<0.001	3.859	1.980	7.520	0.007	2.686	1.314	5.49
3 or more comorbidities	<0.001	8.724	2.850	26.702	0.002	6.268	1.968	19.967

Figure 1.

P157

RISK FACTORS FOR THROMBOSIS IN PATIENTS AGED > 60 YEARS WITH ESSENTIAL THROMBOCYTHEMIA WITHOUT PREVIOUS THROMBOTIC EVENTS

R. Latagliata[1], A. Andriani[2], M. Breccia[3], I. Carmosino[3], F. Vozella[4], A. Romano[5], A.L. Biagi[6], L. Maurillo[7], M. Trawinska[8], K. Paciaroni[9], M. Santopietro[10], S. Leonetti Crescenzi[11], A. D'Addosio[12], C. Tatarelli[13], A. Di Veroli[1], E. Rossi[14], M. Montanaro[1]

[1]Hematology, Belcolle Hospital; [2]Hematology, Spaziani Hospital; [3]Hematology of Translational and Precision Medicine, Policlinico Umberto I, Sapienza University; [4]UOC of Hematology and Stem cell transplantation, Campus Biomedico; [5]UOC Ematologia and Transplants of "Istituto Nazionale Tumori. Regina Elena"; [6]S.M. Goretti Hospital – Polo Pontino "Sapienza" University; [7]Hematology, Policlinico Tor Vergata & Department of Biomedicine and Prevention, Tor Vergata; University; [8]UOC of Hematology, Sant'Eugenio Hospital, ASL Roma 2; [9]UOSD Hematology, ASL Roma 1; [10]Hematology and Hematopoietic Stem Cells Transplant Unit, AO San Camillo-Forlanini; [11]Hematology and Stem Cell Transplant, San Giovanni-Addolorata Hospital; [12]UOC Service of immunology and Transfusion Medicine, Villa San Pietro Hospital; [13]Hematology, Sant'Andrea University Hospital, Sapienza; [14]Fondazione Policlinico Universitario A. Gemelli - IRCCS, Italy

Background: Thrombotic events are the major complications in patients (pts) with Essential Thrombocythemia (ET). Occurrence of thrombotic events before ET diagnosis is a worldwide recognised risk factor for thrombosis in the follow-up of ET pts: age > 60 years is another risk factor, but its role in pts without previous thrombotic events needs to be further defined with the addition of other potential risk factors.

Methods: To assess prognostic role of different putative risk factors for thrombosis in a wide cohort of elderly pts, we revised clinical features, follow-up and thrombotic events in 956 ET pts aged > 60 years

diagnosed from 1/2000 to 12/2016 and enrolled in the retrospective and prospective registries of Latial Group for the Study of Myeloproliferative Neoplasms.

Table 1. Patient clinical features at diagnosis in the entire cohort and according to presence of thrombotic events before ET diagnosis

	ALL PATIENTS	GROUP A (previous thrombosis before ET diagnosis)	GROUP B (no previous thrombosis before ET diagnosis)	p
Patients, n° (%)	956	191 (20.0)	765 (80.0)	
M/F, n° (%)	352/604 (36.8/63.2)	79/112 (41.4/58.6)	273/492 (35.7/64.3)	0.146
Median age, years (IQR)	72.3 (67.1 – 78.1)	71.8 (67.2 – 78.2)	72.4 (67.1 – 78.0)	0.316
Median Hb, g/dl (IQR)	14.0 (12.0 – 15.0)	14.0 (12.5 – 15.1)	14.0 (13.0 – 15.0)	0.822
Median Hct, % (IQR)	43.0 (39.0 – 46.0)	43.0 (39.0 – 46.0)	43.0 (40.0 – 46.0)	0.980
Median WBC, x 10^9/l (IQR)	8.78 (7.14 – 10.76)	9.22 (7.10 – 11.47)	8.63 (7.17 – 10.52)	**0.008**
Median PLT, x 10^9/l (IQR)	761 (620 – 943)	736 (606 – 939)	766 (623 – 944)	0.385
Spleen enlargement, n° (%): No < 5 cm ≥ 5 cm Not evaluable	802 (85.7) 121 (12.9) 13 (1.4) 20	149 (81.0) 32 (17.4) 3 (1.6) 7	653 (86.8) 89 (11.8) 10 (1.4) 13	0.121
Hypertension, Y/Evaluable (%)	395/644 (61.3)	94/143 (65.7)	301/501 (60.1)	0.221
Diabetes, Y/Evaluable (%)	79/644 (12.3)	19/143 (13.3)	60/501 (12.0)	0.673
Dyslipidaemia, Y/Evaluable (%)	124/644 (19.3)	36/143 (25.4)	88/501 (17.6)	**0.038**
Smoke, Y/Evaluable (%)	143/644 (22.2)	38/143 (26.6)	105/501 (21.0)	0.154
JAK2 V617F, WT/Mut (%)	235/546 (30.1/69.9)	38/112 (25.4/74.6)	197/434 (31.3/68.7)	0.158
JAK2 V617F allele burden, Median value, % (IQR)	19,0 (7.6 – 35.2)	21.8 (11.2 – 40.6)	17,3 (6.8 – 34.2)	0.171

P158

REAL-LIFE IMPACT OF RUXOLITINIB IN MYELOFIBROSIS: LONG TERM RESULTS OF A MONOCENTRIC-RETROSPECTIVE STUDY

G. Ciotti[1,2], S. Pepe[1], E. Scalzulli[1], I. Carmosino[1], P. Musiu[1], C. Ielo[1], C. Luise[1], M. Martelli[1], M. Breccia[1]

[1]Department of Translational and precision medicine - Az. Policlinico Umberto I - La Sapienza University; [2]Onco Hematology, Department of Oncology - Veneto Institute of Oncology IOV - IRCCS, Italy

Ruxolitinib (RUX) is the first JAK1/2 inhibitor approved for myelofibrosis. Although several studies have shown efficacy on splenomegaly and symptom control, the withdrawal rate is still high. Furthermore, timing of treatment start and its impact on survival is still a matter of debate. We retrospectively evaluated 137 pts treated with RUX from January 2011 to July 2021. Responses were defined according to IWG-MRT/ELN 2013 criteria. A reduction in palpable spleen volume of 20-50% from baseline was defined as a partial response. EFS was defined as the time from RUX start to discontinuation for any cause. Median age was 66,4 (range 32,5 – 83,7). Median follow-up (FU) was 38,2 months (range 2,5-112,7). Splenic ORR was 62% and 59% at 6 and 24 months, respectively; median time to best response was 8,4 months. Higher starting dose (>5mg BID) seems to correlate to early response (6,2 *vs* 9 months, p=0,07); palpable spleen ≥10cm was associated with a lower ORR (47% *vs* 70% at 1-year, p=0.011). At all time points, a significant symptoms response was confirmed. Hematological AEs were more severe in the first 3 months, thereafter median Hb and PLT values remain stable though significantly reduced from baseline (p<0,001). At last FU, 43,7% of patients had permanently discontinued RUX. The first cause of discontinuation (27%) was allo-HSCT. Loss of response and refractoriness accounted for 17% with only 3 pts refractory to RUX. Overall, 34 pts died. Deaths were mainly attributable to infections (42.4%), followed by progression into AML (21.2%). No drug-related deaths were reported and 33% of the deaths were not attributable to the disease. Survival at 24 and 60 months was 92% and 62,2%, respectively. A starting dose <5mg BID was associated with a lower OS (38.5 months *vs* NR, p=0,006). Survival was also reduced in pts who had discontinued RUX for any cause (48,2 months *vs* NR, p<0,001). The negative prognostic role of discontinuation was confirmed in multivariate analysis (HR 24.03, p<0,001). Median EFS was 47,7 months (range 40,5 – 55,1). Transfusion-dependence at RUX start was associated with shorter EFS (27,8 *vs* 56,2 months, p = 0,013). A lower EFS was also seen in patients with a palpable spleen ≥5cm at baseline (44,5 months *vs* NR, p = 0,06).

The efficacy of RUX is confirmed also in the real-life setting with a favorable safety profile. Earlier initiation of treatment and higher starting dose correlates with better efficacy, survival and later discontinuation.

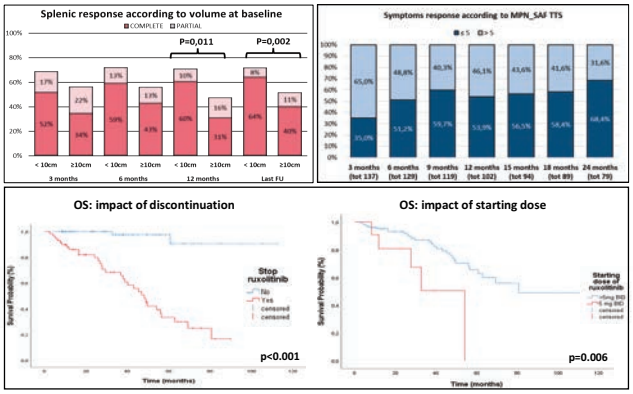


Figure 1.

P159

COVID-19 MORTALITY RATES IN CML PATIENTS

I. Civettini[1,2], F. Brioschi[2], G.P.M. Zambrotta[1,2], C. Gambacorti-Passerini[1,2]

[1]Department of Medicine and Surgery, University of Milan-Bicocca; [2]Haematology Division, San Gerardo Hospital, Italy

Background: The advent of the COVID-19 pandemic had a considerable impact among haematological patients, with high mortality rates as reported by Passamonti *et al*. (4). The same authors, however, highlighted that patients with chronic myeloid leukemia (CML) receiving TKI were alive at data cutoff and were at low risk of mortality. These findings were not confirmed by the CANDID (7) study in which a 13.7% COVID-19 mortality rate was reported among CML patients. This value was later resized by Breccia et al. who reported a lower mortality rate of 5.5%, but still higher than the general population (2.9%) (3).

Aims: To evaluate COVID-19 severity and mortality rates in CML patients.

Methods: We retrospectively evaluated CML patients treated at our institution (Ospedale San Gerardo, Monza) with a laboratory-confirmed SARS-CoV-2 infection diagnosed from February 2020 to April 2022 (26 months). We included only adult patients (aged ≥18 years). We evaluated: presenting symptoms, COVID-19 severity (refered to hospitalization or admission to ICU) and mortality.

Results: Out of a total of 325 CML patients treated at our institution, we recorded 49 SARS-CoV-2 positive patients (15,1%, 6.9/100 person years). Female patients were 26 (53%) and male were 23 (47%). The median age was 55.9 years old. Of the 49 confirmed infections, 9 patients

(18.4%; CI: 10-31) were asymptomatic and 29 (59,2%; CI:45-72%) had mild symptoms (median age of 52,9 years old). 8 patients (16.3%, C.I. 8.5-29) required hospitalization and 3 (6,1% CI: 2.1-16) were admitted to the Intensive Care Unit (ICU) (median age of 66,1 years old). All the 3 patients admitted to ICU were not vaccinated. No deaths were recorded (0%, 95% CI: 0-5.8).

Conclusions: If we compare the death rate observed in our small series (0%, 95% CI: 0-7.7) with the one reported for the Italian population (1.1 %) from February 2020 to April 2022 (1), no significant differences exist. The median age at COVID-19 diagnosis was 56 years old, but it raised to 66 among patients who required hospitalization or ICU admission. It should be considered that the excess of mortality observed in previous studies in CML patients is more strictly related with the older age of the analyzed population, rather than the haematological disease itself. After all, the fact that CML patients receiving TKI enjoy a normal life expectancy (5;6) should also be applied to CML patients with COVID-19.

P160

FIRST REPORT OF TOLERABILITY AND LONG-TERM EFFICACY OF PEG-INTERFERON ALPHA ASSOCIATED WITH ZOLENDRONATE IN THE TREATMENT OF BONE LOSS SECONDARY TO INDOLENT SYSTEMIC MASTOCYTOSIS

L. Crosera[1], M. Bonifacio[1,2], I. Tanasi[1,2], G. Orsolini[2,3], A. Bernardelli[1], P. Bonadonna[2,4], M. Krampera[1], M. Rossini[2,3], R. Zanotti[1,2]

[1]Hematology Unit, Department of Medicine, Azienda Ospedaliera Universitaria Integrata di Verona, Verona, Italy; [2]Gruppo interdisciplinare per lo studio della Mastocitosi (GISM), Azienda Ospedaliera Universitaria Integrata di Verona, Verona, Italy; [3]Rheumatology Unit, Department of Medicine, Azienda Ospedaliera Universitaria Integrata di Verona, Verona, Italy; [4]Allergy Unit, Department of Medicine, Azienda Ospedaliera Universitaria Integrata di Verona, Verona, Italy

Systemic mastocytosis (SM) is a rare neoplastic disease characterized by the proliferation and pathological accumulation of mast cells in various organs and tissues. Bone involvement is frequently reported in SM, including bone pain, osteopenia, osteoporosis, fragility fractures, osteosclerosis or mixed pattern. Antiresorptive drugs are the standard-of-care. In small case series of patients with severe osteoporosis secondary to SM, the use of subcutaneous α-interferon combined with bisphosphonates was associated to good efficacy, but poor tolerability and high dropout rates. Moreover, the optimal dose and duration of IFN-α therapy for SM remain still unclear. Pegylated interferon-α (Peg-IFNα) has a prolonged serum half-life and is associated to an improved tolerability. The use of Peg-IFNα in SM has never been reported to date. We describe 3 male patients, aged 46, 43 and 49 years, all diagnosed with indolent SM and severe bone involvement. Before treatment, patient 1 had a mixed pattern of small osteolytic and osteosclerotic lesions while patients 2 and 3 had multiple vertebral fractures (5 and 7 respectively). All reported severe bone pain. Serum tryptase (sT) before treatment was 143, 39.4 and 24.8 ng/mL respectively. T- and Z-score measured at spine were -1.3, -2.7, -4.4, and -1.2, -1.7, -2.3, respectively. After informed consent about off-label use and having verified that they had no contraindications to interferon, patient 1 was treated with Peg-IFNα2b at 80 mcg/week and patients 2 and 3 with Peg-IFNα2a at 90 mcg/week for 1 year associated with zoledronate i.v. 5 mg yearly for at least 5 years. Median follow-up was 97 months (range 95-99). Paracetamol and/or low dose of steroids were administrated only in the first few weeks. Peg-IFNα was never discontinued and dose was temporarily reduced for mild cytopenia or flu-like symptoms as needed.

A progressive reduction of sT over time was documented in all patients (Figure 1). T-score at spine after two years showed an increase of +0.5, +0.2, +1.9, respectively. At the last follow-up T-score increase was +0.5, +0.6 and +2.3, respectively. No patient developed new fractures or required other cytoreductive treatments. All patients reported partial/near complete remission of bone pain.

Our data suggest acceptable safety and long-term efficacy of Peg-IFNα associate to zoledronate in the treatment of severe bone involvement associated to indolent SM.

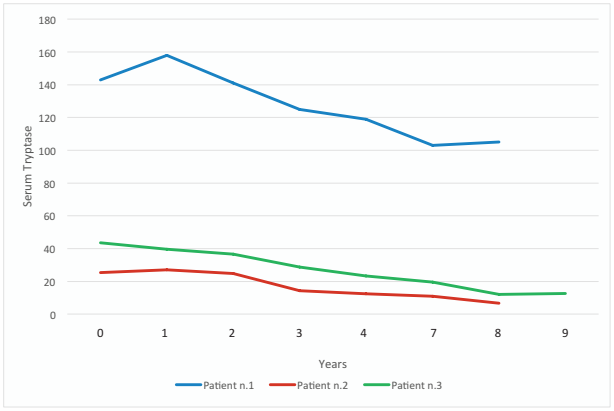


Figure 1. Tryptase levels at baseline and after treatment with Peg-IFN associated with zoledronate.

P161

HUMORAL AND CELLULAR RESPONSES AFTER BOOSTER DOSE OF COVID-19 VACCINATION IN MPN PATIENTS ON RUXOLITINIB THERAPY

A. Atanasio[1,2], A. Vanni[2], L. Maggi[2], S. Pilerci[2], A. Mazzoni[2], F. Crupi[1,2], S. Tekle[2,3], M.G. Colao[4], M. Borella[1,2], G.M. Rossolini[2,4], A.M. Vannucchi[1,2], F. Annunziato[2,5], P. Guglielmelli[1,2]

[1]CRIMM, Centre of Research and Innovation in Myeloproliferative Neoplasms, University of Florence, Italy; [2]Department of Experimental and Clinical Medicine, University of Florence, Italy; [3]Infectious and Tropical Diseases Unit, Careggi University Hospital, Italy; [4]Microbiology and Virology Unit, Careggi University Hospital, Italy; [5]Flow Cytometry Diagnostic Center and Immunotherapy (CDCI), Careggi University Hospital, Italy

Introduction: We previously reported that MPN patients (pts) on ruxolitinib (RUX) treatment achieved a reduced humoral response rate after the first COVID vaccination compared to pts with no treatment or hydroxyurea (HU) and a healthy control group (Guglielmelli *et al*. AJH 2021). Here, we present new data from the same cohort concerning humoral and spike-specific B and T cell responses throughout the complete vaccination cycle, in order to further analyse the effects of RUX on COVID-19 mRNA vaccination response.

Methods: We prospectively assessed serologic and cell-mediated specific immunologic responses throughout a full cycle of SARS-CoV-2 mRNA vaccine (two initial doses and one "booster" dose) in 23 patients with PV (n=7), ET (n=6) and MF (n=10) according to the following timepoints: T0 (before first dose), T1 (before second dose, 21-28 days after first dose), T2 (3 months after second dose), T3 (2 months after booster dose).

Results: Among the 23 pts included in the study, 13 were on a stable dose of RUX since >3 months (RUX-group; median duration, 7.3yr), while in the non-RUX group 5 were not currently treated and 5 under HU. Median RUX dose was 20 mg daily. Figure 1 shows levels of anti-SARS-CoV-2 antibodies (Abs) and frequency of spike-specific CD19+ B cells and CD4+/CD154+/cytokine+ T cells at different timepoints. In general, the extent of specific Abs was significantly lower in the RUX-group compared to non-RUX pts for the first two vaccine doses, but after the booster dose the difference was no longer significant for neutralizing Abs. Interestingly, T helper cell-mediated response was similarly diminished in the RUX-group while it was comparable to controls for B cells.

Conclusions: These results confirm preliminary data on the negative effect of RUX treatment on COVID-19 mRNA vaccination response in MPN pts. Notably, this can improve after the administration of a third dose. Overall, our findings reinforce that MPN pts should be vaccinated with a booster dose to achieve a better protection, especially while on RUX treatment. These findings also suggest that RUX-mediated TCR/JAK/STAT inhibition might impair T helper cells interactions with B cells, reducing overall proinflammatory cytokine release and Ab production.

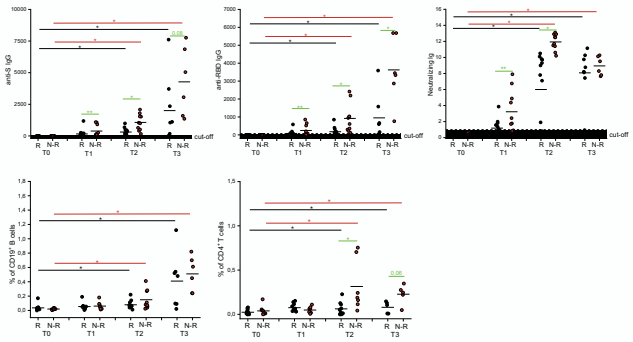


Figure 1. Serologic and cellular response to mRNA COVID19 vaccination in MPN patients treated with ruxolitinib (R) vs non-ruxolitinib (N-R): Black lines represent mean values, dotted lines represent cut-off values. Black and red asterisks refer to paired statistics within each study group compared to T0. Green asterisks refer to unpair statistics between R and N-R group. *= p<0.05 calculated with Wilcoxon-Signed Rank test. **=p<0.01 calculated with Mann-Whitney test. Standard diagnostic ELISA assay measured binding Ab unit (BAU)/mL for anti-S and anti-RBD Ab, and relative index for neutralizing Abs. Frequency of spike-specific CD19+ B cells were evaluated by immunofluorimetric assay. Frequency of CD4+ T cells reactive to SARS-CoV-2 was defined by expression of CD154 and at least one cytokine among IFN-γ, IL-2 and TNF-α (CD4+CD154+cytokine+) by functional immunofluorimetric assay.

P162

CLINICAL AND MOLECULAR FEATURES OF THE PATIENTS WITH IDIOPATHIC ERYTHROCYTOSIS

E.M. Elli*[1], M. Mauri*[2] D. D'Aliberti[2], I. Crespiatico[2], D. Fontana[2], S. Redaelli[2], S. Pelucchi[2], B. Manghisi[1,2], F. Cavalca[1,2], A. Ripamonti[1,2], F. Brioschi[1], S. Palamini[3], F. Mottadelli[4], D. Ramazzotti[2], A. Piperno[2], C. Gambacorti-Passerini[1,2], R. Piazza[1,2] *co-first authors

[1]Divisione di Ematologia e Unità trapianto di midollo osseo, Ospedale San Gerardo; [2]Dipartimento di Medicina e Chirurgia, Università Milano-Bicocca; [3]Centro Ricerca Tettamanti, Ospedale San Gerardo; [4]Fondazione Monza e Brianza per il Bambino e la sua Mamma (MBBM), Ospedale San Gerardo, Italy

Background: Polycythemia Vera (PV) is typically caused by JAK2V617F or exon 12 JAK2 mutations. Little is known about polycythemia cases where no JAK2 variants can be detected and no other causes of primary or acquired erythrocytosis can be identified. This condition is defined as Idiopathic Erythrocytosis (IE).

Material and methods: We evaluated clinical-laboratory parameters of a cohort of 56 IE patients (pts), regularly followed up at the Hematology Unit of our Institution, between 1999 and 2021. We determined their molecular profile using a high-depth targeted oncopanel on peripheral blood coupled with paired blood/buccal-DNA exome-sequencing. Concerning the treatment, all pts were managed with phlebotomies, to maintain hematocrit below 50%. No cytoreduction was used at onset, only low dose aspirin in pts with concomitant risk vascular factors.

Results: Principal clinical-laboratory features of IE pts at diagnosis are showed in Table 1A. Compared to PV (Randi, 2015), IE pts were mostly males, younger and presented normal/higher serum erythropoietin levels. Interestingly, ferritin levels were higher in our cohort (median 115 ng/ml) than we expected in PV pts (Ginzburg, 2018). According to molecular profiling (Table 1B), we identified 17 Low Mutation Burden somatic variants in 13 (23.2%) pts, principally involving *DNMT3A* and *TET2*. Notably, a large part of the cohort (76.8%) showed no evidence of clonal hematopoiesis (CH). These findings opened-up the possibility of an underlying genetic disorder functionally connected with congenital erythrocytosis but characterized by adult onset and limited penetrance. By using ad hoc statistical analyses, we identified recurrent germline variants in 43 (76.8%) pts occurring mainly on JAK/STAT, Hypoxia and Iron metabolism pathways (Table 1C). In particular, a high fraction of pts (50%) resulted HFE mutated. After a median follow-up of 7.7 years, 6 (10.7%) thrombotic events were reported during follow-up. Eight (14.3%) pts required introduction of cytoreduction. Only 2 (3.6%) myelofibrotic evolutions was observed. No pts presented leukemic transformation.

Conclusion: Our data suggest that IE are, in large part, genetic disorders with few pts showing evidence of low burden CH. In most IE we identified recurrent germline variants occurring mainly on JAK/STAT, Hypoxia and Iron metabolism pathways. To validate our data, the generation of cellular models is ongoing.

Table 1. Clinical and molecular profile of Idiopatic Erytrocytosis.

Tab 1A. Clinical and laboratory features at diagnosis		N= 56 pts
Male/female, n (%)		46/10 (82.1/17.9)
Age (years), median (range)		55.6 (16.2-77.3)
Hb (g/dl), median (range)		18 (16.2-23.1)
Hematocrit (%), median (range)		52.3 (47-67.6)
MCV (fl), median (range)		87 (76-100.4)
WBC count (×109/L), median (range)		7.3 (4.3-15.6)
PLT count (×109/L), median (range)		202 (100-347)
Serum erythropoietin (U/L), median (range)		8.8 (1-25.5)
Ferritin level (ng/mL), median (range)		115 (2-363)
Palpable splenomegaly, n (%)		2 (3.6)
Previous thrombosis, n (%)		9 (16)
Antiplatelet therapy, n (%)		42 (75)
Deaths, n (%)		3 (5.3)
Tab 1B. Somatic mutations (in 13 pts); *VAF (Variant allele frequency) < 10%:		
Genes	**mutated patients, n (%)**	**protein change; n**
DNMT3A	9 (16)	p.Tyr584*; 1
		p. Arg749Cys; 1
		p.Gly484Arg; 1
		p.Arg736His; 1
		p.Val563Met; 1
		p.Arg882His; 1
		p.Cys818Tyr; 1
		c.1429+1G>A (splicing site); 1
		p.Gln356Argfs*51; 1
TET2	3 (5.4)	p.Pro401del; 1
		p.Arg1167Gly; /p.Gln1624*; 1
		p.Gln701Argfs*3; 1
IDH2	1 (1.8)	p.Asp200His; 1
SF3B1	1 (1.8)	p.Lys700Glu; 1
PTPN1	1 (1.8)	p.Lys389Gln; 1
JAK2	1 (1.8)	p.Lys539Leu; 1
Tab 1C. Germline variants (in 43 pts)		
Genes	**mutated patients, n (%)**	**protein change, n**
HFE	28 (50)	p.His63Asp +/-: 20
		p.His63Asp +/+: 1
		p.Cys282Tyr +/-: 6
		p.Cys282Tyr/p.His63Asp: 1
HIF-1A	17 (30)	p.Pro582Ser +/-: 17
EPAS-1	3 (5.4)	p.Phe540Leu +/-: 2
		p.Phe374Tyr +/-: 1
JAK2	7 (12.5)	p.Ile982Leu +/-: 2
		p.Asn1108Ser +/-: 2
		p.Gly571Ser +/-: 1
		c.1513+4A>G (splicing site) +/-: 1
		p.Thr668Ile +/-: 1
JAK3	4 (7.1)	p.Val722Ile +/-: 4
C-KIT	3 (5.4)	p.Val530Ile +/-: 2
		p.Arg956Gln +/-: 1
TET2	1 (1.8)	p.Tyr867His/p.Met17001Ile: 1
ASXL1	1 (1.8)	p.Pro1322Arg +/-: 1
CSF3R	1 (1.8)	p.Ala119Thr +/-: 1
ZRSR2	1 (1.8)	p.Gly438_Arg442 dup +/-: 1
FGFR3	1 (1.8)	p.Ala312Val +/-: 1
SDHD	1 (1.8)	p.His50Arg +/-: 1

P163

MYELOID NEOPLASM WITH EOSINOPHILIA AND A RARE REARRANGEMENT OF PLATELET-DERIVED GROWTH FACTOR RECEPTOR BETA GENE (PDGFR-B)

G. Lazzaro[1], A. Calvisi[1], M. Bacciocchi[1], M. Monne[1], A. Uras[1], A. Figus,[2] A. Cucca[1], A Bianchi[1], M. Murineddu[1], A. Di Francesco[1], G. Piras[1], A.D. Palmas[1]

[1]UOC Hematology 1, Ospedale "San Francesco" ASL NUORO; [2]UOC Radiology 2 , Ospedale "San Francesco" ASL NUORO, Italy

PDGFR-b rearrangements are related to myeloid/lymphoid neoplasms with eosinophilia, a rarely entity redefined by WHO in 2016. Despite the rarity of presentation, these conditions have an excellent response to Imatinib. The first fusion gene partner discovered was ETV6 [t(5;12)(q32;p13.2)], while all other partners are rare and often found in single cases. Here we report a case of myeloid neoplasm with an important eosinophilic component with PDE4DIP::PDGFRb rearrangement A 25-year-old woman came to our attention for anemia (Hb:10,1 g/dl) and leukocytosis (WBC:15200/mmc) with hypereosinophilia (Eo:1900/mmc). She presented with a mild splenomegaly and perimalleolar edema and reported severe bilateral knee pain. Bone marrow aspirate and biopsy were consistent with a myeloid neoplasm with eosinophilic component. Knee MRI showed bone marrow replacement involving tibia and femur bilaterally, suggesting a hematological malignancy process. Molecular biology testing were negative for BCR-ABL fusion gene and FIP1L1-PDGFRa, JAK2, MPL, CALR mutations, while fluorescence in situ hybridization with a breakapart probe detected a PDGFRb gene rearrangement. NGS RNA fusion panel approach identified PDE4DIP::PDGFRb fusion as a result of translocation t(1;5)(q23;q31). A diagnosis of 'myeloid neoplasm with eosinophilia and PDGFRb rearrangement' was done. Treatment with Imatinib mesylate 100 mg/die was started. After two weeks of therapy blood counts reverted to normal and bone pain improved. At a 12 months follow-up a complete remission was achieved: knee pain disappeared, MRI normalized, FISH and NGS analysis documented a complete absence of the PDGFRb rearrangement previously detected. According to literature, beside ETV6, other partner genes rearranged with PDGFRb such as NUMA1, KAZN, and CSNK2A1 were reported rare. So far t(1;5)(q23;q31) involving PDE4DIP gene has only been reported in four patients affected by myeloid neoplasm with eosinophilia, all of them infants. This is the first reported case in a 25 years-old female patient and with knee localization. Early diagnosis with molecular detection of PDGFR-B rearrangements, as well as a prompt treatment with Imatinib mesylate, allowed to obtain a brilliant and rapid response. As only few data are available in literature, and considering the young age of presentation of the disease, the duration of the molecular response and the possibility of a safe treatment discontinuation remain a matter of debate.

P164

DEPICTING THE PHENOTYPICAL AND GENETIC CHARACTERISTICS OF PATIENTS PRESENTING WITH JAK2 WILD TYPE ERYTHROCYTOSIS

A. Zagaria[1], F. Tarantini[1], P. Orsini[1], C. Cumbo[1], E. Parciante[1], L. Anelli[1], N. Coccaro[1], C.F. Minervini[1], G. Tota[1], I. Redavid[1], M.R. Conserva[1], A. Ricco[1], I. Attolico[1], G. Specchia[2], P. Musto[1], F. Albano[1]

[1]Department of Emergency and Organ Transplantation (D.E.T.O.) - Hematology and Stem Cell Transplantation Unit - University of Bari "Aldo Moro"; [2]School of Medicine, University of Bari "Aldo Moro", Italy

Introduction: JAK2 wild type (WT) erythrocytosis includes inherited and acquired conditions, representing a diagnostic and clinical challenge. Our group has previously demonstrated an association between JAK2 WT erythrocytosis and the simultaneous presence of two single nucleotide polymorphisms (SNPs) (JAK2 GGCC_46/1 haplotype and CALR rs1049481_G allele). We extended the case series and evaluated the association of both SNPs with JAK2 WT erythrocytosis; furthermore, we hypothesized a correlation with EPO levels and investigated the occurrence of additional gene mutations.

Methods: Peripheral blood samples from 80 JAK2 WT erythrocytosis patients (pts) were analyzed. The association analysis was performed with the SNPassoc R package, and it was measured by the odds ratio (OR) and p-value under five genetic models: codominant, dominant, recessive, overdominant and log-additive. Next-generation sequencing (NGS) analysis on 44/80 (55%) pts with JAK2 haplotype and/or CALR rs1049481_G allele with normal EPO level was performed; a panel encompassing 26 target genes frequently mutated in myeloid malignancies was used.

Results: Sixty-nine of the 80 pts had at least one SNP. Considering the entire cohort of pts, a significant positive association between JAK2 haplotype and erythrocytosis risk was observed under the dominant model (OR=2.29, p=0.0007576). We incorporated several covariates to adjust the association test and improve its accuracy. Erythrocytosis risk is higher by introducing three specific covariates (CALR rs1049481_alleleG, sex and EPO level) individually (OR=2.3, p=0.0007354; OR=2.62, p=0.000255; OR=2.73, p=0.000153, respectively) or in combination (OR=3.13, p=0.000051). In detail, the association is strengthened by CALR rs1049481_alleleG, male sex and normal EPO level. The NGS analysis showed the presence of 22 genetic variants affecting 7 genes (ASXL1, TET2, DNMT3A, JAK2, KIT, RUNX1, ANKRD26) in 17/44 cases (38.6%). ASXL1 was the most frequently mutated gene (6/44, 14%), followed by TET2 (5/44, 11%) and DNMT3A (4/44, 9%).

Conclusion: Our preliminary data suggest that male pts presenting with JAK2 WT erythrocytosis and with normal EPO levels can benefit from the search for germline polymorphisms combination in JAK2 and CALR driver genes for a better diagnostic profiling. Moreover, 38% of pts with this genetic background have mutations in typical driver genes of myeloid neoplasm, which are thought to contribute to the pathogenic mechanisms of polycythemia vera.

P165

RUXOLITINIB ADHERENCE IN MYELOFIBROSIS AND POLYCYTHEMIA VERA: THE "RAMP" STUDY

F. Palandri[1], D. Bartoletti[1,2], E.M. Elli[3], M.M. Trawinska[4], A. Iurlo[5], M. Bonifacio[6], G. Caocci[7], F. Mendicino[8], R. Latagliata[9], C. Mazzoni[1,2], A.D. Romagnoli[1,2], B. Garibaldi[10], A. Ripamonti[3], D. Cattaneo[5], E. Tamellini[6], E. Abruzzese[4], M. Krampera[6], N. Vianelli[1], M. Cavo[1,2], G. Auteri[1,2], M. Breccia[11], G.A. Palumbo[12]

[1]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli"; [2]Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale, Università di Bologna; [3]Ospedale San Gerardo, ASST Monza; [4]Ospedale S. Eugenio, Università Tor Vergata; [5]Foundation IRCCS Ca' Granda, Ospedale Maggiore Policlinico; [6]A.O.U. Integrata Verona; [7]Polo oncologico "A. Businco", Università degli studi di Cagliari; [8]Dipartimento di Emato-Oncologia, A.O. Annunziata; [9]Ospedale Belcolle; [10]Scuola di Specializzazione in Ematologia, Università degli Studi di Catania; [11]A.O.U. Policlinico Umberto I, Università degli Studi di Roma "La Sapienza"; [12]Dipartimento di Scienze Mediche, Chirurgiche e Tecnologie Avanzate "G.F. Ingrassia", Università di Catania, Italy

Ruxolitinib (RUX) is beneficial in myelofibrosis (MF) and polycythemia vera (PV) patients (pts). The Adherence to Refills and Medications Scale (ARMS) (Kripalani S, Value Health 2009) and the Distress Thermometer (DT) (Donovan KA, Psycho-oncology 2014) measure drug

adherence and psychological distress, respectively. After IRB approval, the RAMP (Rux adherence in MF and PV) multicenter prospective observational study included 189 consecutive RUX-treated pts with MF (75%) or PV (25%), that completed ≥1 ARMS/DT test, with the aim to evaluate: 1) RUX adherence (ADH) and features associated to ADH; 2) level of distress and its association to ADH; 3) impact of ADH/distress on response. Pts completed the ARMS/DT tests at the earliest convenient time (wk0), irrespective of the time of RUX start, and again after 4 (wk4), 8 (wk8), 12 (wk12), and 24 (wk24) weeks. Patients were stratified by timing of ADH assessment (EARLY-ADH: within 12 months from RUX start). Six out of 11 ARMS questions investigated intentional ADH. At wk0, the mean ARMS score was 13.16±1.95; 50.3% were high adherent (H-ADH, ARMS <14); 78.7% of low adherent (L-ADH, ARMS ≥14) pts had intentional L-ADH. Mean DT score was 2.88±2.79, with 19.6% of pts with high DT (H-DT, score 6-10) and 80.4% with low DT (L-DT, score 0-5). In univariate analysis, H-ADH was associated to: female sex (p=0.003), L-DT (p=0.004), Total Symptoms score (TSS)≥1 (p=0.04), and EARLY-ADH (p=0.04). Female sex (p=0.005), L-DT (p=0.001) and EARLY-ADH (p=0.03) remained associated to H-ADH in multivariable analysis (MVA). In MF pts, female sex (p=0.007), L-DT (p=0.001), and PLT <200 x10^9/L at wk0 (p=0.01) were associated to H-ADH in MVA. Overall, 143 (75.7%) of pts completed ARMS/DT tests at all time-points (Figure 1). The percentage of full completers with H-ADH tended to increase over time (from 46.9% at wk0 to 51.8% at wk24), while pts with H-DT decreased (from 22.3% to 17.8%). Stable H-DT (12.5% of pts) was associated to stable L-ADH (38.3%, p=0.001). At wk24, spleen/symptoms response was more frequent in stable H-ADH pts (p=0.05) and in stable L-DT pts (p=0.04). The RAMP study highlights that L-ADH to RUX, mainly intentional, remains an unmet clinical need, particularly in male pts and with H-DT. Notably, L-ADH was associated to worse responses. While L-ADH was most observed in pts evaluated ≥12 months from RUX start, periodic ARMS7 administration increased ADH, suggesting that this measure may improve pts compliance.

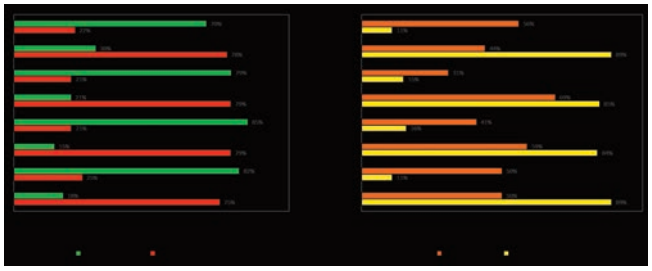


Figure 1.

P166

CLINICAL CHARACTERISTICS AT ONSET AND TREATMENT APPROACHES IN YOUNG AND ELDERLY PATIENTS WITH ESSENTIAL THROMBOCITEMIA (ET): EVALUATION OF RETROSPECTIVE AND PROSPECTIVE LAZIAL DATABASES

A. Andriani[1], M. Breccia[2], I. Carmosino[2], E. Cerchiara[3], A. Romano[4], A.L. Biagi[5], L. Maurillo[6], M. Trawinska[7], K. Paciaroni[8], M. Santopietro[9], S. Leonetti Crescenzi[10], M. De Muro[1], A. D'Addosio[11], C. Tatarelli[12], A. Di Veroli[14], E. Rossi[13], R. Latagliata[14], M. Montanaro[14]

[1]Hematology, Spaziani Hospital, Frosinone; [2]Hematology of Translational and Precision Medicine, Policlinico Umberto I, Sapienza University; Rome; [3]UOC of Hematology and Stem cell transplantation, Campus Biomedico, Rome; [4]UOC Ematologia and Transplants of "Istituto Nazionale Tumori. Regina Elena", Rome; [5]S.M. Goretti Hospital – Polo Pontino "La Sapienza" University, Latina; [6]Hematology, Policlinico Tor Vergata & Department of Biomedicine and Prevention, Tor Vergata University, Rome; [7]UOC of Hematology, Sant'Eugenio Hospital, ASL Roma 2, Rome; [8]UOSD Hematology, ASL Roma 1, Rome; [9]Hematology and Hematopoietic Stem Cells Transplant Unit, AO San Camillo-Forlanini Rome; [10]Hematology and Stem Cell Transplant, St. Giovanni Addolorata Hospital, Rome; [11]UOC Service of immunology and Transfusion Medicine, Villa San Pietro Hosp., Rome; [12]Hematology, Sant'Andrea University Hospital, Sapienza, Rome; [13]Fondazione Policlinico Universitario A. Gemelli - IRCCS, Rome; [14]Hematology, Belcolle Hospital, Viterbo

Background: Essential Thrombocythemia (ET) is the most common Myeloproliferative Neoplasm (MPN): clinical features at diagnosis as well as treatment approaches are different between young and elderly patients (pts), with a worldwide accepted age cut-off of 60 years (yrs).

Aim: To describe clinical features in a large regional cohort of young and elderly pts with ET, we evaluate all pts recorded in the retrospective and prospective databases of Latial Group for MPN study from January 2000 to December 2016.

Table 1. Cardiovascular risk factors and treatment approaches in ET patients according to age.

	Patients over 60 years old: 992			Patients under 60 years old: 622		
CARDIO-VASCULAR RISK FACTORS	0 RF	139 (20.5%)	678	0 RF	180 (42.3%)	426
	1 RF	341 (50.3%)		1 RF	161 (37.8%)	
	2 RF	159 (23.5%)		2 RF	64 (15.0%)	
	≥3 RF	39 (5.8%)		≥3 RF	21 (4.9%)	
	UNKNOWN	314		UNKNOWN	197	
Cytoreductive Treatment	None	58 (7.5%)	775	None	224 (43.8%)	512
	HU	697 (89.9%)		HU	206 (40.2%)	
	ANA	4 (0.5%)		ANA	36 (7.1%)	
	IFN	9 (1.2%)		IFN	40 (7.8%)	
	OTHER	7 (0.9%)		OTHER	6 (0.1%)	
	UNKNOWN	217		UNKNOWN	110	
Antithrombotic Treatment	ASA	572 (75.6%)	757	ASA	400 (81.1%)	493
	TAO	27 (3.6%)		TAO	9 (0.2%)	
	NOAC	2		NOAC	0	
	OTHERs	(TK, PL ,IBU, LMWH) 91		OTHERs	(TK, PL, IBU, LMWH) 31	
	SEQUENTIAL	31 (4.1%)		SEQUENTIAL	19	
	COMBINATION	2		COMBINATION	0	
	NONE	32 (4.2%)		NONE	34 (6.9%)	
	UNKNOWN	235		UNKNOWN	130	

Results: A whole cohort of 1614 pts [median age 66 yrs, interquartile range (IQR) 51 - 75] was analysed. Patients were divided into two groups; Group A with 622 pts aged < 60 yrs. and Group B with 992 pts aged ≥ 60 yrs. Median follow-up was 64 and 60 months, respectively. In both groups female sex was prevalent (63.2%). JAK-2 V617F positivity was 60% in young *vs* 69.7% in elderly pts, with a median allele burden < 20% (9.6% and 19.3%, respectively). Spleen enlargement was reported in 15.8% young *vs* 14.1% elderly (p=0.326), median leukocytes count was 8.35 in young *vs* 8.70 x 10^9/l in elderly (p= 0.021) and median platelet count was 727 x 10^9/l in young *vs* 755 x 10^9/l in elderly (p=0.041). Previous thrombotic events were reported more frequently in elderly (20.0%) than in young pts (12.2%) (p< 0.001), with a 2/3 ratio in favor of arterial events; however, previous splanchnic thromboses were more frequent in young pts. In the Table are reported cardio-vascular risk factors (CVF) (smoke, diabetes, hypertension, dyslipidaemia) and treatments: as expected, CVF were more frequent in elderly, with at least 1 CVF reported 79.5% in elderly *vs* 57.7% in young pts (p<0.001). Antithrombotic treatment was administered in 92.6% of young and 96.1% of elderly (p=0.007): as expected, cytoreductive treatments were started in approximal all elderly pts (92.5%) compared to 57.2% of younger pts (p<0.001).

Conclusions: Real-life observation of a large cohort of unselected ET pts showed that in all Centres of the Lazio region international guidelines for treatment approach were correctly applied.

P167

JAK2 UNMUTATED ERYTHROCYTOSIS: IMPACT OF AGE ON CLINICAL-LABORATORY FEATURES AND MANAGEMENT

M. Bortolotti[1], C. Bucelli[2], D. Cattaneo[1,2], E. Fermo[2], C. Vercellati[2], A. Marcello[2], D. Consonni[2], U. Gianelli[2,3], A. Iurlo[2]

[1]Department of Oncology and Hemato-Oncology, University of Milan; [2]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico; [3]Department of Pathophisiology and Transplantation, University of Milan, Italy

JAK2-unmutated or secondary erythrocytosis (SE) encompasses both hereditary and acquired conditions. Management of SE has been conflicted by unfounded concerns mainly regarding thrombotic risk and treatment. With the aim to describe clinical-laboratory features, treatment approach and outcome of SE patients (pts), we conducted a single-centre retrospective study involving 55 pts. Inclusion criteria were a confirmed erythrocytosis according to 2016 WHO classification thresholds for Polycythemia Vera (PV) and a wild type JAK2 (both exon 14 and 12) mutational status. We excluded pts with a clear cause of secondary erythrocytosis. Selected continuous and categorical variables were compared among groups (pts < and > 40 years) using univariate statistics. Statistical analyses were performed with Stata 16 (StataCorp. 2019). As shown in Table 1, 47 (85%) pts were males with a median age at diagnosis of 39 years; 13 (24%) were active smokers.

Table 1.

Variables	Patients (n= 55)
Age at diagnosis, years; median (range)	39 (15-76)
Males; n (%)	47 (85)
Smoke - Active; n (%) - Previous; n (%) - Never; n (%) "n" evaluable = 55 (100%)	 13 (24) 15 (27) 27 (49)
Previous history of thrombosis; n (%) "n" evaluable = 55 (100%)	5 (9)
Hyperviscosity symptoms at diagnosis; n (%) "n" evaluable = 55 (100%)	14 (25)
Splenomegaly at diagnosis; n (%) "n" evaluable = 50 (91%)	7 (14)
Serum erythropoietin level, UI/l; median (range) "n" evaluable = 54 (98%)	8.7 (<1-51.4)
Hemoglobin, g/dl; median (range) "n" evaluable = 55 (100%)	17.8 (16.0-20.1)
Hematocrit; median (range) "n" evaluable = 55 (100%)	51.5 (48.2-69.1)
Bone marrow aspirate and biopsy; n (%) - signs of erythroid hyperplasia; n (%)	23 (42) 14 (61)
Myeloid next generation sequencing (NGS), n (%) positive; n (%) - oncogenetic variants (DNMT3A, TP53); n (%) - undetermined significance variants (TET2, EZH2, ETV6); n (%)	22 (40) 10 (46) 6 (27) 4 (19)
Congenital screening; n (%) - positive; n (%)	29 (53) 0 (0)
Therapy regimens (exposure, ever) - Phlebotomy; n (%) - Acetylsalicylic acid; n (%) -- 100 mg/d; n (%) -- 75 mg/d; n (%) - both - no therapy	 23 (42) 22 (40) 16 (73) 6 (27) 14 (25) 24 (44)
Thrombotic events; n (%) - at diagnosis; n (%) - during follow-up; n (%)	4 (4) 3 (5) 1 (2)
Hemorrhagic events; n (%)	1 (2)
Follow-up in years; median (range)	4.7 (0.3-28.5)
Deaths; n (%)	0 (0)

A previous history of thrombosis was detected in 5 (9%). Hyperviscosity symptoms were reported in 14 (25%) pts at diagnosis and 7 (14%) had splenomegaly. Median Hb/Hct values at diagnosis were 17.8 g/dl and 51.5%, respectively. Median erythropoietin (Epo) serum levels were 8.7 U/l and resulted below normal limits in 30% of pts. Bone marrow biopsy was available for 23 (42%) pts with signs of erythroid hyperplasia in 61%. Myeloid NGS panel was performed in 22 (40%) pts and revealed variants in 10 (6 with oncogenetic potential and 4 of undetermined significance). Screening for congenital causes of erythrocytosis was performed in 29 (53%) but none was suggestive. Regarding treatment, 23 (42%) pts received at least 1 phlebotomy and 22 (40%) antiplatelet agents. Triggers for phlebotomy were symptoms in 4 pts while a variable Hct threshold (from 45 to 55%) was used in 15. After a median follow-up of 4.7 years (0.3-28.5) we registered 4 (4%) thrombotic events (of whom 3 at diagnosis), 1 hemorrhagic complication and no fatalities. Statistical analysis brought out a trend towards a lower Epo level in younger, symptomatic and NGS mutated pts. Furthermore, antiplatelet agents and phlebotomy were more frequently used in elderly. To the best of our knowledge, this study represents the largest single centre series of SE: even if our data suggest an indolent course, the lack of clear evidence on management and evolution highlight the importance to maintain under control mainly pts younger with NGS mutated or low Epo levels.

P168

PLATELET ACTIVATION MECHANISM IN ESSENTIAL THROMBOCYTHEMIA: ROLE OF ANTI-ENDOTHELIAL CELL ANTIBODIES (AECA)

R. Cacciola[1], V. Vecchio[2], E. Gentilini Cacciola[3], E. Cacciola[4]

[1]Haemostasis Unit, Department of Clinical and Experimental Medicine, [2]University of Catania, Italy, Medical School of Medicine, [3]University of Catania, Italy, Public Health and Infectious Diseases, [4]Sapienza University, Rome, Italy, Medical, Surgical Sciences and Advanced Technologies "G.F. Ingrassia, University of Catania, Italy

Essential Thrombocythemia (ET) is a Philadelphia-negative chronic myeloproliferative neoplasm (MPN) characterized by platelet activation and thrombosis. Platelet activation is linked to inflammatory endothelial activation. Inflammation causes autoimmunity. Autoimmunity causes cytotoxixc anti-endothelial cell antibodies (AECA). If in ET there is platelet activation linked to autoimmune endothelial activation deserves to be investigated. Therefore, we investigated AECA, Endothelial Leukocyte Adhesion Molecule-1 (ELAM-1), Intercellular Adhesion Molecule-1 (ICAM-1), and von Willebrand Factor antigen (VWF:Ag) as markers of endothelial activation and P-selectin as marker of platelet activation. In addition, we evaluated the contribute of AECA to vascular injury by antibody-dependent cellular cytotoxicity. This study included 60 JAK2V617F negative WHO-defined ET patients (25 men and 35 women, mean age 55 years, range 30-50). The mean duration of disease was 8 years (range 2-10 years). All patients were on low-dose aspirin. None had previous thrombosis, cardiovascular risk factors or hereditary thrombophilia. Nobody had autoimmune or inflammatory diseases. 50 blood donors age-and sex matched served as controls. Of 60 patients, after a median follow-up of 6.5 years, 40/60 (67%) (15 men, 25 women; mean age 50 years (range 35-50) had thrombosis, including 15 transient ischemic attack (TIA), 10 stroke, and 15 myocardial infarction (MI). 20/60 (33%) (12 men, 8 women; mean age 52 years (range 30-52) did not develop thrombosis. Magnetic Resonance Imaging (MRI), and electrocardiogram were used to diagnose TIA, stroke, and MI, respectively. AECA, ELAM-1, ICAM-1, VWF:Ag, and P-selectin were measured by ELISA. Cyotoxicity assay was also performed. The patients with thrombosis were AECA positive (IgG ELISA Ratio 24.1±10.1) *vs* the patients without thrombosis (IgG ELISA Ratio 1.7±2.0) and controls IgG ER values (1.6±2.2.). ELAM-1 and ICAM-1 and VWF:Ag were elevated in patients with thrombosis (65±5 ng/ml and 185±10 ng/ml and 80±10 ng/mL) *vs* those without thrombosis (31±1 ng/ml and 91±10 ng/mL and 26±2 ng/mL) and controls (24±5 ng/ml and 79±10 ng/mL and 17±2 ng/mL)

as well as P-selectin (80±10 ng/mL *vs* 25±10 ng/mL *vs* 20±5 ng/mL). Cytotoxicity assay was positive in patients with thrombosis. A positive correlation there was between AECA and P-selectin and thrombosis. These results suggest an additional mechanism of platelet activation in ET patients with unexplained thrombosis.

P169

THE PROGNOSTIC ROLE OF NEUTROPHIL-PLATELET RATIO AND NEUTROPHIL-LYMPHOCYTE RATIO IN RUXOLITINIB-TREATED PRIMARY MYELOFIBROSIS PATIENTS

M. Santoro[1], A. Romano[2], S. Mancuso[1], D. Sirocchi, E. Gigliotta[3], M. Mattana[1], G.A. Palumbo[2], S. Siragusa[1]

[1]Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties (PROMISE), Hematology Unit, University of Palermo, Palermo, Italy; [2]UOC Ematologia AOU Policlinico di Catania, Catania, Italy; [3]Hematology Division University Hospital Policlinico "Paolo Giaccone", Palermo, Italy

Until today, there are no biological predictors of ruxolitinib response in myelofibrosis patients. An elevated ratio between absolute neutrophil count and absolute lymphocyte count (NLR, neutrophil to lymphocyte ratio) is a marker of inflammation and is known to be associated with progression-free survival (PFS) and overall survival (OS) in other diseases. Similarly, a high ratio between absolute neutrophil count and platelet count (NPR, neutrophil-to-platelet ratio) was studied in other diseases and linked to detrimental prognosis. High NLR and PLR were associated with worse OS and PFR in different non-hematological diseases (both neoplasms and infective diseases), but failed to achieve significance in predicting prognosis of Hodgkin Lymphoma patients. In myeloproliferative diseases, an elevated NLR was associated with the incidence of venous thrombosis, but not with other variables. Recently ruxolitinib have demonstrated to improve not only quality of life, but also overall survival in patients with myelofibrosis. The aim of our study is to evaluate whether NLR and NPR may predict a better overall survival in patients with primary myelofibrosis (PMF) treated with ruxolitinib. Data from 154 patients with PMF treated with ruxolitinib in real life were retrospectively collected and divided into two cohorts (#1, study cohort, and #2, validation cohort) in relation to the hematology center the patients referred to (cohort #1 Palermo, cohort#2 Catania). We excluded patients preventively treated with steroids, diagnosed with HIV or an active autoimmune disease, in order to remove biases from the determination of NLR and NPR (neutrophilia of lymphopenia non-PMF determined). Cutoff values were mutated from other studies and adapted when necessary to our group of patients. For NLR the cutoff value was 6 according to previous studies, for NPR the cutoff value was considered as 100, being it the 75° percentile in both cohorts. Median follow-up was 50 months. NLR (<6 *vs* ≥6) distinguished patients with a better OS in cohort #1 but not in cohort #2. On the other hand, NPR ≥100 identified patients with a worse OS in both cohorts, with statistical significance (HR = 20.2 and p= 0.003 in cohort #1; HR = 3.1 and p = 0.006 in cohort #2). NLR≥6 and NPR≥100 are easy-to-use and potentially useful biomarkers in patients with myelofibrosis and indication to ruxolitinib, to identify patients with a worse OS. Evaluation in prospective trials are needed to achieve stronger data in this field.

P170

COEXISTENCE OF CLONAL B LYMPHOCYTE DISORDERS AND MYELOPROLIFERATIVE DISEASES WITH JAK2 GENE MUTATION: ASSESSMENT OF INCIDENCE

D. Avino, M. Di Rosa, M. Di Perna, F. Castelgrande, A. Cascone, M. Casciello, A. Di Palma, V. Belsito, M. Lucignano, C. Califano

UOC Ematologia, Presidio Ospedaliero Andrea Tortora, Italy

The incidence of secondary neoplasia or another tumor of the hematopoietic system is increased in individuals with myeloproliferative neoplasia (MPN) with JAK2 gene mutation. Coexistence of MPN and Lymphoproliferative Disorders (LPD) in the same patient has been reported sporadically in the literature. In this work retrospectively evaluated the incidence of LPD in 265 patients who had received a diagnosis of MPN JAK2+ at our facility; moreover, in 99 patients diagnosed with MPN JAK2+ we investigated the presence of a subclinical condition defined as monoclonal B lymphocytosis (MBL). The retrospective case series showed the presence of LPD in 26 patients (9.8%) with a male/female ratio of 1:2.

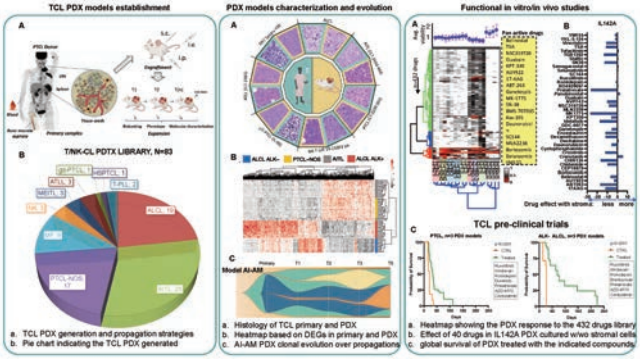


Figure 1.

In particular: 9 (3.4%) developed a Chronic Lymphatic Leukemia/Lymphoma (LLC/LNH), 2 (0.7%) Multiple Myeloma (MM) and 15 (5.6%) a Monoclonal Gammopathy of undetermined significance (MGUS). In most cases, the diagnoses of MPN and LPD were concomitant; the two cases of MM were unexpectedly diagnosed 13 and 14 years after the diagnosis of PV. Of the 99 MPN JAK2+ patients, 18 (18%) showed the presence of clonal restriction of surface immunoglobulins. 4 patients diagnosed with MDS/MPN-RS-T JAK2+ were also included in this study and all 4 showed the presence of a lymphocyte B clone. The increased incidence of MGUS and MPN in our patients may be due to the increased incidence of MGUS in the general population. Further studies are needed to identify cases of MGUS and MBL at higher risk of progression, and the presence of the JAK2 mutation may be an added risk factor. On the basis of this experience, given that clinically there may be an overlap of signs and symptoms that may be common to MPN and LPD, evaluation of the protein panel and the search for lymphocyte B clones at the diagnosis of MPN could represent a simple and inexpensive system to identify and better monitor patients at risk of developing LPD. 4 patients, were diagnosed with solid neoplasia prior or subsequent to the diagnosis of hematologic disease; one of the patients who presented MM post PV was diagnosed with pulmonary neoplasia. Indirectly, this finding supports the theory of global genetic instability of pluripotent hematopoietic progenitors in Myeloproliferative Neoplasms.

P171

SIGNIFICANT IMPROVEMENT OF THE SPIKE-SPECIFIC ANTIBODY AND MEMORY B CELL RESPONSE AFTER THIRD DOSE OF MRNA SARS-COV-2 VACCINES IN MYELOFIBROSIS PATIENTS

A. Santoni[1], F. Fiorino[2], M. Simoncelli[1], A. Ciabattini[2], A. Sicuranza[1], G. Pastore[2], J. Polvere[2], S. Galimberti[3], S. Auddino[2], C. Baratè[3], V. Sammartano[1], D. Medaglini[2], M. Bocchia[1]

[1]Hematology Unit, Department of Medical Science, Surgery and Neuroscience, Azienda Ospedaliero Universitaria Senese, University of Siena; [2]Laboratory of Molecular Microbiology and Biotechnology, Department of Medical Biotechnologies, University of Siena; [3]Hematology Unit, Department of Clinical and Experimental Medicine, Azienda Ospedaliero Universitaria Pisana, University of Pisa, Italy

Immunization with mRNA SARS-CoV-2 vaccines has been highly recommended in fragile subjects, including patients (pts) with myelofibrosis (MF). MF pts may receive clinical benefits from Ruxolitinib (Ruxo), a JAK1/JAK2 inhibitor that deeply reduces inflammatory cytokine production and impairs to some extent cellular immune responses. We earlier demonstrated that after 2 doses of mRNA SARS-CoV-2 vaccine, MF pts, especially under Ruxo treatment, developed spike-specific IgG with slower kinetics compared to healthy subjects. This impairment furnished a strong rationale for a 3rd vaccine dose.

Here, we profile both antibody and memory B cell spike-specific immune response in MF pts with or without Ruxo treatment after the 2nd and 3rd dose of mRNA SARS-CoV-2 vaccines BNT162b2 (BioNTech) and mRNA-1273 (Moderna). Of a total of 39 MF pts enrolled in the study and receiving 3 doses of mRNA anti-SARS-CoV-2 vaccine, induced immune response was evaluated both after 2nd and 3rd dose in 19/39 pts. Spike-specific antibody titers were detected by ELISA and ACE2/RBD binding inhibition was tested with a SARS-CoV 2 surrogate virus neutralization test kit. Multiparametric flow cytometry was used to identify SARS-CoV-2-specific B-cells. The number of pts showing anti-spike IgG arised from 15/19 (79%) after 2nd dose to 17/19 (89%) after 3rd dose with a mean antibody titer increasing from 10467 of 37861 accordingly. The percentage of MF pts who developed a positive inhibition activity (>30%) after 2nd dose was 47% (9/19) and it increased to 84% (16/19) after 3rd dose. Even spike-specific B cells showed a consistent increase being detected in 38% (7/19) of pts after 2nd dose and in 74% (14/19) after 3rd dose. Analyzing vaccine induced response according to treatment, 8/19 (42%) MF pts were on Ruxo, while 11/19 (58%) received hydroxyurea or supportive therapy. Of note, 100% (8/8) of Ruxo treated and 82% (9/11) of untreated pts developed spike-specific plasma IgG response after 3rd dose, despite with a lower mean titer in the Ruxo group (16800 versus 53178). Furthermore, we detected spike specific B cell in 87% (7/8) of Ruxo treated pts and 64% (7/11) of untreated pts, with ACE2/RBD inhibition binding activity evident in 87% (7/8) and 82% (9/11) of pts, respectively. In summary, our study demonstrates the capacity of 3rd mRNA vaccine dose to boosting inhibition binding activity, memory B cell response and anti-spike IgG response in all MF pts, regardless the treatment with Ruxo.

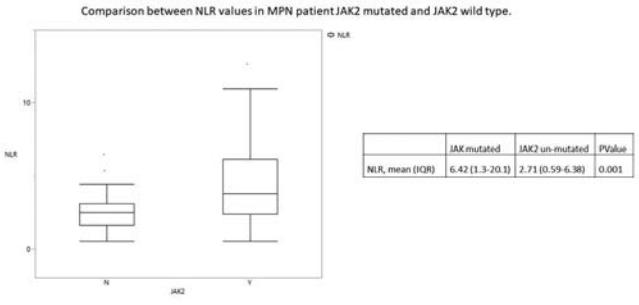
P172

CORRELATION BETWEEN NEUTROPHIL-TO-LYMPHOCYTE RATIO AND JAK2 V617F MUTATION IN MPN PATIENTS WITH THROMBOSIS

E. Morsia, E. Torre, F. Marrara, G. Goteri, P. Antonella, A. Olivieri, S. Rupoli

Clinica di Ematologia, Ospedali Riuniti di Ancona, Università Politecnica delle Marche, Italy

Myeloproliferative neoplasms (MPN) are a heterogenous group of hematopoietic stem cell disorders with a natural history marked by vascular complications. The pathogenesis of thrombosis results from a complex interplay of disease-related and patient-related factors in which the systemic inflammation has a pivotal role. In the least years, neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) emerged as inflammatory status markers and they were associated with poor survival in cancers and with higher mortality in major cardiac events. Recently, a sub-analysis of ECLAP study demonstrated that NLR is an independent risk factor for venous thrombosis in PV patients. The aim of this study is analyzed in a cohort of 113 patients with MPN according to WHO 2016 and at least a thrombotic event after the diagnosis, the role of NLR and PLR as inflammatory biomarkers in the clinical presentation and the outcome of these patients. Patients and disease features are summarized in Table 1. During a median follow up of 94.3 months (range, 2.4-416.0), arterial and venous thrombosis occurred in 29 (26%) and 84 (74%) patients with MPN, respectively. MPN patients whom will develop an arterial event are older (pV=0.046), with more cardiovascular risk factors (pV=0.001), higher JAK2 V617F allelic burden in PCR (pV=0.041) and higher monocytes level (pV=0.001) at diagnosis compared to those with venous thrombosis. No significantly differences in terms of NLR and PLR were observed comparing MPN patients with arterial or venous events during the follow-up (pV=0.23 and 0.38, respectively). Moreover, in our cohort of patients NLR and PLR are not correlated with recurrence thrombosis rate or overall survival. Finally, we find a correlation between NLR values and JAK2 V617 mutation (Figure1). Patients with JAK2 V617F as MPN driver mutation and a thrombotic event presented higher NLR values compared to those with different driver mutation (CALR, MPL, or triple negative). In conclusion, our data suggested a different role of inflammation in thrombogenesis of MPN according to molecular landscape, underlying the central role of inflammation in JAK2 mutated patients with thrombosis and the likely presence of different mechanisms in the pathogenesis of thrombosis in JAK2 wild type patients.



	JAK mutated	JAK2 un-mutated	PValue
NLR, mean (IQR)	6.42 (1.3-20.1)	2.71 (0.59-6.38)	0.001

Figure 1.

P173

MPN WITH CONCOMITANT MGUS DIAGNOSIS: A RETROSPECTIVE STUDY

C. Fatigati, F. Antonucci, L. De Fazio, R. Iannotta, M. Lamagna, A. Fiumarella, A. Leone, F. Muriano, G. Scariati, V. Martinelli, F. Pane, N. Pugliese

University of Naples Federico II, Italy

Patients with Ph-negative MPN may harbor MGUS and MM. The clinical and molecular determinants of this co-occurrence are still uncertain. This study wants to evaluate the correlation between MGUS and MPN related features and clinical course. We retrospectively analyzed clinical data from 448 consecutive patients with a diagnosis of MPN (revised ac-

cording to 2016 WHO criteria) performed from 1989 to 2020 at our Institution. Data collection included molecular and cytogenetic analysis, clinical history (including thrombotic events) and therapy during the entire MPN follow-up. Among the 448 consecutive patients, 33 (7.4%) displayed both MPN and MGUS (33 females and 10 males). MPN diagnosis were ET (36%), MF (33%), PV (25%), or pre-MF (6%), the median age was 61 yrs (28-84); 25 (75.8 %) patients harbored JAK2V617F mutation, 3 (9.1%) patients type I CALR mutation, 1 patient (3%) W515K MPL mutation (3%), and 4 (12.1%) were triple negative. For 30 patients MPN diagnosis incurred before (57.6%) or synchronous (33%) with MGUS diagnosis, only 3 patients (9.1%) had MGUS diagnosed before MPN. Serum M protein consisted in a majority of IgG (84.8%, 14 cases ʎ e 14 ƙ light chain), 2 cases of IgA and 1 case of IgM protein with a median count of 1.04 plasma-cells in bone marrow aspirate at diagnosis. After a median follow-up of 7 yrs (1 to 30 yrs), 5 patients (15.2%) originated a second hematological malignancy (3 (10%) developed LNH, 1 MM and 1 developed AML) and 2 patients (6.1%) evolved in MF. Molecular and cytogenetic analysis, clinical history and MPN specific therapies don't seem to influence the clinical course. There are few publications highlighting coexistence of MGUS in MPN patients. Little is known about the underlying molecular mechanisms and there aren't guidelines clarifying whether a particular treatment or follow-up is necessary. In our MPN cohort the incidence of MGUS is higher than general population. Although, this data can be influenced by a more accurate hematological follow-up, including serum protein electrophoresis, we can't exclude a real increased rate of MGUS among MPN patients. Interestingly, in our cohort the percentage of patients who developed second hematological malignancies seemed slightly higher than literature data MPN patients without MGUS. Further studies with case-control cohort are necessary to better understand the possible detrimental influence between MPN and MGUS.

P174

A RARE CASE OF ACML ASSOCIATED WITH CNS INVOLVEMENT AND WITH AGGRESSIVE CLINICAL COURSE

D. Lame, M. Pianelli, E. Morsia, A. Carturan, G. Goteri, S. Mancini, A. Olivieri, A. Poloni

AOU Ospedali Riuniti di Ancona, Italy

The presence of neutrophilic leukocytosis may underlie a wide variety of diseases. Some rare causes of neutrophilia might be chronic neutrophilic leukemia (CNL) and atypical chronic myeloid leukemia (aCML).

Here we report a case of a 78-year-old woman who came to our ER due to severe leukocytosis 74.410/m^3, with ANC 52830/mm^3, lymphocytes 5950/mm^3, eosinophils 740/mm^3, monocytes 1490/mm^3, promyelocytes 2%, myelocytes and metamyelocytes 14%, thrombocytopenia (P) 24.000/mm^3 and anemia (Hb 6,3 g/dl) on a routine check-up. The patient was asymptomatic and the last exams available showed a mild leukopenia and thrombocytopenia. The abdominal echography showed mild splenomegaly (15.5cm). In the hypothesis of a Myeloproliferative Neoplasm in the blast phase, it was administered Hydroxycarbamide 1 g/die and the patient was given support therapy. The patient underwent bone marrow (BM) examinations: (i) ago aspirate showed hypercytosic BM dominated by a myeloid hyperplasia of 70% with reduced maturation of the myeloid lineage without blast excess and a reduced and dysplastic erythroid lineage. The megakaryocytes were not suggestive of a PMF; (ii) normal karyotype (iii) JAK2V617F and BCR-ABL were negative. (iv) BM biopsy showed hypercytosic with emphasized granulopoiesis and 2% of immature precursors; (v) NGS showed: CSF3R T618I, IDH2 R140Q and STAG2 R1033T. One week later, the patient presented mental deterioration. On the blood exams: WBC 34500/m^3, Hb 9,5 g/dl, P 14.000/m^3. The patient underwent a cranial CT and RMN that showed multiple lesions of 11mm in the brain parenchyma, cerebellum and encephalic trunk. Another week later, the clinical presentations worsened: she was in a comatous state and feverish 40°C unresponsive to steroid therapy. During these days the WBC went on doubling, until they reached the following values WBC 195.740/mm3, ANC 133.100/mm^3, blasts 2%. In a very short time the patient died. Autopsy showed a leukemic and hemorrhage infiltration in multiple organs and in the BM a cellularity of 100% represented by myeloid elements with a slowdown maturation with blasts 5%. According to WHO 2016 this case can be reported as an aCML, an MDS/MPN overlap syndrome that is difficult to differentiate from a CNL. It is characterized by leukocytosis with dysplastic neutrophilia and an increase of their precursors, hypercellular BM with granulocytic dysplasia and blasts <20%. The presence of CSF3R mut is uncommon, but it does not rule out the diagnosis of aCML.

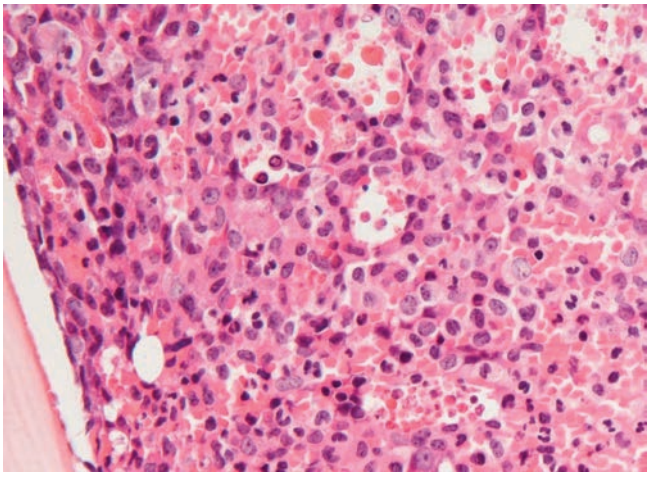


Figure 1.

P175

ABSTRACT NOT PUBLISHABLE

Chronic myeloid leukemia, myelodysplastic syndromes, cytogenetics and molecular genetics

P176

ABSTRACT NOT PUBLISHABLE

P177

THALASSEMIA CARRIER STATUS IS ASSOCIATED WITH A BETTER LIPOPROTEIN PROFILE IN PATIENTS WITH CHRONIC MYELOID LEUKEMIA TREATED WITH TYROSINE KINASES INHIBITORS

O. Mulas, G. Caocci, S. Chiriu, L. Nissardi, D. Mantovani, G. La Nasa

Ematologia e Centro Trapianti Midollo Osseo, Ospedale Businco, ARNAS G. Brotzu, Dipartimento di Scienze Mediche e Salute Pubblica, Università di Cagliari, Italy

Introduction: Beta-thalassemia major is a common monogenic disease characterized by abnormal hemoglobin structure. Thalassemia carrier status (Tcs) is a clinically silent condition characterized by mild anemia and hypochromic microcytosis widespread in the Mediterranean area. Pieces of evidence showed that the subjects with this defect have lower levels of cholesterol and a lower incidence of thrombotic events. Tyrosine kinases inhibitors (TKI), in particular second and third-generation classes, were associated with dyslipidemia in chronic myeloid leukemia (CML).

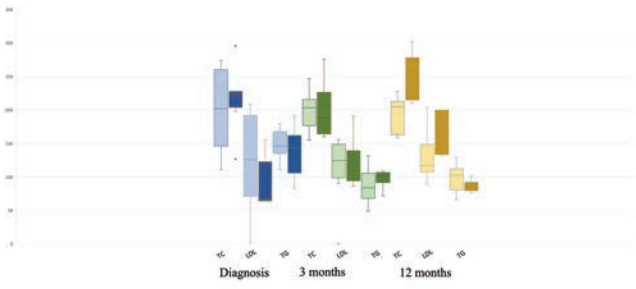


Figure1: Box plot diagram showing the distribution of lipoproteins levels (total cholesterol, low-density lipoprotein, and triglycerides at diagnosis, 3 and 12 months of TKI treatment in patients with CML. Light color = thalassemia carrier status group; dark color = control group

Figure 1.

Objectives: This study aims to compare the mean lipid levels in CML patients with or without Tcs, treated with TKI.

Methods: Twenty-one CML patients with Tcs and 19 normocytemic were evaluated in our institution between December 2003 and June 2021. The lipoprotein profile, including total cholesterol (TC), low-density lipoprotein (LDL), and triglycerides (TG), were collected at diagnosis, 3 and 12 months after starting TKI.

Results: A total of 40 patients were recruited. The median follow-up was 40 months (range 6-98). Overall, 22 (55%) patients received imatinib as the first line of therapy, 6 (15%) dasatinib, and 12 (30%) nilotinib. Neither of the patients had a previous history of dyslipidemia. In the Tcs group, 10 patients (47,6%) were male, 16 (84,2%) in the control group. The mean age at diagnosis was 51 years (24-86) in Tcs group, 48 years (20-79) in the control group. Overall, at diagnosis, in Tcs patients, the mean levels of TC, LDL and TG were 199mg/dl, 105 mg/dl and 149 mg/dl, respectively. In the control group, we found TC 216mg/dl, LDL 94mg/dl and TG 137mg/dl (P=NS). After 3 months of therapy, an increase of lipid values was detected in the control group (TC 209mg/dl, LDL 124mg/dl TG 96mg/dl) but it was less evident in the Tcs group (TC 199mg/dl, LDL 128 mg/dl, TG 87 mg/dl). This trend was confirmed after 12 months of treatment with TC 196mg/dl and 250mg/dl (P=0.01), LDL 132 mg/dl and 167mg/dl, TG 99 mg/dl and 77mg/dl in the Tcs group and control group, respectively. The boxplot was shown in Figure 1.

Conclusions: Our results suggest that the condition of Tcs is associated with a better lipid profile after TKI treatment. In this context, CML patients with Tcs condition seem less exposed to thrombotic risk in comparison with the control group and could be treated with TKIs associated with higher incidence of cardiovascular complications. Further studies are needed on this CML subgroup.

P178

CONCOMITANT ADMNITSRATION OF METFORMIN AND TYROSINE KINASE INHIBITORS IN CHRONIC PHASE CHRONIC MYELOID LEUKEMIA PATIENTS: A POSSIBLE SYNERIGISTIC EFFECT?

C. Luise, E. Scalzulli, C. Ielo, P. Musiu, G.M. Assanto, M. Martelli, M. Breccia

Hematology, Department of Translational and Precision Medicine, Sapienza University, Italy

The introduction of tyrosine kinase inhibitors (TKIs) has revolutionized the outcome of chronic myeloid leukemia (CML) patients; nevertheless, a proportion of patients do not respond adequately to therapy due to intolerance or resistance, and this represent an unmet medical need. Recently, there have been considerable research advances on the antileukemic mechanisms of the antidiabetic drug metformin. In CML, BCR-ABL fusion protein abnormally regulates various downstream signaling pathways, such as SRC, STAT5, PI3K/AKT/mTOR, and others, resulting in an increased proliferation, decreased apoptosis, or reduced growth factor dependence of tumor cells. Metformin is a widely prescribed glucose-lowering agent, and in preclinical studies has been shown to suppress cell viability, induce apoptosis, and downregulate the mTORC1 signaling pathway in resistant CML cells, suggesting a potential synergism between the two drugs. We conducted a retrospective single-center study to evaluate the outcome of CML patients treated with TKIs and concomitant metformin administration. Our analysis included 402 newly diagnosed chronic phase CML patients treated with all available TKIs, including 24 diabetic patients, whose 19 in treatment with metformin (Table 1).

Table 1. Baseline characteristics.

	Metformin group n (%)	No metformin group n (%)
	19 (5)	383 (95)
Age, years (range)	69.7 (45.6-79.4)	57.6 (20.4-86.9)
Male Female	10 (53) 9 (47)	209 (54.5) 174 (45.5)
Sokal score: • High • Intermediate • Low	 0 14 (73) 5 (26)	 33 (9) 165 (43) 181 (47)
First line TKI therapy: • Imatinib • Dasatinib • Nilotinib	 12 (63) 7 (37) 0	 294 (77) 30 (8) 59 (15)

Imatinib was administered in more than 60% of the diabetic patients. Considering the 2 cohort of patients (metformin and no metformin), we observed no significant difference in overall survival (179 *vs* 151 months, p= 0.315) and event free survival (110 *vs* 107 months, p= 0.563), regardless of TKI treatment. However, 11/19 evaluable patients of metformin

group (58%) achieved at least an MMR at 12 months comparing to 53% in no metformin group (p=0.176). DMR (MR4-MR4.5) were reached in 40% of metformin group and 22% in no metformin group, at last evaluation (p=0.03). In the metformin arm were reported 89% of grade 1-2 adverse events versus 65% in non metformin one (hematological toxicities were described in 30% in both cohorts). Forty-five patients (11%) were resistant to first line treatment, no one belonged to metformin group. In conclusion, our experience, with the limitation of a relatively small sample size of diabetic patients treated concomitantly with metformin, shows that the concomitant use of TKI and metformin may have a synergistic effect, increasing the proportion of patients achieving a DMR. However, further investigations are needed to confirm the clinical antileukemic benefit of the combination.

P179

IRF4 GENE DYSREGULATION IN CHRONIC MYELOID LEUKEMIA: CULPRIT OR BYSTANDER?

F. Tarantini[1], C. Cumbo[1], E. Parciante[1], L. Anelli[1], A. Zagaria[1], N. Coccaro[1], C.F. Minervini[1], G. Tota[1], I. Redavid[1], M.R. Conserva[1], I. Attolico[1], A. Russo Rossi[1], G. Specchia[2], P. Musto[1], F. Albano[1]

[1]Department of Emergency and Organ Transplantation (D.E.T.O.) - Hematology and Stem Cell Transplantation Unit - University of Bari "Aldo Moro"; [2]School of Medicine, University of Bari "Aldo Moro", Italy

Introduction: Interferon regulatory factor 4 (IRF4) is involved in the differentiation of granulocytes, macrophages and myeloid-derived suppressor cells (MDSCs). Its downregulation in chronic myeloid leukemia (CML) in the pre-tyrosine kinase inhibitors (TKI) era is demonstrated. We evaluated IRF4 expression kinetics in CML follow-up to elucidate its possible pathogenesis role.

Methods: We evaluated 130 samples: 113 peripheral blood (PB) from 38 CML patients (pts), K-562 cell line, 16 healthy controls (HC) PB. IRF4 ddPCR absolute quantification was performed. The quantification was calculated as the ratio between IRF4 and GUSB number of transcript copies (I/G). Statistical analyses were performed with GraphPad Prism 8.3.

Results: IRF4 was downregulated in K-562 cells (median 0.0010 I/G, p=0.0025) and CML pts at diagnosis (median 0.0125 I/G, p<0.0001) compared to HC PB (median 0.2594 I/G). Re-evaluation at the time of the best molecular response (MR) in 31 CML pts upon TKI treatment showed a 10-fold higher value (median 0.1544 I/G) than at diagnosis but lower than HC (p=0.0012). The IRF4 expression in pts achieving their best MR in >5 years was comparable to HC. Conversely, in pts reaching the best MR in <5 years, IRF4 expression remained lower than HC (median 0.1276 I/G, p<0.0001). Upon initiation of TKI, a significant increase of IRF4 expression was detectable after three months of treatment (median 0.2214 I/G, p=0.0002) compared to diagnosis, while minor fluctuations were detected after 6, 12 months, and at the time of best MR. Moreover, we evaluated seven patients attempting a "treatment-free remission" (TFR); of them, 4/7 relapsed (loss of MR3) within six months. Interestingly, at that time, IRF4 expression fell under the normal lower range value (median 0.1213 I/G, p=0.085) and raised to normal values after TKI resumption (median 0.2442 I/G, p=0.42). The remaining pts in TFR showed no significant IRF4 fluctuations at different time points.

Conclusion: Considering its complex functions (i.e., inhibition of granulocytes differentiation, modulation of immune surveillance through the MDSCs and macrophages), IRF4 could play a key role in CML biology. Our preliminary data show that IRF4 expression in CML may be affected by TKI treatment and, probably, associated with different factors (i.e., time exposure to TKI), thus suggesting a biological role that needs further study. The IRF4 gene expression role in the TFR duration deserves to be further investigated.

P180

LOW-DOSE TKIS IN CHONIC MYELOID LEUKEMIA PATIENTS: A CAMPUS CML REAL-LIFE STUDY

A. Iurlo[1], D. Cattaneo[1,2], S. Artuso[1], C. Bucelli[1], E. Abruzzese[3], V. Accurso[4], M. Annunziata[5], S. Barulli[6], G. Beltrami[7], M. Bergamaschi[8], G. Binotto[9], M. Bocchia[10], M. Bonifacio[11], G. Caocci[12], I. Capodanno[13], M. Caramella[14], F. Castagnetti[15], F. Cavazzini[16], E. Crisà[17], M.S. De Candia[18], C. Elena[19], S. Galimberti[20], A. Gozzini[21], M. Crugnola[22], M. Iezza[15], G. La Barba[23], R. Latagliata[24], L. Levato[25], G. Loglisci[26], L. Luciano[27], F. Lunghi[28], D. Luzi[29], A. Maggi[30], A. Malato[31], B. Martino[32], M.C. Miggiano[33], P. Murgano[34], M. Pizzuti[35], P. Pregno[36], D. Rapezzi[37], G. Rege-Cambrin[38], S. Russo[39], R. Sancetta[40], G. Sanpaolo[41], A.R. Scortechini[42], F. Sorà[43], P. Sportoletti[44], F. Stagno[45], A. Tafuri[46], M. Tiribelli[47], C. Fava[48], G. Rosti[49], R. Foà[50], G. Saglio[48], M. Breccia[50]

[1]Hematology Division, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico; [2]Department of Oncology and Hemato-Oncology, University of Milan; [3]Hematology Division, Sant'Eugenio Hospital; [4]Hematology Division, University Hospital Policlinico "Paolo Giaccone"; [5]Division of Hematology, AORN Cardarelli; [6]Hematology and Hematopoietic Stem Cell Transplant Center, AORMN; [7]Hematology and Bone Marrow Transplantation Unit, IRCCS Ospedale Policlinico San Martino; [8]Department of Internal Medicine, Santa Corona Hospital; [9]Department of Medicine, Hematology and Clinical Immunology, Padua School of Medicine; [10]Hematology Unit, Azienda Ospedaliera Universitaria Senese; [11]Department of Medicine, Section of Hematology, University of Verona; [12]Hematology Unit, Businco Hospital, University of Cagliari; [13]Hematology Unit, Azienda Unità Sanitaria Locale-IRCCS; [14]Division of Hamatology, ASST Grande Ospedale Metropolitano, Niguarda; [15]Institute of Hematology "L. and A. Seràgnoli", Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna, "S. Orsola-Malpighi" Hospital; [16]Hematology Unit, Azienda Ospedaliero-Universitaria "S. Anna"; [17]Division of Hematology, Department of Translational Medicine, Università del Piemonte Orientale and Azienda Ospedaliero-Universitaria Maggiore della Carità; [18]Hematology Unit, Hospital A. Perrino; [19]Hematology Unit, Fondazione IRCCS Policlinico S. Matteo; [20]Department of Clinical and Experimental Medicine, University of Pisa; [21]Division of Hematology, AOU Careggi; [22]Hematology Unit, Università degli Studi di Parma; [23]Hematology Unit, Azienda USL di Pescara; [24]Division of Hematology, Belcolle Hospital; [25]Hematology Unit, Ospedale Catanzaro; [26]Hematology Unit, Ospedale Lecce; [27]Division of Hematology, Department of Clinical Medicine and Surgery, Federico II University; [28]Hematology Unit, Ospedale S. Raffaele; [29]Hematology Unit, A.O. Santa Maria; [30]Division of Hematology, Hospital "S.G. Moscati"; [31]Hematology Unit, Ospedali Riuniti 'Villa Sofia-Cervello'; [32]Hematology Unit, Grande Ospedale Metropolitano-G.O.M. Bianchi-Melacrino-Morelli; [33]Division of Hematology, San Bortolo Hospital; [34]Division of Hematology, Sant'Elia Hospital; [35]Hematology Unit, Ospedale Potenza; [36]Division of Hematology, AOU Città della Salute e della Scienza; [37]Hematology Unit, Ospedale Cuneo; [38]Division of Internal Medicine and Hematology, San Luigi Gonzaga Hospital, Orbassano; [39]Division of Hematology, Dipartimento di Patologia Umana dell'Adulto e dell'Età Evolutiva, Policlinico G. Martino, University of Messina; [40]Hematology Unit, Ospedale Mestre; [41]Department of Hematology and Stem Cell Transplantation Unit, IRCCS Casa Sollievo della Sofferenza Hospital; [42]Division of Hematology, Department of Molecular and Clinical Sciences, Polytechnic University of Marche; [43]Institute of Hematology, Università Cattolica Sacro Cuore; [44]Hematology Unit, Ospedale Perugia; [45]Hematology Section and BMT Unit, AOU Policlinico 'Rodolico-San Marco'; [46]Division of Hematology, Azienda Ospedaliera Universitaria Sant'Andrea; [47]Division of Hematology and BMT, Department of Medical and Morphological Research, University of Udine; [48]Department of Clinical and Biological Sciences, University of Torino; [49]Scientific Direction, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori"; [50]Hematology, Department of Precision and Translational Medicine, Policlinico Umberto 1, Sapienza University

Introduction: In chronic myeloid leukemia (CML) long-term exposure to TKIs has been associated with chronic adverse events (AEs) that can negatively impact on patients' quality of life (QoL) and may promote relevant morbidity and mortality. The TKI dose is usually reduced after the emergence of AEs but also in the setting of a dose optimization process aimed at reducing the risk of AEs, improving QoL as well as at promoting and maintaining a deep molecular response.

Aim: To explore the use of TKIs at a reduced dose in CML patients by Italian hematologists.

Methods: In September 2020 a questionnaire was sent to the 54 Italian hematology centers participating in the Campus CML. This interactive network of hematologists expert in the field of CML aims at sharing experiences and improving all steps of CML management through a continued education process. The online survey consisted of questions on the use of reduced doses of TKIs in the daily clinical practice.

Results: The survey was completed by 49 (90.7%) of the 54 centers involved. Most Italian hematologists (62.5%) started TKI treatment at the standard dose, with possible dose reductions during the follow-up. All centers reported CML patients managed on low-dose TKIs: overall, in 1.741 of the 5.108 (34.1%) regularly followed CML-chronic phase patients. More specifically, a reduction in TKI dose occurred in 714 (27.0%) out of 2.648 patients treated with imatinib, 344/1.133 (30.4%) with nilotinib, 305/813 (37.5%) with dasatinib, 211/294 (71.8%) with bosutinib and 167/220 (75.9%) with ponatinib. The TKI dose was reduced in most patients (1.208, 69.4%) because of AEs or comorbidities, while in the remaining patients (533, 30.6%) TKIs were de-escalated after achieving the optimal molecular target.

Conclusions: In this large series of real-life CML patients managed in Italy, treatment with low-dose TKI represents an important reality. As expected, bosutinib and ponatinib are the drugs most frequently used at a reduced dose. It is important to underline that treatment with TKIs was usually started at the standard dose (except for elderly patients or for patients with significant comorbidities), with almost 30% of TKI dose reductions carried out in the clinical practice to optimize long-term treatment after achieving an optimal molecular response. The updated results will be presented.

P181

CHOICE OF TYROSINE KINASE INHIBITOR AND EARLY EVENTS DURING THE FIRST YEAR OF THERAPY IN NEWLY DIAGNOSED CHRONIC PHASE CML PATIENTS WITH CONCOMITANT DIABETES: A "CAMPUS CML" STUDY

I. Capodanno[1], M. Tiribelli[2], M.C. Miggiano[3], C. Bucelli[4], F. Cavazzini[5], S. Leonetti Crescenzi[6], S. Russo[7], E. Scalzulli[8], A. Bernardelli[9], L. Luciano[10], O. Mulas[11], G. Loglisci[12], C. Elena[13], U. Pizzano[2], I. Attolico[14], G. Binotto[15], E. Crisà[16], P. Sportoletti[17], A. Di Veroli[18], A.R. Scortechini[19], A.P. Leporace[20], M. Basile[21], M. Crugnola[22], F. Stagno[23], P. Murgano[24], D. Rapezzi[25], D. Luzi[26], A. Iurlo[4], M. Bocchia[27], C. Fava[28], A. Malato[29], S. Galimberti[30], I. Vincelli[31], M. Trawinska[32], M. Pizzuti[33], G. Caocci[11], M. Bonifacio[9], G. Saglio[34], G. Specchia[14], M. Breccia[8], R. Latagliata[18]

[1]Hematology Unit, Azienda Unità Sanitaria Locale-IRCCS; [2]Division of Hematology and BMT, Department of Medical Area, University of Udine; [3]Hematology Department, San Bortolo Hospital; [4]Division of Hematology, Foundation IRCCS Ca' Granda-Ospedale Maggiore Policlinico; [5]Hematology Unit, University of Ferrara; [6]Hematology, San Giovanni Hospital; [7]Hematology, University of Messina; [8]Department of Cellular Biotechnologies and Hematology, "Sapienza" University ; [9]Department of Medicine, Section of Hematology, University of Verona; [10]Hematology, University Federico II; [11]Department of Medical Sciences and Public Health, University of Cagliari; [12]Hematology, Vito Fazzi Hospital; [13]Hematology, Policlinico San Matteo, University of Pavia; [14]Hematology and Transplantation Unit, University of Bari; [15]Department of Medicine, Hematology and Clinical Immunology, University of Padua; [16]Hematology, Ospedale Maggiore; [17]Hematology, University of Perugia; [18]Hematology Unit, Ospedale Belcolle; [19]Hematology Unit, Azienda Ospedaliero Universitaria Ospedali Riuniti; [20]Hematology Unit Azienda Ospedaliero Universitaria Sant'Andrea; [21]Hematology, San Giuseppe Moscati Hospital; [22]Hematology, University of Parma; [23]Hematology, Ferrarotto Hospital; [24]Division of Hematology, Sant'Elia Hospital; [25]Hematology, AO Santa Croce e Carle; [26]Onco-Hematology Department, AO Santa Maria; [27]Hematology, AOU Senese; [28]Hematology, Mauriziano Hospital; [29]Hematology, Cervello Hospital; [30]Hematology, University of Pisa; [31]Hematology, Bianchi-Melacrino-Morelli Hospital; [32]Hematology, Sant'Eugenio Hospital; [33]Hematology, San Carlo Hospital

Background: Tyrosine kinase inhibitors (TKIs) have dramatically changed the treatment of chronic myeloid leukemia (CML). Most of data on the TKIs safety derive from sponsored controlled trials, where patients with multiple comorbidities had fewer opportunities to be included. Many questions about the management of newly diagnosed CML can only be answered by analysing large cohorts in real world practice.

Methods To evaluate the choice of TKI and the incidence of early events during the 1st year of therapy in newly diagnosed chronic phase CML patients with concomitant diabetes, we retrospectively studied 1732 CP-CML patients diagnosed from 1/2012 to 12/2019 at 33 Italian Hematology Centres and treated with frontline imatinib (IM) or second-generation TKIs (2G). Among these, 197 patients (11.4%) had concomitant diabetes.

Table 1. Clinical features of the whole cohort and according to concomitant diabetes.

	All patients (1732)	Patients without diabetes (1535)	Patients with diabetes (197)	p
Gender, M/F (%)	1011/721 (58.4 – 41.6)	880/655 (57.3 – 42.7)	130/67 (66.0 – 34.0)	**0.020**
Median age (years) (IQR)	59.7 (46.8 – 71.2)	58.4 (44.9 – 69.9)	69.4 (58.8 – 76.6)	**<0.001**
Hb, g/dl (IQR)	12.7 (11.0 – 14.2)	12.7 (10.9 – 14.1)	12.7 (11.4 – 14.3)	0.826
WBC, x 10^9/l (IQR)	57.2 (28.5 – 133.0)	59.3 (28.7 – 142.3)	44.9 (24.2 – 90.2)	**0.008**
PLTS, x 10^9/l (IQR)	355 (241 – 561)	355 (245 – 563)	349 (232 – 556)	0.852
Spleen, n° evaluable (%):	1687	1498	189	
Not palpable	935 (55.4)	825 (55.1)	110 (58.2)	
< 5 cm below costal margin	479 (28.4)	421 (28.1)	58 (30.7)	0.244
≥ 5 cm below costal margin	273 (16.2)	252 (16.8)	21 (11.1)	
Sokal score, n° evaluable (%):	1709	1513	196	
Low	667 (39.0)	618 (40.8)	50 (25.5)	
Intermediate	787 (46.1)	673 (44.5)	113 (57.7)	**<0.001**
High	255 (14.9)	222 (14.7)	33 (16.8)	
ELTS score, n° evaluable (%):	1681	1489	192	
Low	966 (57.3)	876 (58.9)	91 (47.4)	
Intermediate	522 (31.2)	446 (29.9)	77 (40.1)	**0.019**
High	193 (11.5)	167 (11.2)	24 (12.5)	
Arterial hypertension, n° (%)	668 (38.6)	527 (34.4)	141 (71.6)	**<0.001**
Previous neoplasm, n° (%)	229 (13.2)	193 (12.6)	36 (18.3)	**0.027**
COPD, n° (%)	131 (7.6)	98 (6.4)	33 (16.8)	**<0.001**
Ischemic heart disease, n° (%)	117 (6.8)	80 (5.2)	37 (18.8)	**<0.001**
Cerebrovascular events, n° (%)	48 (2.8)	38 (2.5)	10 (5.1)	**0.037**
Concomitant drugs, n° evaluable (%):	1717	1520	197	
0 - 2	1113 (64.8)	1077 (70.8)	36 (18.3)	
3 – 5	376 (21.9)	291 (19.1)	85 (43.1)	**<0.001**
> 5	228 (13.3)	152 (10.1)	76 (38.6)	
Frontline TKI, n° (%):				
Imatinib	973 (56.1)	831 (54.0)	142 (72.0)	
Dasatinib	280 (16.2)	234 (15.3)	46 (23.4)	**<0.001**
Nilotinib	479 (27.7)	470 (30.7)	9 (4.6)	

Results: The main clinical features at diagnosis of the entire cohort and in patients with diabetes are reported in the Table. Compared with non-diabetic patients, subjects with diabetes were older, had higher Sokal and ELTS scores (Sokal intermediate + high 74.5% *vs* 59.2%, ELTS intermediate + high 62.6% *vs* 41.1%) and were more likely affected by other comorbidities as arterial hypertension, COPD, ischemic heart disease/cerebrovascular events and previous neoplasms: as a consequence, diabetic patients reported a higher number of concomitant drugs (> 5 in 38.6% *vs* 10.1%, p<0.001). The number of white blood cells at diagnosis was lower in diabetic patients (44.9x109/l *vs* 59.3 x10^9/l, p=0.008)). Significant differences were observed in the choice of frontline TKI: com-

paring diabetic with non-diabetic patients, IM was prescribed in 72% *vs* 54%, dasatinib in 23.4% *vs* 15.3% and nilotinib in 4.6% *vs* 30.7% of cases (p<0.001). There were 51 early events (25.9%) in the 1st year of treatment leading to permanent frontline TKI discontinuation in the diabetic patients, compared to 285 (18.7%) in non-diabetic patients (p=0.037). One-year cumulative incidence of TKI permanent discontinuation was 25.9% (95%CI 19.8 – 32.0) in diabetic patients compared to 18.5% (95%CI 16.6 – 20.4) in non-diabetic patients (p=0.015).

Conclusions: This real-world study on over 1700 CML patients shows that concomitant diabetes is an important factor in newly diagnosed CML patients, affecting both the clinical presentation and the frontline treatment choice: in addition, concomitant diabetes is linked to a high incidence of early events and frontline TKI permanent discontinuation.

P182

EVALUATION OF SEROLOGICAL RESPONSE TO ANTI-SARS-COV-2 MRNA VACCINATION IN CHRONIC MYELOID LEUKEMIA (CML) PATIENTS (PTS)

S.P. Pascale[1], R. Nuccorini[1], T. Pierri[2], R. Di Mare[1], L. Fabio[1], E. Lerose[1], M.A. Merlino[1], P. Schiavo[1], A. Amendola[1], G. Brucoli[2], M.D. Caputo[1], I. Chitarrelli[1], M. Cimminiello[1], S. Coluzzi[1], N. Filardi[1], A. Matturro[1], D. Vertone[1], M. Poggiaspalla[5], F. Malaspina[5], G. Musuraca[5], G. Coralluzzo[1], B. D'Araia[3], C. Bitetti[3], C. Musto[2], A.P. Bellettieri[4], G. Martinelli[5], C. Cerchione[5], M. Pizzuti[1]

[1]UOC di Ematologia, Azienda Ospedaliera Regionale "San Carlo", Potenza, Italy; [2]UO di Medicina Trasfusionale, Azienda Ospedaliera Regionale "San Carlo", Potenza, Italy; [3]UOS di Ematologia, Presidio Ospedaliero "Madonna delle Grazie", Matera, Italy; [4]Direzione Sanitaria, Azienda Ospedaliera Regionale "San Carlo", Potenza, Italy; [5]Direzione Scientifica, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Meldola, Italy; [6]UO di Ematologia, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Meldola, Italy

Background: Italy launched its COVID-19 vaccination campaign on 27 December 2020.As expected,several studies highlighted that serological response of hematological patients (pts) was reduced compared to healthy subjects,due to the state of immunosuppression because of both underlying disease and administered therapy.However CML pts demonstrated to have a good serological response to anti-SARS-COV-2 mRNA vaccination (BNT162b2).

Methods: We studied serological response to BNT162b2 in a setting of CML pts after 30-45 days post first cycle of vaccination and post administration of booster. Anti-SARS-CoV-2 IgG titers were evaluated by the AdviseDx SARS-CoV-2 IgG II assay (Abbott). A total of 44 CML pts were included in the study (median age 63,19-88).25 pts were treated with Imatinib while 19 received 2ndand 3rd generation Tyrosine Kinase Inhibitors (TKI).6 pts were in MR2 while the others had reached a MR3 or a deep molecular response (DMR).A comparison with 33 healthy health workers of San Carlo Hospital in Potenza (median age 40,28-66) was foreseen.

Results: In the control group mean titer of anti-SARS-CoV-2 IgG was 11876 (range 171-40000),while in our cohort of CML pts we observed an IgG titer not significantly different compared with the control arm (mean 8700,5,range 105–27951).We observed levels of IgG greater in pts who had received 2nd and 3rd generation TKI than in pts who had used Imatinib (1130,8 *vs* 6532,7),this data was confirmed also after booster dose.Although this trend was not statistically significant,it could be influenced by different median age between two groups of pts (Imatinib 66 *vs* 2nd and 3rd generation TKI 57 years) and it should be confirmed on a larger sample size.Pts who had achieved at maximum MR3 showed IgG titers greater than pts in DMR (13326 *vs* 6926) but it warrants further studies on large scale.We also evaluated serological response after booster dose in 36 pts,34 of them showed a further increase of anti-SARS-CoV-2 IgG titer.Mean concentration after 3rd dose was 22179,mean increase compared to the titer after the 2nd dose,expressed as the ratio between the two values,was 3,5 while in the control group the mean titer of IgG after booster was 24443,5 (5756,5–40000) with a mean increase ratio of 2,6.

Conclusions: Our study demonstrated a good serological response to BNT162b2 for CML pts and this laboratory data was also confirmed by clinical observation of CML pts with COVID-19,all of whom recovered without the need for special care.

P183

CHRONIC MYELOID LEUKEMIA DISCONTINUATION THERAPY: RQ-PCR VERSUS DIGITAL DROPLET PCR IN LONG TFR

L. De Fazio[1], R. Reina[1], M. Lamagna[1], D. Lisi[1], A. Potenza[2], R. Visconti[2], S. Errichiello[2], B. Izzo[2], F. Pane[1], L. Luciano[1]

[1]Hematology Unit, Department of Clinical Medicine and Surgery, University Federico II; [2]Department of Molecular Medicine and Biotechnology, University Federico II & Ceinge Advanced Biotechnologies, Italy

Chronic myeloid leukemia (CML) represents a unique hematological condition as tyrosine kinase inhibitors (TKIs) have allowed long term survival. The establishment of standardized molecular response cut offs and the concept of deep molecular response as measured through RQ-PCR have paved the path to therapy discontinuation. Literature suggests RQ-PCR may not be the best tool to evaluate minimal residual disease when interrupting treatment and during therapy discontinuation, proposing digital PCR as a method with higher sensitivity.

Aims: This study aims to compare the length of treatment until therapy discontinuation according to first line treatment and to assess if digital droplet PCR (dd-PCR) can improve molecular follow up of long treatment free remission (TFR) patients over 5 years of therapy discontinuation.

Methods: We analized the comparative results of RQ-PCR and dd-PCR of peripheral blood samples of 10 CML patients (6F; 4M, median age 59,8 years) from our institution in long term TFR (minimum of 5 years) in sustained deep molecular response. Samples were divided according to first line therapy and subsequent changes: seven patients were treated with Imatinib (five until discontinuation of therapy, one switched to Nilotinib and one to Dasatinib because of the E244 mutation); three with IFN (one until discontinuation, two shifted to Imatinib in second line).

Results: The mean length of treatment before discontinuation was 152±50 months; duration of therapy was longer for patients who received first-line treatment with IFN *vs* TKI; whereas, shorter duration was observed among those who received more than one line of medication. Paired sample t-test revealed no significant differences between RQ-PCR and dd-PCR (t= 0.307; p=0.767).

Conclusions: In this small sample of CML long TFR patients length of treatment until discontinuation was shorter for patients treated with TKI. Molecular response was similar as measured by dd-PCR and RQ-PCR. Results could be consequence of our small sample, perhaps it may also be due to a selected CML court. To clarify these points, it would be useful to expand the sample and to evaluate possible factors influencing disease control in long-term TFR, such as CD26+ cell count and immunological microenvironment.

P184

DIELECTROPHORESIS FOR THE DETECTION OF MINIMAL RESIDUAL DISEASE IN HEMATOLOGICAL MALIGNANCIES: A PILOT STUDY

G. Scandura[1], P.G. Bonacci[2], G. Caruso[2], S. Petralia[2], C. Pandino[1], N. Musso[3], A. Romano[1], M. Camarda[3,4]

[1]Department of General Surgery and Medical-Surgical Specialties, University of Catania, Catania, Italy; [2]Department of Biotechnological and Biomedical Sciences, University of Catania, Catania, Italy; [3]STLab srl, Catania; [4]Consiglio Nazionale delle Ricerche – Istituto per la Microelettronica e Microsistemi (CNR-IMM), Italy

Introduction: Minimal residual disease (MRD) is defined as the small number of cancer cells that persist in patients during the period of complete remission (CR). Since the correlation between the level of MRD and the probability of relapse seems to be stronger than for any other prognostic factor including age, sex, type of mutation and treatment used, it represents a highly informative factor for estimating the probability of relapse in haematological diseases. The recently diagnostic techniques as NGF and NGS have a sensitivity of 10−5/10−6, but they still show some technical issues for MRD evaluation due heterogeneity and operator-dependence of NGF, and the lack of clonal marker by molecular approaches in about one third of patients which limits NGS. These limitations mentioned above can be overcome by dielectrophoresis (DEP), a label-free technique based on the capacity of polarizable particles to move when placed in an ionic medium and exposed to an electric field. Since cells separation is also influenced by morphological and cytoplasmic parameters, the DEP-FFF buffer effects were investigated *in vitro* in CML cell line.

Methods: CML cell line (K562) was treated with DEP-FFF buffer (Aqueous solution of 9.5% Sucrose, 0.1 mg/ml Glucose, 0.1 % BSA, 1mM PBS pH7.0, 0.1mM Ca-Acetate, 0.5mM Mg-Acetate and conductivity of 33 mS/m). Since DEP separation takes place at room temperature for a period of 1h, morphological changes were assessed at different time points (0', 15', 30', 45', 60') using imaging flow cytofluorimetry. Gene expression was carried out by qRT-PCR. Proliferation capacity was evaluated by MTT assay.

Results: Incubation with DEP-FFF buffer did not affect the main morphological parameters (circularity, diameter and area) of single cells. Moreover, the lack of stress granules in the cytoplasm measured as cytoplasmic granularity (side scatter), suggests that buffer composition does not induce stress. Interestingly, the gene expression analysis showed GAPDH and iNOS downregulation suggesting that buffers composition impacts cellular metabolism. Since metabolism is closely related to cell growth, we finally tested the capacity of cells to recover their growth after the time spent in DEP-FFF buffer. The results showed a reduction of proliferation after 24h.

Conclusion: Our study suggests that DEP-FFF buffer does not induce morphological changes and stress in CML cells, but can affect metabolism impacting the recovery of cell growth.

P185

CHOICE OF TYROSINE KINASE INHIBITOR AND EARLY EVENTS DURING THE FIRST YEAR OF THERAPY IN NEWLY DIAGNOSED CHRONIC PHASE CML PATIENTS WITH PREVIOUS NEOPLASIA: A "CAMPUS CML" STUDY

I. Capodanno[1], M. Tiribelli[2], M.C. Miggiano[3], C. Bucelli[4], F. Cavazzini[5], S. Leonetti Crescenzi[6], S. Russo[7], E. Scalzulli[8], A. Bernardelli[9], L. Luciano[10], O. Mulas[11], G. Loglisci[12], C. Elena[13], U. Pizzano[2], I. Attolico[14], G. Binotto[15], E. Crisà[16], P. Sportoletti[17], A. Di Veroli[18], A.R. Scortechini[19], A.P. Leporace[20], M. Basile[21], M. Crugnola[22], F. Stagno[23], P. Murgano[24], D. Rapezzi[25], D. Luzi[26], A. Iurlo[4], M. Bocchia[27], C. Fava[28], A. Malato[29], S. Galimberti[30], I. Vincelli[31], M. Trawinska[32], M. Pizzuti[33], G. Caocci[11], M. Bonifacio[9], G. Saglio[34], G. Specchia[14], M. Breccia[8], R. Latagliata[18]

[1]Hematology Unit, Azienda Unità Sanitaria Locale-IRCCS; [2]Division of Hematology and BMT, Department of Medical Area, University of Udine; [3]Hematology Department, San Bortolo Hospital; [4]Division of Hematology, Foundation IRCCS Ca' Granda-Ospedale Maggiore Policlinico; [5]Hematology Unit, University of Ferrara; [6]Hematology, San Giovanni Hospital; [7]Hematology, University of Messina; [8]Department of Cellular Biotechnologies and Hematology, "Sapienza" University ; [9]Department of Medicine, Section of Hematology, University of Verona; [10]Hematology, University Federico II; [11]Department of Medical Sciences and Public Health, University of Cagliari; [12]Hematology, Vito Fazzi Hospital; [13]Hematology, Policlinico San Matteo, University of Pavia; [14]Hematology and Transplantation Unit, University of Bari; [15]Department of Medicine, Hematology and Clinical Immunology, University of Padua; [16]Hematology, Ospedale Maggiore; [17]Hematology, University of Perugia; [18]Hematology Unit, Ospedale Belcolle; [19]Hematology Unit, Azienda Ospedaliero Universitaria Ospedali Riuniti; [20]Hematology Unit Azienda Ospedaliero Universitaria Sant'Andrea; [21]Hematology, San Giuseppe Moscati Hospital; [22]Hematology, University of Parma; [23]Hematology, Ferrarotto Hospital; [24]Division of Hematology, Sant'Elia Hospital; [25]Hematology, AO Santa Croce e Carle; [26]Onco-Hematology Department, AO Santa Maria; [27]Hematology, AOU Senese; [28]Hematology, Mauriziano Hospital; [29]Hematology, Cervello Hospital; [30]Hematology, University of Pisa; [31]Hematology, Bianchi-Melacrino-Morelli Hospital; [32]Hematology, Sant'Eugenio Hospital; [33]Hematology, San Carlo Hospital; [34]Department of Clinical and Biological Sciences, University of Turin, Italy

Background: Tyrosine kinase inhibitors (TKIs) have dramatically changed the treatment of chronic myeloid leukemia (CML). Most of data on the TKIs safety derive from sponsored controlled trials, where patients with multiple comorbidities had fewer opportunities to be included. Many questions about the management of newly diagnosed CML can only be answered by analysing large cohorts in real world practice.

Methods: To evaluate the choice of TKI and the incidence of early events during the 1st year of therapy in newly diagnosed chronic phase CML patients with a story of previous neoplasia, we retrospectively studied 1732 CP-CML patients diagnosed from 1/2012 to 12/2019 at 33 Italian Hematology Centres and treated with frontline imatinib (IM) or second-generation TKIs (2G). Among these, 229 patients (13.3%) had a previous neoplasia.

Results: The main clinical features at diagnosis of the entire cohort and in patients with or without previous neoplasia are reported in the Table. Patients with previous neoplasia were older ($p<0.001$), had a lower disease burden [lower WBC median count ($p<0.001$), higher median Hb value ($p=0.014$), lower rate of patients with spleen enlargement ($p<0.001$)] and were more likely affected by arterial hypertension ($p<0.001$), diabetes ($p=0.025$) and cerebrovascular events ($p=0.045$). The choice of frontline TKI was significantly different comparing patients with and without previous neoplasia: IM was prescribed in 72.1% *vs* 53.7%, dasatinib in 12.2% *vs* 16.8% and nilotinib in 29.5% *vs* 15.7% of

cases (p<0.001). In patients with previous neoplasia were reported 43 early events leading to permanent frontline TKI discontinuation (18.7%) in the 1st year of treatment, compared to 296 (19.7%) in patients without previous neoplasia (p=0.122). One-year cumulative incidence of TKI permanent discontinuation was 18.8% (95%CI 13.7 – 23.9) in patients with previous neoplasia compared to 19.4% (95%CI 17.4 – 21.3) in patients without previous neoplasia (p=0.833).

Conclusions: This real-world study on over 1700 CML patients shows that a previous neoplasia is an important factor in newly diagnosed CML patients, as concern the clinical presentation and the frontline treatment choice: however, previous neoplasia does not seem to worsen the incidence of early events and the rate of frontline TKI permanent discontinuation.

Table 1. Clinical features of the whole cohort and according previous neoplasia

	All patients (1732)	Patients without previous neoplasia (1503)	Patients with previous neoplasia (229)	p
Gender, M/F (%)	1011/721 (58.4 – 41.6)	866/637 (57.6 – 42.4)	144/85 (62.9 – 37.1)	0.133
Median age (years) (IQR)	59.7 (46.8 – 71.2)	58.1 (45.1 – 69.9)	68.4 (60.1 – 75.2)	**<0.001**
Hb, g/dl (IQR)	12.7 (11.0 – 14.2)	12.6 (10.9 – 14.1)	13.1 (11.8 – 14.4)	**0.014**
WBC, x 10^9/l (IQR)	57.2 (28.5 – 133.0)	60.8 (29.0 – 146.1)	41.3 (25.8 – 81.9)	**<0.001**
PLTS, x 10^9/l (IQR)	355 (241 – 561)	359 (245 – 564)	335 (230 – 556)	0.145
Spleen, n° evaluable (%):	1687	1467	220	
Not palpable	935 (55.4)	775 (52.8)	160 (72.7)	
< 5 cm below costal margin	479 (28.4)	436 (29.7)	43 (19.6)	**<0.001**
≥ 5 cm below costal margin	273 (16.2)	256 (17.5)	17 (7.7)	
Sokal score, n° evaluable (%):	1709	1489	220	
Low	667 (39.0)	594 (39.9)	74 (33.6)	
Intermediate	787 (46.1)	681 (45.8)	105 (47.7)	0.080
High	255 (14.9)	214 (14.3)	41 (18.7)	
ELTS score, n° evaluable (%):	1681	1467	214	
Low	966 (57.3)	861 (58.7)	109 (50.9)	
Intermediate	522 (31.2)	440 (30.0)	81 (37.9)	0.081
High	193 (11.5)	166 (11.3)	24 (11.2)	
Arterial hypertension, n° (%)	668 (38.6)	540 (36.0)	128 (55.9)	**<0.001**
Diabetes, n° (%)	197 (11.4)	161 (10.7)	36 (15.7)	**0.027**
COPD, n° (%)	131 (7.6)	109 (7.3)	22 (9.6)	0.213
Ischemic heart disease, n° (%)	117 (6.8)	98 (6.5)	19 (8.3)	0.322
Cerebrovascular events, n° (%)	48 (2.8)	37 (2.5)	11 (4.8)	**0.045**
Concomitant drugs, n° evaluable (%):	1717	1491	226	
0 - 2	1113 (64.8)	1008 (67.6)	105 (46.5)	
3 – 5	376 (21.9)	309 (20.7)	67 (29.6)	**<0.001**
> 5	228 (13.3)	174 (11.7)	54 (23.9)	
Frontline TKI, n° (%):				
Imatinib	973 (56.1)	808 (53.7)	165 (72.1)	
Dasatinib	280 (16.2)	252 (16.8)	28 (12.2)	**<0.001**
Nilotinib	479 (27.7)	443 (29.5)	36 (15.7)	

P186

PREVALENCE AND CLINICAL SIGNIFICANCE OF AUTOANTIBODY POSITIVITY IN PATIENTS WITH LOW-RISK MYELODYSPLASTIC SYNDROMES: A SINGLE CENTER EXPERIENCE

F. Versino[1], F. Serpenti[1], N. Revelli[2], W. Barcellini[2], B. Fattizzo[1]

[1]Università degli Studi di Milano;[2]UO Ematologia, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Italy

Accumulating evidence shows a link between myelodysplastic syndromes, especially low-risk ones (LR-MDS), and autoimmunity, including the detection of anti-erythrocyte (anti-RBC) and anti-platelets (anti-PLT) autoantibodies (Ab) in some patients. In this study we aimed at evaluating the prevalence of anti-RBC and anti-PLT Ab in a single-center LR-MDS series, and their relationship with clinical features, immunosuppressive treatment, and response (according to IWG 2018). All LR-MDS patients diagnosed from 2001 until time of writing, screened for Ab, were retrospectively included. Among 79 subjects (median follow up of 54.5 months, 3-244) at least one Ab was found in 34 (43%), more frequently anti-PLT (22/40) than anti-RBC (13/50 tested cases). By dividing positive (Ab+) from negative (Ab-) patients, thrombocytopenia (50% *vs* 26.6%) and marrow hypocellularity (28.6% *vs* 11.1%) were more frequent in the former, while other bone marrow features, cytogenetics, and mutations by NGS were similar. Comprehensive evaluation identified 10 patients with overt autoimmune (AI) disease (13%): 6 hemolytic anemia (AIHA), 3 immune thrombocytopenia (ITP), and 1 Evans syndrome (ES). Overall, 31 patients were treated with steroids, mainly in the Ab+ group (55.9% *vs* 26.7%); reasons were Ab- cytopenia (10), altered hemolytic markers (8), thrombocytopenia (8), and constitutional symptoms (5). Median prednisone dose was 25 mg/day (5-65): 8 patients with overt AI disease received prednisone 1 mg/kg/day, whilst doses <0.5 mg/Kg/day were used for Ab- cytopenia/constitutional symptoms. Seventeen subjects (54%) responded, without a significant difference between Ab+ and Ab-. Anti-RBC Ab+ patients showed better response rate as compared to Ab- or anti-PLT Ab+ ones (61.5% *vs* 18.2%). Interestingly, MDS-ES patient firstly responded to steroids for ITP and subsequently to rituximab for AIHA. These data confirm that more than 40% of LR-MDS patients display Ab positivity, but only about 10% show overt AI disease. Steroid therapy triggered by Ab positivity (>50% cases) alleviated cytopenia in nearly 60% of cases, particularly anti-RBC+ ones. These data suggest testing anti-RBC and anti-PLT Ab in patients with LR-MDS since, along with clinical evaluation, may indicate a beneficial use of immunosuppressive therapy.

Table 1. General Characteristics and Patient outcome. MDS = Myelodysplastic Syndrome; MLD = Multilineage Dysplasia; RS MLD = Multilineage Dysplasia with Ring Sideroblasts; IPSS = International Prognostic Scoring System; Thrombocytopenia = (PLT <100x10^9/L); NGS = Next Generation Sequencing (tested for myeloid mutations); BM = Bone Marrow.

	Ab+ (n=34) (43%)	Ab- (n=45) (57%)	*p-value*
Median age, years (range)	72.5 (42-92)	76 (36-88)	ns
MDS MLD, N(%)	18 (52.9)	11 (24.4)	0.008
MDS RS MLD, N(%)	1 (2.9)	8 (17.8)	0.03
IPSS, N(%)			
low	20 (58.9)	29 (64.4)	ns
intermediate-1	14 (41.1)	16 (35.6)	ns
Thrombocytopenia, N(%)	17 (50)	12 (26.6)	0.04
BM Hypocellularity, N(%)	**n=28** 8 (28.6)	**n=36** 4 (11.1)	ns
BM Lymphoid Infiltrate, N(%)	20 (58.8)	26 (57.8)	ns
Cytogenetics, N(%)	**n=33**	**n=45**	
Normal	25 (75.8)	38 (84.4)	ns
Abnormal	8 (24.2)	7 (15.6)	ns
NGS, N(%)	**n=16**	**n=25**	
Normal	6 (37.5)	10 (40)	ns
1 mutation	4 (25)	8 (32)	ns
>1 mutations	6 (37.5)	7 (28)	ns
Steroids N(%)	19 (55.9)	12 (26.7)	0.008
Response	11 (57.9)	6 (50)	ns
Need for >1 steroid course	5 (14.7)	1 (2.2)	0.04
Need for therapy after steroid	7 (36.8)	6 (50)	ns

P187

CHRONIC TRANSFUSION NEED AS A RISK FACTOR FOR SEVERE INFECTIONS IN PATIENTS WITH MYELODYSPLASTIC SYNDROMES

M. Pianelli, E. Morsia, D. Lame, A. Carturan, A. Oliveri, A. Poloni

Clinica di Ematologia, Ospedali Riuniti Ancona, Italy

Background: Patients with myelodysplastic syndromes (MDS) have an high risk of developing infections, which still represent the most frequent complications and the main cause of mortality and morbidity. We conducted a retrospective study with the aim of evaluating the epidemiology of infectious events and finding the risk factors in a cohort of patients affected by MDS.

Patients and methods: We analyzed 200 patients with MDS or LMMC followed at our Institution in the last 15 years. Diagnosis was made according to 2016 WHO classification. The risk was assessed based on R-IPSS criteria. Transfusion-dependency was defined as a transfusion

burden of ≥ 4 units/8 weeks.

Results: MDS-MLD was the most common form of disease (70 patients, 35%), followed by MDS-SLD (23 patients, 11.5%), MDS-5q- (19 patients, 9.5%), MDS-EB1 (19 patients, 9.5%), MDS-EB2 (17 patients, 8.5%), MDS-RS with unilinear (6 patients, 3%) and with multilinear (15 patients, 7.5%) dysplasia, MDS unclassifiable (1 patients, 0.5%). Prognosis assessment showed very low (19%) and low (49.7%) risk MDS predominate. We detected 65 cases of infections of higher than third grade according to WHO. Pneumonia was the most frequent infection (36 cases), especially of bacterial origin. Risk factors associated with infections ≥ G3 in multivariate analysis were comorbidities (ORR 1.4, pV=0.017), neutropenia (ORR 3.9, pV=0.026) and transfusion-dependence (ORR 5.3, pV=0.001). In our cohort, 28% of patients underwent chronic transfusions: 40% of these patients had very low or low MDS and 23% had intermediate MDS. Moreover, transfusion-dependence also has impacted on survival. At a median follow up of 30 months (range 0.8-161), the median overall survival was 57 months and unreached in patients without and with transfusion dependency, respectively. Our data confirmed the role of comorbidities, neutropenia as a risk factor for severe infections, and, for the first time, the transfusion-dependence.

Conclusion: Our study showed that transfusion dependency is not only indication of poor survival but also is an important risk factor for infections in MDS patients. Given this finding, the transfusion dependent MDS patients could be considered high risk for infections, requiring closer clinical monitoring, an early use of iron-chelating agents and tailored prophylactic measures against infections.

P188

ANEMIA IS A MARKER OF POOR PROGNOSIS IN UNFIT CHRONIC MYELOMONOCYTIC LEUKEMIA PATIENTS TREATED WITH AZACITIDINE

F. Cavalca [1,2], A. Ripamonti [1,2], F.A. Brioschi[2], C. Gambacorti-Passerini[1,2], E.M. Elli[2]

[1]Department of Medicine and Surgery, University of Milano-Bicocca; [2]Hematology Division and Bone Marrow Unit, San Gerardo Hospital, Italy

Background: Chronic myelomonocytic leukemia (CMML) is a clonal myelodysplastic/myeloproliferative neoplasm typically affecting the elderly, characterized by clinical heterogeneity and elevated risk for transformation into acute myeloid leukemia (AML). Treatment of unfit elderly patients (pts) affected by CMML still represents today a clinical challenge: in many cases to these pts is offered only supportive care. Here we present our real-life experience in treating these pts with 5-azacitidine (AZA).

Methods: We retrospectively analyzed 14 consecutive pts followed at our institution between 2010 and 2022, with a diagnosis of CMML (according to WHO criteria) treated with AZA and declared unfit to intensive therapies (*e.g.*, intensive chemotherapy or stem cell transplantation). We collected data regarding clinical and biological features of disease, in order evaluate response rate and outcome predictors.

Results: 14 pts received AZA after a median time from diagnosis of 1.3 (range 0,1-9,1) years. Median age at AZA start was 75.5 (range 63.9-80.4) years. According to WHO subtypes, at AZA start the most of pts (78.5%) were classified as CMML-2. Six pts had proliferative variant, 8 (57.2%) presented myelodysplastic variant of CMML. At AZA start, 5 pts (35.7%) had Hb <9 g/dl and 7 pts (50%) had PLT < 50.000/mm^3. Median number of AZA cycles administered was 13 (range 2-37). According to IWG 2006 criteria, 12 pts achieved a response (85,7%), including 5 complete remissions (30,7%). Median time to obtain the best response was 4 months (range 1-8). Ten pts (71.4%) lost response to AZA, after a median time of 18.7 months (range 3.7-47.6). Five (35.7%) pts had a progression to AML after a median time of 22.3 months (range 6.8-29.9). In term of outcome, median progression free survival (PFS) from AZA start was 16.5 months (range 3.7-67.8). Median survival from the AZA start was 19.7 months (range 8.8-67.8). No unexpected toxicity was reported. Increased bone marrow blast percentage (> 10%), proliferative features and low platelets (< 50.000/mm^3) at AZA start had no significant correlations with survival or PFS. Only anemia at AZA start (Hb <9 g/dl) correlated with significant poor outcome (p<0.001; Figure1).

Conclusion: CMML pts are often elderly and unfit to intensive treatment. In our experience, AZA treatment has been shown to be effective and non-toxic for these pts, with a high response rate. We have identified anemia at AZA start as a marker of poor prognosis.

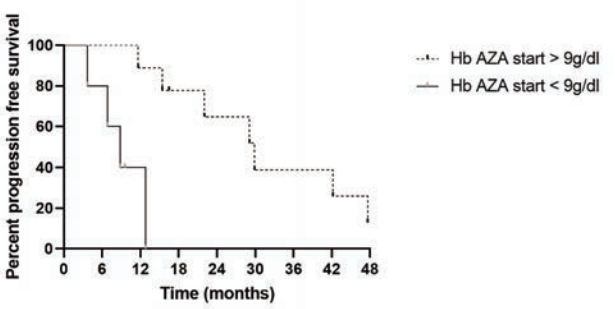


Figure 1.

P189

CHRONIC MYELOMONOCYTIC LEUKEMIA DIAGNOSIS BY FLOW CYTOMETRY: ANCONA EXPERIENCE

D. Lame, M. Caprino, E. Marinelli Busilacchi, N. Viola, E. Morsia, M. Pianelli, A. Olivieri, A. Poloni

AOU Ospedali Riuniti di Ancona, Italy

Chronic myelomonocytic leukemia (CMML) is a myeloid neoplasm characterized by dysplasia, abnormal production of monocytic cells with an elevated risk of leukemic evolution. According to WHO, CMML patients present a persistent (≥3 months) absolute PB monocytosis (≥1×109/L) and relative monocytosis (≥10% of PB leukocytes), with exclusion of CML, classical MPN and all other hematologic neoplasms and a blast cell count <20% in PB and/or BM. In addition, morphological and/or histopathological evidence for diagnostic dysplasia ≥1 of the three major BM cell lineages must be present. If dysplasia is absent or not diagnostic (<10%), the presence of cytogenetic or molecular alterations or flow cytometry (FC) abnormalities may be employed as co-criteria of the diagnosis of CMML. FC is helpful to confirm the monocyte and blast cell counts. In addition, FC is useful for confirming the presence of distinct monocyte populations. Based on the expression of CD14 and CD16, monocytes are classified into classical (MO1) (CD14+/CD16−), intermediate (MO2) (CD14+/CD16+) and non-classical (MO3) (CD14-/CD16+). FC analysis of PB monocytes were proposed as a quick and efficient tool for distinguishing CMML from reactive monocytosis, by highlighting an increase in the MO1 fraction above 94% and a decrease of the percentage of MO3. Using FC, we evaluated PB and BM samples from 20 patients with confirmed diagnose of CMML and 20 PB sample from patients with other myeloid malignancies with monocytosis (MPN-monocytosis) (n=8) and reactive monocytosis (n=12). Among these patients, 15/20 (75%) of CMML patients displayed MO1 ≥94%, while MO1≥94% was observed in 1/12 (8%) of the patients with reactive monocytosis and in 1/8 (12) of the patients with MPN-monocytosis. MO3 fraction was always <5% in CMML patients, but >5% in 19/20 (95%) of the other cases. BM samples from CMML patients showed similar percentage of MO1 and MO3 compared to PB samples. Commonly PB and BM monocytes display aberrant expression of CD56. Furthermore, it was detectable a fraction of non-maturing neutrophils

(CD66b+/CD11b-) in nearly half of patients. We are now revaluating our frozen samples for the presence of Slan in MO2 fraction.

In conclusion, this little real-life experience of routinely FC study on PB and BM samples is similar to the studies described in the literature and it confirms the comparable expression of MO1 in both samples, suggesting the indistinct use of PM and BM assay in the CMML patients setting.

P190

SUPPORTIVE CARE IN LOW-RISK MYELODYSPLASTIC SYNDROMES: ROLE OF ERYTHROPOIESIS STIMULATING AGENTS (ESAS)

C. Cerchione[1], F. Alfinito[2], I. Soriente[3], A.M. D'Arco[3], P. Danise[3], G. Cerciello[3], G. Musuraca[1], A. Lucchesi[1], V. Di Battista[1], D. Cangini[1], M.B. Giannini[1], S. Ronconi[1], M. Ceccolini[1], F. Pane[2], G. Martinelli[1]

[1]Hematology Unit, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS; [2]Hematology, AOU Federico II; [3]Hematology, Ospedale di Pagani, Italy

Erythropoiesis stimulating agents (ESAs) are the frontline treatment in low-risk anemic MDS patients and an employment of this therapy in the earlier stage of the disease can delay the need for RBC transfusion. It's matter of debate whether the clinical response is a result of proliferation and maturation of the dysplastic clone or stimulation of residual normal erythropoiesis by ESAs. Macrocytosis is one of the cytological hallmarks of dyserithropoiesis in MDS: an analysis of the erythropoietic response to ESAs therapy in a cohort of anemic non trasfusion-dependent MDS patients, enrolled in a retrospective register, RECAMDS, subgroup of Italian register, was performed. 183 patients, treated with standard-dose ESAs, have been retrospectively analyzed. Data analysis was performed, according to IWG 2006 criteria, at the baseline, after 3 and 6 months of continuous treatment, with a subanalysis of the patients according to WHO and R-IPSS risk stratification. ESAs were started at mean Hb concentration of 9.31 g/dl, mean serum EPO concentration: 51 mU/L, after a mean time from diagnosis of 6 months (r.1-118). ORR was 83.6% (153/183), no difference among WHO and IPSS subgroups was found: 132/183 (72.1%) achieved response after 3 months of treatment, while other 21/183 (11.2%) after 6 months. 19 patients with stable disease (non-responders, according to IWG criteria), in which treatment was continued, achieved response after 9 months. In the macrocytic-responders group 83.2% exhibits again macrocytosis after 3 months, while 16.8% become normocytic. In the normocytic-responders group 89.8% exhibits again normocytosis, while 10.2% become macrocytic: in these patients, after 3 months, there was a contemporary worsening in neutropenia and thrombocytopenia, with transfusion-dependence, regarded as first signs of progression of disease. Non-responders were 30/183 (16.3%): in the macrocytic non-responders group 89% exhibit again macrocytosis after 3 months, while 11% become normocytic; in the normocytic group 76% exhibits again macrocytosis, while 24% become normocytic. These preliminary data can suggest that, in the majority of MDS patients responsive to ESAs, the increase of Hb concentration occurs mainly stimulating erythroid production in MDS clones; in the minority of patients probably it happens recruiting residual polyclonal erythropoiesis. It is interesting to note that stimulating effects of ESAs last even when the expression of dysplasia progresses.

P191

SEVERE CHRONIC PRIMARY NEUTROPENIA: FINDINGS FROM A CASE SERIES OF PATIENTS UNDERWENT EXTENSIVE DIAGNOSTIC EVALUATION INCLUDING GENETIC ANALYSIS

K. Paciaroni[1], F. Pulvirenti[2], E. Sangiorgi[3], S. Licci[4], N. Villiva'[1], L. Cicconi[1], F. Celesti[1], F. Simula[1], A.Tordi[1], T. Caravita di Toritto[1]

[1]UOSD Ematologia, ASL Roma 1; [2]UOD Immunodeficienze Primitive AOU Policlinico Umberto I; [3]Istituto di Medicina Genomica, Fondazione Policlinico Universitario A. Gemelli IRCCS - Università Cattolica del Sacro Cuore; [4]Pathology Unit, San Filippo Neri Hospital

Severe chronic primary neutropenia (CPN) is a rare entity and a well-known risk factor for susceptibility to bacterial infections. We report here the characteristics and outcomes of 3 severe CPN patients who underwent to an extensive work up including genetic analysis. Clinical, hematologic, immunologic, biochemical and genetic characteristics are detailed in the Tables. All 3 patients were female and Case 1 and 2 revealed family history positive for haematological and/or immunologic disease. Recurrent aphtous stomatitis, perirectal infections and vaginal infections were experienced in all three patients. The severe infectious complications affected 2 patients: case 1 experienced the complete thooth loose as consequences of recurrent oral infections while case 2 developed pneumonia requiring admission in hospital. A clonal rearrangement of the T-cell receptor genes was identified in the peripheral blood of all 3 patients although the lymphocyte immunophenotyping showed a normal distribution of B and T subset and natural killer cells. The bone marrow biopsies showed the increased number of cytotoxic lymphocytes CD3+CD8+ in all cases and a late maturation arrest in case 1 and case 3. All 3 patients were tested for variants in the adenosine deaminase 2 (ADA2) protein, which is associated to the first molecularly described monogenic vasculitis syndrome that includes hematological manifestations as hypogammaglobinemia and neutropenia. Case 1 resulted carrier of the homozygous pathogenic variant of ADA2. Extending the genetic analysis, we detected other two family members carriers of the same variants, one of them with natural killer lymphocytosis and hypogammaglobulinemia. Clinical course is actually followed at our Institution: the case 1 is receiving regular GCSf therapy with efficacy, the case 2 is on immunosuppressive treatment with Metothrexate. To date no severe bacterial infection has been reported. In conclusion all our CPN cases were found in female patients with T-cell clone. The present experience suggests that a complete hematologic and immunologic evaluation is necessary to ascertain the CPN diagnosis. The genetic analysis for variants in the ADA2 gene might be included in the diagnostic assessment ,especially in cases with a family history positive for haematological and/or vascular diseases, in order to support more specific diagnosis, to find other family members carrying the same variants and open up the possibility to use a more targeted treatment.

Table 1. Clinical, hematologic, immunologic, biochemical and genetic characteristics.

PATIENTS	CASE 1	CASE 2	CASE 3
AGE AT DIAGNOSIS	57	31	21
SEX	F	F	F
NEUTROPHIL COUNT (mm^3)	0-200	800-1200	200-400
DURATION OF OBSERVATION	4 YEARS	28 YEARS	8 YEARS
INFECTIONS	• APHTOUS STOMATITIS • RECURRENT VAGINAL INFECTIONS • PERIRECTAL INFECTIONS • GINGIVITIS AND PERIODONTITIS • RECURRENT FEVER EPISODES (> 3 TIMES/YEAR) • DEEP SKIN TISSUE INFECTIONS • GASTROINTESTINAL SYMTOMS • OTITIS • HERPES ZOSTER REACTIVATION	• APHTOUS STOMATITIS • RECURRENT VAGINAL INFECTIONS • PERIRECTAL INFECTIONS • • RECURRENT FEVER EPISODES (≥ 3 TIMES/YEAR) • RECURRENT BRONCHITIS TREATING BY ORAL ANTIBIOTIC (> 3 TIMES/YEAR) • GASTROINTESTINAL SYMTOMS • HERPES ZOSTER REACTIVATION	• APHTOUS STOMATITIS • RECURRENT VAGINAL INFECTIONS • PERIRECTAL INFECTIONS
INFECTIOUS COMPLICATIONS	EDENTULOUS	PNEUMONIA REQUIRING HOSPITAL ADMISSION	NONE
FAMILIAR HISTORY	SISTER WITH NK LYMPHOCITOSIS and HYPOGAMMAGLOBULINAEMIA CONSANGUINEUS	BROTHER WITH HYPOGAMMAGLOBULINAEMIA	NONE

	PARENTS		
SIEROLOGY for virus	HBV: NEG HCV: NEG HIV: NEG EBV: POSITIVE IgG CMV: POSITIVE IgG	HBV: NEG HCV: NEG HIV: NEG EBV: POSITIVE IgG CMV: POSITIVE IgG	HBV: NEG HCV: NEG HIV: NEG EBV: POSITIVE IgG CMV: POSITIVE IgG
Biological autoimmunity	ANA: NEG ANTIi-dsDNA: NEG ASMA: NEG AMA: NEG RHEUMATOID FACTOR: POS	ANA: NEG ANTIi-dsDNA: NEG ASMA: NEG AMA: NEG RHEUMATOID FACTOR: NEG	ANA: NEG ANTIi-dsDNA: NEG ASMA: NEG AMA: NEG RHEUMATOID FACTOR: NEG
GAMMAGLOBULINE	IGG 987, IgA 125, IgM 180	IGG 807, IgA 120, IgM 211	IgG 1481, IgA 294, IgM 269
VITAMINIC ASSET (B12, folate)	NORMAL	NORMAL	NORMAL
T-CELL RECEPTOR	POSITIVE (181pb)	POSITIVE (180pb)	POSITIVE (180pb)
lymphocyte immunophenotyping	CD3+ 90% (1.570/mm3) NK CD16+CD56+:2% (36/mm3) CD4/CD8 1.2	CD3+ 81% (2.3707mm3) NK CD16+CD56+ 9% (274/mm3) CD4/CD8 2.9	CD3 90% (1866/mm3) NK CD16+CD 56+ 4% (84/mm3) CD4/CD8 1.2
BONE MARROW SWEAR	LATE MATURATION ARREST	NO AVAILABLE	LATE MATURATION ARREST
BONE MARROW BIOPSY	INCREASED CELLULARITY, MATURATION ARREST INCREASED NUMBER OF CYTOTOXIC LYMPHOCYTES T CD3+CD8+	NORMAL CELLULARITY, MATURATION ARREST INCREASED NUMBER OF CYTOTOXIC LYMPHOCYTES T CD3+CD8+	INCREASED CELLULARITY, MATURATION ARREST INCREASED NUMBER OF CYTOTOXIC LYMPHOCYTES T CD3+CD8+
CARIOYIPE	46 XX	46 XX	46 XX
EPN CLONE	NEGATIVE	NEGATIVE	NEGATIVE
ELANE TEST	NO DONE	NO DONE	NEGATIVE
MUTATION OF THE ADENOSINE DEAMINASI 2 GENE	PRESENT IN HOMOZYGOUS GENOTYPE	WILD GENE	WILD GENE
DIAGNOSYS	SEVERE CHRONIC PRIMARY NEUTROPENIA ASSOCIATE WITH T-CELL CLONE AND HOMOZIGOUS GENOTYPE FOR DEFICIT OF ADENOSINE DEAMINASI TYIPE 2 (DADA2)	SEVERE CHRONIC PRIMARY NEUTROPENIA ASSOCIATE WITH T-CELL CLONE	SEVERE CHRONIC PRIMARY NEUTROPENIA ASSOCIATE WITH T-CELL CLONE
TERAPY	• G-CSF 12MU x 3 TIMES A WEEK • PROPHYLAXIS THERAPY FOR *PNEUMOCISTIS CARINII* TWICWE A WEEK • ON GOING ASSESMENT FOR A POSSIBLE	• METHOTREXATE 10 MG A WEEK • PROPHYLAXIS THERAPY FOR *PNEUMOCISTIS CARINII* TWICWE A WEEK	NONE
	THERAPY WITH ANTI-TUMOR NECROSIS FACTOR AS INDICATED IN DEFICIT OF ADA 2		

P192

HEMOCYTOMETRIC ASPECTS OF ERYTHROPOIESIS IN RESPONSE TO THE ADMINISTRATION OF LUSPATERCEPT (REBLOZYL), THE NEW AGENT OF ERYTHROID MATURATION, IN LOW-RISK PATIENTS WITH MYELODYSPLASTIC SYNDROME WITH RING SIDEROBLASTS

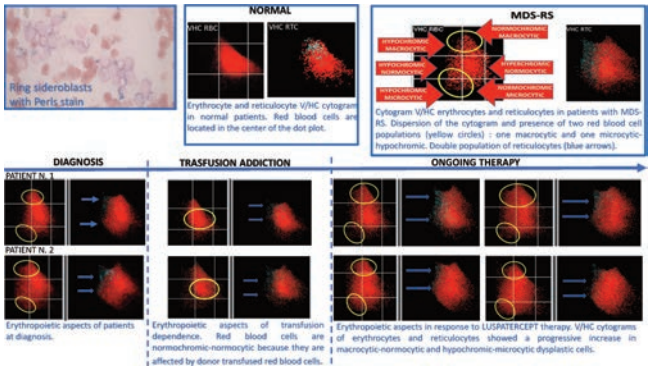
D. Avino, M. Casciello, C. Califano, M. Di Rosa, A. Di Palma, P. Danise

U.O.C. Ematologica Presidio Ospedaliero A. Tortora, Italy

MDS-RS (Myelodysplastic Syndrome Ring Sideroblasts) is a low-risk type of myelodysplastic syndrome characterized by the presence of ≥15% ring sideroblasts or ≥5% if the SF3B1 mutation is present. The pathogenetic mechanism underlying MDS-RS is a defect in the metabolism of mitochondrial iron which is present in an aberrant form of mitochondrial ferritin. Peripheral blood smears of patients with MDS-RS show a dimorphic morphological pattern, characterized in part by macrocytic-normochromic red blood cells and in part by hypochromic-microcytic red blood cells. This pattern is well evident on the volume/concentration hemoglobin cytograms provided by Advia Siemens haematology analysers. The presence of two populations of red blood cells is indicative of two different and simultaneous types of erythropoiesis: one megaloblastic and the other one coming from deficient iron supply that depends mainly on an intrinsic defect of erythropoiesis. Through hemocytometry it was possible to highlight the characteristics of erythropoiesis in two patients undergoing therapy with Luspatercept, the new agent of erythroid maturation. Luspatercept consists of a recombinant fusion protein that, by binding to TGF-β, inhibits cell apoptosis signals and induces erythroid maturation by differentiating progenitors in late stage and improving anaemia. Response to therapy was assessed in terms of increased haemoglobin levels and reduced transfusion requirements. Erythrocyte cytograms showed a progressive increase in macrocytic-normochromic and hypochromic-microcityc dysplastic cells

in responder patients. This double population of erythrocytes originates from a double population of reticulocytes as can be observed on reticulocyte V/CH cytograms. These results suggest that Luspatercept is likely to exercise its action on dysplastic clones and non on normal residual clones.

Figure 1.



P193

CASE REPORT: A NOVEL IN-FRAME DELETION IN THE JUXAMEMBRANE DOMAIN OF THE FLT3 GENE IN ADULT PATIENTS WITH ACUTE MYELOID LEUKEMIA

G. Parise[1], G. Iaquinta[1], S. Angeloni[1], G. Luzi[2], M. Ragazzo[1], L. Rigacci[2], P. Grammatico[1]

[1]U.O.C. Laboratorio di Genetica Medica, Sapienza Università degli Studi di Roma, Azienda Ospedaliera San Camillo-Forlanini, Roma; [2]U.O.C. di Ematologia e Trapianti di Cellule Staminali, Azienda Ospedaliera San Camillo-Forlanini, Roma, Italy

The FMS-like tyrosine kinase 3 gene (FLT3) encodes a receptor tyrosine kinase, expressed in early hematopoietic progenitors, and plays a key role in controlling survival, proliferation and differentiation of hematopoietic cells. Activating mutations of this gene have been highly discussed in myeloid malignancies, mainly in acute myeloid leukemia (AML) in which are identified in approximately one third of newly diagnosed patients. The internal tandem duplication (ITD), located within the receptor's autoinhibitory juxatamembrane domain (JMD), represents the most common type of FLT3 mutation; it presents with a high leukemic burden and confers a poor prognosis in patients with AML. Point mutations within the activation loop of the tyrosine kinase domain (TKD) mark another class of gain-of-function FLT3 mutations. Both mutant FLT3 molecules are activated through ligand-independent dimerization and trans-phosphorylation and cause a constitutive activation of downstream signaling pathways such as the ERK and STAT5. Several FLT3 tyrosine kinase inhibitors have been developed in the last few years, but midostaurin is currently the only one approved for the upfront treatment of FLT3 mutated AML. In this study, we describe a novel FLT3 in-frame variant (c.1770_1775delCTACGT; p.Y591_V592del) identified in an AML patient through Sanger sequencing and consisting in a deletion of 6 nucleotides in the JMD, where the FLT3-ITDs usually localize. This mutation targets key residues in the JMD involved in the interactions within FLT3 that regulate its activation. We conducted a review of published cases and series for FLT-3 JMD mutations, however, there are limited functional data for JMD mutations, especially deletions. Our analysis leads us to propose a new class of FLT3 mutations that may impact patient care and highlights the importance of conducting further research to define the role of FLT3 mutations other than ITD in modulating disease phenotype, prognosis and response to therapy.

P194

LOW JAK2 V617F ALLELE BURDEN, POSITIVE: DIAGNOSTIC STUDIES AND INDICATIONS

F. Culurgioni, S.T. Cirina, S. Uda, C. Musiu, V. Capponi, G. Caocci, G. La Nasa

S.C. Ematologia e CTMO, Ospedale Oncologico "A. Businco", ARNAS "G, Brotzu" Cagliari, Italy

The myeloproliferative neoplasms (MPNs) are neoplastic pathologies that affect hematopoietic stem cells and are characterized by uncontrolled proliferation of mature myeloid cells. Approximately 70% of patients with myeloproliferative neoplasms carry a point mutation in the JAK2 gene. The JAK2 V617F mutation was discovered in 2005 and it consists in a point mutation in exon 14of JAK2, which involves the replacement of the amino acid valine with the amino acid phenylalanine at the level of codon 617 of the pseudo-kinase domain (JH2). The result of this mutation is the interruption of the autoinhibitory activity of the pseudokinase domain and the consequent constitutive activation of the kinase domain (JH1).

The purpose of this studies the quantification of the JAK2 V617F mutation in patients with suspected MPN from 2017 to 2019 in the S.C Hematology and CTMO of the Businco Hospital in Cagliari.

The analyzes were carried out on 593 peripheral blood samples and, after being analyzed, they were divided into 4 groups based on the percentage of mutated JAK2 V617F alleles: negative, gray zone, positive with low JAK2 V617F allele burden, positive. Particular attention was paid to the group of patients whose JAK2 V617F allelic quantification value fell in the gray area (2% of patients).

Further molecular investigation performed on these patients showed the presence of the W515L mutation in the MPLgene in 12,5% of the samples and an insertion in the CALR gene in 14,2% of the patients.

PUBLISHED ONLY

SP01

COVID-19 IN PATIENTS WITH HAEMATOLOGICAL MALIGNANCY: AN ITALIAN SINGLE CENTER EXPERIENCE

A. Rago, F. Celesti, A. Siniscalchi, T. Caravita di Toritto

UOSD Ematologia ASL Roma 1, Italy

A novel severe acute respiratory syndrome (SARS)-like coronavirus (SARS-CoV-2) has emerged as a human pathogen, causing global pandemic and resulting in 6 million worldwide. Because of immunosuppression, the potential threat of COVID-19 to cancer patients is significant and a higher mortality rate has been documented for multiple cancers worldwide. Immunosuppression is particularly evident in hematological malignancies (HMs) such as leukemias, myelodysplastic syndromes (MDS), myeloproliferative neoplasms (MPNs), lymphomas, and multiple myeloma (MM).Advanced age (≥60 years) and non-White race were identified as risk factors for death. Authorized COVID-19 vaccines are safe and effective in the general population. Given the high case fatality rate among patients with HMs, prioritisation of COVID-19 vaccines for this group might appear straightforward. We report data on 33 patients (pts) with HMs referred to a single center as out-patient between 01/2021 and 04/2022. The distribution of positive COVID-19 based on the waves of infections is as follows: 1/33 during first, 1/33 during second, 1/32 during third and 30/33 fourth waves, respectively. The only 2/33 pts developed pneumonia and 1/33 is died for COVID-19 (che vuol dire?). 14/33 pts were treated with monoclonal antibody for COVID-19. 32/33 patients were on active therapy at the time of COVID-19 diagnosis, and pts received a median of 1.4 therapies (range 0-3). The median age of infected pts was 65 (range, 22-86 years), 23/33 pts were older than 60 years and 21/33 were female. Among all the pts, 3/6 were already hospitalized at the time of symptoms, but none of them received mechanical ventilation. The most common symptoms at diagnosis were fever (n = 4) and cough (n =5); 22/33 had not symptoms. 21/33 pts were affected by multiple myeloma (MM), 4/33 MPN, 8/33 patient had a Lymphoproliferative disorders such as NHL and CLL. The four MPNs pts were treated at the time of COVID-19 diagnosis, with hydroxyurea (1/32) and imatinib (1/32). The pts with NHL were in anti-CD20 antibody and ibrutinib therapy, while the 10/21 MM patient were treated with Daratumumab-Lenalidomide and dexametasone (Dara-Len-Dex), Len+Dex 8/21, 1/21 with VMP (velcade-Melphalan-Prednsione); Dara alone 1/21 and Dex alone 1/21. In all the patients, the origin of COVID-19 infection was un-know. 30/33 pts had COVID-19 vaccines (29/30 Pzifer and 1/30 Moderna) and 3 pts were not vaccinated, one of this died during infection. In conclusion, in our study hematological pts appear to be vulnerable to covid-19 infection and although the number of confirmed COVID-19 was globally low, we noticed a significantly increase in the fourth wave. Therefore in this out-patient setting, persisting the pandemic phase, it is still important to maintain social distancing and reducing in hospital admission, as it is a potential risk factors for COVID-19 infection.

SP02

DOES COVID-19 INFECTION TRIGGER ROSAI DORFMAN DISEASE? A CASE REPORT

C. Marcon, R. Mullai, C. Filì, V. Simeon, V. Di Luca, G. Lamon, R. Mestroni, D. Lazzarotto, R. Fanin

Division of Hematology and Stem Cell Transplantation, University Hospital ASUFC

Rosai-Dorfman disease (RDD) is an extremely rare histiocytic disorder presenting both with lymphadenopathies and extranodal masses. The ultimate pathogenetic driver remains unknown but a possible correlation with viral infections (such as Parvovirus B19, HHV 6 and EBV) has been suggested. A woman, 59 years old, presenting with fever and massive abdominal lymphadenomegaly and supraclavicular, nuchal, latero-cervical lymphadenopathies, was admitted to our Hospital to investigate the outset of a possible lymphoproliferative disease. At admission blood count showed: marked absolute lymphopenia (210/mmc), neutrophilia (15.360/mmc), mild anemia (Hb 9.9 g/dL) and severe thrombocytopenia (12.000/mmc); blood chemistry provided high inflammatory indexes (PCR 180 mg/L, PCT 2.67 ng/mL, ferritin 3611 ng/mL, IL6 214 pg/mL). Bone marrow biopsy revealed only megakaryocyte hyperplasia. The patient was vaccinated with 2 doses of Comirnaty vaccine (last one 4 months before). After three days from admission, without any contact with positive subjects, the patient's molecular swab for SarsCoV2 turned positive, with persistence of clinical and bio-humoral alterations. Two lymph node biopsies were programmed to get a definitive diagnosis, requiring time to be performed and validated. Meanwhile steroids, immunoglobulins, TPO mimetics and single-dose Rituximab were administered in order to treat persistent and transfusion refractory thrombocytopenia. No rise of platelet count or significant clinical benefit were obtained. Progressively the patient developed a moderate NIH-grade pneumonia, 31 days after 1st positivity. SarsCoV2 was isolated even in bronchoalveolar lavage, which revealed an over infection of Aspergillus, *K. Pneumoniae* and *S. Aureus.* High-flow oxygen, antimicrobial therapy and hyperimmune plasma infusions, provided mild clinical improvement. Conclusive histological diagnosis of RDD, without identification of BRAF mutations, allowed introduction of a treatment based on methotrexate and 6-mercaptopurine, determining a slow but progressive platelet count recovery and ameliorating of infective symptoms, even if SarsCov2 swab was still positive (three month since 1st positivity).

Diagnosis of rare diseases are known to be difficult and affected people often develop various complications. Concerning our patient, it cannot be excluded that SarsCoV2 infection has played a role in generating and sustaining a pathogenetic pro-inflammatory trigger for the development of RDD.

SP03

EFFECTIVENESS OF ANTI SARS COV2 MONOCLONAL ANTIBODY IN HIGHLY IMMUNOCOMPROMISED PATIENTS AFFECTED BY SEVERE HEMATOLOGICAL DISEASES

R. Bianco[1], S. Iaccarino[1], G. Farina[1], A. Camera[1], M. Iovine[1], M. Troiano[1], A. Annecchiarico[2], E. Lupoli[3], F. Frigeri[1]

[1]Hematology Unit of AORN S. Anna and San Sebastiano; [2]Health Management Unit of AORN S. Anna and San Sebastiano; [3]Pharmacy Unit of AORN S. Anna and San Sebastiano, Italy

COVID 19 infection could increase the mortality rate in hematological disorders (HD) due to a delay of the scheduled chemotherapeutic regimen until viral disease resolution. It should be considered an additional life-threatening risk factor in this setting of pts. Here, we present the clinical features and outcomes of five patients affected by severe HD, hos-

pitalized in our Hematological Unit from March to May 2021 who showed a COVID-19 infection at the molecular swab which in our strategy was routinely performed once a week. Patients were affected by High Grade Non Hodgkin Lymphoma (N=3) Acute Myeloid Leukemia (N=1) and one acute graft versus host disease (GVHD) occurred post haploidentical bone marrow transplant for a refractory AML (N=1). All pts were male with a median age of 50 years and all of them were in aplastic phase after high intensive immune-chemotherapy. Molecular swabs confirmed a SARS COV2 Delta variant in all of them. All patients were asymptomatic and no one had received an anti SARS COV 2 vaccine. Monoclonal antibody (Bamlanivimab-Etesevimab) treatment was started within 5 days (median 3 days) without any relevant side effect. Patients were monitored by molecular swab every 3 days and a log-reduction curve of viral load was calculated and a negative test was obtained in a median time of 14 days. No COVID 19 related deaths occurred and all patients could continue planned chemotherapeutic regimen without relevant delays on schedule. Data presented showed the effectiveness of molecular swab monitoring which allow a prompt starting of monoclonal therapy, resulting in a rapid resolution of COVID 19 infection without a significant interference with the scheduled time of chemotherapeutic regimens.

SP04

GEOTRICHUM CLAVATUM INFECTION POST ALLOGENIC STEM CELL TRANSPLANTATION IN HEMATOLOGICAL PATIENTS: TWO CASE REPORTS

A. Rinaldi[1], L. Prezioso[1], B. Cambo'[1], M. Giaimo[1], B. Dalla Palma[1], D.Vallisa[1,2]

[1]Ematologia e Ctmo Azienda Ospedaliera - Universitaria Parma; [2]Ospedale G. Da Saliceto-Piacenza; Ematologia e Ctmo-Parma, Italy

Geotrhicum clavatum (G.C.) infection is a rare and lifethreatining event in immunocompromised patients. Bloodstream infections, skin lesions and pulmonary involvement are the most frequent manifestations. Mortality is high, ranging from 57% to 80%.

There is no optimal antifungal treatment: guidelines recommend liposomal B amphotericine (L-AMB) with or without co-administered flucytosine or with voriconazole; synergism with Isavuconazole (ISA) has to be confirmed. Here we describe two cases of G.C. infection in post transplant setting.

Table 1.

	Case 1	Case 2
Age	61	29
Sex	Male	Female
Diagnosis	AML MDS related	ETP-ALL
Treatment	Azacitidine; CPX351	HyperCVAD; GIMEMA LAL0904; VENETOCLAX-Bortezomib; HSCT (MUD/ TBF/ ATG-R-CSA-MMF) Relapse: DLI; Venetoclax-Bortezomib; Nelarabina; FLA-IDA; II HSCT (haplo PTCy)
Conditionig regimen HSCT	MAC : TBF	MAC: TBI+ FLUDA
GVHD Prophylaxis	CSA+MTX and ATG	PTCy+ CSA +MMF
Antifungal prophylaxis	Posaconazole (induction) micafungine (HSCT)	Posaconazole (induction) micafungine (HSCT)
Engrafment	During infection period	During infection period
Fungal insulation	Bloodstrem and cerebrospinal fluid	Bloodstream
Clinical manifestation	Hyperpyrexia, neurological symptoms	Hyperpyrexia and concomitant lung infection
Treatment	Liposomal amphotericin B + isavuconazole	Liposomal amphotericin B; isavuconazole
Outcome	Death	Resolution

Case 1: 61 y.o.man, in good general condition and overweight was diagnosed with post MDS-AML after two courses of therapy with azacitidine in Oct. 2019. He received chemotherapy (CHT) with CPX351 followed by hematopoietic stem cell transplantation (HSCT) from 10/10 matched unrelated donor (MUD). After HSCT severe mucositis and fever unresponsive to antibiotics occurred, with isolation of G.C. from blood culture at day+16. Therapy with L-AMB was promptly started. Clinical conditions suddenly worse because of development of neurological symptoms and then coma. Brain CT and MRI documented the presence of infectious foci in the basal nuclei. G.C. was isolated also in cerebrospinal fluid. Due to the lack of response to L-AMB, ISA was added. On day +17 granulocyte engraftment was documented. Unfortunately patient died at day +20 post HSCT.

Case 2: 29 y.o. woman, with an history of substances abuse, was diagnosed with early T precursor acute lymphoblastic leukemia (ETP-ALL) in Dec 2017. She received high dose CHT followed by 10/10 MUD-HSCT in 2018. One year later she relapsed . After salvage CHT, second HSCT from an haploidentical donor was performed. During peri-engraftment period (day +13), breakthrough infection occurred with isolation from the blood cultures of G.C. L-AMB was started with resolution of fever. Due to the presence of pleural effusion and basal thickening on the CT scan, bronchoalveolar lavage was performed with positivity for galactomannan. L-AMB was continued until discharge, switching to ISA as outpatients treatment.

Conclusion: G.C. is a rare and potential fatal infectious event. Prolonged period of severe neutropenia, despite systemic antifungal prophylaxis, certainly contribute to the development of this infection. Despite the similar therapeutic approach, the outcome of our two patients was conditioned by the different organ involvment. The peculiar aspects of two patients are summarized in Table 1.

SP05

SEVERE HYPERCALCEMIA AND SKELETAL INVOLVEMENT IN A PATIENT WITH RELAPSED/REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA: RARE EVENTS? CASE REPORT AND LITERATURE REVIEW

O. Battisti[1], M.G. Franzese[2], L. Ciuffreda[2], G. Palumbo[2], R. Cammarota[2], V.F. Fesce[2], G. Spinosa[2], A. Liso[3], L. Melillo[2]

[1]Department of Emergency and Organ Transplantation, University School of Medicine; [2]Department of Hematology, Hospital Riuniti; [3]Department of Medical and Surgical Sciences, University of Foggia, Italy

Background: The hypercalcemia associated with malignancy is the most frequent cause of hypercalcemia in hospitalized patients; in most cases it is symptomatic and associated with poor prognosis. The skeletal involvement in Chronic Lymphocytic Leukemia (CLL) has been considered a rare event for a long time; in literature some cases of lytic bone lesions in patients affected by CLL have already been described. In approximately 20 cases in the literature according to a recent review, patients with CLL present bone lesions too (Bacchiarri F. et al., 2022 Apr 4, Clin. Case Reports).

Patient concerns: We present the case of a 53-year-old female patient, affected by CLL stage IV Rai/C Binet with significant anemia and thrombocytopenia (unmutated IGHV, mutated TP53), in whom a severe and symptomatic hypercalcemia has occurred one week after the beginning of the second line therapy with venetoclax. The X-ray of right and left femurs, carried out due to deep pain at lower limbs, showed a thin area of radiotransparence at the third proximal diaphyseal of the right femur. The bone scintigraphy has detected a pathologically inhomogeneous distribution of osteotropic tracer in multiple sites; the Positron Emission Tomography has revealed pathological FDG uptake in the whole axile and appendicular skeleton. In addition to the hypercalcemia, we have detected suppressed PTH and elevated levels of IL-6.

Intervention: The patient has been treated with intense hydration, di-

uretics and bisphosphonates. Moreover, we have interrupted the therapy with venetoclax until the resolution of the hypercalcemia, in suspected drug-related adverse event.

Outcomes and conclusions: The calcium levels have returned to normal. Oncological evaluations have excluded the presence of concomitant second malignancies. The patient has re-initiated venetoclax without further problems and then she has started rituximab; in addition, she has been submitted to HLA typing for an eventual allogeneic hematopoietic stem cell transplantation. Five months after the beginning of the therapy, the patient's general clinical conditions are good and no new episodes of hypercalcemia have occurred. In our opinion, the pathological mechanism underlying the hypercalcemia and the skeletal involvement in patients affected by CLL deserve to be studied accurately in the future.

Key words: chronic lymphocytic leukemia, hypercalcemia, skeletal involvement, venetoclax

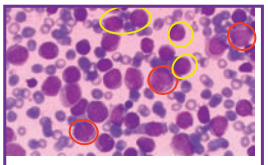
SP06

MIXED PHENOTYPE ACUTE LEUKEMIA (MPAL): DESCRIPTION OF DIAGNOSTIC PATHWAYS AND IMPACT ON TREATMENT CHOICES IN A PATIENT WITH BILINEAR ACUTE LEUKEMIA B/MYELOID PHILADELPHIA CHROMOSOME POSITIVE

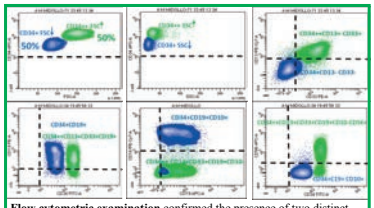
D. Avino, A. Cascone, M. Di Perna, A. Di Palma, V. Maglione, L. Ammirati, B. Vannata, C. Cimmino, C. Califano

UOC Ematologia Presidio Ospedaliero A. Tortora, Italy

MPALs are acute leukemia with poor prognosis in which blasts express antigens from more than one cell line. In bilinear MPAL two blasts populations of different lines coexist while in bipenotypic MPAL there is a single population of blasts which expresses markers of different cell lines. A 39-year-old male came to our hospital for fever, asthenia, tachycardia, and visual disturbances. The blood count showed marked leukocytosis (WBC:314000/µL), anemia (Hb:75 g/L) and thrombocytopenia (PLT:24000/µL). The peripheral blood and bone marrow morphological examination showed two populations of blasts, one of small size, poor agranulate basophilic cytoplasm and one of medium-large size with cytoplasmic granules suggestive of acute bilinear leukemia. Flow cytometric examination confirmed the presence of two distinct populations of pathological cells with different physical and phenotypic characteristics: the first (50%) with a low SSC and immunophenotype CD34+CD45dimCD19+CD10+CD20+/-TdT+cyCD79a+HLA-DR+ and the second with major SSC CD34++CD45dimCD33+ CD13+CD117+/-CD7+/-CD56+CD19+CD11c+CD36+/-CD64+/-MPO+. The cytogenetic study revealed the t(9;22) and the molecular analysis revealed the presence of the BCR-ABL1. The patient started ALL-based Hyper-CVAD induction chemotherapy in combination with Dasatinib. A hematological remission has been obtained but not a major cytogenetic and molecular response for this reason it was decided to switch to Ponatinib.



Bone marrow smear: presence of two populations of blasts, one of small size, poor agranulate basophilic cytoplasm (yellow circles) and one of medium-large size with cytoplasmic granules (red circles).



Flow cytometric examination confirmed the presence of two distinct population of pathological cells: the first (50%) (blue) with FSC↓ SSC↓ and immunophenotype CD34+CD45dimCD19+CD10+CD20+/-TdT+cyCD79a+HLA-DR+ and the second (50%) (green) with FSC↑ SSC↑ and immunophenotype CD34++CD45dimCD33+CD13+CD117+/-CD7+/-CD56+CD19+CD11c+CD36+/-CD64+/-MPO+.

At the onset of progressive leukocytosis (WBC:12160/µL) and thrombocytopenia (PLT:63000/µL) he performed a bone marrow re-evaluation which showed a relapse of the disease with 75% predominantly myeloid blasts (95%) and the appearance of an anomaly additional cytogenetics: the trisomy of chromosome 21. The patient started the rescue chemotherapy according to FLA-IDA scheme in association with Ponatinib, obtaining hematological remission again but not cytogenetic and molecular response. Patient refused the trasplant program. Approximately 4 months after remission, worsening hyperleukocytosis (WBC:71950/µL), anemia (Hb:103g/L) and marked thrombocytopenia (PLT:11000/µL) was observed, suggesting a loss of response to therapy and a relapse of disease. The patient started the compassionate therapy with Venetoclax in combination with Ponatinib without any benefit. The patient died after 4 months. The therapeutic approach for MPAL patients is not unique and there is no clear evidence whether they respond better to induction regimens for ALL or AML.

SP07

FISH ANALYSIS FOR DETECTION OF C-MYC, BCL2 AND BCL6 REARRANGEMENTS IN HIGH-GRADE B CELL LYMPHOMAS ON PARAFFIN-EMBEDDED TISSUE

C. Fabbricatore[1], I. Caliendo[1], L. Sparano[2], L. Barone[1], M. Langella[1], R. Rosamilio[1], G. Morelli[1], G. Malferà[1], C. Attianese[1], A. Ruggiero[1], F. Puopolo[1], C. Califano[1]

[1].U.O.C. di Ematologia ed Autotrapianto di Cellule Staminali Emopoietiche; [2]U.O.C. Anatomia e istologia patologica, Italy

Introduction: High-grade B-cell lymphoma (HGBL) is a newly defined entity in the latest World Health Organization Classification.This category includes HGBL with MYC and BCL2 and/or BCL6 rearrangements, defined as "double-hit" or "triple-hit"(HGBL-DH/TH).Accurate diagnosis would appear to mandate Fluorescence In Situ Hybridization (FISH) for all tumors with diffuse large B-cell lymphoma (DLBCL) morphology. Here, we present the results of performing FISH to paraffin-embedded tissues, with a panel of probes including MYC, BCL2 and BCL6, to document related gene translocation and overexpression.

Methods: FISH analysis was performed on 4 µm tissue sections using FISH DNA break-apart probes and Vysis IntelliFISH Kit (Vysis).A total of 10 cases were examined using LSI C-MYC Break Apart FISH Probe kit, LSI BCL2 Break Apart FISH Probe Kit, LSI BCL6 Break Apart FISH Probe Kit. Briefly, the tissue slide was de-paraffined and rehydrated prior to the procedure. After treatment with protease solution, FISH DNA Probes were added to the tissue sections and hybridized for over night followed by stringent wash. Assessment of signals was performed using Leica Fluorescent microscope with the Cytovision software at x100 magnification. The cases performed depend on the availability of tissue block hence the total cases for each gene were different. The FISH analyses results were divided into signal patterns normal, translocated (>20% of the whole tumour population), gain copies (>20% of the whole tumour population) and both translocated and overexpression category. All slide specimens were analized by pathologist and integrated with clinical information. Cut-off score for MYC overexpression in immunohistochemistry (IHC) was : ≥30%. In addition, the presence of a high percentage of tumor cells positive for Ki-67 staining is evaluated.

Results: In this study, two patients showed MYC rearrangement while eight patients exhibited no MYC rearrangement. Of the MYC rearranged cases, one case concurrently bore bcl2 rearrangement (HGBL-DH). Only overexpression of BCL2 and BCL6 rearrangement, rispectly, was found in one patient and two patients.

Discussion: Over the last decade, FISH has become a firmly established technique in the diagnosis and assessment of lymphoid malignancies, to identify chromosomal abnormalities, that predicting a more aggressive course of the disease.This data can serve as a plataform for future studies to have better outcomes with more intensive and targeted therapies.

SP08

EFFICACY OF BRENTUXIMAB-VEDOTIN PLUS DHAP REGIMEN FOLLOWED BY AUTOLOGOUS STEM CELLS TRANSPLANTATION AS SALVAGE TREATMENT FOR REFRACTORY "GRAY ZONE" LYMPHOMA. A CASE REPORT

G. Monaco, G. Farina, S. Iaccarino, A. Camera, R. Bianco, F. Frigeri

UOC Ematologia AORN Sant'Anna e San Sebastiano, Italy

Gray zone lymphoma (GZL) is a rare type of lymphoma with intermediate features between diffuse large B cell lymphoma and classical Hodgkin disease. Prognosis is very poor. There are no standardized therapeutic strategies, especially for relapsed/refractory (R/R) patients. Few evidences, about efficacy of the anti CD-30 antibody drug conjugate Brentuximab Vedotin (BV) for GZL's treatment, are reported. CASE REPORT. In October 2020, a 21-years-old woman showed sovraclavear lymphoadenopathy associated with fever, loss of weight and nocturnal sweats. Chest radiography and total body computerized tomography (TB-CT) evidenced a bulky mediastinal disease, pleural effusion and a left sovraclavear limphoadenopaty, extending up to the paracardiac region. Mediastinal biopsy was performed and the histology revealed a GZL. A stage IV disease was documented after total body Positron Emission Tomography (PET) which showed high metabolic activity in nodal sites, mediastinum and right ovary. First line therapy with 6 cycles of DA-EPOCH-R regimen (Dose adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, rituximab) was performed. High dose methotrexate was added at the second and third cycles for CNS prophylaxis. Restaging post chemotherapy revealed a refractory disease for persistence of mediastinum and nodal uptake even if a reduction of mass volume. A second line polychemotherapy according to BV-DHAP regimen (BV plus dexamethasone, cytarabine and cisplatin), was started as bridging treatment to autologous stem cells transplantation (ASCT). After the first cycle, the patient obtained a very good partial response, converted to a complete remission at the end of third cycle. At this time, patient underwent ASCT, after high dose conditioning regimen with FEAM regimen (fotemustine, etoposide, cytarabine, melphalan). Restaging post ASCT confirmed a complete metabolic response with a further reduction of mass volume. At our knowledge this is the first report of a successfully salvage therapy by BV-DHAP plus ASCT in a refractory GZL. Our case suggests that BV-DHAP is an effective and safe regimen allowing peripheral blood stem cells (PBSC) collection, that could be proposed as a valid bridging therapy in R/R GZL.

SP09

CYCLOPHOSPHAMIDE ADDITION TO POMALIDOMIDE, BORTEZOMIB AND DEXAMETHASONE IN HEAVILY PRETREATED MULTIPLE MYELOMA, A CLINICAL REPORT

L. De Padua, D. Gangemi, G. Tomei, A. Carbone, S. Vaccarini, R. Sala

UOC Hematology, F. Spaziani Hospital, Italy

In June 2012 a 68-years-old hypertensive and dyslipidemic man admitted to hospital with pneumoniae. The blood work showed hemoglobin 9.9 g/dL, creatinine 1.7 mgdL and IgGK M-protein 5.6 g/dL. A magnetic resonance imaging revealed spine and pelvic diffuse lytic lesions. He was diagnosticated with stage III, ISS II multiple myeloma. His performance status (ECOG) was 2. He was treated with melphalan, bortezomib and prednisone obtaining partial remission. In March 2013 he started lenalidomide 25 mg and dexamethasone (dex). He experienced grade 3 neutropenia requiring granulocyte colony-stimulating factor (G-CSF) support. After 30 cycle he admitted to hospital with a community-acquired pneumoniae. Lenalidomide was reduced to 15 mg/day. In November 2017 after 46 cycles the disease progressed: M-protein increased to 2.7 g/dl, costal lytic lesions detected on computed tomography (CT), bone marrow massively infiltrated. At the age of 73 (ECOG 1) the patient started daratumumab and oral dex obtaining functional well-being despite the stable disease. After 20 cycles in December 2019, the M-protein increased to 3.4 g/dL with all other results unchanged. Until July 2020 we added 8 cycles of twice weekly bortezomib to oral dex and monthly administration of daratumumab. The patient experienced grade 3 neutropenia and two events of bronchitis requiring antibiotics and G-CSF support. In January 2021 undergoing therapy with oral dex and daratumumab, he reported fatigue (ECOG 2) and severe lower back pain with functional limitation. A CT scan revealed diffuse lytic lesions. The M protein increased to 3.6 g/dL. In February 2021 we started pomalidomide 4 mg (days 1-14), bortezomib 1,3 mg/m^2 on days 1,4,8,11 and oral dex 20 mg on days 1,2,4,5,8,9,11,12 of a 21 days cycle. Special attention to neuropathy and hyperglycemia was tracked closely. The patient showed stable disease with ECOG improvement. After 8 cycles bortezomib was continued on days 1 and 8. The patient developed grade 3 neutropenia requiring G-CSF support. After 13 cycles in November 2021, we added oral cyclophosphamide 300 mg on days 2 and 9 and weekly G-CSF (days 4, 11 and 18). The patient experienced one event of bronchitis without hospitalization. In April 2022 after 20 cycles M-protein was decreased to 1.8 g/dL with other results unchanged. The patient is functionally doing very well (ECOG 0). Our findings showed efficacy and safety of this combination in a heavily pretreated old patient with multiple myeloma.

SP10

GAUCHER DISEASE AND MULTIPLE MYELOMA: A SYNCHRONOUS DIAGNOSIS

A. Rago[1], A. Tordi[1], E. Verrecchia[2], R. Manna[3], A.M. Di Francesco[3], C. Zizzo[4], G. Duro[4], M. Offidani[5], T. Caravita di Toritto[1]

[1]UOSD Ematologia ASL ROMA1, Roma; [2]UOC continuità assistenziale, Fondazione Policlinico Universitario A. Gemelli IRCCS; [3]Centro di ricerca delle febbri periodiche e malattie rare, università cattolica del sacro cuore, Roma; [4]Istituto di per la Ricerca e l'Innovazione Biomedica CNR-Palermo, Palermo; [5]Clinca di Ematologia, Ospedali Riuniti di Ancona, Ancona, Italy

Type 1 Gaucher disease (GD1) is the most frequent lysosomal storage disease and corresponds to an inherited deficiency of glucocerebrosidase. Due to excessive accumulation of glucocerebroside in bone marrow, both cytopenia and bone lesions may occur. The incidence of malignant disorders has been evoked in non-neuronopathic type I GD. More particularly, many case reports have been published that describe the association between GD1 and multiple myeloma (MM). Here, we report a case of MM patient who have a synchronous diagnosis of GD and MM. 75-year-old male with no significant history but MGUS, presented to the hospital with abnormal renal function anemia, and lower back pain The patient presented with a normocytic anemia, hemoglobin of 9.3. On CT imaging, the patient had innumerable osteolytic lesions, predominantly in the pelvis, no splenomegaly. The patient was subsequently found to have an IgG kappa M-spike of 3.36 gr/dl. Bone marrow biopsy was obtained and was consistent with plasma cell myeloma. Upon immunophenotypic analysis, monoclonal IgG kappa (CD38 bright) population was present at 20-30% of the bone marrow. Further evaluation on FISH and cytogenetics was negative. Patient was started an induction first line therapy with DRD (daratumumab, lenalidomide and dexamethasone). During treatment, into an observational protocol, the patient was testing for GD (Dried Blood Spots-DBS) and was found to be a carrier of atypical GD. Peripheral blood specimen was sent of revealing low enzymatic glucocerebrosidase activity resulted 2 mol/h/ml (normal range >2,5 nmol/h/ml); therefore GBA molecular analysis revealed an heterozygous of the p.Arg209Cys (p.R209C) and p.Leu483Pro (p.L483P) variant. The patient underwent to further evaluation to search sign and symptoms at-

tributable to GD. Patient had a past medical history of anemia fo unknown origin, and recently complained for bone pain, which was attributed to osteolytes lesions. Abdomen ultrasound didn't report hepatosplenomegaly. GD biomarkers resulted normal (chitotriosidase, ferritin) except for LysoGB1 (14.6 ng/ml, normal range <6,8 mg/ml).The need to undertake specific therapy for Gaucher disease is still being evaluated. At this time, no clinical report are reported about the contemporary therapy with ERT and monoclonal antibody and Lenalidomide in MM patient.

SP11

HIGH RISK MYELODYSPLASTIC SYNDROME DEVELOPING AFTER CAR T- CELL THERAPY IN A PATIENT WITH RELAPSED DIFFUSE LARGE B CELL LYMPHOMA

E. Accorsi Buttini[1], M. Farina[1], L. Lorenzi[2], V. Radici[1], A. Turra[1], E. Morello[1], N. Polverelli[1], F. Colnaghi[1], C. Almici[3], E. Ferrari[3], A. Bianchetti[3], A. Leoni[1], F. Re[4], K. Bosio[4], S. Bernardi[4], M. Malagola[1], A. Re[5], D. Russo[1]

[1]Unit of Blood Diseases and Bone Marrow Transplantation, Cell Therapies and Hematology Research Program, Department of Clinical and Experimental Science, University of Brescia, ASST Spedali Civili di Brescia; [2]Department of Molecular and Translational Medicine, Section of Pathology, University of Brescia, ASST Spedali Civili di Brescia; [3]Stem Cell Laboratory, Section of Hematology and Blood Coagulation, Clinical Chemistry Laboratory, Diagnostics Department, ASST Spedali Civili di Brescia; [4]Research Center Ail (CRE A), Chair of Hematology Department of Clinical and Experimental Science, University of Brescia, ASST Spedali Civili di Brescia; [5]Hematology Unit, ASST Spedali Civili di Brescia, Italy

Chimeric antigen receptor (CAR)T- cell therapy showed exciting efficacy in relapsed and refractory B malignancies. Hematotoxicity after CAR T-cell is represented by early and late cytopenias and hypogammaglobulinemia. We report here a case of high risk myelodysplastic syndrome (MDS) developed after CAR-T cell therapy for relapsed diffuse large B cell lymphoma (DLBCL). In August 2019, a 57 year-old woman was diagnosed with germinal-center BCL-2 single rearrangement DLBCL, stage IVs-A, IPI score 3, CSN-IPI 4. Bone marrow (BM) biopsy showed B-cell lymphoma infiltrate (25% of cellularity) in a context of normocellular marrow. She was treated with 4 cycles of R-CHOP and one more cycle of R-MAD, achieving a PET complete remission (CR). Following chemotherapy, the BM biopsy revealed a hyperplastic erythropoiesis with hypoplastic megakaryo-granulopoiesis without lymphoma infiltration. Intensification with HD-AraC and ASCT was performed on April 2020. Eight months later the patient relapsed with multiple adenopathies and was evaluated for CAR T-cell therapy. After two R-ESHAP cycles, Tisagenlecleucel was infused in April 2021 without any early adverse event. Six months later, the patient was in CT-PET CR but developed a progressive pancytopenia (grade III anemia, grade IV thrombocytopenia, grade III neutropenia according to CTCAE) requiring G-CSF, erythrocyte and platelet support. On January 2022, a BM biopsy revealed a multilineage dysplasia with chromosome 7 deletion (not present two months after CAR T cell infusion) and with no gene mutations on NGS. Diagnosis of high revised-IPSS risk MDS was made and azacitidine was started as bridge to allogeneic transplantation. Acute and long term hematologic toxicities after CAR-T therapy are reported in the literature. Early cytopenia is probably related to cytokine mediated myelosuppression and to lymphodepleting therapy. Late cytopenia seems to correlate with BM stem cell reserve resulting from previous chemotherapy lines and high baseline level of inflammation markers. Chromosome 7 deletion is considered one of the hallmark features of therapy related MDS but up to now, no cases of secondary malignancy were attributed to previous CAR T treatment. This case highlights the need to monitor hematopoesis (with BM biopsy, cytogenetics, NGS) in all candidates to CAR T at different time points in order to understand if cellular therapy itself may play a role in development of clonal hematopoiesis or secondary myeloid diseases.

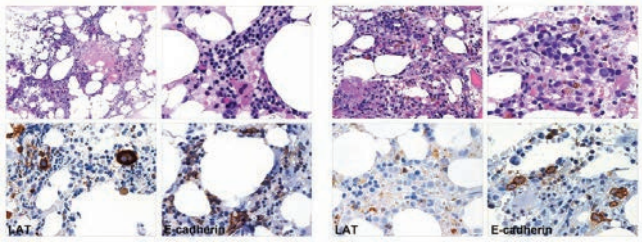


Figure 1.

SP12

KENNEDY'S DISEASE AND MYELODISPLASTIC SYNDROME: A POSSIBLE NEW ENTITY IN MYELOID NEOPLASM GERMLINE PREDISPOSITION ? A CASE REPORT.

A.L. Piccioni[1], S. Fenu[1], M.T. Voso[2], M. Inghilleri[3], E. Fabiani[2], P. Panetta[2], B. Anaclerico[1], P. Anticoli Borza[1], V. Bongarzoni[1], M. Cedrone[1], E. Ceresoli[1], E. Finolezzi[1], S. Leonetti Crescenzi[1], A. Tamburini[1], L. Cudillo[1]

[1]UOC Ematologia e Trapianto di cellule staminali AO S. Giovanni Addolorata Roma; [2]Dipartimento di Biomedicina e Prevenzione, Università di Roma Tor Vergata; [3]Centro di Malattie Rare Neuromuscolari Dipartimento di Neuroscienze Umane Università di Roma "La Sapienza", Italy

Introduction: The introduction of next-generation sequencing (NGS) into the diagnostic work-up in Myeloid Neoplasm has revealed that the myelodysplastic syndrome (MDS) or Acute Myeloid Leukemia (AML) hereditary are more common than previously thought in adult patients(5-15%). Thus, myeloid neoplasm with germline predisposition were included as a new dedicated entity in WHO 2016, but there are other rare disorders that lead to bone marrow failure not yet included in this classification.We report a case of bone marrow failure syndrome (IBMFS),associated with Kennedy disease(MK),which developed MDS then AML. MK, or bulbospinal muscular atrophy, is a rare motor neuron disease associated with a mutation of the androgen receptor gene on the long arm of the cr.X

Clinical case: 66-year-old Caucasian man with isolated persistent neutropenia came to our observation in March 2013.In medical history, he was diagnosed with Kennedy's disease from the age of 33.Bone marrow cytomorphology showed trilinear dysplasia with myeloblast 4%. Cytogenetics demonstred normal karyotype (46,XY). The diagnosis was MDS-MLD (WHO classification 2008), risk assessment was R-IPSS and WPSS low. In February 2018, was observed an increased number of blast cells (11%) on cytomorphology,CD45+CD33+CD34+CD117+HLADR+ in flow cytometry. Cytogenetics confermed 46,XY.The MDS-EB2 ELN 2017 was diagnosed. The patient underwent therapy with 5-azacitidine 75 mg/m^2 daily schedule for 5+2 days at 4-week intervals receiving thirty-four cycles with partial remission. In December 2021 was diagnosed with acute myeloid leukemia AML-MRC ELN 2017 forty-six months after MDS-MLD diagnosis.The bone marrow sample shoved 25 % blasts. Cytogenetics confermed 46, XY. NGS is in table. Patient received therapy with decitabine 20 mg/m^2/day for five every 28 days and venetoclax 100 mg/day for 21 days. He performed two courses from February 2022 with complete remission.

Conclusions: To date have not yet been described in the literature cases of MK associated with IBMFS. A new entity of MK-related germline mutations could be hypothesized that could predispose to the myelodysplasia or acute leukemia when associated with additional somatic muta-

tions such as ASXL1.The study of the molecular biology profile of IBMFS-related MDS could be useful to stratify these diseases into dedicated risk categories and to better evaluate the predictive value of mutations such as ASXL1, TET2, DNMT3A when associated with X-linked genetic alterations.

Table 1. NGS mutational analysis.

Gene	Target region (exon)	Gene	Target region (exon)	Gene	Target region (exon)	Gene	Target region (exon)	Gene	Target region (exon)
ABL	4-9	*CSF3R*	all	*IDH1*	4	*NPM1*	10,11	*SRSF2*	1
ASXL1	9,11,12	*DNMT3A*	all	*IDH2*	4	*NRAS*	2,3	*TET2*	all
BRAF	15	*ETV6*	all	*JAK2*	all	*PTPN11*	3,7-13	*TP53*	all
CALR	9	*EZH2*	all	*KIT*	2,8-11,3,17,18	*RUNX1*	all	*U2AF1*	2,6
CBL	8,9	*FLT3*	13-15 and 20	*KRAS*	2,3	*SETBP1*	4	*WT1*	6-10
CEBPA	all	*HRAS*	2,3	*MPL*	10	*SF3B1*	10-16	*ZRSF2*	all

Risultati giudicati di interesse clinico:

Gene	Tipo Alterazione	Risultato Alterazione	Chr	c.DNA	Proteina	Dettaglio	VAF (%)
ASXL1	INDEL	Frameshift	20	c.1900_1922del	p.(Glu635Argfs*15)	E635R*15	37,1
EZH2	SNV	Missense	7	c.2069G>A	p.(Arg690His)	R690H	6,1
EZH2	SNV	splice_donor -2	7	c.728+2T>C	p.(?)		6,1
SRSF2	SNV	Missense	17	c.284C>A	p.(Pro95His)	P95H	33,2

SP13

SAFETY OF BONE MARROW HEMATOPOIETIC STEM CELL COLLECTION FROM A SARS-COV2 POSITIVE DONOR: A SINGLE EXPERIENCE DURING THE ITALIAN PANDEMIC

G. Magliano, B. De Marco, G. Bertani, L. Pezzetti, L. Intropido, G. Travi, E. Volpato, R. Crocchiolo, G. Grillo, R. Cairoli

Department of Haematology, Niguarda Cancer Center, ASST Grande Ospedale Metropolitano Niguarda, Italy

Background: The worldwide pandemic caused by SARS-COV2 virus has brought significative burden on the health care system, including programs performing allogeneic hematopoietic stem cell transplantation (HSCT). We present the case of a safe bone marrow collection procedure from a SARS-COV2 positive donor.

Methods: A 54 year-old woman, who came to our attention in September 2020, was diagnosed with severe aplastic anemia. The 55 year-old patient's brother was selected as HLA haploidentical donor. Despite a first negative molecular test on nasopharyngeal swab, a new pre-operative test, performed on the basis of hospital policy, revealed positivity for SARS-COV2. The donor was completely asymptomatic. Considering the urgent need to treat our patient, as the general clinical conditions were rapidly worsening due to infectious complications, we decided not to stop the transplant procedure. Conditioning regimen was cyclophosphamide 300 mg/mq+fludarabine 30 mg/mq (days -6 to-3), GvHD prophylaxis was antithymocyte globulin 3,75 mg/Kg (days -1 and 0), total body irradiation (TBI) 400 cGy (day -1).

Results: Bone marrow harvesting was performed in an operating room which provided airborne infection isolation routine. The medical team wore enhanced personal protection equipment. The procedure was free from complications. SARS-COV2 RNA on the product was found negative in real-time PCR. Being asymptomatic, the donor was dismissed the day after the procedure to domiciliar isolation. Our patient received the processed product, which consisted in CD34+ 3.54 x 10^6/kg cells. The recipient was negative for SARS-COV2 on nasopharyngeal swab after stem cell infusion.

Conclusions: Our case enlightens a successful bone marrow harvesting procedure from a SARS-COV2 positive donor, which was organised in urgent clinical need, and demonstrates that transplantation from asymptomatic positive donors is feasible and safe, as viral transmission did not happen since the stem cell product was RT-PCR negative. Despite the current EBMT recommendations suggesting to avoid stem cell donation from positive individuals, donor care and selection should be revisited, as SARS-COV2 positivity itself might not be an exclusion criteria for bone marrow donation. Further data are needed to assess whether harvested marrow could transmit SARS-CoV2. Specific measures are also needed to provide the safety of the bone marrow collection medical team.

SP14

VENETOCLAX PLUS HYPOMETHYLATING AGENTS (HMAS) AS A TREATMENT OF ACUTE MYELOID LEUKEMIA (AML) PATIENTS WHO RELAPSE AFTER ALLOGENEIC HEMATOPOIETIC STEM CELLS TRANSPLANTATION ALLO-HSCT)

A. Spina, M.A. Urbano, F.I. Merchionne, E. Rinaldi, G. Mele, G. Guaragna, C. Romano, D. Pastore

UOC EMATOLOGIA , Ospedale "Antonio Perrino" - Brindisi, Italy

Introduction: Venetoclax is used in combination with HMAs to treat adult patients with newly diagnosed AML who are not candidates for intensive induction chemotherapy or who are 75 or older. Here we report our experience of 4 patients treated with venetoclax plus HMA with relapse of AML after allo-HSCT. Patients and methods: in our centre, 4 patients suffering from relapse of AML after allo-HSCT underwent HMAs plus venetoclax. Two patients received azacitidine as HMA and two patients decitabine. The median age of the patients was 55.5 (21-64); two were men and two were women. At relapse, median bone marrow blasts was 37.5 % (20-55), WBC 1.050/mmc (700-9.900), Hgb 8 g/dl (7,5-11) and platelets of 22.500/mmc (15.000-80.000).

Results: The median of the courses of therapy administered was 4 (range 1-6). One patient had graft versus host disease (GVHD) during therapy. The overall response rate (ORR) was 50%. One patient achieved complete remission, one patient partial remission, one patient stable disease and another one was refractory. Median overall survival (OS) was calculated from start of venetoclax plus HMA to death or last follow-up and was 7 months (3-11). The adverse events found were infectious (pneumonia in 75%, sepsis in 25%, undetected fever 25%). Two patients died from disease progression and two are alive; the former relapsed, the latter had a disease progression. Conclusions: The combination venetoclax plus HMA was effective and well tolerated even in patients with relapse of AML after allo-HSCT. Obviously, a study on a large sample of patients is needed to better evaluate the effectiveness of the treatment and the management of its toxicity, to acquire information on any changes in chimerism and finally to manage GVHD during therapy.

SP15

REACTIVE HEMOPHAGOCYTIC SYNDROME IN THE CONTEXT OF ACUTE GRAFT-VERSUS-HOST DISEASE AND SARS-COV-2 INFECTION

A. Vincenzi[1], F. D'Agostino[1], A. Fiore[1], L. Fusco[2], M. Foggia[2,3], A. Buonomo[2,3], C. Califano[4], I. Gentile[2,3], F. Pane[1,2], G. Battipaglia[1,2]

[1]Federico II University of Naples, Hematology Unit, Naples; [2]Department of Clinical Medicine and Surgery, Federico II University of Naples, Naples; [3]Federico II University of Naples, Infectious Disease Unit, Naples; [4]Onco-Ematologia Ospedale Pagani, Salerno, Italy

Reactive hemophagocytic syndrome is a life-threatening hyperinflammatory syndrome that can occur in several situations, including graft versus host disease (GVHD) after haematopoietic stem cell transplantation (HSCT). The syndrome has also been described in patients with COVID-19. Treatments include steroids and JAK-2 inhibitors, *e.g.* Ruxolitinib.

A 59-year old woman was diagnosed with secondary acute myeloid leukemia evolving from 5q- myelodysplastic syndrome in June 2021. Being refractory to chemotherapy, she underwent haploidentical HSCT

with active disease (10% blasts).

Neutrophil and platelet engraftment occurred on days (d) 19 and 27, respectively.

On d29 she developed grade II skin acute GVHD, successfully treated with methylprednisolone 1 mg/kg.

On d44 paucisymptomatic SARS-CoV2 infection was documented and treated with monoclonal antibodies in our COVID-19 Infectious disease Unit.

On d72, a Campylobacter infection was documented and treated with Azithromycin.

On d83, due to clinical worsening with reappearance of abundant diarrhea, the patient was hospitalized in the COVID19 Infectious Disease Unit. Biochemistry showed hyperbilirubinemia (peak 15,64 mg/dl), hypertrigliceridemia (peak 932 mg/dl), severe pancytopenia, elevated serum ferritin (>2000 ng/ml) and CRP (231 mg/L). A bone marrow aspirate was performed showing complete remission (CR) but trilinear dysplasia with histiocytes and clear figures of active hemophagocytosis (Figure 1). H-Score result was 225, with probability of reactive hemophagocytosis being 96-98%.

Methylprednisolone dose was increased to 2 mg/kg to treat hepatic and gut severe acute GVHD. Due to steroid-refractoriness, off-label treatment with Ruxolitinib was introduced at 10 mg BID, allowing CR of gut and partial remission of hepatic GVHD.

Due to the persistent pancytopenia, at d112 a second bone marrow aspiration was performed, confirming CR and also a significant reduction in hemophagocytosis figures.

At d115, while the patient was still SARS-CoV2 positive, bilirubin levels peaked again and rapid clinical deterioration occurred, preventing introduction of other treatments. The patient died on d119 after HSCT.

Post-transplant reactive hemophagocytic syndrome diagnosis requires high suspicion and prompt treatment. This case raises questions about the possible role of SARS-CoV2 in triggering GVHD in its severe form, together with reactive hemophagocytosis.

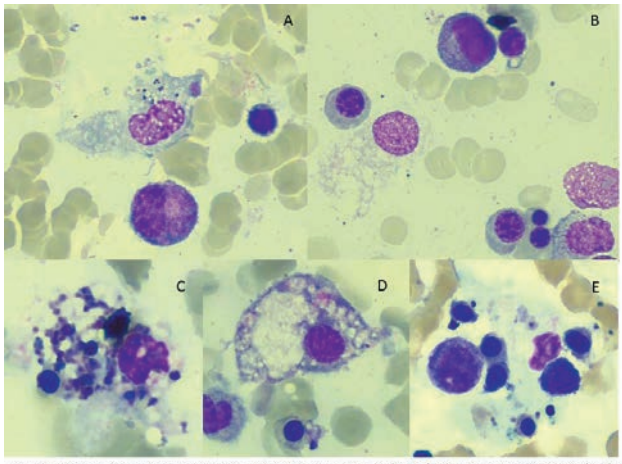


Fig. 1 Bone marrow aspirate revealing activated macrophages (A,B,D) with figures of siderosis (A,C) and hemophagocitosis (E). Dysplastic erythroid and myeloid precursors were observed (A, B).

Figure 1.

SP16

MAINTENANCE THERAPY WITH PONATINIB FOR AN EXTENDED PERIOD OF TIME AFTER A DOUBLE ALLOGENEIC PERIPHERAL STEM CELLS TRANSPLANT IN A PATIENT WITH PHILADELPHIA CHROMOSOME-POSITIVE ACUTE LYMPHOBLASTIC LEUKEMIA (PH+ ALL)

A. Spina, M.A. Urbano, F.I. Merchionne, G. Guaragna, G. Mele, M.L. Di Noi, C. Schifone, E. Rinaldi, M.P. D'Errico, M.R. Coppi, C. Romano, D. Pastore

UOC Ematologia , Ospedale "Antonio Perrino" - Brindisi, Italy

Introduction: The use of third-generation tyrosine kinase inhibitor ponatinib post-allogeneic hematopoietic stem cell transplant is still limited and its preventive effect on relapse is not well-known. We report our experience on the use of ponatinib after a second allogeneic transplant in a patient with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL).

Case report: A 52 year old man in December 2011 received a diagnosis of Ph+ ALL, p 210, at high risk for leukocytosis and underwent induction therapy with steroid and dasatinib (140 mg per day), achieving a complete haematological and cytogenetic response; however, the molecular disease persisted. Therefore in June 2012 he underwent allogeneic transplantation of stem cells from an unrelated donor (1 antigenic mismatch on the DPB1 locus). After the transplant, he underwent "maintenance" therapy with Dasatinib until March 2013, achieving complete molecular remission. In July 2013, disease recurrence and confirmation of the ABL mutational analysis of the V299L mutation. Therefore the patient started ponatinib therapy until November 2013 and achieved complete morphological remission. In the same period he underwent the II allogeneic stem cell transplant from related donor (son) HLA matching: 5/10. In April 2014 he resumed the "maintenance" therapy with ponatinib 15 mg per day (well tolerated) until March 2022 maintaining a deep molecular response (Figure 1). In conclusion, the "maintenance" therapy with ponatinib, after allogeneic transplantation, in our case proved to be effective and safe for a long follow-up of 96 months. However, studies on a large sample of patients are needed to evaluate the appropriate dosage and duration of administration of the third generation inhibitor after an allogeneic transplant in subjects with Ph+ ALL.

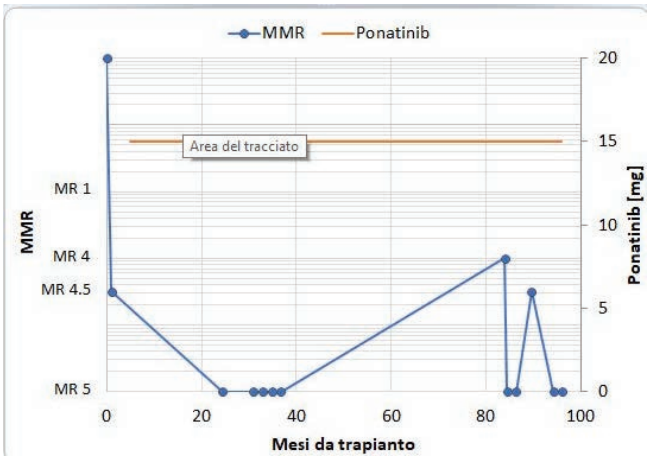


Figure 1.

SP17

EARLY DEVELOPMENT OF CRANIOPHARINGYOMA AFTER ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION IN AN ADULT PATIENT AFFECTED BY ACUTE MYELOID LEUKEMIA

G. Magliano, B. De Marco, G. Bertani, R. Greco, V. Mancini, G. Grillo, R. Cairoli

Department of Haematology, Niguarda Cancer Center, ASST Grande Ospedale Metropolitano Niguarda, Italy

Background: Second solid cancers are a considerable late complication in hematopoietic stem cell transplantation (HSCT) survivors and are associated with substantial morbidity and mortality. The cumulative incidence is reported up to 14.9% at 15 years post HSCT. Brain tumors and their development are seldom described in this setting.

Methods: a 60 years old woman, affected by late relapse of NPM-1 positive acute myeloid leukemia, was allografted in February 2021 in our Division. Her past medical history included hemicrania and empty sella. During the hospitalization for reinduction chemotherapy, in order to study a clinical picture of diabetes insipidus and hypothyroidism, we performed a brain MRI, which documented a small cystic lesion, extending in the sellar and supra-sellar region, T2 hyperintense and T1 hypointense. As there were not signs of bone involvement, nor hemorrhage, and in the absence of neurological symptoms, endocrine therapy was started. Considering the urgent need to treat AML, we continued the programmed cycles and brought the patient to haploidentical and reduced-intensity (thiotepa, fludarabine and melphalan) transplant. GvHD prophylaxis was cyclophosphamide 50 mg/Kg days +3-4, cyclosporine from day +5 and MMF from day +5 to +35. As we obtained full engraftment and no signs of aGvHD, we dismissed the patient.

Results: during outpatient follow up, CR was documented and immunosuppressive therapy was partially tapered. Four months after allo HSCT, the patient showed an abrupt right eye blindess, associated with mental confusion and abulia. We repeated brain MRI which documented a wide expansion of the lesion, involving the pituitary stalk, the third ventricle and the optic chiasm. The lesion was removed with a transsphenoidal approach. Histological diagnosis of craniopharingyoma, adamantinomatous subtype, was made. The patient eventually died of surgical complications.

Conclusions: we described the case of an apparently not significant brain lesion, which revealed to be a low grade tumor, usually with an indolent growth, which rapidly spread during the period of immune suppression due to allo HSCT. Moreover, this happened only a few months after transplant. We need more information concerning the effects of immune suppression on CNS tumors. In the meantime we suggest a strict follow up for early detection and a multidisciplinary approach before and after HSCT.

NEW PHARMACOLOGIC APPROACHES TO SICKLE CELL DISEASE (SCD)

L. De Franceschi

Dipartimento di Medicina, Università di Verona & AOUI Verona; Policlinico GB Rossi, Verona, Italy

Sickle cell disease (SCD) is an hemoglobinopathy which affects approximately 100,000 individuals in the United States and almost 20,000-25,000 subjects in Europe, mainly immigrants from endemic areas such as Sub-Saharan Africa to European countries.[1,2] In the last two decades, the availability of mouse models for SCD has allowed both characterization of the pathogenesis of sickle cell related organ damage(s) and identification of pathophysiology-based new therapeutic options in addition to hydroxyurea (HU).[1-3] These can be divided into (Figure 1):

- Agents which reduce/prevent sickle red cell dehydration or red cell sickling or HbF inducers to delay;
- Agents targeting SCD vasculopathy and sickle cell-endothelial adhesive events;
- Anti-oxidant molecules.

Among the agents preventing red cell sickling, the oral direct anti-sickling agent GBT440 has been shown to be beneficial in SCD. GBT440 (or voxelotor) blocks HbS intermolecular contacts, preventing the generation of HbS fibers and red cell sickling. A phase III clinical trial is on-going to evaluate whether the preliminary evidence of beneficial clinical effects might be transferable in patients with severe, symptomatic SCD (NCT03036813). In addition, FDA has recently defined voxelotor as breakthrough therapy for SCD.[4] Voxelotor (900-1500 mg/die) results in sustained and persistent increased in Hb and an improvement in patients' quality of life evaluated with clinical global impression scale change (CGI-C) in patients with SCD. Noteworthy, Minniti C et al have reported a significant improvement in leg ulcers in patients with SCD at 24 and 72 weeks of treatment with Voxelotor (900-1500 mg/die).[5]

Metabolomic studies on red cells have further linked cell energy as ATP with red cell survival and red cell features especially in pathologic condition such as SCD or β-thalassemia. The recent development of pyruvate kinase (PK) activators such as Mitapivat (PKLR and PKM2 activator) and Etavapivat (PKLR activator) to treat patients with chronic hemolytic anemia due to PK deficiency represent a new therapeutic option to improve survival of pathologic red cells such as SCD but also b-thalassemic erythrocytes.[6] Clinical trials with Mitapivat (NCT04610866) and Etavapivat (NCT03815695) on patients with SCD are ongoing. Ad interim results indicate an improvement of anemia and chronic hemolysis in SCD patients treated with either Mitapivat or Etavapivat.

In SCD, anti-adherence therapeutic strategies might represent an interesting, novel therapeutic strategy to prevent the generation of acute VOCs and to lessen SCD related organ damage (Figure 1). Among anti-adherence molecules, growing attention has been devoted to Crizanlizumab is a humanized P-Selectin antibody, which has been tested in a multinational double-blind placebo-controlled trial (SUSTAIN, #NCT0185361).[7,8] SCD subjects were treated with Crizanlizumab either 2.5 or 5 mg/Kg every 4 weeks. Crizanlizumab at the dosage of 5 mg/Kg every 4 weeks reduced the number of pain crisis and increased the time between VOCs in SCD independently from possible preceding HU treatment.[7-9] Noteworthy, SCD patients treated with Crizanlizumb show a statistic significant 50% reduction in days per year on parental opioids compared to placebo group. Collectively, these data indicate crizanlizumab as new therapeutic option to limit/prevent sickle cell related acute complication, possibly interfering with SCD natural history.

SCD is also characterized by a highly pro-oxidant environment due to the elevated production of reactive oxygen species (ROS) generated by increased levels of pathological free heme and iron and a reduction in anti-oxidant systems such as GSH. L-Glutamine is a likely anti-oxidant agent in SCD. Glutamine is involved in GSH metabolism since it preserves NADPH levels required for GSH recycling, and it is the precursor for nicotinamide adenine dinucleotide (NAD) and arginine. Recently, a multicenter, randomize, placebo-controlled double-blind phase III clinical trial with L-glutamine (0.3 g/Kg twice a day) involving 230 SS and /Sbeta^0 patients with ≥ 2 pain crisis showed that L-glutamine supplementation reduced the mean number and length of hospitalization, associated with increased median time to the first crisis.[10] Both studies have several limitations such as (i) the high rate of patient drop-out; (ii) the presence of fatal events due to multiorgan failure in L-glutamine arm; (iii) the lack of effects on hematologic parameters and hemolytic indices; and (iv) the absence of clear data on L-glutamine mechanism of action.

In conclusion, we are living in a new era for SCD characterized by emerging of novel treatments for SCD and the amelioration of survival of SCD patients, which requires a holistic approach to ensure an improvement of patient quality of life. This might re-direct clinician and scientist to also consider the new field of combinatorial therapy with or without HU for SCD. In addition, long-term studies should be designed and support to evaluate the real impact of these new molecules on natural history of SCD.

References

1. Matte A, Cappellini MD, Iolascon A, Enrica F, De Franceschi L. Emerging drugs in randomized controlled trials for sickle cell disease: are we on the brink of a new era in research and treatment? Expert Opin Investig Drugs. 2020;29(1):23-31.
2. Matte A, Zorzi F, Mazzi F, et al. New Therapeutic Options for the Treatment of Sickle Cell Disease. Mediterr J Hematol Infect Dis. 2019;11(1):e2019002.
3. Telen MJ. Developing new pharmacotherapeutic approaches to treating sickle-cell disease. ISBT Sci Ser. 2017;12(1):239-247.
4. Torres L, Conran N. Emerging pharmacotherapeutic approaches for the management of sickle cell disease. Expert Opin Pharmacother. 2019;20(2):173-

186.
5. Minniti CP, Knight-Madden J, Tonda M, et al. The impact of voxelotor treatment on leg ulcers in patients with sickle cell disease. Am J Hematol. 2021;96(4):E126-E128.
6. Matte A, Federti E, Kung C, et al. The pyruvate kinase activator mitapivat reduces hemolysis and improves anemia in a beta-thalassemia mouse model. J Clin Invest. 2021;131(10).
7. Ataga KI, Kutlar A, Kanter J, et al. Crizanlizumab for the Prevention of Pain Crises in Sickle Cell Disease. N Engl J Med. 2017;376(5):429-439.
8. Ataga KI, Kutlar A, Kanter J. Crizanlizumab in Sickle Cell Disease. N Engl J Med. 2017;376(18):1796.
9. Slomski A. Crizanlizumab Prevents Sickle Cell Pain Crises. Jama. 2017;317(8):798.
10. Niihara Y, Miller ST, Kanter J, et al. A Phase 3 Trial of l-Glutamine in Sickle Cell Disease. N Engl J Med. 2018;379(3):226-235.

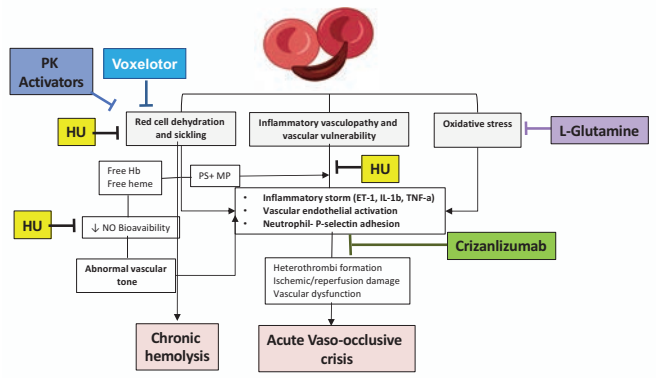


Figure 1. Schematic diagram of the mechanisms of action of pathophysiology based new therapeutic options for treatment of sickle cell disease and sickle cell vasculopathy as well as for hydroxyurea (HU). Hb: hemoglobin; HbF: fetal hemoglobin; PS: phosphatidyl-serine; MP: microparticles; ET-1: endothelin-1, IL-1β: interleukin-1, TNF-α: tumor necrosis factor-alpha; NO: nitric oxide.

THE NEW FRONTIER OF CURATIVE TREATMENTS IN SICKLE CELL ANEMIA

M. Algeri

Dipartimento di Onco-Ematologia e Terapia Cellulare e Genica, IRCCS Ospedale Pediatrico Bambino Gesù, Roma, Italy

Sickle cell disease (SCD) is one of the most common severe disorders in the world and its incidence is expected to increase over time, thereby representing a growing burden on global health resource. Hematopoietic stem cell transplantation (HSCT) offers patients with SCD a curative option, although its broad application is significantly limited by donor availability and transplant-related mortality and morbidity, specifically graft rejection, graft-versus-host disease (GVHD) and other treatment-related toxic effects. Autologous transplantation of gene-modified hematopoietic stem/progenitor cells (HSPCs) is a theoretic universal cure for SCD that could eliminate major limitations of allogeneic transplantation. Autologous gene therapies in development for SCD aim to address the underlying genetic cause of disease either by increasing the expression of an antisickling β-like globin or increasing endogenous HbF expression using gene addition or gene-editing strategies. All current protocols to treat SCD by autologous HSCT include 3 major steps: (a) isolation of patient HSPCs; (b) *ex vivo* genetic manipulation of $CD34^+$ cells to correct the SCD mutation; (c) myeloablative conditioning to create a receptive bone marrow niche, followed by infusion of the modified HSPCs. The first reported gene therapy cure for SCD used a lentiviral vector encoding the antisickling β-globin variant $\beta^{A\text{-}T87Q}$. Recently published interim results of 25 patients enrolled in a phase 1-2 study investing this approach have shown that one-time treatment had an effect on the pathophysiological features of SCD, leading to the complete resolution of severe vaso-occlusive events (VOCs). Two subject treated with this product before the adjustment of stem cell harvest and manufacturing developed clonal myeloid neoplasms, albeit without evidence of insertional oncogenesis. Genome-editing nuclease (such as CRISPR/Cas9) may be employed to induced RBC γ-globin transcription and HbF expression by disabling an erythroid-specific BCL11A gene enhancer. Preliminary results from a clinical study testing this strategy are promising, with 31 patients with SCD no longer having severe VOCs after gene-edited HPSCs infusion. Transduction of SCD donor CD34+ cells with a microRNA-adapted short hairpin RNA that suppresses BCL11A expression is another attractive strategy to increase the production of HbF. Six subjects have been treated in a clinical trial using this approach with encouraging preliminary results.

References

Abraham AA and Tisdale JF. Gene therapy for sickle cell disease: moving from the bench to the bedside. Blood 2021; 138 (11): 932–941.
Kunter J, et al. Biologic and Clinical Efficacy of LentiGlobin for Sickle Cell Disease. N Engl J Med 2022; 386:617-628.
Goyal S, et al. Acute myeloid leukemia case after gene therapy for sickle cell disease. N Engl J Med 2022;386:138-147.
Locatelli F, et al. Efficacy and safety of a single dose of CTX001 for transfusion-dependent beta-thalassemia and severe sickle cell disease. EHA Congress 2022, Abstract LB2367
Esrick eB, et al. Post-Transcriptional Genetic Silencing of BCL11A to Treat Sickle Cell Disease. N Engl J Med 2021; 384:205-215

WHAT IS TODAY'S ROLE OF TRANSFUSION THERAPY IN SCD?

D. Venturelli

Department of Transfusion Medicine, University Hospital Modena, Modena, Italy

Sickle cell disease (SCD) is an inherited blood disorder caused by a point mutation in the beta globin gene resulting in the production of insoluble sickle hemoglobin (HbS). HbS polymerizes when deoxigenated resulting in erythrocyte sickling and membrane damage. These abnormalities lead to hemolysis, chronic anemia, inflammation and vaso-occlusion which are responsible for the acute and chronic manifestations of SCD.[1,2]

Red Blood Cell (RBC) transfusion is a key component in SCD management with a therapeutic (for life-threatenig SCD complications) or a prophylactic (to decrease the incidence of specific SCD-related complications) intent.[3] Guidelines on transfusion management for SCD are limited by the small number of well-designed studies.[4-6] The choice of performing simple or exchange transfusion (manual or automated) is partly dependent on the underlying condition (Table 1).The goal of transfusion in SCD patients is to reduce the increased blood viscosity. In acute conditions, this is achieved with an hematocrit (Hct) not higher than 30% and the HbS <30%. For chronic indications, Hct and HbS are targeted in a 33-36% and 30–50% range, respectively. Over their lifetime, most individuals with SCD are exposed to various transfusion regimens and thus are at risk of developing transfusion complications.

In addition to those typically associated with transfusions such as febrile nonhemolytic transfusion reactions and allergic reactions, SCD patients have increased risk of alloimmunization, autoimmunization, iron overload and delayed hemolytic reactions (DHTR) with hyperhemolysis.[7-8] Since the frequency of RBC antigens is heavily influenced by race, mismatches between donors and recipient are frequent in SCD patients and their presence increases the likelihood of allo-immunization.[9] Thus, extended RBC antigen profiles and antibody screenings should be performed in all SCD patients before transfusions.

The use of transfusion therapy should be based on symptomatic anemia and hemodynamic unbalances rather than the hemoglobin (Hb) value. Simple transfusions in children and adults should be performed if the Hb level is at least 2 g/dL below the patient's baseline and there are new symptoms associated with anemia, or there is a trend of decreasing

Hb over several days without a compensatory increase in reticulocyte count.[10] It is important to avoid unnecessary transfusions in uncomplicated vaso-occlusive episodes because the acute inflammatory state may increase the risk of red cell allo-immunization.

Conclusions. Blood transfusions are essential components in the therapy of SCD patients with severe or acute episodes of anemia and/or severe vaso- occlusive events, They are also utilized for prevention of stroke and perioperative complications. For other clinical conditions in SCD patients, the benefit of transfusion therapy is still unclear. Blood transfusions are not usually recommended to correct chronic anemia in patients with stable SCD. Since the frequent use of transfusions is associated with numerous complications, they should be offered following specific guidelines and tailored to the individual needs.

Table 1.

INDICATION	TYPE OF TRANSFUSION
ACUTE TRANSFUSION INDICATION	
Symptomatic anemia: aplastic crisis, acute splenic sequestration	Simple transfusion : expert consensus
Acute clinical stroke or TIA	Exchange transfusion
Acute hepatic sequestration/ intrahepatic cholestasis	Simple or exchange transfusion :expert consensus
ACS (acute chest syndrome)	Simple or exchange transfusion : moderate-recurrent-expert consensus Exchange transfusion: severe-expert consensus
Acute multiorgan failure	Simple or exchange transfusion
Preoperative (surgeries lasting > 1 hour and require general anesthesia)	Simple or exchange transfusion ; randomized clinical trial
Pregnancy: severe or frequent SCD-related complications or high risk pregnancy	Simple or exchange transfusion : expert consensus
CHRONIC TRANSFUSION INDICATION	
Primary stroke prevention	Simple or exchange transfusion : randomized clinical trial
Secondary stroke prevention	Simple or exchange transfusion : randomized clinical trial
Recurrent VOC	Simple or exchange transfusion

References

1. Ware R.E, de Montalembert M, Tshilolo L, Abbond MR. Sickle cell disease. Lancet 2017, 390:311-23.
2. Kavanagh P.L; Fasipe T.A and Wun T.Sickle cell disease. A review.JAMA 2022,328(1) 57-69.
3. Sharma D, Ogbenna AA, Kassim A and Andrew J. Transfusion support in patients with sickle cell disease. Semin. Hematol.2020:39-50.
4. Chou ST, Alsawas M, Fasano RM, et al. American Society of Hematology 2020 guidelines for sickle cell disease: transfusion support. Blood Adv. 2020;4(2):327-355.
5. Han H, Hensch L. and Tubman V.N Hematology Indications for transfusion in the management of sickle cell disease 2021 696-702
6. Tanhehco Y.C, Shi PA and Schwartz J.Transfusion therapy in sickle cell disease Ann.Blood 2022;7,9
7. Linder.GE and Chou ST. Red cell transfusion and allommunization in sickle cell disease .Haematologica 2021:106 (7):1805-1815
8. Pirenne F. The cause and pathogenesis of hemolytic transfusion reactions in sickle-cell disease. Curr Opin Hematol. 2019;26(6):488-494.
9. Vichinsky EP, Earles A, Johnson RA, Hoag MS, Williams A, Lubin B. Alloimmunization in sickle cell anemia and transfusion of racially unmatched blood. New Eng J Med 1990;322:1617–21.
10. DeBaun MR and Chou ST. Red blood cell transfusion in sickle cell disease: indications and transfusion tecniques. UpToDate. 2022:1-40.

THROMBOPHILIA SCREENING: INDICATIONS AND LIMITATIONS IN 2022

E. Rossi

Sezione di Ematologia, Dipartimento di Scienze Radiologiche ed Ematologiche, Università Cattolica del Sacro Cuore, Roma; Dipartimento di Diagnostica per Immagini, Radioterapia Oncologica ed Ematologia, Fondazione Policlinico A. Gemelli IRCCS, Roma

Thrombophilic abnormalities are significantly associated with an increased risk of venous thromboembolism (VTE) and weakly with arterial thrombosis, fetal loss, and obstetric complications. In the past 30 years, knowledge in this field has dramatically increased with the identification of several gene variants causing hypercoagulability. The two main mechanisms are loss-of-function of anticoagulant proteins and gain-of-function of procoagulants, the latter owing to increased synthesis or impaired downregulation of a normal protein or, more rarely, to the synthesis of a functionally hyperactive molecule (Table 1). Diagnosis of inherited thrombophilia rarely affects the acute or long-term management of VTE. However, the risk of recurrent VTE is increased in patients with deficiency of natural anticoagulants (antithrombin, protein C, and protein S), in homozygotes for gain-of-function mutations, and in antiphospholipid syndrome. Long-term anticoagulation with vitamin K antagonists or direct oral anticoagulants can reduce the high incidence of recurrence in these patients. Because of the increased risk of VTE during pregnancy and the puerperium, thrombophilia screening is indicated in selected patients with a positive family history of VTE. It is controversial if inherited thrombophilia is associated with early or late fetal losses or placental complications. Antithrombotic drugs LMWH and low-dose aspirin may have a potential therapeutic benefit in patients with recurrent pregnancy loss and thrombophilia, but further placebo-controlled trials are urgently needed to clarify this issue. Although a supra-additive effect for the risk of VTE is observed between oral contraceptives and thrombophilia, the absolute incidence of VTE is low in premenopausal women, and universal screening strategies are unlikely to be cost-effective. Antiphospholipid antibodies are associated with arterial thrombosis, whereas screening for heritable thrombophilias is not helpful in this setting. However, subgroup analysis indicates that they may play a role in young patients and children. Screening for inherited thrombophilia in thrombosis-free individuals is indicated only for relatives of a proband who is anticoagulant-deficient or has a family history of VTE. In families with thrombophilia and VTE, primary antithrombotic prophylaxis during risk situations such as surgery or immobilization lowers the rate of incident VTE.

Table 1. Aadapted from Martinelli *et al.,* Nat Rev Cardiol 2014.

Mechanisms associated with inherited thrombophilia
Known mechanisms
Loss-of-function ▪Antithrombin deficiency ▪Protein C deficiency ▪Protein S deficiency
Gain-of-function ▪Factor V Leiden ▪Prothrombin G20210A ▪High factor VIII level ▪Non-O blood group ▪Dysfibrinogenaemia
Postulated mechanisms
▪Low tissue factor pathway inhibitor level ▪High fibrinogen level ▪High factor IX level ▪High factor X level ▪High factor XI level ▪Resistance to antithrombin ▪Global hypofibrinolysis ▪High thrombin activatable fibrinolysis inhibitor level ▪Hyperhomocysteinaemia

References

De Stefano V, Rossi E, Paciaroni K, Leone G. Screening for inherited thrombophilia: indications and therapeutic implications. Haematologica. 2002;87(10):1095-108. .

De Stefano V, Rossi E. Testing for inherited thrombophilia and consequences for antithrombotic prophylaxis in patients with venous thromboembolism and their relatives. A review of the Guidelines from Scientific Societies and Working Groups. Thromb Haemost. 2013;110(4):697-705.

De Stefano V, Grandone E, Martinelli I. Recommendations for prophylaxis of pregnancy-related venous thromboembolism in carriers of inherited thrombophilia. Comment on the 2012 ACCP guidelines. J Thromb Haemost. 2013;11(9):1779-81.

Martinelli I, De Stefano V, Mannucci PM. Inherited risk factors for venous thromboembolism. Nat Rev Cardiol. 2014;11(3):140-56.
Stevens SM, Woller SC, Bauer KA, Kasthuri R, Cushman M, Streiff M, Lim W, Douketis JD. Guidance for the evaluation and treatment of hereditary and acquired thrombophilia. J Thromb Thrombolysis. 2016;41(1):154-64.
Middeldorp S. Inherited thrombophilia: a double-edged sword. Hematology Am Soc Hematol Educ Program. 2016;2016(1):1-9.
American College of Obstetricians and Gynecologists' Committee on Practice Bulletins–Obstetrics. ACOG Practice Bulletin No. 197: Inherited Thrombophilias in Pregnancy. Obstet Gynecol. 2018 ; 132(1):e18-e34.
Nowak-Göttl U, van Ommen H, Kenet G. Thrombophilia testing in children: What and when should be tested? Thromb Res. 2018;164:75-78.
Colucci G, Tsakiris DA. Thrombophilia screening revisited: an issue of personalized medicine. J Thromb Thrombolysis. 2020;49(4):618-629.
Salehi Omran S, Hartman A, Zakai NA, Navi BB. Thrombophilia Testing After Ischemic Stroke: Why, When, and What? Stroke. 2021;52(5):1874-1884.

INFLAMMASOMES AND TROMBOPHILIA

A. Lucchesi,[1] G. Micucci,[1] G. Giordano,[2] M. Napolitano[3]

[1]Hematology Unit, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori"Meldola; [2]Internal Medicine Division, Hematology Service, Regional Hospital "A. Cardarelli", Campobasso; [3]Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties and Haematology Unit, University Hospital "P. Giaccone", Palermo, Italy

Inflammatory conditions are known to be a major contributor to hypercoagulable states. The concept of 'thromboinflammation' is undoubtedly complex, since there are multiple biological factors and mechanisms involved, but it can be generically defined as a pathological response within the vascular system that follows vessel injury, tissue invasion by pathogens or sterile inflammation (of non-infectious origin). The consequence is acute organ damage due to ischaemia. In certain disorders, of which myeloproliferative neoplasms (MPNs) and autoimmune diseases (ADs) constitute a model, the aberrant mechanism of response to such insults is perpetually enabled by inflammasomes, in particular NLRP3 and AIM2. Inflammasomes are fundamental elements of the innate immune system, consisting of protein scaffolds whose task is to promote the cleavage action of caspases, and to convert pro-interleukins into mature cytokines. The epilogue of inflammasomes' activity is pyroptosis, a highly inflammatory form of programmed lytic cell death, which is followed by the release of high amounts of procoagulant substances. In particular, tissue factor (TF) is released in the form of circulating microvesicles, triggering thrombin through the extrinsic coagulation pathway. Thrombin in turn exhibits a protease activity, responsible for the irreversible triggering of protease activated receptors (PARs) on platelets and endothelial cells, leading to the rapid conversion of fibrinogen to fibrin, smooth muscle contraction, cell migration and proliferation, and matrix deposition. PARs downstream signals do indeed have a crosstalk with the TGF-ß pathway (also boosted by those cytokines resulting from the action of caspase-1, namely IL-1ß and IL-18). The system has obviously the function of wound repair, but its perpetual function in the absence of injury or bleeding is responsible for a state of hypercoagulability and promotion of fibrosis. Our research team called this pathogenetic model 'the circulating wound' and demonstrated a preferential use of the extrinsic coagulation pathway in myelofibrosis, a disease clinically characterised by thrombosis, dysimmunity, inflammation, bone marrow fibrosis and a tendency to clonal progression. Lastly, the NLRP3 inflammasome assembly is also responsible for other thromboinflammation phenomena such as NETosis, i.e. the release of nuclear filaments by neutrophils, which, in addition to trapping pathogens, interact directly with platelets through P-selectin, initiating thrombus formation. All these processes have often been described vaguely or incompletely, therefore more studies are needed to provide further elucidation of the connection between inflammasome activation and thrombosis.

References

1. Guo L, Rondina MT. The Era of Thromboinflammation: Platelets Are Dynamic Sensors and Effector Cells During Infectious Diseases. Front Immunol. 2019 Sep 13;10:2204. doi: 10.3389/fimmu.2019.02204. PMID: 31572400; PMCID: PMC6753373.
2. Wu C, Lu W, Zhang Y, Zhang G, Shi X, Hisada Y, Grover SP, Zhang X, Li L, Xiang B, Shi J, Li XA, Daugherty A, Smyth SS, Kirchhofer D, Shiroishi T, Shao F, Mackman N, Wei Y, Li Z. Inflammasome Activation Triggers Blood Clotting and Host Death through Pyroptosis. Immunity. 2019 Jun 18;50(6):1401-1411.e4. doi: 10.1016/j.immuni.2019.04.003. Epub 2019 May 7. PMID: 31076358; PMCID: PMC6791531.
3. Chanchal S, Mishra A, Singh MK, Ashraf MZ. Understanding Inflammatory Responses in the Manifestation of Prothrombotic Phenotypes. Front Cell Dev Biol. 2020 Feb 14;8:73. doi: 10.3389/fcell.2020.00073. PMID: 32117993; PMCID: PMC7033430.
4. Di Battista V, Bochicchio MT, Giordano G, Napolitano M, Lucchesi A. Genetics and Pathogenetic Role of Inflammasomes in Philadelphia Negative Chronic Myeloproliferative Neoplasms: A Narrative Review. Int J Mol Sci. 2021 Jan 8;22(2):561. doi: 10.3390/ijms22020561. PMID: 33429941; PMCID: PMC7827003.
5. Lucchesi A, Napolitano R, Bochicchio MT, Giordano G, Napolitano M. Platelets Contribution to Thrombin Generation in Philadelphia-Negative Myeloproliferative Neoplasms: The "Circulating Wound" Model. Int J Mol Sci. 2021 Oct 20;22(21):11343. doi: 10.3390/ijms222111343. PMID: 34768772; PMCID: PMC8583863.
6. Lucchesi A. et al, Outcomes of global coagulation assays in patients with Philadelphia-negative myeloproliferative neoplasms with respect to their clinical and genetic determinants of clonal evolution. EHA Library. 06/10/22; 357852; P992
7. Bhuria V, Baldauf CK, Schraven B, Fischer T. Thromboinflammation in Myeloproliferative Neoplasms (MPN)-A Puzzle Still to Be Solved. Int J Mol Sci. 2022 Mar 16;23(6):3206. doi: 10.3390/ijms23063206. PMID: 35328626; PMCID: PMC8954909.

VENOUS THROMBOEMBOLISM IN ACUTE LEUKEMIA: FROM PATHOPHYSIOLOGY TO TREATMENT

M. Napolitano,[1] A. Lucchesi,[2] S. Siragusa[1]

[1]Promise Department, University of Palermo, Italy; [2]Hematology Unit, IRCCS Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) "Dino Amadori", Meldola (FC), Italy

Venous-thromboembolism (VTE) is a potentially life-threatening disease; available evidences, mainly based on small single center studies, suggest that the risk of VTE in acute leukemia (AL) patients is as high as that reported for solid tumours. During the course of AL, the incidence of VTE has been observed to vary widely, from 2% up to 12%; this may be due to the characteristics of different analysed leukemia types, cohorts and timeframes. The pathogenesis of VTE in AL is multifactorial (Figure 1)and based on: type of leukemia; type of treatment; patients related factors and concomitant risk factors including infections or central venous catheter.[1]n addition, leukemic stem cells are able to release procoagulant, proinflammatory and angiogenic factors.[2,3] A recent study evaluating the risk and predictor factors of VTE in elderly patients with acute myeloid leukemia (AML) has reported that a history of VTE, before AML diagnosis, significantly increases the risk of VTE related to AML and overall mortality.[4] Available studies on the treatment of VTE in the setting of AL have been recently revised. The reported recurrence rate of VTE was quite heterogenous (0-29%), based on duration of treatment and follow up. A statistically significant higher risk of bleeding among patients treated for VTE was however not observed.[5] The safety and efficacy of anticoagulant treatment in patient with AL has not been formally explored and specific data are lacking. Severe thrombocytopenia and coagulopathies in these subjects make treatment of VTE challenging for the risk of death related to VTE and the high bleeding risk.[6,7] Recently released guidelines from the Italian Society of Haematology (SIE), developed for VTE prophylaxis in haematological malignancies, do not recommend routine prophylaxis of VTE in patients with AL in general. In acute lymphoblastic leukemia, during treatment with asparaginase, prophylaxis with low molecular weight heparin (LMWH) is recommended in association with antithrombin administration to maintain

antithrombin target levels of 80-120%.[8] We have shown in a retrospective national study,[9] the feasibility of anticoagulation in patients at high bleeding risk for severe thrombocytopenia and AL related coagulopathy. A consensus developed by the Gruppo Italiano Malattie Ematologiche dell'Adulto has identified the platelet cut-off for safe administration of LMWH in thrombocytopenic adult patients with haematologic malignancies affected by acute or non-acute VTE.[10] The lack of high-quality evidences for high risk patients like those affected by AL imposes great caution on the use of direct oral anticoagulants in AL.

References

1. Annibali O, Napolitano M, Avvisati G, Siragusa S. Incidence of venous thromboembolism and use of anticoagulation in hematological malignancies: Critical review of the literature. Crit Rev Oncol Hematol. 2018 Apr;124:41-50. doi: 10.1016/j.critrevonc.2018.02.003.
2. Grignani G, Maiolo A. Cytokines and hemostasis. Haematologica. 2000 Sep;85(9):967-72.
3. Falanga A, Marchetti M. Anticancer treatment and thrombosis. Thromb Res. 2012 Mar;129(3):353-9. doi: 10.1016/j.thromres.2011.10.025.
4. Gangaraju R, Gahagan A, Bhatia S, Kenzik K. Venous-thromboembolism in elderly patients with acute myeloid leukemia. Thromb Res. 2021 Apr;200:9-11. doi: 10.1016/j.thromres.2020.12.032.
5. Ahrari A, Al-Ani F, Wang YP, Lazo-Langner A. Treatment of venous thromboembolism in acute leukemia: A systematic review. Thromb Res. 2019 Jun;178:1-6. doi:10.1016/j.thromres.2019.03.014
6. Gonzalez XAA, Bayne HEF, Al-Ogaili A, et al. Comparsion of in-patient outcomes and mortality of venous thromboembolism related hospitalizations between solid and hematological malignancies: a nationwide inpatient sample database analysis. Phlebology 2018;33:704.
7. Cornelissen LL, Kreuger AL, Caram-Deelder C, et al. Thrombocytopenia and the effect of platelet transfusions on the occurrence of intracranial hemorrhage in patients with acute leukemia - a nested case-control study. Ann Hematol 2020 doi: 10.1007/s00277-020-04298-7.
8. https://www.siematologia.it/linee-guida-sie.html
9. Napolitano M, Valore L, Malato A, et al. Management of venous thromboembolism in patients with acute leukemia at high bleeding risk: a multi-center study. Leuk Lymphoma. 2016;57(1):116-9. doi: 10.3109/10428194.2015.1046864.
10. Napolitano M, Saccullo G, Marietta M, et al; Platelet cut-off for anticoagulant therapy in thrombocytopenic patients with blood cancer and venous thromboembolism: an expert consensus. Blood Transfus. 2019 May;17(3):171-180. doi: 10.2450/2018.0143-18

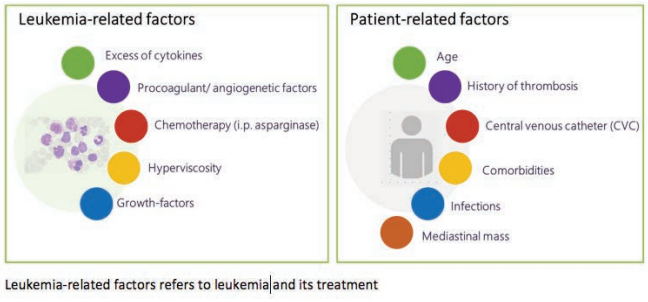


Figure 1. Risk factors of venous thromboembolism in acute leukemia

IRON FILES IRON: ROLE OF ALTERATIONS IN IRON METABOLISM IN THE MYELODYSPLASTIC MICROENVIRONMENT

F. Pilo

Hematology Unit and Transplant Center. "A. Businco" Hospital, Cagliari, Italy

Background

Iron is fundamental for many cellular functions such as the cell cycle of growth and replication, metabolism and DNA synthesis/repair. However, the ability to gain and lose electrons gives iron the possibility of participating in potentially harmful free radical-generating reactions, producing reactive oxygen species (ROS). There is now a substantial body of literature supporting the role of ROS in the pathogenesis of many diseases and in particular those related to cell proliferation and differentiation such as the myelodysplastic syndromes (MDS). Iron overload, caused by ineffective erythropoiesis, increased gastrointestinal iron intake and transfusion dependency allow us to consider the MDS as the ideal disease model to try to understand the complex relationship between the haemopoietic niche, microenvironment, oxidative stress and inadequate haemopoiesis.[1]

The link between hematopoietic niche functionality and iron toxicity

Several studies showed in vitro how oxidative stress influences the fate of haematopoietic stem cells by compromising migration, development, self-renewal and cell cycle status.[2] The hypoxic conditions and several environmental factors (HIF1, COX2, PGE2, CCXCR4, CXCL12) participate to maintain low ROS levels. Increases in ROS levels, drives stem cell differentiation to short term repopulating cells and further on to myeloid differentiation. Exceedingly high ROS levels, as may occur during important oxidative stress conditions such as chronic inflammation or iron overload, can promote stem cell exhaustion and subsequent apoptosis. Haematopoietic stem cells quiescent and active state is a balance between ROS levels 'too much' or 'too little' ROS seems be a determining factor in the fate of many pathways critical to cell survival and proliferation. In essence ROS balance may determinate stem cell destiny.[3] Similar effects have been described with osteogenic progenitors and differentiation of mesenchymal stem and progenitor cells.[4,5] A disturbed microenvironment (including osteogenic elements) might affect haematopoietic stem cell growth modifying the cross talking between the haematopoietic niche components.[6] In a myelodysplastic mouse model, authors reported decreased osteoblasts and osteoclasts number and decreased bone formation rate. In particular, they identified iron overload as responsible for osteoblast inhibition and increases in osteoclasts. They concluded that oxidative stress is involved in the pathogenesis of bone loss during iron excess and that oxidative stress may affect the relationship between haematopoietic cells and the microenvironment in MDS.[6]

Aspects of haematopoiesis that may be associated with altered levels of ROS

Haematological improvement during iron chelation

In 2013, Chai and colleagues showed that iron overload markedly decreased the ratio of immature haematopoietic cells and reduced HSPCc clonogenic capacity. Iron overload increased ROS levels of HSPCs through the NOX4/ROS/P38 MAPK signalling pathway. Interestingly, these effects were abrogated by treating mouse HSPCs with iron chelator or the powerful antioxidant N- acetyl-cysteine (NAC), suggesting that iron overload may be closely related to high oxidative stress. Similar results were found using bone marrow mesenchymal cells (BM-MSCs) in a similar murine model. In an iron overload situation, BM-MSCs exhibited proliferation-differentiation deficiencies and osteoblastic commitment deficiencies. Immunohistochemical analysis demonstrated that chemokine stromal cell-derived factor-1, stem cell factor-1, and vascular endothelial growth factor-1 expression were down regulated. Furthermore, bone marrow mononuclear cells (BMMNCs) co-cultured with iron had decreased colony forming unit (CFU) counts suggesting that iron could lead to decreased haemopoietic supporting functions of BM-MSCs. [7-8]

Bone marrow transplantation engraftment

Recently a murine model was used to investigate the possible relationship between iron overload and engraftment post-allogeneic haematopoietic stem cell transplant (HSCT) demonstring that recipient mice of iron-overloaded donor, had lower levels of myeloid B and T-lymphocytic lineage engraftments compared to the recipient mice of normal donor. It was also showed that oxidative stress could affect the engraftment of HSC from a normal donor by modifying microenvironment and remarkably reducing expression of CXCL12, VCAM-1, Kit-ligand, erythropoietin and thrombopoietin.

Clonal evolution

Inadequate ROS homeostasis, resulting in oxidative stress and genetic instability in haematopoietic stem cells and myeloid progenitors, has been linked with leukemic progression. MDS are essentially a clonal disease of the elderly, characterized by increased genetic instability and as such are an ideal model to explore the role of iron in the clonal evolution phenomenon. Iron loading in irradiated B6D2F1 mice accelerated leukemia development added driver mutation. However, there was a progressive decrease in AML risk for irradiated mice with increase in iron burden from 7.5 to 15 to 30 mg. Furthermore, analysis of BMCs from irradiated mice at earlier intervals revealed accelerated dysregulation of signaling pathways upon iron loading.[10]

Conclusions

Deciphering ROS homeostasis in haematopoietic stem cells will provide a better understanding of the part played by iron in switching HSC from quiescence to activation and vice versa and will also clarify on its possible role in the initiation and/or development of leukaemia. The difficulty comes when we try to translate this knowledge and transform it into a clinical trial with a therapeutic end point. Essentially, all the data on the relationship between iron, ROS and haematopoiesis comes almost exclusively from basic research or from murine models that have very different characteristics from trials in patients.

References

1. Pilo F, Angelucci E A storm in the niche: Iron, oxidative stress and haemopoiesis.Blood Rev. 2018 Jan;32(1):29-35.
2. Ludin A, Gur-Cohen S, Golan K, Kaufmann KB, Itkin T, Medaglia C, et al. Reactive oxygen species regulate hematopoietic stem cell self-renewal, migration and development, as well as their bone marrow microenvironment. Antioxid Redox Signal 2014;21:1605–19.
3. Ye Z-W, Zhang J, Townsend DM, Tew KD. Oxidative stress, redox regulation and diseases of cellular differentiation. Biochim Biophys Acta 1850;2015:1607–21.
4. Balogh E, Tolnai E, Nagy BJ, Nagy B, Balla G, Balla J, et al. Iron overload inhibits osteogenic commitment and differentiation of mesenchymal stem cells via the in- duction of ferritin. Biochim Biophys Acta 1862;2016:1640–9.
5. Borriello A, Caldarelli I, Speranza MC, Scianguetta S, Tramontano A, Bencivenga D, et al. Iron overload enhances human mesenchymal stromal cell growth and hampers matrix calcification. Biochim Biophys Acta 1860;2016:1211–23.
6. Bulycheva E, Rauner M, Medyouf H, Theurl I, Bornhauser M, Hofbauer LC, et al. Myelodysplasia is in the niche: novel concepts and emerging therapies. Leukemia 2015;29:259–68.
7. Chai X, Zhao M, Li D, Meng J, Lu W, Mu J, et al. Establishment of an mouse model of iron-overload and its impact on bone marrow hematopoiesis. Zhongguo Yi Xue Ke Xue Yuan Xue Bao2013;35:547–52.
8. Chai X, Li D, Cao X, Zhang Y, Mu J, Lu W, et al. ROS-mediated iron overload injures the hematopoiesis of bone marrow by damaging hematopoietic stem/progenitor cells in mice. Sci Rep 2015;7:41900.
9. kabe H, Suzuki T, Uehara E, Ueda M, Nagai T, Ozawa K. The bone marrow he- matopoietic microenvironment is impaired in iron-overloaded mice. Eur J Haematol 2014;93:118–28.
10. Chan et al. The effects of secondary iron overload and iron chelation on a radiation-induced acute myeloid leukemia mouse model BMC Cancer (2021) 21:509

THE ROLE OF MINIMAL RESIDUAL DISEASE IN ACUTE LYMPHOBLASTIC LEUKEMIA

S. Chiaretti

Division of hematology, Dept. of Translational and precision medicine, Sapienza University of Rome, Italy

Acute lymphoblastic leukemia (ALL) is the most frequent neoplasm in children and is rarer in adults, even though a second peak of incidence from the 6th decade onwards is recorded. In the last decades, there was a dramatic improvement in the outcome of ALL patients, initially limited to the pediatric age and, more recently also in adult ALL, with long term outcomes approaching 80-90% in children and 50% in adults (excluding the elderly), respectively. The main reasons for this improvement are represented by the adoption of multi-chemotherapeutic and intensive treatments for Philadelphia negative (Ph-) cases, and a TKi-based approach for as well Philadelphia positive (Ph+) ALL, and a risk stratification based not only on clinical parameters at the onset of disease, but according to minimal residual disease (MRD). MRD is defined as any approach capable of detecting residual cells beyond the limit of cytomorphology. Its importance relies on the fact that MRD can: a) distinguish between patients at high vs low risk of relapse, b) permit to increase/ switch therapy in persistently MRD positive or with MRD recurrence patients to prevent an overt hematologic relapse; b) allocate patients to allogeneic transplantation in a biologically-driven fashion. Presently, MRD can be evaluated using different approaches, namely immunophenotype, and polymerase chain reaction (PCR) amplification-based methods, that use either fusion gene transcripts, if present, or patient-specific markers (immunoglobulin/T-cell receptor (IG/TR) gene rearrangements). All these methods present advantage and disadvantages, summarized in Table 1. The current effort is to improve the limit of sensivity.

Table 1.

	IG/TR RQ-PCR	Fusion genes RQ-PCR	Flow cytometry
Applicability	>90%	30-40%	>90%
Sensitivity	$10^{-4}/10^{-5}$	$10^{-4}/10^{-5}$	$10^{-3}/10^{-4}$
Pros	High sensitivity Potentially applicable to all patients Standardized	High sensitivity Target stability Fast and relatively easy	Infomative of the whole sample population Fast and standardized
Cons	Time consuming Hampered by clonal evoluation Large amounts of diagnostic DNA Relatively expensive	RNA instability Cross-contamination Standardized on DNA, less standardized on RNA	Relatively sensitive Requires high skill Hampered by the amount of cells Possible misinterpretation for hematopoietic reconstitution Relatively expensive

However, while it is well established that in both Ph- negative as well Philadelphia positive ALL is one of the most, if not the most predictive marker of relapse, we are facing the fact that some patients will relapse despite an achievement of MRD negativity, suggesting that other biological factors might contribute to disease recurrence or that the limit of sensitivity of current approaches is not sufficiently sensitive: for the latter issue, novel approaches, mostly represented by next generation sequencing (NGS) and digital droplet PCR (ddPCR) are being evaluated, and their clinical potential evaluated. These topics will be discussed at the congress site.

References

1. Berry DA, Zhou S, Higley H, et al. Association of Minimal Residual Disease With Clinical Outcome in Pediatric and Adult Acute Lymphoblastic Leukemia: A Meta-analysis. JAMA Oncol. 2017;3:e170580.
2. Coccaro N, Anelli L, Zagaria A, et al. Droplet digital PCR is a robust tool for monitoring minimal residual disease in adult Philadelphia-positive acute lymphoblastic leukemia. J Mol Diagn 2018, 20,474-482.
3. Della Starza I, Nunes V, Cavalli M, et al. Comparative analysis between RQ-PCR and digital-droplet-PCR of immunoglobulin/Tcell receptor gene rearrangements to monitor minimal residual disease in acute lymphoblastic leukaemia. Br J Haematol 2016, 174, 541–549.
4. Della Starza I, De Novi LA, Santoro A, et al. Digital Droplet PCR Is a Reliable Tool to Improve Minimal Residual Disease Stratification in Adult Philadelphia-Negative Acute Lymphoblastic Leukemia. J Mol Diagn 2022, S1525-1578.
5. Coccaro N, Anelli L, Zagaria A., et al. Droplet digital PCR is a robust tool for monitoring minimal residual disease in adult Philadelphia-positive acute lymphoblastic leukemia. J Mol Diagn 2018, 20,474-482.
6. Ansuinelli M, Della Starza I, Lauretti A, et al. Applicability of droplet digital polymerase chain reaction for minimal residual disease in Philadelphia-positive acute lymphoblastic leukaemia. Hematol Oncol 2021, 39, 680-686.
7. Ladetto M, Brïggemann M, Monitillo L, et al. Next-generation sequencing and real-time quantitative PCR for minimal residual disease detection in B-cell disorders. Leukemia 2014,28,1299–1307.
8. Kotrova M, Muzikova K, Mejstrikova E, et al. The predictive strength of next-

generation sequencing MRD detection for relapse compared with current methods in childhood ALL. Blood 2015, 126,1045–1047.
9. Kotrova M, van der Velden VHJ, van Dongen, JJM, et al. Next-generation sequencing indicates false-positive MRD results and better predicts prognosis after SCT in patients with childhood ALL. Bone Marrow Transplant 2017, 52, 962–968.

KINETIC EVALUATION OF MINIMAL RESIDUAL DISEASE IN LYMPHOMA

S. Ferrero,[1,2] F. Cordero,[3] E. Genuardi[1]

[1]Department of Molecular Biotechnologies and Health Sciences, Hematology Division, University of Torino, Torino; [2]Hematology Division, AOU "Città della Salute e della Scienza di Torino", Torino; [3]Department of Computer Science, University of Torino, Torino, Italy

Minimal residual disease (MRD) detection is a validated outcome predictor in follicular (FL) and mantle cell lymphoma (MCL).[1-2] Many efforts have been spent to identify the best-performing MRD time point for outcome prediction;[1,6] unfortunately, given the different induction regimens employed in different trials, a direct comparison of MRD time points might be difficult. Moreover, it is hardly conceivable that a single time point could capture the entire natural history of such chronic and complex diseases.

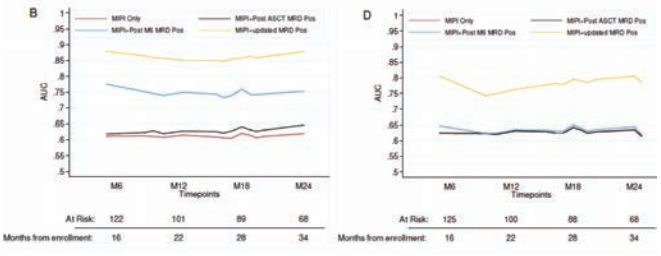


Figure 1. Time-varying AUCs of TTP. MIPI only (red) and different MIPI-adjusted kinetic MRD models are shown: BM (B) and PB (D) by RQ-PCR. Abbreviations: AUC, area under the curve; TTP, time to progression; RQ-PCR, Real time Quantitative Polymerase Chain Reaction; MIPI, mantle cell international prognostic index; M6, six months from transplant; ASCT, autologous stem cell transplantation; MRD POS, positive minimal residual disease.

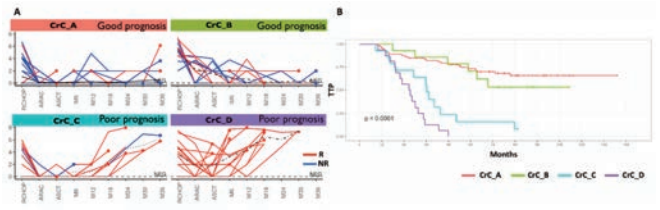


Figure 2. (A) CrC based on BM MRD results. (B) TTP stratified by CrC on BM. CrC, CONNECTOR risk cluster; BM, bone marrow; MRD, minimal residual disease; TTP, time to progression. R, relapse; NR, no relapse.

Recently, the clinical relevance of repeated MRD monitoring has been described in a large, prospective clinical trial for youngers MCL patients.[7] Starting from simple MRD accumulation patterns,[2] the Authors developed a dynamic model encompassing both MCL international prognostic index (MIPI) and a time-varying, regularly updated MRD analysis, taking particularly into account the dismal prognostic value of MRD reappearance after treatment termination. This kinetic model outperformed static predictive models in terms of area under the curve (AUC, Figure 1). This approach is further strengthened by the observation that in kinetic analysis peripheral blood (PB) might represent a fully adequate tissue source, sparing patients from undergoing repeated bone marrow (BM) examinations. Strikingly, very similar results have been obtained in an independent first-line trial in FL:[8] the high predictive value of punctual MRD analysis at multiple pre-planned time points was further improved by a kinetic approach; moreover, BM allowed better prediction at the early time points but, starting from month 12 after end of induction PB was superimposable to BM, allowing effective and reliable long-term non-invasive MRD monitoring.[9]

Nonetheless, complex patterns of MRD kinetics over time might generate interpretation issues and hamper an easy-to-use application of this predictive biomarker. To overcome the limitation of empirical analysis, novel automated computational frameworks, such as CONNECTOR (https://qbioturin.github.io/connector/), are under development, to facilitate the interpretation of MRD kinetics and stratify patients in risk classes based on a solid, algorithm-derived, classification, without knowledge of any clinical or outcome data (Figure 2). Such clusterization proved effective using BM, PB, and mixed tissues and validation of results on independent trials is currently ongoing.[10]

In conclusion, several recently published data reveal that MRD in MCL and FL should be approached in a kinetic manner: this is probably the best way to exploit all the bulk of information and provides a powerful risk stratification tool, suitable for MRD-guided treatment. These issues deserve primary consideration, both in the analysis of MRD data of current trials and in planning future clinical studies.

References

1. Pott C, Hoster E, Delfau-Larue M-H, et al. Molecular remission is an independent predictor of clinical outcome in patients with mantle cell lymphoma after combined immunochemotherapy: a European MCL intergroup study. Blood. 2010;115(16):3215-3223.
2. Ladetto M, Lobetti-Bodoni C, Mantoan B, et al. Fondazione Italiana Linfomi. Persistence of minimal residual disease in bone marrow predicts outcome in follicular lymphomas treated with a rituximab-intensive program. Blood. 2013;122(23):3759-3766
3. Kolstad A, Pedersen LB, Eskelund CW, et al. Molecular monitoring after autologous stem cell transplantation and preemptive rituximab treatment of molecular relapse; results from the nordic mantle cell lymphoma studies (MCL2 and MCL3) with median follow-up of 8.5 years. Biol Blood Marrow Transplant. 2017;23(3):428-435.
4. Gressin R, Daguindau N, Tempescul A, et al. A phase 2 study of rituximab, bendamustine, bortezomib and dexamethasone for first-line treatment of older patients with mantle cell lymphoma. Haematologica. 2019;104(1):138-146.
5. Hoster E, Pott C. Minimal residual disease in mantle cell lymphoma: insights into biology and impact on treatment. Hematology Am Soc Hematol Educ Program. 2016;2016(1):437-445.
6. Callanan MB, Macintyre E, Delfau-Larue M H et al. Predictive power of early, sequential MRD monitoring in peripheral blood and bone marrow in patients with mantle cell lymphoma following autologous stem cell transplantation with or without rituximab maintenance; final results from the Lyma-MRD project, conducted on behalf of the Lysa group. Blood. 2020;136 (Suppl 1):12-13.
7. Ferrero S, Grimaldi D, Genuardi E, et al. Punctual and kinetic MRD analysis from the Fondazione Italiana Linfomi MCL0208 phase III trial in mantle cell lymphoma. Blood. 2022; 23: Online ahead of print.
8. Luminari S, Manni M, Galimberti S, et al. Response-adapted postinduction strategy in patients with advanced-stage follicular lymphoma: the FOLL12 study. J Clin Oncol 2022; 40(7):729-739.
9. Ladetto M, Ferrero S, Del Giudice I, et al. A comprehensive and systematic analysis of Minimal Residual Disease (MRD) monitoring in follicular lymphoma: results from the Fondazione Italiana Linfomi (FIL) FOLL12 trial. Blood 2021;138 (Suppl 1):41-43.
10. Cordero F, Ferrero S, Pernice S, et al. "Dissecting MRD kinetics by automated computational analysis to improve outcome prediction in mantle cell lymphoma: a bioinformatic substudy from the Fondazione Italiana Linfomi (FIL) MCL0208 clinical trial. 64th American Society of Hematology Annual Meeting & Exposition 2022; abstract submitted.

THE NEW FRONTIERS OF MOLECULAR DIAGNOSIS IN HEMORRAGIC PATHOLOGIES AND COAGULATION

M. Pinotti, A. Branchini, D. Balestra, F. Bernardi

Università di Ferrara, Dipartimento di Scienze della Vita e Biotecnologie, Italy

The advent of next generation sequencing revolutionized the genetic characterization of inherited hemorrhagic coagulation factor disorders and provided a huge amount of gene variations, many of them of uncertain significance. On the other hand, the characterization of their pathogenic role, and most importantly of the residual expression levels associated with them in patients, are crucial to classify patients, and the ability to discriminate between "null" and "not null" conditions has relevant pathophysiological implications.

In coagulation factor VIII (FVIII) deficiency (Hemophilia A, HA), the most frequent complication in patients undergoing replacement therapy is the development of inhibitory antibodies against the infused FVIII. Among the several components determining the susceptibility to develop inhibitors, the F8 gene mutation plays a key role with "null" mutations being associated with the highest risk. In this scenario, the advent of recombinant DNA technologies and the *in vitro* expression of recombinant gene variants opened the way for the elucidation of several molecular mechanisms accounting for residual levels, which help explaining the patients' phenotype and response to treatment.

Paradigmatic examples are represented by nonsense mutations that are commonly considered "null" genetic conditions but unexpectedly appear to confer a remarkably lower risk to develop inhibitors than expected. Through a systematic study of a large panel of nonsense mutations associated with Hemophilia we demonstrated that, depending on the nucleotide features and position, these mutations might account for residual expression levels through a mechanism called "ribosome readthough". Splicing mutations at conserved splice sites are also commonly considered "null" but, though a variety of alternative splicing mechanisms they might produce residual expression levels. While for hemophilia trace levels (<1%) have a limited impact on patients' phenotype, in factor VII deficiency, whose absence is lethal, they explain survival.

In this lecture we will discuss these aspects and their pathophysiological relevance.

References

1. Lombardi S, Testa MF, Pinotti M, Branchini A. Molecular Insights into Determinants of Translational Readthrough and Implications for Nonsense Suppression Approaches. Int J Mol Sci. 2020 Dec 11;21(24):9449. doi: 10.3390/ijms21249449.
2. Ferraresi P, Balestra D, Guittard C, Buthiau D, Pan-Petesh B, Maestri I, Farah R, Pinotti M, Giansily-Blaizot M. Next-generation sequencing and recombinant expression characterized aberrant splicing mechanisms and provided correction strategies in factor VII deficiency. Haematologica. 2020 Mar;105(3):829-837. doi: 10.3324/haematol.2019.217539. Epub 2019 Jul 4.
3. Balestra D, Maestri I, Branchini A, Ferrarese M, Bernardi F, Pinotti M. An Altered Splicing Registry Explains the Differential ExSpeU1-Mediated Rescue of Splicing Mutations Causing Haemophilia A. Front Genet. 2019 Oct 10;10:974. doi: 10.3389/fgene.2019.00974. eCollection 2019.
5. Scalet D, Maestri I, Branchini A, Bernardi F, Pinotti M, Balestra D. Disease-causing variants of the conserved +2T of 5' splice sites can be rescued by engineered U1snRNAs. Hum Mutat. 2019 Jan;40(1):48-52. doi: 10.1002/humu.23680. Epub 2018 Nov 19.
5. Branchini A, Ferrarese M, Campioni M, Castaman G, Mari R, Bernardi F, Pinotti M. Specific factor IX mRNA and protein features favor drug-induced readthrough over recurrent nonsense mutations. Blood. 2017 Apr 20;129(16):2303-2307. doi: 10.1182/blood-2016-09-738641. Epub 2017 Feb 14.
6. Branchini A, Ferrarese M, Lombardi S, Mari R, Bernardi F, Pinotti M. Differential functional readthrough over homozygous nonsense mutations contributes to the bleeding phenotype in coagulation factor VII deficiency. J Thromb Haemost. 2016 Oct;14(10):1994-2000. doi: 10.1111/jth.13443. Epub 2016 Sep 19.

B CELL LYMPHOMA: FROM CYTOGENETICS TO GENOMICS ON THE WAY TO PRECISION MEDICINE

R. Dalla-Favera

Institute for Cancer Genetics, Columbia University, New York, NY, USA

During the last four decades enormous progress has been made toward understanding the pathogenesis of cancer, including several types of B cell lymphoma. Initial cytogenetic characterization, which defined the critical role of chromosomal translocations in distinct B cell lymphoma subtypes, were followed by the identification of the genes involved in the translocations, and the elucidation of their role in normal B cell development and lymphomagenesis. A major turning point was then represented by the development of next-generation sequencing technologies, which allowed the comprehensive definition of the repertoire of somatic gene alterations associated with major lymphoma subtypes. Paralleling these studies, a critical advancement came from the precise identification of the cell-of-origin of B cell lymphomas, and in particular the discovery that (except for a fraction of mantle-cell lymphoma cases) these tumors derive from the germinal-center (GC), the site where B cells are selected to become antigen-specific memory B cells and plasma cells increased their affinity for the antigen via immunoglobulin somatic hypermutation (SHM) and class-switch recombination (CSR). These advances are exemplified by the progress in Diffuse-Large B-cell Lymphoma (DLBCL), the most common subtype of human lymphoma. In this entity, transcriptomic analysis has led to the identification of multiple subtypes reflecting the derivation from distinct stages of the GC reaction, including the GCB- and ABC-DLBCL. Which are associated with distinct genetic lesions and differential response to chemotherapy , indicating the involvement of separate oncogenic pathways. More recently, further refinement to the DLBCL classification was provided by the identification of several genetic subgroups based on the presence of co-occurring genetic alterations, which also show distinct clinical outcomes, with implications for differential therapeutic targeting. While the association of individual DLBCL subtypes with clinical outcome suggests the clinical relevance of this new taxonomy, not all patients can be classified; moreover, these schemas are based on the analysis of coding regions, which represent only 2-3% of the genome. Thus, further genetic complexity of pathogenetic relevance may reside in the non-coding regulatory portion of the genome.

The final part of the lecture will review recent discoveries in the analysis of the non-coding, regulatory portion of the DLBCL genome. We have found that chromatin domains corresponding to active super-enhancers (SEs), the major regulatory elements of gene expression, are highly and specifically hypermutated in over 90% of DLBCL samples. Hypermutation is caused by the abnormal activity of Activation Induced Deaminase (AID), the enzyme that normally catalyzes the physiologic hypermutation of immunoglobulin genes to create antibody diversity in the GC. Hypermutated SEs are linked to genes encoding B-cell developmental regulators and oncogenes, including BCL6, BCL2 and CXCR4. We identified specific mutations that prevent their binding and transcriptional downregulation by specific transcriptional repressors. Genetic correction of selected mutations restores repressor DNA-binding, downregulates target gene expression, and leads to the counter-selection of cells harboring corrected alleles, indicating oncogenic dependency from the SE mutations. This pervasive SE mutational mechanism reveals a new major set of genetic lesions deregulating gene expression, which expands the involvement of known oncogenes in DLBCL pathogenesis and identifies new deregulated gene targets of therapeutic relevance. We anticipate that this new layer of genetic alterations will contribute to a more comprehensive classification of DLBCL, with implications for precision therapeutic targeting.

References

1. Basso, K., Dalla-Favera, R. Germinal Centres and B cell lymphomagenesis. Nat Revm Immunol. 15(3):172-84, 2015
2. Pasqualucci, L., Dalla-Favera, R. Genetics of diffuse large B-cell lymphoma. Blood m131(21):2307-2319. 2018
3. Bal, E., Kumar, R., Hadigol, M., Holmes, A.B., Hilton, L.K., Loh, J.W., Dreval, K., Wong, J.C.H., Vlasevska, S., Corinaldesi, C., Soni, R., K., Basso, K., Morin, R.D., Khiabanian, H., Pasqualucci, L., Dalla-Favera, R. Super-enhancer hypermutation alters oncogene expression in B cell lymphoma. Nature 10.1038/s41586-022-04906-8, 2022 (online ahead of print)

INHERITED THROMBOCYTOPENIAS

F. Melazzini

Department of Internal Medicine and Medical Therapeutics, University of Pavia, Pavia, Italy; Department of Internal Medicine, IRCCS San Matteo Hospital Foundation, Pavia, Italy

Inherited thrombocytopenias (ITs) have been considered for a long time exceedingly rare disorders, and bleeding diathesis has been addressed as the main clinical issue impacting the lives of patients affected.

Since the beginning of this century, thanks to the identification of dozens of new forms, the number of known ITs raised to more than 40. It has been revealed that most patients have mild or no bleeding tendency at all, because the most prevalent disorders are usually characterized by moderate or mild thrombocytopenia and no severe defect of platelet function.[1]

In many cases, thrombocytopenia is an incidental finding, and misdiagnosis with immune thrombocytopenia (ITP) may lead to unnecessary treatments, such as immunosuppressive drugs or splenectomy, which not only do not increase platelet count, but also may cause severe side effects.[2-4]

Almost half of the genetic defects causing low platelet count could not only induce other congenital manifestations, but also predispose to acquire life-threatening additional diseases over the course of life. For instance, mutations in *RUNX1*, *ANKRD26* and *ETV6* predispose to hematological malignancies. *MYH9* mutations result in congenital thrombocytopenia and increase the risk of developing kidney failure, cataracts and hearing loss at a later stage, while *MPL* mutations cause a congenital thrombocytopenia that usually evolves into bone marrow failure.[5]

The clinical picture of ITs, therefore, has become much more variegated and complex than the term inherited thrombocytopenia would suggest. Furthermore, clinical studies showed that treatments other than platelet transfusion can greatly benefit affected subjects.

The rarity of ITs and difficulties for their diagnosis have so far discouraged population studies to identify the frequency of these conditions. However, physicians dealing with blood diseases should expect to examine a significant number of individuals with ITs during their professional life.

Identification of patients with ITs is essential for evaluation of their prognosis, enabling effective genetic counselling, personalizing follow-up and giving appropriate treatments in case of development of additional diseases that can be prevented or successfully treated at their onset. Careful clinical evaluation and peripheral blood film examination are extremely useful tools in guiding the diagnostic process and identifying the candidate genes to be sequenced.[6]

References

1. Balduini CL, Melazzini F, Pecci A. Inherited thrombocytopenias-recent advances in clinical and molecular aspects. Platelets 2017; 28: 3–13
2. Noris P, Schlegel N, Klersy C, Heller PG, Civaschi E, Pujol-Moix N, et al. Analysis of 339 pregnancies in 181 women with 13 different forms of inherited thrombocytopenia. Haematologica, 99 (8) (2014), pp. 1387-1394
3. Noris P, Perrotta S, Seri M, Pecci A, Gnan C, Loffredo G, et al. Mutations in ANKRD26 are responsible for a frequent form of inherited thrombocytopenia: analysis of 78 patients from 21 families Blood, 117 (24) (2011), pp. 6673-6680
4. Pecci A, Ma X, Savoia A, Adelstein RS. MYH9: Structure, functions and role of non-muscle myosin IIA in human disease. Gene, 664 (2018), pp. 152-167
5. Melazzini F, Zaninetti C, Balduini CL. Bleeding is not the main clinical issue in many patients with inherited thrombocytopaenias. Haemophilia, 23 (5) (2017), pp. 673-681
6. Pecci A, Balduini CL. Inherited thrombocytopenias: an updated guide for clinicians. Blood Rev. 2021 Jul;48:100784.

ROLE OF BISPECIFIC ANTOBODIES IN ACUTE LEUKEMIAS

A. Venditti

Hematology, Department of Biomedicine and Prevention, University Tor Vergata; Department of Onco-Hematology, Azienda Policlinico Tor Vergata, Rome, Italy

Bispecific antibodies (BsAbs) represent a broad family of molecular constructs that have the unique ability to allow the synchronous coupling of two different antigens.[1,2] Bispecific T-Cell Engagers (BiTEs) belong to the BsAbs category which binds one cancer cell antigen and one immune-effector cell antigen.[1-3] The mechanism of action of BiTEs is depicted in Figure 1.

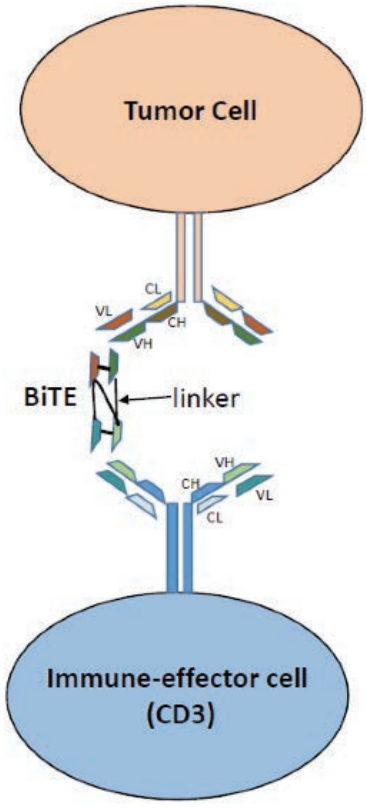


Figure 1. BiTE consists of the combination of the variable heavy and light chain of a tumor-associated and immune-effector cell (T-cell) antigen. The chains are connected through a linker, which guarantees the stability and flexibility of the construct.

Although several versions of BiTEs were developed, the basic mode of action remains the same. In fact, BiTEs consist of a single heavy and light chain of the variable region of a cancer and immune-effector cell (CD3) antigen, this construct is known as diabody. Upon antigen binding, BiTEs bridge the cancer and immune-effector cell, leading to the formation of a "cytolytic synapse". This is a critical step for T-cell engagement and cytokine release, which promotes cancer cell lysis.[4] Recent variants of BiTEs include Dual Affinity Retargeting antibodies (DART), Bi- and Tri-specific Killer Engager antibodies (BiKEs and TriKEs) (Figure 2).[1,2]

Blinatumomab is the first and only BiTE so far approved for the treatment of acute leukemia. In the TOWER Trial, 405 adults patients with R/R ph' negative ALL were randomized to receive blinatumomab or chemotherapy, overall survival (OS) being the primary end-point.[5] In this heavily pre-treated cohort of patients, median duration of OS was significantly longer in the blinatumomab arm than in the control one (7.7 vs 4 months; HR 0.71; P=0.01). In the translational research paralleling the clinical design of the trial, it was demonstrated that the baseline T cell percentage was a predictor of MRD response, when receiving blinatumomab.[6] In the ALCANTARA phase II trial, 16 (36%) of 45 adult patients with R/R Ph+ positive ALL achieved CR/CRh after 1-2 cycles of blinatumomab. Seven of the responders (44%) proceeded to HSCT.[7] In the DALBA phase II trial, 63 adult patients with newly diagnosed Ph+ positive ALL were given dasatinib/steroids, followed by 2 cycles of blinatumomab. The frequency of bone marrow molecular response was the primary end-point; 98% of the patients achieved a CR, with 29% reaching a molecular response after dasatinib. This figure increased up to 60%, following the 2 cycles of blinatumomab.[8] Future developments and directions include combination of blinatumomab with chemotherapy or with new TKi such as ponatinib. The role of BiTEs (anti-CLEC12A; AMG330) and DARTs (Flotetuzumab) in acute myeloid leukemia will be also discussed.[9]

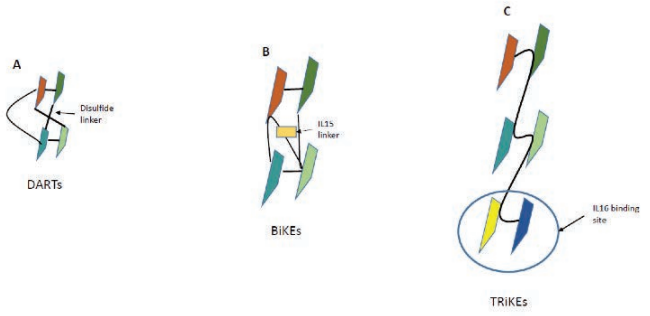


Figure 2. DARTs have the same structure than BiTEs with the addition of a disulfide linker, which confers more stability to the construct (A). BIKEs contain an IL15 linker (yellow box in B). TRIKEs are equipped with an additional binding site for IL16 (C). BIKES and TRIKEs have been specifically developed to drive natural killer engagement.

References

1. Tian Z, Liu M, Zhang Y, Wang X. Bispecific T cell engagers: an emerging therapy for management of hematologic malignancies. J Hematol Oncol 2021;14(75):1-18.
2. Allen C, Zeidan AM, Bewersdorf JP. BiTEs, DARTS, BiKEs and TriKEs—Are Antibody Based Therapies Changing the Future Treatment of AML? Life 2021;11(465):1-17.
3. Kühl L, Aschmoneit N, Kontermann RE, Seifert O. The ELG technology to generate Ig-like bispecific antibodies. MABS 2022;14(1)(e2063043):1-13.
4. Baeuerle PA, Reinhardt C. Bispecific T-Cell Engaging Antibodies for Cancer Therapy. Cancer Res; 2009, 69, 4941.
5. Kantarjian H, Stein A, Gokbuget N, et al. Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia. NEJM 2017;376:836-847.
6. Wei A, Ribera JM, Larson RA, et al. Biomarkers associated with blinatumomab outcomes in acute lymphoblastic leukemia. Leukemia 2021; 5:2220–2231.
7. Martinelli G, Boissel N, Chevallier P, et al. Complete Hematologic and Molecular Response in Adult Patients With Relapsed/Refractory Philadelphia Chromosome–Positive B-Precursor Acute Lymphoblastic Leukemia Following Treatment With Blinatumomab: Results From a Phase II, Single-Arm, Multicenter Study. JCO 2017; 35(16):1795-1802.
8. Foà R, Bassan R, Vitale A, et al. Dasatinib–Blinatumomab for Ph-Positive Acute Lymphoblastic Leukemia in Adults. NEJM 2020; 383(18):1613-1623.
9. Daver N, Alotaibi AS, Bucklein V, Subkleve M. T-cell-based immunotherapy of acute myeloid leukemia: current concepts and future developments. Leukemia 2021; 35:1843–1863.

THE ROLE OF BI-SPECIFIC ANTIBODIES IN MULTIPLE MYELOMA

E. Zamagni, M. Cavo[1,2]

[1]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli", Bologna, Italy; [2]Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale, Università di Bologna, Bologna, Italy

Bispecific antibodies (BsAbs) are molecules capable of binding to the CD3 antigen, expressed on T lymphocytes, and to target antigens (Ag) expressed on the surface of target cells, resulting in a bridge between T lymphocytes and target cells, capable of guiding the immune response (with consequent destruction of the target) towards a pathological cell population.[1] At the moment there are no BsAbs approved for use in patients with multiple myeloma (MM), however several trials are underway, aimed at evaluating the short- and long-term efficacy and toxicity of these drugs in patients with relapsed/refractory (RRMM).

The more affected target is currently B cell maturation antigen (BCMA), a transmembrane protein, belonging to the family of tumor necrosis factor receptors, which, when stimulated by its BAFF and APRIL ligands, is able to induce cell proliferation, survival and differentiation of B lymphocytes into plasma cells (PCs) and which is selectively expressed by PCs, in particular if clonal.[2]

Teclistamab (Tec) is a humanized IgG4 class BsAb designed to bind simultaneously to BCMA and CD3. A phase I/II study has been recently published, showing high efficacy, with an overall response rate (ORR) of 63% and median duration of response of 18 months in patients treated with 5 prior lines of therapy (LOT), and a 52% ORR in a sub-group of patients previously treated with other anti-BCMA agents (Table 1).[3] Several other phase II and III studies are currently on-going, combining Tec with other standards of care, and comparing them with approved triplets in RRMM from the second line of therapy.

Other BsAbs have been developed against BCMA and are currently in different stages of development (Table 1).

Talquetamab is a first in class T-cell redirecting bispecific antibody targeting both CD3 and GPRC5D, an orphan receptor that is highly expressed in malignant plasma cells and has limited expression in normal human tissues.[4] A phase I study is currently exploring the efficacy and safety of 2 subcutaneous doses of Talquetamab in 130 RRMM, treated with a median of 6 prior LOT, including patients pre-treated with an anti BCMA agent, showing an ORR of 63-70% (Table 1).

A third target has been explored, FCRH5 (FC receptor-homolog 5), another Ag selectively expressed by the B lineage, mainly on MM PCs, where it's near ubiquitous.[5] Cevostamab, the first-in-class BsAb targeting FCRH5, is under investigation in an on-going phase I study for patients with RRMM, including those exposed to prior anti BCMA agents, showing ecouraging efficacy and safety results (Table 1).[6]

Peculiar toxicities are associated with this treatment, some acute, such as cytokine release syndrome (CRS) and neurotoxicity (ICANS) and some chronic, such as immune suppression, linked to hypo-gammaglobulinemia and B-cell killing.[7] The first is a hyper-inflammatory reaction, characterized by fever and in severe cases hypotension and/or hypoxia. The second is a transient alteration of the state of alertness and cognitive functions, especially language; these complications require close monitoring of vital functions and, if worsening, early therapy with cytokine blocking drugs (Tocilizumab, anti-IL6) and/or corticosteroids. Moreover, target-specific toxicities, such as mucosal and cutaneous damage when GPRC5D is affected, may be present (Table 1).

References

1. Shah N, Chari A, Scott E, et al. B-cell maturation antigen (BCMA) in multiple myeloma: rationale for targeting and current therapeutic approaches. Leukemia. 2020 Apr;34(4):985-1005
2. Sanchez L, Dardac A, Madduri D et al. B-cell maturation antigen (BCMA) in

multiple myeloma: the new frontier of targeted therapies. Ther Adv Hematol. 2021 Jan 30 ecollection
3. Moreau P, Garfall AL, van de Donk NWCJ et al. Teclistamab in Relapsed or Refractory Multiple Myeloma. N Engl J Med. 2022 Jun, online ahead of print
4. Minnema MC, Krishnan A, Berdeja JC, et al. Talquetamab, a G protein-coupled receptor family C group 5 member D x CD3 bispecific antibody in relapsed/refractory multiple myeloma: updated efficacy and safety results from Monumental-1, Hema Sphere 2022, S182
5. Li J, Stagg NJ, Johnston J, et al. Membrane-Proximal Epitope Facilitates Efficient T Cell Synapse Formation by Anti-FcRH5/CD3 and Is a Requirement for Myeloma Cell Killing. Cancer Cell. 2017 Mar 13;31(3):383-395
6. Trudel S, Cohen AD, Krishnan AY et al. Cevostamab Monotherapy Continues to Show Clinically Meaningful Activity and Manageable Safety in Patients with Heavily Pre-Treated Relapsed/Refractory Multiple Myeloma (RRMM): Updated Results from an Ongoing Phase I Study. Blood 2021;138 (Suppl 1):157
7. Lee DW, Santomasso BD, Locke FL, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biol Blood Marrow Transplant. 2019 Apr;25(4):625-638

Table 1. Efficacy results of main Bs Abs in RRMM.

	Teclistamab[1] (n=165)	AMG701[2] (n=85)	REGN5458[3] (n=49)	TNB-383B[4] (n=58)	CC-93269[5] (n=30)	Elranatamab[6] (n=30)	Talquetamab[7] (n=82)	Cevostamab[8] (n=53)
Target	BCMA	BCMA	BCMA	BCMA	BCMA	BCMA	GPRC5D	FcRH5
Administration	SC, QW	IV, QW	IV, QW then Q2W	IV, Q3W	IV, QW then Q2W	SC, QW	SC, QW/Q2W 405/800 µg/kg	IV, Q3W
Median prior LoT	5 (2-14)	6 (2-25)	5 (2-17)	6 (3-15)	5 (3-13)	8 (3-15)	6 (2-17)/5 (2-17)	6 (2-15)
Triple refractory	77.6%	62%	100%	64%	67%	87%	76%/77%	72%
CRS, G≥3	72%, 0.6%	64%, 9%	38%, 0%	69%, 3%	77%, 3%	73%, 0%	76%, 1%/79%, 0	76%, 2%
Neurotoxicity, G≥3	14.5%, 0.6%	NR	12%, 0	NR	NR	NR	NR	28%, 0
ORR	63%	26%	51%	50.7%	89% at 6-10 mg	83% at RP2D	70%/64%	53%
CR	CR 7%	17% ≥VGPR	43% ≥VGPR	43% ≥CR	44% at 6-10 mg	30%	7%/11.4%	18%
MRD – (10^{-5})	44 out of 54	6 out of 7	4 out of 10	NR	12 out of 13	3 patients	NR	6 out of 7

*There are no head-to-head comparisons of these data and naïve comparison should be conducted with caution
BCMA, B-cell maturation antigen; CR, complete response; CRS, cytokine release syndrome; IV, intravenous; LoT, lines of treatment; NR, not reported; RP2D, recommended phase 2 dose; SC, subcutaneous; MRD, minimal residual disease; NT, neurotoxicity; ORR, overall response rate; QW, weekly, Q2W/Q3W, every 2/3 weeks; VGPR, very good partial response

[1]Nooka A et al. ASCO 2022;abstract 8007; [2]Harrison S et al. ASH 2020;abstract 181; [3]Zonder J, et al. COMy 2022;abstract only; [4]Kumar S et al. ASH 2021;abstract 900; [5]Costa L et al. ASH 2019;abstract 143; [6]Bahlis N et al. ASCO 2021;abstract 8006; [7]Minnema M et al. ASCO 2022;abstract 8015; [8]Cohen A et al. ASH 2020;abstract 292

RECENT PROGRESS IN THE PATHOGENESIS OF CHRONIC MYELOID LEUKEMIA

S. Bernardi

[1]Department of Clinical and Experimental Sciences, University of Brescia, Bone Marrow Transplant Unit, ASST Spedali Civili, Brescia, Italy; [2]Centro di Ricerca Emato-Oncologica AIL (CREA), ASST Spedali Civili, Brescia, Italy

Chronic myeloid leukaemia (CML) is a blood cancer due to a reciprocal translocation, resulting in a BCR-ABL1 oncogene. Although tyrosine kinase inhibitors (TKI) have been successfully used to treat CML, there are still cases of resistance. The resistance occurred mainly due to the mutation in the tyrosine kinase domain of the BCR-ABL1 gene. However, there are still many cases with unknown causes of resistance as the etiopathology of CML are not fully understood. Thus, it is crucial to figure out the complete pathogenesis of CML.[1] Here it is going to be presented an overview concerning the most recent evidences about CML pathogenesis.

Firstly, numbers of studies have revealed the mechanisms of CML pathogenesis which involves several key signalling pathways, including the MAPK, JAK-STAT, PI3K/AKT, EGFR, ERBB, TGF-b, METTL3/METTL14, HIF1α and TP53 pathways.[2,3] The identification of these BCR-ABL1 interactors and regulators has better elucidated the dynamic of leukemia onset and progression, even if other mechanisms must be investigated. In example, the leukemic stem cells (LSC) counterpart is insensitive to TKI. This strongly suggests that their survival is independent of BCR-ABL1 activity, relying on other factors, including interactions with the bone marrow (BM) microenvironment. Bone morphogenetic proteins (BMP) seems one of the most interesting elements driving the persistence of LSC and sustaining the pathogenesis even in case of relapse.[4] Additional elements sustaining CML pathogenesis are microRNA (miRNA).[5] Among them, hsa-miR-155-5p presents a dynamic regulatory aspect by modulating the BCR-ABL1-mediated leukemogenesis. In fact, hsa-miR-155-5p targets E2F2, KRAS and FLI1, affecting MAPK signaling.[6] Finally yet importantly, there are several evidences about the immunological landscape and dysfunctions permitting the development of CML clones, the survival of LSC and the relapse.[7]

To note, different CML zebrafish, D. melanogaster, and mouse models have been recently developed. These biological tools will help the investigation of multiple aspects supporting and influencing the leukemogenesis and the development of CML[8,9] improving the knowledge in the further years.

References

1. J.F. Apperly "Chronic myeloid leukaemia", Lancet, 2015
2. V. Singh et al "The Molecular Role of HIF1α Is Elucidated in Chronic Myeloid Leukemia", Front Onc, 2022
3. Z. Ianniello et al "New insight into the catalytic -dependent and –independent roles of METTL3 in sustaining aberrant translation in chronic myeloid leukemia", Cell Death and Disease, 2021
4. S. Jeanpierre et al, "The quiescent fraction of chronic myeloid leukemic stem cells depends on BMPR1B, Stat3 and BMP4-niche signals to persist in patients in remission", Hematologica, 2021
5. M. H. Elias et al, "A Systematic Review of Candidate miRNAs, Its Targeted Genes and Pathways in Chronic Myeloid Leukemia–An Integrated Bioinformatical Analysis", Front in Oncology, 2022
6. I. Soltani et al "Potential functions of hsa-miR-155-5p and core genes in chronic myeloid leukemia and emerging role in human cancer: A joint bioinformatics analysis", Genomics, 2021
7. Y. Hsieh et al "Improving outcomes in chronic myeloid leukemia through harnessing the immunological landscape", Leukemia, 2021
8. R. Bernardoni et al "A new BCR-ABL1 Drosophila model as a powerful tool to elucidate the pathogenesis and progression of chronic myeloid leukemia", Hematologica, 2019
9. D. Zizioli and S. Bernardi et al "Development of BCR-ABL1 Transgenic Zebrafish Model Reproducing Chronic Myeloid Leukemia (CML) Like-Disease and Providing a New Insight into CML Mechanisms", Cells, 2021

TREATMENT OPTIMIZATION IN CHRONIC MYELOID LEUKEMIA: HOW CAN WE INCREASE THE PROBABILITY OF TREATMENT-FREE REMISSION?

F. Castagnetti

Istituto di Ematologia "Seràgnoli", IRCCS Azienda Ospedaliero-Universitaria di Bologna, Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale, Università di Bologna, Bologna, Italy

Introduction and background

Tyrosine kinase inhibitors (TKIs) significantly improved the survival of CML patients, making it very close to normal[1,2]. Recently, the expectations have changed and the emerging primary goal of therapy, at least in selected patients, is the achievement of a treatment-free remission (TFR).[1] Unfortunately, the probability of achieving a stable deep molecular response (DMR), pre-requisite to attempt treatment discontinuation (D/C), is approximately 40-50% and in real-life experiences no more than 10-20% CML patients are able to attain TFR.[1,2] A debate on treatment policies able to maximize the probability of TFR is open.[3]

First-line treatment

Second generation (2G)-TKIs induced higher and deeper responses, but may be associated with higher toxicity, if compared to imatinib.[4,5] The ELN recommendations do not provide simple criteria to choose a specific first line inhibitor for each patient.[2] On the contrary, in the view of treatment D/C, the GIMEMA CML Working Party (WP) provided practical suggestions on how to choose. The patient's age and the ELTS score should be considered (Figure 1): 2G-TKIs should be preferred in patients < 40 years and in patients 41–65 years with non-low risk (comorbidities should be taken into account).[1] However, TFR should be pursued in all patients, including those treated with imatinib, if criteria for treatment D/C are reached.[1,3] The probability of achieving TFR may depend on several factors, but therapy duration and DMR duration were the most relevant variables.[3,6-9]

Second-line treatment

According to ELN and GIMEMA Recommendations, the decision to change treatment depends on the response at milestones[1,2] (Figure 2). When the goal is TFR, the GIMEMA panel suggested to change if BCR::ABL1 >10% at 3 and 6 months, >1% at 12 months, and >0.1% at 24 months (warning if BCR::ABL1 >0.01%).[2] The choice of second-line treatment (and beyond) is influenced by the reasons for switching, the presence of BCR::ABL1 mutations, and the type of first-line TKI. If a stable DMR is achieved, a treated discontinuation may be attempted, but in the case of resistance to previous lines, the chances of reaching a TFR are low.[3,10]

Conclusions

Despite the large number of studies, several issues on TFR remain unsolved. In particular, the role of 2G-TKIs, 3G-TKIs and new drugs in maximizing the probability of TFR without increasing toxicity has not been clarified yet. Moreover, the mechanisms behind the immunological control of CML need to be elucitated.

	18-40 yrs	41-65 yrs	66-80 yrs	> 80 yrs
Low risk	2GTKIs	IM – 2GTKIs	IM	IM
Intermediate risk	2GTKIs	2GTKIs	IM – 2GTKIs	IM
High risk	2GTKIs	2GTKIs	IM – 2GTKIs	IM

2GTKIs: second generation tyrosine kinase inhibitors; IM: imatinib; yrs: years

Baccarani et al. Blood Advances 2019

Figure 1. First-line treatment according to GIMEMA recommendations.

	RESPONSE	GIMEMA 2019	ELN 2020
3 months	Optimal	≤ 10	≤ 10
	Warning	-	> 10
	Failure	**> 10 (confirmed)**	-
6 months	Optimal	≤ 1	≤ 1
	Warning	1-10	1-10
	Failure	**> 10**	> 10
12 months	Optimal	≤ 0.1	≤ 0.1
	Warning	0.1 - 1	0.1 - 1
	Failure	**> 1**	> 1
24 months	Optimal	≤ 0.01	≤ 0.1
	Warning	0.1 - 0.01	0.1 - 1
	Failure	**> 0.1**	> 1

Baccarani et al. Blood Advances 2019
Hochhaus et al. Leukemia 2020

Figure 2. Definition of response to first- and second-line therapy

References

1. Baccarani M, Abruzzese E, Accurso V, et al. Managing chronic myeloid leukemia for treatment-free remission: a proposal from the GIMEMA CML WP. Blood Adv. 2019;3:4280-90.
2. Hochhaus A, Baccarani M, Silver RT, et al. European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia. Leukemia. 2020;34:966–84.
3. Castagnetti F, Binotto G, Capodanno I, et al. Making Treatment-Free Remission (TFR) Easier in Chronic Myeloid Leukemia: Fact-Checking and Practical Management Tools. Target Oncol. 2021;16:823-38.
4. Gugliotta G, Castagnetti F, Breccia M, et al. Treatment-free remission in chronic myeloid leukemia patients treated front-line with nilotinib: 10-year follow-up of the GIMEMA CML 0307 study. Haematologica. 2022 Apr 7. doi: 10.3324/haematol.2021.280175.
5. Kantarjian HM, Hughes TP, Larson RA, et al. Long-term outcomes with frontline nilotinib versus imatinib in newly diagnosed chronic myeloid leukemia in chronic phase: ENESTnd 10-year analysis. Leukemia. 2021;35:440-53.
6. Saussele S, Richter J, Guilhot J, et al. Discontinuation of tyrosine kinase inhibitor therapy in chronic myeloid leukaemia (EURO-SKI): a prespecified interim analysis of a prospective, multicentre, non-randomised, trial. Lancet Oncol. 2018 Jun;19(6):747-757.
7. Richter J, Lübking A, Söderlund S, et al. Molecular status 36 months after TKI discontinuation in CML is highly predictive for subsequent loss of MMR-final report from AFTER-SKI. Leukemia. 2021;35:2416-18.
8. Radich JP, Hochhaus A, Masszi T, et al. Treatment-free remission following frontline nilotinib in patients with chronic phase chronic myeloid leukemia:

5-year update of the ENESTfreedom trial. Leukemia. 2021 May;35(5):1344-1355.
9. Shah NP, García-Gutiérrez V, Jiménez-Velasco A, et al. Dasatinib discontinuation in patients with chronic-phase chronic myeloid leukemia and stable deep molecular response: the DASFREE study. Leuk Lymphoma. 2020;61:650-9.
10. Hughes TP, Clementino NC, Fominykh M, et al. Long-term treatment-free remission in patients with chronic myeloid leukemia after second-line nilotinib: ENESTop 5-year update. Leukemia. 2021;35:1631-42.

THE LONG-TERM MANAGEMENT OF PATIENTS NOT ELIGIBLE TO STOP TREATMENT WITH THYROSIN-KINASE INHIBITORS

M. Breccia

Az. Policlinico Umberto I- Sapienza Università, Roma, Italy

Approximately 35-38% of patients with chronic myeloid leukemia (CML) treated with a second generation first-line inhibitor (2gen TKI) and approximately 22% of patients treated with imatinib may be candidates for discontinuation, as they achieved a deep and stable molecular response.[1] Most patients are therefore destined to continue long-term treatment. All available TKIs have off-target effects: there has been evidence of more serious adverse events (AEs) which in some patients can cause significant morbidity over time and increased mortality. About 20% of patients may suffer from long-term complications, requiring a therapeutic switch to another TKI without possible cross-intolerance or dose reduction.[2] To reduce persistent adverse events (AEs) related to long-term exposure to TKI treatment, several studies have focused on the efficacy of TKI dose optimization, improving quality of life without compromising the achievement and maintenance of responses and, finally, the attempt of treatment free remission (TFR). Studies such as DESTINY or NILO-RED, which optimize dosage, have shown that most patients have maintained or improved molecular responses.[3] The OPTIC study finally demonstrated that the correct starting dose of ponatinib is 45 mg but immediately after reaching at least a ratio <1%, it is possible to reduce it to 15 mg, maintaining efficacy even in patients with increased molecular load with reduced cardiovascular toxicity.[4]

Considering the potential benefits and risks of each TKI and the specific goals on a case-by-case basis, a proactive therapeutic change can be considered to deepen the response: the timing of the change remains a controversial topic, but regular monitoring and early change are associated with a better outcome.[5,6] The recent results of the ENESTPath study showed that switching from imatinib in patients already on CCyR but not in profound response to a 2gen TKI, about 35% of patients improved the depth of the molecular response able to participate in a TFR program.[7]

New compounds are on the horizon for highly pretreated patients resistant and / or intolerant to multiple lines of treatment: among these, the FDA has already approved the first example of a STAMP inhibitor, asciminib, capable of acting on the myristoyl site. Results from recent sponsored studies and real-world data showed that the drug rescued patients in 3rd or subsequent lines of therapy with reduced and manageable toxicity, with no evidence of off-target effects.[8,9] Experimental therapies are also underway to eradicate or silence residual leukemia through active immune surveillance.[10]

References

1. Hochhaus A, Saglio G, Hughes TP, et al. Long-term benefits and risks of frontline nilotinib vs imatinib for chronic myeloid leukemia in chronic phase: 5-year update of the randomized ENESTnd trial. Leukemia. 2016;30(5):1044-54.
2. Steegmann JL, Baccarani M, Breccia M, et al. European LeukemiaNet recommendations for the management and avoidance of adverse events of treatment in chronic myeloid leukaemia. Leukemia. 30:1648-167(2016)
3. Breccia M, Scalzulli E, Pepe S, et al. Future management of chronic myeloid leukemia: from dose optimization to new agents. Curr Cancer Drug Targets 2022, Jun 13 (Epub ahead of print)
4. Cortes J, Apperley J, Lomaia E, et al. Ponatinib dose-ranging study in chronic phase chronic myeloid leukemia: a randomized, open-label phase 2 clinical trial. Blood 2021; 138(21): 2042-2050
5. Quintás-Cardama A, Jabbour EJ. Considerations for early switch to nilotinib or dasatinib in patients with chronic myeloid leukemia with inadequate response to first-line imatinib. Leuk Res. 2013;37(5):487-95.
6. Garcia-Gutierrez V, Breccia M, Jabbour E, et al. A clinician perspective on the treatment of chronic myeloid leukemia in the chronic phase. J Hematol Oncol 2022; 15: 90
7. Rea D, Kyrcz-Krzemien S, Sportoletti P, et al. Treatment free remission (TFR) after two different durations of nilotinib consolidation in patients with chronic myeloid leukemia previously treated with imatinib: Enestpath study results. Blood 2021; 138: suppl 1, 635
8. Hughes TP, Mauro MJ, Cortes JE, et al. Asciminib in chronic myeloid leukemia after ABL kinase inhibitor failure. N Engl J Med 2019; 381: 2315-2326
9. Shanmuganathan N, Hughes TP. Asciminib for chronic myeloid leukemia: next questions. Br J Haematol 2022; Jun 21 (Epub ahead of print)
10. Hochhaus A, Ernst T. TKI discontinuation in CML: how do we make more patients eligible? How do we increase the chances of a successful treatment-free remission? Hematology Am Soc Hematol Educ Program 2021: 106-112

NEW THERAPEUTIC APPROACHES IN MANTLE CELL LYMPHOMA

C. Visco

Department of Medicine, Section of Hematology, University of Verona, Verona, Italy

Mantle cell lymphoma (MCL) is a rare B-cell non-Hodgkin lymphoma characterized by clinical and biological heterogeneity. Risk stratification at the time of diagnosis has become critical. Together with the Mantle Cell Lymphoma International Prognostic Index-Combined (MIPI-c), which integrates an estimate of proliferation (Ki67 index), the presence of blastoid morphology, and/or TP53 mutation are associated with suboptimal response to intensive chemoimmunotherapy and dismal survival outcomes. Given their excellent activity in the relapsed/refractory setting, increasingly, biologically targeted therapeutics—such as covalent Bruton tyrosine kinase inhibitors, lenalidomide, and venetoclax—are being incorporated into "chemotherapy-free" regimens and in combination with established chemoimmunotherapy backbones for treatment-naïve mantle cell lymphoma. There is a strong need for risk-adapted treatment programs, that tailor treatment according to baseline prognostic factors since first diagnosis and incorporate minimal residual disease assessment, as initially proposed in the elderly population by the Fondazione Italiana Linfomi V-RBAC study. Such studies present an opportunity to move beyond the historical fitness-based treatment selection paradigm and approach a more personalized, tailored treatment.

Several unsolved problems remain in relapsed/refractory patients, mainly represented by the above mentioned high-risk biological features and by Bruton tyrosine kinase inhibitors failure. In this setting promising standard or investigational therapies exist, including CAR T-cell therapy (including brexucabtagene autoleucel and lisocabtagene maraleucel), bispecific antibody therapy targeting CD20-CD3, zilovertamab vedotin (an antibody-drug conjugate that targets ROR1), and noncovalent Bruton tyrosine kinase inhibitor (*i.e.* pirtobrutinib). These new therapies have shown promising efficacy, even among high-risk patients, including patients with early refractoriness to standard approaches.

With the therapeutic landscape that is rapidly evolving, a comprehensive biologic characterization since initial diagnosis is highly encouraged in patients with MCL. The presence of high-risk features indicates that clinical trial participation is strongly recommended. Furthermore, early referral for consideration of CAR T-cell therapy is advisable, as similar efficacy has been observed with CAR T-cell therapy across subgroups.

References

Hoster E, Rosenwald A, Berger F, et al. Prognostic value of Ki-67 index, cytology, and growth pattern in mantle-cell lymphoma: results from randomized trials of the European Mantle Cell Lymphoma Network. J Clin Oncol.

2016;34:1386-1394.
Aukema SM, Hoster E, Rosenwald A, et al. Expression of TP53 is associated with the outcome of MCL independent of MIPI and Ki-67 in trials of the European MCL Network. Blood. 2018;131:417-420.
Eskelund CW, Dahl C, Hansen JW, et al. TP53 mutations identify younger mantle cell lymphoma patients who do not benefit from intensive chemoimmunotherapy. Blood. 2017;130:1903-1910
Visco C, Tisi MC, Evangelista A, et al; Fondazione Italiana Linfomi and the Mantle Cell Lymphoma Network. Time to progression of mantle cell lymphoma after high-dose cytarabine-based regimens defines patients risk for death. Br J Haematol. 2019;185:940-944
Wang ML, Lee H, Chuang H, et al. Ibrutinib in combination with rituximab in relapsed or refractory mantle cell lymphoma: a single-centre, open-label, phase 2 trial. Lancet Oncol. 2016;17:48-56.
Wang M, Munoz J, Goy A, et al. KTE-X19 CAR T-cell therapy in relapsed or refractory mantle-cell lymphoma. N Engl J Med. 2020;382:1331-1342.
Tam CS, Opat S, Simpson D, et al. Zanubrutinib for the treatment of relapsed or refractory mantle cell lymphoma. Blood Adv. 2021;5:2577-2585.
Palomba ML, Gordon LI, Siddiqi T, et al. Safety and preliminary efficacy in patients with relapsed/refractory mantle cell lymphoma receiving lisocabtagene maraleucel in transcend NHL 001. Blood. 2020;136(suppl 1):10-11.
Hutchings M, Morschhauser F, Iacoboni G, et al. Glofitamab, a novel, bivalent CD20-targeting T-cell-engaging bispecific antibody, induces durable complete remissions in relapsed or refractory B-cell lymphoma: a phase I trial. J Clin Oncol. 2021;39:1959-1970.

IMMUNOTHERAPY FOR THE TREATMENT OF RELAPSED/REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA

C. Carlo-Stella,[1,2] E. Calabretta[1,2]

[1]Department of Biomedical Sciences, Humanitas University, Rozzano (Milano), Italy; [2]Department of Oncology and Hematology, Humanitas Cancer Center, IRCCS Humanitas Research Hospital, Rozzano (Milano), Italy

Although the majority of patients with untreated Diffuse Large B-cell Lymphoma (DLBCL) are efficiently cured, 35% to 40% of them experience primary refractory or relapsing (r/r) disease. Conventional chemotherapy-based salvage therapy, including autologous stem cell transplantation (ASCT), can produce durable disease control in less than half of eligible patients, leaving the rest with a dismal prognosis. Recently, a wide variety of novel immunotherapies, targeted therapies, and cellular therapies have flourished, allowing for an unprecedented clinical improvement for these patients (Table 1).

Specifically, genetically modified autologous T cells targeting CD19 (CAR T-cells) have shown that direct promotion of T cell-mediated cell death can lead to clinically meaningful remissions. Recently, these products have been compared to standard-of-care first salvage therapy in randomized phase III trials,[1-3] with promising, yet conflicting, efficacy, that has led to the FDA approval of two of such products for r/r DLBCL within 12 months of frontline therapy. In the same setting, the combination of the CD19-targeting agent Tafasitamab and Lenalidomide reported an ORR of 60% (43% CR rate) and included mainly patients ineligible for ASCT.[4]

Beyond second-line, numerous targeted and immunotherapy-based agents have shown considerable efficacy with an acceptable safety profile. These include Loncastuximab tesirine, a humanized CD19-targeting antibody-drug conjugate (ADC) with a reported ORR of 48% (24% CR rate),[5] the anti-CD79 ADC Polatuzumab, which has been approved for clinical use in combination with Bendamustine/Rituximab (ORR 45%, CR 40%)[6] and Selinexor, an inhibitor of the nuclear export receptor XPO1.[7]

Lastly, bispecific agents targeting CD20 and CD3 are of great interest. They are designed to bring T cells close to tumor cells to trigger T-cell-mediated cytotoxicity with the potential to circumvent some of the challenges of CAR-T cell therapy. Several CD20/CD3 bispecific T-cell engagers are currently in advanced clinical development and detailed safety and efficacy data have been reported for Glofitamab,[8] Epcoritamab,[9] and Mosunetuzumab.[10] With such an increasing availability of novel therapeutic agents, the current challenge is to identify the correct sequence of such therapies, the patient population that may best benefit from each type of therapy, and, possibly, the addition to standard treatment to achieve higher rates of frontline cure.

Table 1. Novel FDA/EMA approved therapies for the treatment of r/r DLBCL.

Agent	Mechanism of action	Indication	Efficacy	Reference
Tisagenlecleucel	Anti-CD19 CAR T-cell, 4-1BB costimulatory domain	r/r DLBCL after ≥2 lines of therapy	ORR 52% CR 40%	(1)
Lisocabtagene Maraleucel	Anti-CD19 CAR T-cell, 4-1BB costimulatory domain	r/r DLBCL after ≥1 lines of therapy*	ORR 86% CR 66%	(2)
Axicabtagene Ciloleucel	Anti-CD19 CAR T-cell, CD28 costimulatory domain	r/r DLBCL after ≥1 lines of therapy*	ORR 83% CR 65%	(3)
Tafasitamab + Lenalidomide	Fc-enhanced CD19 targeting agent + immunomodulatory drug	r/r DLBCL after ≥1 lines of therapy	ORR 60% CR 43%	(4)
Loncastuximab tesirine	Anti-CD19 PBD-ADC	r/r DLBCL after ≥2 lines of therapy	ORR 48.3% CR 24.1%	(5)
Polatuzumab Vedotin + Bendamustine/Rituximab	Anti-CD79b ADC	r/r DLBCL after ≥2 lines of therapy	ORR 43% CR 40%	(6)
Selinexor	XPO1 inhibitor	r/r DLBCL after ≥2 lines of therapy	ORR 28% CR 12%	(7)

*only FDA-approved

References

1. Bishop MR, Dickinson M, Purtill D, Barba P, Santoro A, Hamad N, et al. Second-Line Tisagenlecleucel or Standard Care in Aggressive B-Cell Lymphoma. N Engl J Med. 2022;386(7):629-39.
2. Kamdar M, Solomon SR, Arnason J, Johnston PB, Glass B, Bachanova V, et al. Lisocabtagene maraleucel versus standard of care with salvage chemotherapy followed by autologous stem cell transplantation as second-line treatment in patients with relapsed or refractory large B-cell lymphoma (TRANSFORM): results from an interim analysis of an open-label, randomised, phase 3 trial. Lancet. 2022;399(10343):2294-308.
3. Locke FL, Miklos DB, Jacobson CA, Perales MA, Kersten MJ, Oluwole OO, et al. Axicabtagene Ciloleucel as Second-Line Therapy for Large B-Cell Lymphoma. N Engl J Med. 2022;386(7):640-54.
4. Salles G, Duell J, González Barca E, Tournilhac O, Jurczak W, Liberati AM, et al. Tafasitamab plus lenalidomide in relapsed or refractory diffuse large B-cell lymphoma (L-MIND): a multicentre, prospective, single-arm, phase 2 study. Lancet Oncol. 2020;21(7):978-88.
5. Caimi PF, Ai W, Alderuccio JP, Ardeshna KM, Hamadani M, Hess B, et al. Loncastuximab tesirine in relapsed or refractory diffuse large B-cell lymphoma (LOTIS-2): a multicentre, open-label, single-arm, phase 2 trial. Lancet Oncol. 2021;22(6):790-800.
6. Tilly H, Morschhauser F, Bartlett NL, Mehta A, Salles G, Haioun C, et al. Polatuzumab vedotin in combination with immunochemotherapy in patients with previously untreated diffuse large B-cell lymphoma: an open-label, non-randomised, phase 1b-2 study. Lancet Oncol. 2019;20(7):998-1010.
7. Kalakonda N, Maerevoet M, Cavallo F, Follows G, Goy A, Vermaat JSP, et al. Selinexor in patients with relapsed or refractory diffuse large B-cell lymphoma (SADAL): a single-arm, multinational, multicentre, open-label, phase 2 trial. Lancet Haematol. 2020;7(7):e511-e22.
8. Hutchings M, Morschhauser F, Iacoboni G, Carlo-Stella C, Offner FC, Sureda A, et al. Glofitamab, a Novel, Bivalent CD20-Targeting T-Cell-Engaging Bispecific Antibody, Induces Durable Complete Remissions in Relapsed or Refractory B-Cell Lymphoma: A Phase I Trial. J Clin Oncol. 2021;39(18):1959-70.
9. Hutchings M, Mous R, Clausen MR, Johnson P, Linton KM, Chamuleau MED, et al. Dose escalation of subcutaneous epcoritamab in patients with relapsed or refractory B-cell non-Hodgkin lymphoma: an open-label, phase 1/2 study. Lancet. 2021;398(10306):1157-69.
10. Budde LE, Assouline S, Sehn LH, Schuster SJ, Yoon SS, Yoon DH, et al. Single-Agent Mosunetuzumab Shows Durable Complete Responses in Patients With Relapsed or Refractory B-Cell Lymphomas: Phase I Dose-Escalation Study. J Clin Oncol. 2022;40(5):481-91.

OPTIMIZING TREATMENT APPROACH IN PRIMARY MEDIASTINAL B-CELL LYMPHOMA

A. Broccoli,[1,2] P.L. Zinzani[1,2]

[1]IRCCS Azienda Ospedaliero-Universitaria di Bologna Istituto di Ematologia "Seràgnoli", Bologna, Italy; [2]Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale Università di Bologna, Italy

The modern treatment of primary mediastinal large B-cell lymphoma is based on some recent acquisitions that have refined the approach to both newly diagnosed and relapsed/refractory disease.

Frontline immunochemotherapy with an anthracycline-containing regimen remains the unsurpassed approach of choice.[1] No randomized trials, however, have yet established the best treatment combination to be used frontline. Cyclophosphamide, doxorubicin, vincristine and prednisone plus rituximab given every 14 (R-CHOP14) rather than 21 days produce higher complete responses and a significantly longer progression-free survival.[2] Third-generation regimens, like the methotrexate/etoposide + doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin (MACOP-B/VACOP-B) with the addition of rituximab, produced outcomes similar to R-CHOP14 according to an initial analysis of the IELSG37 trial.[3] The same trial is specifically designed in a randomized fashion to understand whether consolidation radiotherapy may be omitted in patients achieving a complete response after initial chemoimmunotherapy.

Immunotherapy plays a significant role in patients with progressive or relapsed disease. The anti-programmed death-1 (PD-1) blockade with pembrolizumab is now established as a standard of care in patients failing to respond to a first salvage chemotherapy. Pembrolizumab yielded an objective response rate of 45% in the KEYNOTE-170 trial, with a complete response in up to 13% of the cases and a progression-free survival (PFS) rate of 38% at 1 year. Importantly, no patients with a complete response on pembrolizumab experienced disease progression, including cases being off-treatment for at least 1 year.[4] The combination of an anti-PD-1 blocker (nivolumab) with the anti-CD30 drug conjugate brentuximab vedotin enhanced the response rate to 70%, including a complete metabolic response in 43% of treated cases, with median overall survival, PFS and duration of response not reached at a median follow-up of 11 months.[5] Chimeric antigen receptor (CAR) T-cells offer a treatment option in pretreated patients independently of prior checkpoint blockade: published real life experience acknowledges high response rates (78%), mostly consisting of complete remissions (69%), with 78% of patients being alive at 2 years and progression-free in 64% of the cases.[6]

References

1. Broccoli A, Zinzani PL. The unique biology and treatment of primary mediastinal B-cell lymphoma. Best Pract Res Clin Haematol, 2018; 31: 241-250.
2. Camus V, Rossi C, Sesques P, et al. Outcomes after first-line immunochemotherapy for primary mediastinal B-cell lymphoma: a LYSA study. Blood Adv, 2021; 5: 3862-3872.
3. Martelli M, Zucca E, Botto B, et al. Impact of different induction regimens on the outcome of primary mediastinal B cell lymphoma in the prospective IELSG37 trial. Hematol Oncol, 2021; 39 (suppl 2): 90-92.
4. Armand P, Rodig S, Melnichenko V, et al. Pembrolizumab in Relapsed or Refractory Primary Mediastinal Large B-Cell Lymphoma. J Clin Oncol, 2019; 37: 3291-3299.
5. Zinzani PL, Santoro A, Gritti G, et al. Nivolumab Combined With Brentuximab Vedotin for Relapsed/Refractory Primary Mediastinal Large B-Cell Lymphoma: Efficacy and Safety From the Phase II CheckMate 436 Study. J Clin Oncol, 2019; 37: 3081-3089.
6. Crombie JL, Nastoupil L, Redd R, et al. Real-world outcomes of axicabtagene ciloleucel in adult patients with primary mediastinal B-cell lymphoma. Blood Adv, 2021; 5: 3563-3567.

CELLFREE-DNA AS A BIOMARKER IN LYMPHOMAS

D. Rossi[1,2,3]

[1]Experimental Hematology, Institute of Oncology Research, Bellinzona, Switzerland; [2]Division of Hematology, Oncology Institute of Southern Switzerland, Bellinzona, Switzerland; [3]Faculty of Biomedical Sciences, Università della Svizzera Italiana (USI), Lugano, Switzerland

In healthy individuals, cell-free DNA (cfDNA) is defined as freely circulating DNA in plasma released by apostolic cells, while in cancer patients circulating tumor DNA (ctDNA) represents the percentage of tumor-derived cfDNA. Liquid biopsy represents a noninvasive method for the genetic profiling of tumors. The amount of cfDNA in plasma corresponds to several thousand genomic equivalents per ml of plasma and is highly fragmented, while its size ranges from ~40-200 base pairs (bp), with a peak of 166 bp. Upon release, cfDNA is fragmented and nucleosomes, transcription factors and other DNA-binding proteins prevent random cleavage, resulting in specific fragmentation patterns; cfDNA fragmentome can represent both genomic and chromatin features.[1-4] Two different approaches are used to study ctDNA: PCR-based and NGS-based methods, the latter preferred to detect ctDNA in lymphomas. The study of ctDNA may have several clinical applications including diagnosis, prognosis, and monitoring of minimal residual disease. The mutation profile revealed by ctDNA cannot replace the gold standard of histologic diagnosis, however it may be a potential diagnostic tool for particular clinical conditions in lymphoma, such as deep and difficult to surgically reach tumor masses like in the case of Primary CNS lymphoma (PCNSL). In one study, PCR assays targeting MYD88 L265P mutation, which is specific for PSNCL, showed a sensitivity of 60% in plasma samples[5] that could be potentially used also in cerebrospinal fluid samples. With regards to its use as a predictor of prognosis, high ctDNA load at baseline in cancer patients is associated with poor prognosis; in addition several studies have shown that pre-treatment ctDNA levels correlate with Ann Arbor stage, dehydrogenated lactate (LDH) levels, International Prognostic Index (IPI), and total metabolic tumor volume (TMTV). [6-8] Finally, ctDNA allows monitoring of minimal residual disease during treatment and studies have shown that a 2-log-times and 2.5-log reduction in ctDNA levels in patients with HL and DLBCL, respectively, after two cycles of chemotherapy correlates with outcome.[7, 9] In conclusion, ctDNA is a promising and emerging biomarker in lymphoma; it provides genotypic information noninvasively and can measure treatment efficacy by detecting the presence of minimal residual disease. Prospective studies are needed to standardize its use and establish the feasibility of its introduction into clinical practice.

References

1. Roschewski M, Rossi D, Kurtz DM et al. Circulating Tumor DNA in Lymphoma: Principles and Future Directions. Blood Cancer Discov 2022; 3 (1): 5-15.
2. Pirosa MC, Borchmann S, Jardin F et al. Controversies in the Interpretation of Liquid Biopsy Data in Lymphoma. Hemasphere 2022; 6 (6): e727.
3. Mathios D, Johansen JS, Cristiano S et al. Detection and characterization of lung cancer using cell-free DNA fragmentomes. Nat Commun 2021; 12 (1): 5060.
4. Cristiano S, Leal A, Phallen J et al. Genome-wide cell-free DNA fragmentation in patients with cancer. Nature 2019; 570 (7761): 385-389.
5. Hattori K, Sakata-Yanagimoto M, Suehara Y et al. Clinical significance of disease-specific MYD88 mutations in circulating DNA in primary central nervous system lymphoma. Cancer Sci 2018; 109 (1): 225-230.
6. Roschewski M, Dunleavy K, Pittaluga S et al. Circulating tumour DNA and CT monitoring in patients with untreated diffuse large B-cell lymphoma: a correlative biomarker study. Lancet Oncol 2015; 16 (5): 541-549.
7. Kurtz DM, Scherer F, Jin MC et al. Circulating Tumor DNA Measurements As Early Outcome Predictors in Diffuse Large B-Cell Lymphoma. J Clin Oncol 2018; 36 (28): 2845-2853.
8. Bohers E, Viailly PJ, Becker S et al. Non-invasive monitoring of diffuse large B-cell lymphoma by cell-free DNA high-throughput targeted sequencing: analysis of a prospective cohort. Blood Cancer J 2018; 8 (8): 74.
9. Spina V, Bruscaggin A, Cuccaro A et al. Circulating tumor DNA reveals genetics, clonal evolution, and residual disease in classical Hodgkin lymphoma. Blood 2018; 131 (22): 2413-2425.

ALLEGENEIC TRANSPLANTATION IN ACTIVE LEUKEMIAS

F. Bonifazi

Dept of Advanced Cellular Therapies , IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto Seràgnoli, Bologna, Italy

A not negligible proportion of patients with acute leukemia fails to achieve a complete remission (CR) after two courses of intensive chemotherapy (IC) and 50-70% of those achieving CR will eventually relapse. Their prognosis is poor, independently of treatment approach, which remains still controversial, and allogeneic transplantation, although maintains its beneficial role, does not perfom as well as in remission. [1-5]

In 2013 GITMO promoted an academic prospective multicenter study, named GANDALF-01 (GITMO Against Non-responding anD Acute Leukemia Failures for transplant R/R leukemias), aimed to establish the overall survival of transplant from alternative donors (unrelated, haploidentical and from cord blood units) in patients with refractory/relapsed leukemias., after a myeloblative conditioning (MAC), using busulfan, thiotepa and fludarabine. GVHD prophylaxis was stratified according to donor type.[6]

The study enrolled 101 patients; 87 ultimately underwent allo-HSCT. Acute grade II-IV and chronic GVHD occurred in 23 and 10 patients. The incidences of relapse and non-relapse mortality were 49% and 33% at two years. Two-year overall survival of of the transplant population (primary endpoint) was 22%, without significant differences according to disease, donor type and disease history (relapsed *vs* refractory patients). Two-year progression-free survival was 17% respectively. The two-year incidences of relapse and non-relapse mortality were 49% and 33%. Dose intensification with a myeloablative two-alkylating regimen as sole strategy for transplanting refractory/relapsed acute leukemia does seem neither to improve the outcome nor to control disease relapse. A pre-planned relapse prevention such as prophylactic modified or unmodified dono lymphocyte infusions (DLIs), targeted drugs maintenance, immunosuppression modulation,[7] should be included in the transplant strategy and prospectively tested in this patient population.

References

1. Thol F, Schlenk RF, Heuser M, Ganser A. How I treat refractory and early relapsed acute myeloid leukemia. Blood [Internet]. 2015 Jul 16;126(3):319–27. Available from: https://doi.org/10.1182/blood-2014-10-551911
2. Othus M, Appelbaum FR, Petersdorf SH, Kopecky KJ, Slovak M, Nevill T, et al. Fate of Patients with Newly Diagnosed Acute Myeloid Leukemia Who Fail Primary Induction Therapy. Biol Blood Marrow Transplant. 2015;21(3):559–64.
3. Duval M, Klein JP, He W, Cahn JY, Cairo M, Camitta BM, et al. Hematopoietic stem-cell transplantation for acute leukemia in relapse or primary induction failure. J Clin Oncol. 2010;28(23):3730–8.
4. Paul S, Rausch CR, Nasnas PE, Kantarjian H JE. No Title. Clin Adv Hematol Oncol 2019 Mar;17(3)166-175.
5. Todisco E, Ciceri F, Boschini C, Giglio F, Bacigalupo A, Patriarca F, et al. Factors predicting outcome after allogeneic transplant in refractory acute myeloid leukemia: A retrospective analysis of Gruppo Italiano Trapianto di Midollo Osseo (GITMO). Bone Marrow Transplant. 2017;52(7).
6. Bonifazi F, Pavoni C, Peccatori J, Giglio F, Arpinati M, Busca A, et al. Myeloablative conditioning with thiotepa-busulfan-fludarabine does not improve the outcome of patients transplanted with active leukemia: final results of the GITMO prospective trial GANDALF-01. Bone Marrow Transplant. 2022 Jun;57(6):949-958.
7. Loke J, Malladi R, Moss P, Craddock C. The role of allogeneic stem cell transplantation in the management of acute myeloid leukaemia: a triumph of hope and experience. Br J Haematol. 2020;188(1):129–46.

CAR-T CELLS FOR REFRACTORY/RELAPSED LARGE B-CELL AND MANTLE CELL LYMPHOMAS

M. Marchetti,[1] A. Chiappella,[2] M. Guarino,[3] G. Gobbi,[4] M. Martino,[5] A.J.M. Ferreri,[6] L. Fumagalli,[7] R. Saccardi,[8] M. Montanari,[9] M. Martelli,[10] P.L. Zinzani,[11] on behalf of the SIE (Italian Society of Hematology), GITMO, and SIDEM Guideline Working Group

[1]UOC Ematologia, Azienda Ospedaliera S.S. Antonio e Biagio e Cesare Arrigo, Alessandria; [2]Hematology, FondazioneIRCCS Istituto Nazionale dei Tumori, Milano; [3]euro AOU,IRCCS Policlinico S'Orsola, Bologna; [4]Istituto Nazionale dei Tumori di Milano; [5]Stem Cell Transplantation and Cellular TherapiesUnit, Grande Ospedale Metropolitano "Bianchi-Melacrino-Morelli", ReggioCalabria; [6]Onco-Hematology Department, Fondazione Centro SanRaffaele, Milano; [7]Intensive Care Unit, Fondazione IRCCS IstitutoNazionale dei Tumori, Milano: [8]Azienda Ospedaliero UniversitariaCareggi, Firenze, Italy; Ancona; [9]SOD Medicina Trasfusionale, Azienda Ospedaliera Universitaria Ospedali Riunioti di Ancona; [10]Hematology, Department of Translational and Precision Medicine, Sapienza University, Roma; [11]University of Bologna, Istituto Di Ematologia, Bologna, Italy

Chimeric-antigen-receptor-T-cells (CAR-T) are autologous re-engineered lymphocytes capable of inducing durable response rates in a relevant proportion of refractory/relapsed (R/R) aggressive B-cell lymphomas, including diffuse large B-cell lymphoma (DLBCL), primary mediastinal lymphoma (PML), transformed follicular cell lymphoma (tFCL) and mantle –cell lymphoma (MCL). Currently available therapies for such patients do not achieve median progression-free survival (PFS) longer than 12 months, therefore, the potential clinical gain of CAR-T in these patients is huge. Nevertheless, managing CAR-T side effects (AE) is a high-intensity multi-disciplinary clinical activity and therapeutic pathways are still evolving. Finally, the impact of commercial CAR-T on the healthcare budget of hospitals is relevant and sustainability has been questioned. For the above reasons in December 2021 the Italian Society of Hematology proposed a national guideline development project devoted to the management of CAR-T therapies in aggressive B-cell lymphomas: the project was accepted by the National Guideline System (SNLG)[1] and was started in February 2022.

Table 1. List of PICO questions.

code	Population§	Intervention	Comparator	Outcomes
1.1.A	DLBCL R/R, PMCL R/R tFCL	CAR-T	No CAR-T	PFS, OS, QOL Grade 3-4 AE
1.1.B	MCL R/R	CAR-T	No CAR-T	PFS, OS, QOL Grade 3-4 AE
2.1.A	CRS grade 2-4*	Tocilizumab	No tocilizumab	ICANS, NRM LOS-ICU Severe infections
2.1.B	CRS refractory to tocilizumab*	Dexamethasone	No Dexamethasone	ICANS, NRM LOS-ICU Severe infections
2.1.C	CRS & ICANS*	Siltuximab	Tocilizumab	NRM, LOS-ICU Severe infections
2.1.D	CRS refractory to tocilizumab and steroids*	Anakinra	No Anakinra	NRM, ICANS LOS, LOS-ICU
2.2.A	ICANS*	Dexamethasone	No Dexamethasone	Grade 5 ICANS Severe infections LOS Neurological disability
2.2.B	Severe ICANS*	Siltuximab plus Dexamethasone	Dexamethasone	Grade 5 ICANS Severe infections LOS, LOS-ICU Neurological disability
2.2.C	ICANS*	Anakinra	No Anakinra	Grade 5 ICANS Severe infections LOS, LOS-ICU Neurological disability
2.3.A	MAS*	Anakinra	No Anakinra	NRM LOS, LOS-ICU Severe infections
2.4.A	Severe hypogammaglobulinemia*	Intravenous immunoglobulins prophylaxis	No intravenous immunoglobulin prophylaxis	Severe infections LOS

Legend: * after CAR-T for aggressive B-cell lymphomas § adults
LOS = length of hospital stay, LOS-ICU = length of stay in the ICU, NRM = non-relapse mortality, CRS = cytokine release syndrome, MAS = macrophage activating syndrome, ICANS = immune effector cell associated neurotoxicity, PFS = progression-free survival, OS = overall survival, AE = adverse event, QOL =quality of life

The project involved also other scientific societies, namely GITMO and SIDEM, and involved Neurology and Intensive Care specialists, hemonc nurses, apheresis specialists, and senior haematologists involved in the clinical research and practice of CAR-T and lymphomas.

The guidelines development project adhered to GRADE methodological standards, therefore, an Expert Panel agreed on a list of Patient-Intervention-Outcome (PICO) questions (Table 1) and Narrative Questions (Table 2). Subsequently, a systematic search of EMBASE database for published studies was completed in April 2022 and the bibliographic database currently includes 772 records.[2]

The database partitioned the studies into classes according to the disease, study design, and the major topic/outcome. Meta-analyses were specifically selected for supporting PICOs 1.1A and 1.1.B, while additional specific clinical queries were devoted to the use of specific drugs (Anakinra, Siltuximab) for the management of CAR-T side effects. Grey literature was searched for assessing the economic impact of CAR-Ts. EBMT definitions[3] and classifications of AE severity were adopted and harmonization with international guidelines was pursued, while adaptation to country-specific items was also granted.

Recommendations are being developed and will be presented at SIE 2022 Meeting in Rome.

Table 2. List of Narrative Questions.

Code	Question
	Should we EXCLUDE § from CAR-T those adult patients with R/R aggressive B-cell lymphomas and.....
1.1	*... non-active CNS involvement?*
1.2	*... a history of venous thromboembolism?*
1.3	*... a proven MDS?*
1.4	*... disease-correlated ECOG>2?*
1.5	*... age > 70 years?*
1.6	*... tFCL and one prior chemoimmunotherapy line after transformation?*
1.7	*For which patients a bridge therapy (after lymphocyto-apheresis and before lymphodepletion therapy) is recommended?*
1.8	*Is a local (radiotherapy) bridge therapy to be preferred to a systemic one?*
2.1	*Is seizure prophylaxis recommended in candidates to CAR-T? (which drug? Starting when?)*
2.2	*How should we manage patients with post-CAR-T ICANS and intracranial hypertension?*
2.3	*How should we manage patients with ICANS and a state of epilepticus?*
2.4	*When should we perfom a EEG before and after CAR-T infusion?*
2.5	*Which preventive actions for post-CAR-T infections are recommended?*
3.1	*Which is the optimal management of the lymphodepletion process?*
3.2	*Which patients should access ICU after CAR-T infusion?*

Legend: * adults with R/R aggressive B-cell lymphomas § for excessive forecasted toxicity or lack of strong scientific evidence

References

1. www.rayyan.ai
2. snlg.iss.it
3. https://doi.org/10.1016/j.annonc.2021.12.003

POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDERS (PTLD)

P. Comoli,[1,2] S. Basso[1,2] F. Compagno,[2] M. Zecca[2]

[1]Cell Factory, Fondazione IRCCS Policlinico San Matteo, Pavia; [2]Pediatric Hematology/Oncology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

Post-transplant lymphoproliferative disorders (PTLD) are life-threatening complications mainly associated to Epstein-Barr virus (EBV) infection after hematopoietic stem cell transplantation (HSCT).[1-4] PTLD occurs in 1-3.5% of HSCT recipients, although incidence rates may exceed 10% in patients with established risk factors. Although rare, mortality is still relevant, at 30% and 40% of diagnosed cases. The onset of EBV-PTLD is preceded by a pre-clinical phase denoted by increased EBV DNA levels in the peripheral blood.[5,6] Thus, according to international guidelines, prospective monitoring of EBV DNA should be started and continued at least until the fourth posttransplant month. EBV DNA analysis is not a precise predictor of PTLD development, and tailoring screening on the basis of a whole cohort is not always practical. As the other central factor determining progression to PTLD is the lack of a protective immune response, it seems reasonable to associate DNAemia screening with analysis of immune reconstitution.[5]

In the setting of HSCT, there are two strategies to prevent EBV DNAemia. The first is based on interventions on the graft or the patient prior to HSCT, in order to decrease the risk of EBV-infected B cell outgrowth. Post-transplant prophylactic interventions, although attempted, have met with varying results, and are not largely adopted. Preemptive therapy based on EBV DNAemia monitoring is the option of choice to prevent PTLD onset after HSCT. The mainstay of preemptive therapy is anti-CD20 antibody rituximab,[5] that has shown a high rate of success. Among the strategies that boost specific immune reconstitution and immune surveillance, donor-derived or third-party EBV-specific T cells have also shown long-lasting EBV viral load clearance in high percentages of patients.[5,7]

Regarding treatment for overt EBV-PTLD, rituximab and EBV-specific T cell therapy (CTL) are recommended as first-line therapy, while unselected donor lymphocyte infusions (DLI) or chemotherapy are second-line therapy options.[1-4,8] EBV-negative B- and T- cell PTLD cases developing late after HSCT should be regarded as malignant lymphomas, and should, therefore, be treated using protocols for *de novo* lymphoma occurring in the immunocompetent host. Novel therapeutic options are being tested in clinical trials[9] and may contribute to ameliorate outcome in PTLD entities with poor prognosis.

References

1. Styczynski J, van der Velden W, Fox CP, Engelhard D, de la Camara R, Cordonnier C, et al. Management of Epstein-Barr virus infections and post-transplant lymphoproliferative disorders in patients after allogeneic hematopoietic stem cell transplantation: Sixth European Conference on Infections in Leukemia (ECIL-6) guidelines. Haematologica 2016; 101:803-811.
2. Dierickx D, Habermann TM. Post-transplantation lymphoproliferative disorders in adults. N Engl J Med 2018; 378: 549–62.
3. Dharnidharka VR, Webster AC, Martinez OM, Preiksaitis JK, Leblond V, Choquet S. Post-transplant lymphoproliferative disorders. Nat Rev Dis Primers 2016;2:15088.
4. Al Hamed R, Bazarbachi AH, Mohty M. Epstein-Barr virus-related post-transplant lymphoproliferative disease (EBV-associated PTLD) in the setting of allogeneic stem cell transplantation: a comprehensive review from pathogenesis to forthcoming treatment modalities. Bone Marrow Transplant. 2020; 55:25-39.
5. Comoli P, Basso S, Zecca M, Pagliara D, Baldanti F, Bernardo ME, et al. Preemptive therapy of EBV-related lymphoproliferative disease after pediatric haploidentical stem cell transplantation. Am J Transplant. 2007; 7:1648-1655.
6. Baldanti F, Gatti M, Furione M, Paolucci S, Tinelli C, Comoli P, et al. Kinetics of Epstein–Barr virus DNA load in different blood compartments of pediatric recipients of T-cell depleted HLA haploidentical stem cell transplantation. J Clin Microbiol 2008; 46:3672–3677.
7. Bollard CM, Rooney CM, Heslop HE. T-cell therapy in the treatment of post-transplant lymphoproliferative disease. Nat Rev Clin Oncol. 2012; 9:510–519.
8. Trappe RU, Dierickx D, Zimmermann H, et al. Response to Rituximab Induction Is a Predictive Marker in B-Cell Post-Transplant Lymphoproliferative Disorder and Allows Successful Stratification Into Rituximab or R-CHOP Consolidation in an International, Prospective, Multicenter Phase II Trial. J Clin Oncol. 2017;35:536-543.
9. Cheah CY, Fowler NH. Novel agents for relapsed and refractory follicular lymphoma. Best Pract Res Clin Haematol. 2018;31:41-48.

DIAGNOSIS OF INHERITED ANEMIAS IN ADULT PATIENTS

L. De Franceschi

Dipartimento di Medicina, Universita' di Verona & AOUI Verona; Policlinico GB Rossi, Verona, Italy

Anemia is one of the main causes of medical consultation for both in-patients and out-patients care. Although anemia of chronic diseases (ACD) takes the lion's share with 40% of total diagnosis of anemia in adult patients,[1-3] inherited anemias identified in adulthood still represents a challenge for both hematologists and internal medicine physicians. In adults, congenital anemias are generally identified either in emergency

department/intensive care unit such as previously unknown Coombs negative acute hemolytic anemia or in chronic setting such as previously unknown non-hemolytic or hemolytic Coombs negative chronic anemias.

In adult acre, consultation around unexplained anemias should consider that the large part of these patients is generally frustrated by either misdiagnosis or mistreatment.

Thus, an accurate collection of patient history as well as the analysis of the pedigree are crucial parts of the consultation around unexplained anemia. In addition, the rarity of some congenital anemias might further increase the complexity of the making decision process from diagnosis to the therapeutic options.

In chronic setting, clinicians should therefore rest on at least four fixed points: (i) CBC focusing on MCV, MCH, MCHC, RDW plus circulating erythroblasts and reticulocytes; (ii) hemolytic indices; (iii) splenomegaly (y/n), gallbladder stones (y/n); and (iv) the analysis of peripheral blood smears.[4-10] Complementary tests are the iron indices (ferritin & TSAT), the folate and vitamin B plasma levels.

Using real life case collection, we will discuss the more common misinterpretation/misdiagnosis to avoid trail/mistake strategy in making decision process approaching previously unknown acute/ chronic Coombs negative inherited hemolytic anemias.

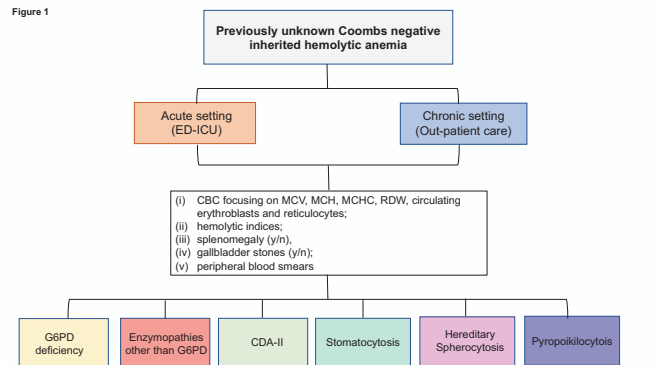


Figure 1. Flow-chart approach to previously unknown acute/ chronic Coombs negative inherited hemolytic anemias in adult patients in both acute and chronic settings. CBC: complete blood count, MCV: mean cell volume, MCH: mean cell hemoglobin, MCHC: mean corpuscular hemoglobin concentration; RDW: red cell distribution width; y/n: yes/no; G6PD: glucose – phosphate dehydrogenase; CDA-II: congenital diserythropoietic anemia type II.

References

1. Kassebaum NJ, Jasrasaria R, Naghavi M, et al. A systematic analysis of global anemia burden from 1990 to 2010. Blood. 2014;123(5):615-624.
2. Weiss G, Ganz T, Goodnough LT. Anemia of inflammation. Blood. 2019;133(1):40-50.
3. De Franceschi L, Iolascon A, Taher A, Cappellini MD. Clinical management of iron deficiency anemia in adults: Systemic review on advances in diagnosis and treatment. Eur J Intern Med. 2017;42:16-23.
4. Andolfo I, Martone S, Rosato BE, et al. Complex Modes of Inheritance in Hereditary Red Blood Cell Disorders: A Case Series Study of 155 Patients. Genes (Basel). 2021;12(7).
5. Iolascon A, Andolfo I, Russo R. Congenital dyserythropoietic anemias. Blood. 2020;136(11):1274-1283.
6. Iolascon A, Andolfo I, Russo R. Advances in understanding the pathogenesis of red cell membrane disorders. Br J Haematol. 2019;187(1):13-24.
7. Gambale A, Iolascon A, Andolfo I, Russo R. Diagnosis and management of congenital dyserythropoietic anemias. Expert Rev Hematol. 2016;9(3):283-296.
8. Andolfo I, Russo R, Gambale A, Iolascon A. New insights on hereditary erythrocyte membrane defects. Haematologica. 2016;101(11):1284-1294.
9. De Franceschi L, Costa E, Dima F, Morandi M, Olivieri O. Glucose-6-phosphate dehydrogenase deficiency associated hemolysis in COVID-19 patients treated with hydroxychloroquine/chloroquine: New case reports coming out. Eur J Intern Med. 2020;80:103.
10. Veneri D, Facchinelli D, Vianello A, et al. Blood smear, a key diagnostic tool in hematology: Lessons from two cases of acute hemolysis in previously undiagnosed G6PD deficiency. Am J Hematol. 2016;91(11):1165-1166.

INDICATIONS FOR ALLOGENIC TRANSPLANTATION IN MYELOPHIBROSIS

B. Mora,[1,2] F. Passamonti[1,2]

[1]Hematology, Ospedale di Circolo, A.S.S.T. Sette Laghi, Varese, Italy; [2]Department of Medicine and Surgery, University of Insubria, Varese, Italy

Survival is considerably short in MF.[1,2] The most recent ELN guidelines recommend that allo-SCT should be performed in young and fit patients whom the estimated OS is less than five years (3) according to prognostic scores as IPSS, DIPSS, DIPSS-plus, MYSEC-PM, this latter for post PV and post ET MF. This curative procedure should be also considered to suitable intermediate-1 risk patients carrying *ASXL1* mutation.[3] In the same risk category, doctors can consider as potential candidate patients either with refractory RBC-transfusion dependent anemia, circulating blasts >2%, or adverse cytogenetics.[4] The NCCN guidelines recommend allo-SCT in PMF for intermediate-2/high risk DIPSS(-plus) and in case of score at least 4 by MIPSS70(-plus v2.0), while in SMF for intermediate-2/high risk MYSEC-PM cases.[5] The second step is to integrate these models with other finalized to assess post SCT outcome. Gagelmann *et al*. recently described a clinical-molecular model (MTSS, *Myelofibrosis Transplant Scoring System*) with the aim of predicting subsequent outcome at the time of referral to allo-SCT.[6] This model could be applied to both PMF and SMF cases and considers the presence of *ASXL1* mutation and the absence of *CALR*/*MP*, age ≥57 years, Karnofsky performance status lower than 90%, PLT and leukocyte count prior to transplantation (<150×10^9/L and >25×10^9/L, respectively) and an HLA-mismatched unrelated donor[6] Patients were therefore grouped in four categories, with a median 5-year OS estimated to be between 90% and 34%. Mortality from allo-SCT complications varied, inversely, from 10% to 57% in the same time interval [86]. Special considerations need conditioning, selection of donors and splenectomy.

References

1. Passamonti F, Cervantes F, Vannucchi AM, Morra E, Rumi E, Pereira A, et al. A dynamic prognostic model to predict survival in primary myelofibrosis: a study by the IWG-MRT (International Working Group for Myeloproliferative Neoplasms Research and Treatment). Blood. 2010;115(9):1703-8.
2. Passamonti F, Giorgino T, Mora B, Guglielmelli P, Rumi E, Maffioli M, et al. A clinical-molecular prognostic model to predict survival in patients with post polycythemia vera and post essential thrombocythemia myelofibrosis. Leukemia. 2017;31(12):2726-31.
3. Barbui T, Tefferi A, Vannucchi AM, Passamonti F, Silver RT, Hoffman R, et al. Philadelphia chromosome-negative classical myeloproliferative neoplasms: revised management recommendations from European LeukemiaNet. Leukemia. 2018;32(5):1057-69.
4. Kröger NM, Deeg JH, Olavarria E, Niederwieser D, Bacigalupo A, Barbui T, et al. Indication and management of allogeneic stem cell transplantation in primary myelofibrosis: a consensus process by an EBMT/ELN international working group. Leukemia. 2015;29(11):2126-33.
5. Network NCC. Myeloproliferative neoplasms. 2021 [Available from https://www.nccn.org/professionals/physician_gls/pdf/mpn.pdf]
6. Gagelmann N, Ditschkowski M, Bogdanov R, Bredin S, Robin M, Cassinat B, et al. Comprehensive clinical-molecular transplant scoring system for myelofibrosis undergoing stem cell transplantation. Blood. 2019;133(20):2233-42.

PROGNOSIS AND TREATMENT STRATEGIES IN MYELOFIBROSIS

A.M. Vannucchi

CRIMM, Centro Ricerca e Innovazione delle malattie Mieloproliferative, Struttura Complessa di Ematologia, ,AOU Careggi e Università degli studi di Firenze, Firenze, Italy

Constitutive activation of the JAK-STAT signaling in MPN, including primary Myelofibrosis (PMF), is sustained by somatic mutations in *JAK2*V617F (50-60%), *CALR* and *MPL*W515x in 20-30% and 5-10%, respectively. *CALR* type-1/1 like mutations are more prevalent than type-2/2 like (70% *vs* 13%) and are associated with favorable survival; con-

versely, a low *JAK2*V617F allele burden is prognostically negative. About 10% lack a known driver mutation, ie are Triple Negative, that is also prognostically negative. Additional mutations affecting genes of DNA methylation, histone modification, mRNA splicing, signaling pathways, and transcription factors, that have prognostic significance independent of clinical IPSS and DIPSS/-plus scores, are found in >50% of cases. Presence of at least 1 mutation in *ASXL1, EZH2, SRSF2, IDH1, IDH2* and *U2AF1* defines a high molecular risk status (HMR),[1] with additional information from the number of mutations (1 *vs* ≥2).[2] Above findings led to the development of integrated scores for patients with PMF, including MIPSS (Mutation-Enhanced International Prognostic Scoring System, plus and v2.0)[3,4] and GIPSS (Genetically Inspired Prognostic Scoring System);[5] secondary MF (MYSEC-PM, Myelofibrosis Secondary to PV and ET-Prognostic Model)[6]; when HSCT is planned (MTSS, Myelofibrosis Transplant Scoring System)[7] (Table 1).

Advances in molecular characterization of MF raised the possibility of developing targeted therapies, and successfully promoted the development of JAK inhibitors (ruxolitinib as the first in class, followed by fedratinib and pacritinib, with momelotinib in advanced development stage). However, available JAKi target the ATP-binding pocket of the JAKs and are not selective for mutant JAK2 protein, explaining the efficacy in *JAK2* wildtype patients. Clonal evolution after ruxolitinib dis-

Table 1. Integrated clinical-molecular prognostic scores in myelofibrosis.

Prognostic Score	Variables (points)	Risk categories (points)	Median survival (years)
MIPSS70	Hemoglobin < 10 g/dL (1) Blasts > 2% (1) Constitutional symptoms (1) Leukocytes > 25 x 10^9/L (2) Platelet count < 100 x 10^9/L (2) BM fibrosis ≥ 2 (1) Non *CALR* type-1 (1) HMR[a] = 1 (1) HMR[a] ≥ 2 (2)	Low (0-1) Intermediate (2-4) High (5-12)	27.7 7.1 2.3
MIPSS70 plus	Hemoglobin < 10 g/dL (1) Blasts > 2% (1) Constitutional symptoms (1) Non *CALR* type-1 (2) HMR[a] = 1 (1) HMR[a] ≥ 2 (2) Unfavourable karyotype[b] (3)	Low (0-2) Intermediate (3) High (4-6) Very high (7-11)	20.0 6.3 3.9 1.7
MIPSS70 plus v2.0	Hemoglobin 8-10 g/dL (1) Hemoglobin <8 g/dL (2) Blasts > 2% (1) Constitutional symptoms (2) Non *CALR* type-1 (2) HMR[a]+*U2AF1* Q157 = 1 (2) HMR[a]+*U2AF1* Q157 ≥ 2 (3) HR Karyotype[c] (3) VHR Karyotype[d] (4)	Very low (0) Low (1-2) Intermediate (3-4) High (5-8) Very high (9-14)	Not reached 10.3 7 3.5 1.8
GIPSS	Non *CALR* type-1 (1) ASXL1 mutation (1) SRSF2 mutation (1) U2AF1 Q157 (1) HR karyotype[c] (1) VHR karyotype[d] (2)	Low (0) Intermediate-1 (1) Intermediate-2 (2) High (3-6)	26.4 8.0 4.2 2.0
MYSEC-PM Passamonti et al.[95]	Hemoglobin < 11 g/dL Blasts ≥ 3% Platelets < 150 x 10^9/L Constitutional symptoms (2) Age at secondary MF (0.15 point/year) *CALR* unmutated genotype (2)	Low (<11) Intermediate-1 (11- <14) Intermediate-2 (14- <16) High (≥ 16)	Not reached 9.3 4.4 2.0
MTSS	Platelets < 150 x 10^9/L (1) Leukocytes > 25 x 10^9/L (1) Karnofsky PS < 90% (1) Age ≥ 57 years (1) HLA-mismatched unrelated donor (2) Non CALR/MPL mutation (2) ASXL1 mutation (1)	Low (0-2) Intermediate (3-4) High (5) Very high (6-9)	5-years OS 83% 5-years OS 64% 5-years OS 37% 5-years OS 22%

Notes:
[a]High molecular risk (HMR) include *ASXL1*, *SRSF2*, *EZH2*, *IDH1/2*.
[b]Unfavourable karyotype defined any abnormal karyotype other than normal karyotype or sole abnormalities of 20q2, 13q2, +9, chromosome 1 translocation/duplication, -Y, or sex chr abnormality other than -Y.
[c] High risk (HR) karyotype include all the abnormalities that are not VHR and favourable (normal karyotype or sole abnormalities of 20q−, 13q−, +9, chromosome 1 translocation/duplication or sex chr abnormality including -Y).
[d]Very high risk (VHR) include single or multiple abnormalities of −7, inv (3), i(17q), 12p−, 11q−, and autosomal trisomies other than +8 or +9.

continuation due to resistance is associated with acquisition of ≥1 mutation in 35% of cases, mostly in *ASXL1*, followed by *TET2*, *EZH2* and *TP53*.[8] Presence of mutations in *ASXL1* and *CBL* and a HMR profile at baseline correlated with shorter time to treatment failure,[9] and mutations in the RAS pathway genes (*NRAS*, *KRAS*, *CBL*) were independent predictors of reduced response to JAKi.[10] Overall, current data indicate that molecular characterization represents a useful tool for prognostication and possibly to contextualize the role of ruxolitinib and other JAKi in the therapeutic algorithm, but therapy is still largely mutation-agnostic, an unmet need to be addressed.

References

1. Vannucchi AM, Lasho TL, Guglielmelli P, et al. Mutations and prognosis in primary myelofibrosis. Leukemia. 2013;27(9):1861-1869.
2. Guglielmelli P, Lasho TL, Rotunno G, et al. The number of prognostically detrimental mutations and prognosis in primary myelofibrosis: an international study of 797 patients. Leukemia. 2014;28(9):1804-1810.
3. Guglielmelli P, Lasho TL, Rotunno G, et al. MIPSS70: Mutation-Enhanced International Prognostic Score System for Transplantation-Age Patients With Primary Myelofibrosis. J Clin Oncol. 2018;36(4):301-318.
4. Tefferi A, Guglielmelli P, Lasho TL, et al. MIPSS70+ Version 2.0: Mutation and Karyotype-Enhanced International Prognostic Scoring System for Primary Myelofibrosis. J Clin Oncol. 2018;36:1769-1770.
5. Tefferi A, Guglielmelli P, Nicolosi M, et al. GIPSS: genetically inspired prognostic scoring system for primary myelofibrosis. Leukemia. 2018;32:1631-1642.
6. Passamonti F, Giorgino T, Mora B, et al. A clinical-molecular prognostic model to predict survival in patients with post polycythemia vera and post essential thrombocythemia myelofibrosis. Leukemia. 2017;31:2725-2731.
7. Gagelmann N, Ditschkowski M, Bogdanov R, et al. Comprehensive clinical-molecular transplant scoring system for myelofibrosis undergoing stem cell transplantation. Blood. 2019;133(20):2233-2242.
8. Newberry KJ, Patel K, Masarova L, et al. Clonal evolution and outcomes in myelofibrosis after ruxolitinib discontinuation. Blood. 2017;130(9):1125-1131.
9. Pacilli A, Rotunno G, Mannarelli C, et al. Mutation landscape in patients with myelofibrosis receiving ruxolitinib or hydroxyurea. Blood Cancer J. 2018;8(12):122.
10. Coltro G, Rotunno G, Mannelli L, et al. RAS/CBL mutations predict resistance to JAK inhibitors in myelofibrosis and are associated with poor prognostic features. Blood Advances. 2020;4(15):3677-3687.

CELLULAR TREATMENT APPROACHES TO THE THALASSEMIA SYNDROMES (TS)

A. Maggio

Campus di Ematologia Franco e Piera Cutino, AOR Villa Sofia-V. Cervello, Palermo, Italy

The TS are congenital disorders, affecting the hematopoietic stem cells (HSCs), characterized by ineffective erythropoiesis (IE) with changes in proliferation and maturation of erythroid cell line. Normally, HSCs regenerate the entire hematopoietic system through regulated fate decisions. The changes in metabolic cofactor bioavailability associated with metabolic switch from glycolysis to mitochondrial oxidative phosphorylation determine a series of DNA-modifying, which, together with coordinated transcriptional changes, regulate the decision between self-renewal and differentiation. Selective pressure triggered by the bone marrow (BM) niche microenvironment, programmed cell death, genotoxic insults from ROS and DNA damage checkpoint-dependent apoptosis, are on the basis of the BM fitness, determining aging clonal related hematopoiesis.[1] These selective pressure factors were even reported on thalassemia BM (Table 1). Approaches, aimed at correction of IE are ongoing. Figure 1 shows drugs targeting IE.Among these, hydroxycarbamide showed, in 1-year-treated thalassemia intermedia pts, a mean Hb increase of 1.5 gr/dl ($P < 0.001$). Overall, 17 of the 24 (70%) patients had an Hb increase of 1.0 gr/dl and were considered responders. Among these, 12 had an increase of 1.5 g/l. Moreover, the three patients with Lepore/b039 genotype had an average Hb increase of 3.1 gr/l (range 2.0–4.5).[2] Ruxolitinib showed spleen volume reduction (-26.83%) in TDT patients.[3] Luspatercept, licensed by AIFA November 24, 2021, showed significantly reduction of transfusion burden by ≥ 33% in wks 13-24 vs placebo (21% *vs* 4.5%). Moreover, a Phase2 study, using luspatercept, mets primary endpoint, suggesting significantly increase of at least 1.0 gr/dl vs placebo over continuous 12 week interval during 12-24 in no-transfused NTDT pts.[4] Kevin K. et al., 2022 showed as mitapivat, an oral pyruvate kinase activator (PKR) , was able to increase Hb > 1.0gr/dl assessed between 4 to 12 weeks, in Phase 2 study of patients with NTDT.[5] Etavopivat, a PKR activator, showed in Phase 1 study proof of mechanism without significant side effects and Phase-2 study in patients with thalassemia and SCD is ongoing (*NCT04987489).*[6] Inhibitors of TMPRSS6 and of Fpn by VIT-2763 completed Phase 1 trial and Phase 2 trial is ongoing for Fpn by VIT-2763.[7] In conclusion, drugs targeting cellular factors are already at the patient's bed. However, Phase 4 and results from other ongoing trials have to be pursued.

Table 1. The causes of dysregulation of haemopoietic stem cells (HSCs) in thalassemia syndromes.

Increasing of:
➢ Phosphoproteins of apoptosis (Cytochrome C, Caspase 6)[1]
➢ Apoptotic effect by Cytokines (IL-1β, TNF, IFNγ)[2] and Unfolded Protein Response (UPR) by impairment UPR function[3]
➢ Activation of Autophagy in erythoblasts[4]
➢ ROS Activation due to α-globin excess[5] and to hemicrome formation[6]
➢ Mitophagy during erythroid differentiation
1.Saranyoo P. et al., J Transl. Med. 2011; 2.Raducka-Jaszul O et al., Int. J. Mol. Sci., 2020; 3.Pathrapol L. et al., Haematologica, 2010; 4. Pathrapol L. et al., Acta haematologica, 2011;5.De Franceschi L., Oxidative Medicine and Cellular Longevity, 2013; 6.Rivella S. et al, Haematologica, 2015; 7.Wu L., Int. J. Hematol., 2016

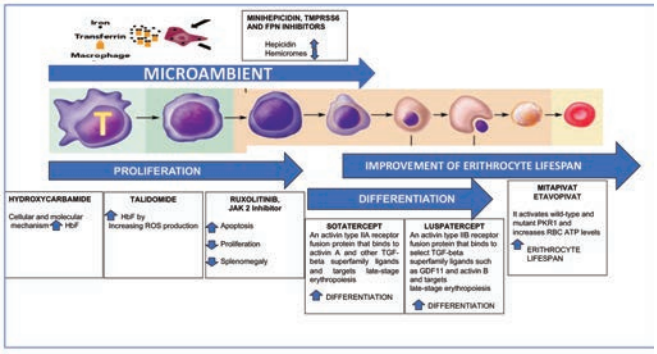


Figure 1. Agents that primarily target ineffective erythropoiesis.

References

1. Masayuki et al. : Dysregulated haematopoietic stem cell behaviour in myeloid leukaemogenesis. Nature Review Cancer, July, 20(7),365-382 .
2. Rigano P.: Desensitization to hydroxycarbamide following long-term treatment of thalassaemia intermedia as observed in vivo and in primary erythroid cultures from treated patients. British Journal of Haematology, 151, 509–515, 2010.
3. Taher A et al.: Efficacy and safety of ruxolitinib in regularly transfused patients with thalassemia: results from a phase 2a study. Blood. 2018 Jan 11;131(2):263-265. doi: 10.1182/blood-2017-06-790121.
4. Taher A. et al.: Luspatercept for the treatment of anaemia in non-transfusion-dependent β-thalassaemia (BEYOND): a phase 2, randomised, double-blind, multicentre, placebo-controlled trial. The Lancet Haematology, August 22, 2022 https://doi.org/10.1016/S2352-3026(22)00208-3.
5. Kevin K. et al.: Safety and efficacy of mitapivat, an oral pyruvate kinase activator, in adults with non-transfusion dependent α-thalassaemia or β-thalas-

saemia:an open-label,multicentre, phase 2 study. The Lancet 2022; 400: 493–501.
6. Forsyth S. et al.: Safety, Pharmacokinetics, and Pharmacodynamics of Etavopivat (FT-4202), an Allosteric Activator of Pyruvate Kinase-R, in Healthy Adults: A Randomized, Placebo-Controlled, Double-Blind, First-in-Human Phase 1 Trial. Clinical Pharmacology in Drug Development 2022, 11(5) 654–665.
7. Vadolas J. Et al. : SLN124, a GalNac-siRNA targeting transmembrane serine protease 6, in combination with deferiprone therapy reduces ineffective erythropoiesis and hepatic iron-overload in a mouse model of beta-thalassaemia. British Journal of Haematology, 2021, 194, 200–210.

Author Index