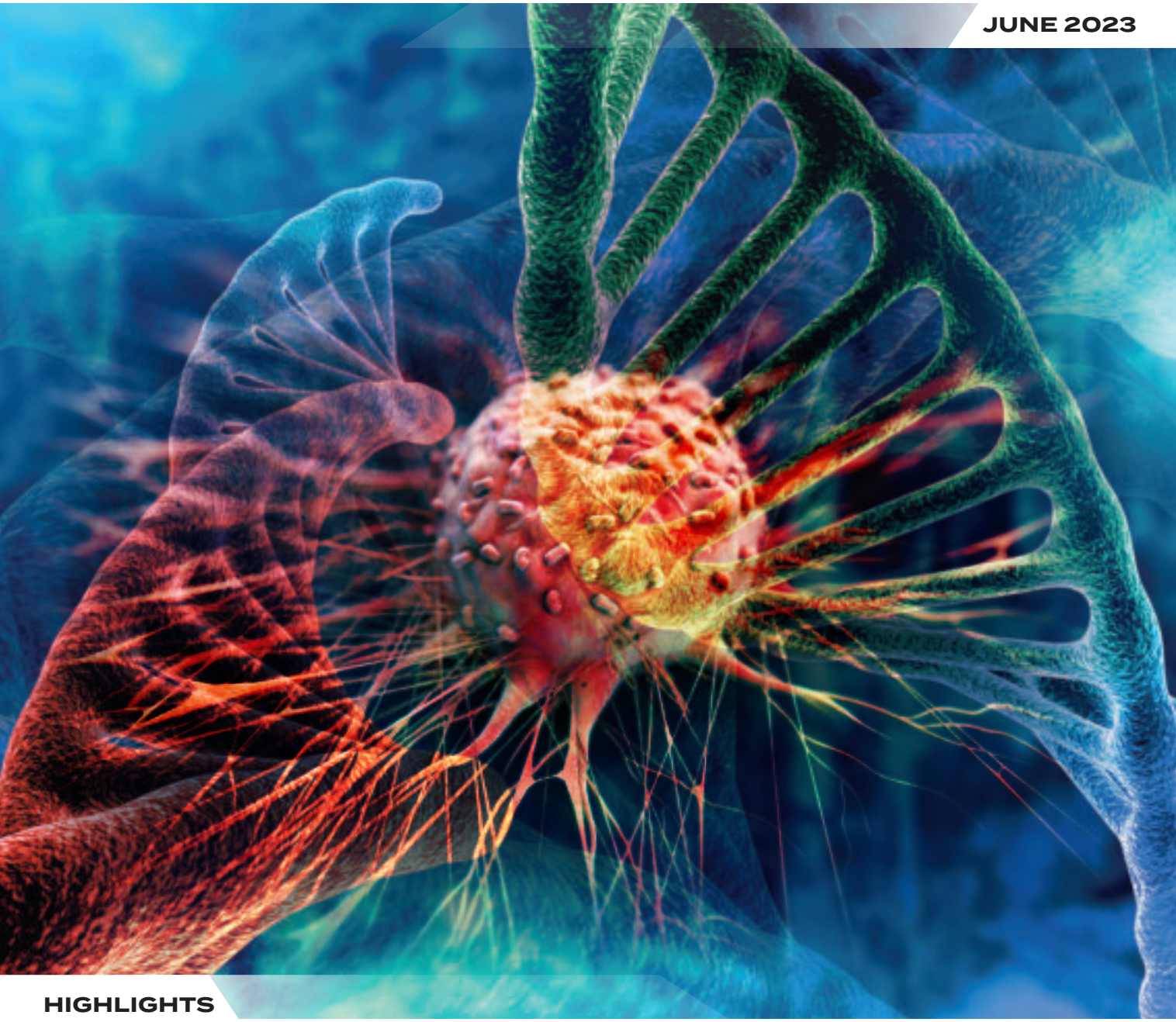
RARE DISEASES REPORT: CANCERS

JUNE 2023



HIGHLIGHTS

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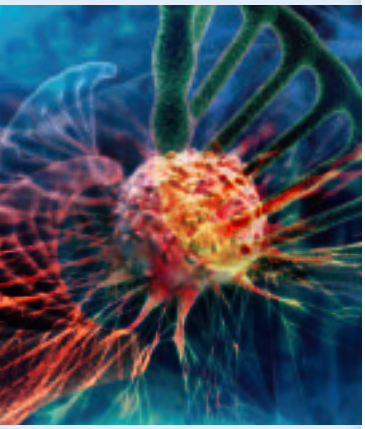

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EDITOR'S NOTE

This edition of *Rare Diseases Report: Cancers* highlights the latest breakthroughs and remaining unmet needs in the management of rare cancers. In addition to celebrating the great progress that has been made in recent years, we also discuss new challenges, such as how the healthcare system can prepare to manage the growing number of rare cancer survivors who are living longer due to improvements in disease management. We hope you enjoy.

– Kerry Hanisch
Executive Editor

Katie Kowalski, MPH

NORD: Making Progress Through Collaboration

For nearly 40 years, the National Organization for Rare Disorders (NORD) has worked to drive meaningful and enduring impact so that people living with rare diseases, including rare cancers, can live their best lives. We are proud to collaborate with MDedge to deliver timely information about rare cancers to healthcare professionals.

Rare cancers are those that affect fewer than 40,000 people per year in the United States. While the incidence of each rare cancer may be low, collectively, they make up a significant proportion (27%) of all cancers.[1] Moreover, rare cancers present unique challenges: they are difficult to identify and often diagnosed at later stages when they are harder to treat. Patients often have trouble finding specialists who are familiar with their rare cancer. Additionally, the availability of effective drugs to treat rare cancers is limited and enrollment in rare cancer clinical trials is challenging due to small, and often not diverse, study populations. Currently, the 5-year survival rate for rare cancers in adults (48.5%) is worse than for common cancers (63.4%).[2]

While people living with rare cancers continue to face daunting obstacles, progress is being made, and there are reasons to hope for a better future. Advances in genomic testing and precision medicine provide increasing evidence that rare cancers can be more efficiently and effectively diagnosed and treated. Genomic tests examine tumor DNA to identify mutations that are unique to an individual's cancer. This genetic information enables a more precise diagnosis and targeted treatment approach. Jim Palma, Co-Lead of the NORD Rare Cancer Coalition, said "There is promise for rare cancer patients due to increased legislative efforts to cover the costs of genomic testing coupled by an increase in FDA approvals for targeted and tissue agnostic therapies."

In 2019, the National Cancer Institute established MyPART, a vast pediatric and adult rare tumor network that aims to bolster patient involvement in research and develop effective therapies through tumor sample collection, shared data, shared samples, new methods to test treatments, and new trial designs. In 2022, MyPART welcomed NORD's Rare Cancer Coalition as an advocacy partner.

Meanwhile, advocacy organizations are giving rare cancer a rising voice. NORD's Rare Cancer Coalition unites rare cancer patient advocacy organizations and helps them drive progress together. The coalition promotes research and awareness through its annual Rare Cancer Day (September 30) campaign. Additionally, NORD has produced over 22 continuing medical education modules on rare cancers in collaboration with PlatformQ Health, providing updates on new therapies and treatment approaches. NORD also offers rare disease reports and educational videos on rare cancers, sessions inclusive of rare cancer topics at the annual NORD Summit, and a quarterly e-newsletter, "Caring for Rare" for healthcare professionals. Please visit us at rarediseases.org to access these resources.

Much work on rare cancers remains to be done, but the progress over recent years points to better outcomes moving forward. We are grateful for the work you do and your dedication to your patients, including those with rare cancers and other rare conditions. We hope you will find the information in this special issue useful for your clinical practice.

– Katie Kowalski, MPH
Associate Director of Education
National Organization for Rare Disorders

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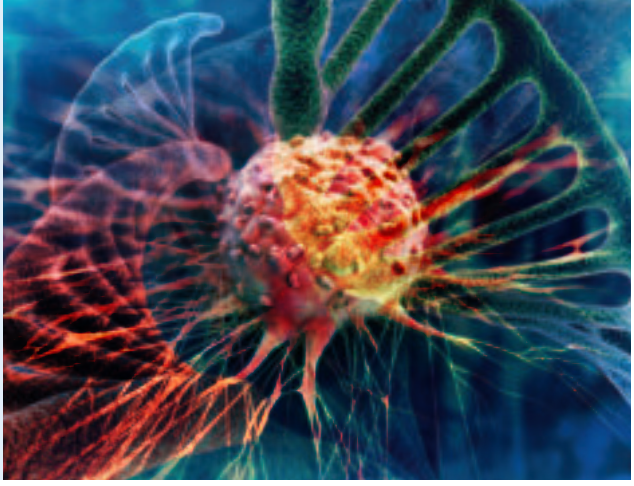
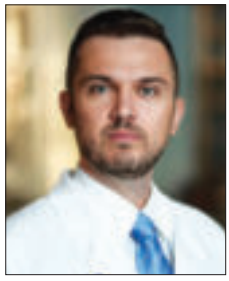


IN THIS ISSUE:

The Complex Challenge of Survival After HPV-Associated Oropharyngeal Cancer



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Case Study

A 65-year-old African American man presented to an Otolaryngology Head and Neck Surgery clinic at a tertiary Veterans Health Administration (VHA) facility for evaluation. The patient recalled a past diagnosis of oropharyngeal cancer (OPC), possibly associated with the human papillomavirus (HPV). After receiving the diagnosis at another VHA facility, the patient opted to seek care at a local, non-VHA facility and received approximately 7 weeks of daily radiation and weekly infusions of chemotherapy.

Six years after his initial diagnosis and treatment, the patient said he had a persistent cough with any meaningful attempts to eat or drink. He also noted he lost at least 10 lbs in the last 3 months and had been hospitalized twice during the past winter. During his second hospitalization he spent 4 days on a ventilator in the intensive care unit.

On examination, the patient appeared frail and cachectic, with significant fibrosis of the neck skin and moderate trismus. His dentition was in poor health, and an in-clinic flexible endoscopy demonstrated clear silent aspiration of oral secretions. Given his failure to thrive, the patient was urgently admitted to the hospital. A modified barium swallow study performed by the head and neck Speech Pathology team demonstrated gross aspiration with all consistencies. After extensive counseling, the patient agreed to the placement of a gastrostomy tube. He was discharged in stable condition with adequate supplies and self-care training. He was advised to continue follow-up in the Head and Neck Cancer Survivorship clinic.

Two years later, in the early phase of the COVID-19 pandemic, the patient was admitted to the hospital with COVID pneumonia. Given the damage to his lungs over the previous decade from recurrent episodes of aspiration pneumonia, the patient succumbed.

An Unexpected, Unrelenting Epidemic

Shifting population dynamics and behaviors have led to an explosion in the incidence of cancers associated with infection by oncogenic subtypes of HPV, among which cancer of the oropharynx represents the most common malignancy.[1,2] OPC now afflicts more than 30,000 new patients in the United States each year.[3] Given current vaccination rates against oncogenic HPV, the overall trend of increasing incidence is not expected to stabilize until the 2040s.[3] Traditional cancers of the head and neck region were previously fatal after 5 years in more than 60% of cases; however, today patients with HPV-associated OPC can expect a more than 80% chance of being alive 5 years after treatment.[4-7] Combining the increasing incidence of OPC with a high chance of oncologic cure has led to an ever-expanding cohort of OPC survivors.

Enthusiasm about a high rate of survival after an HPV-associated OPC diagnosis is now partially dampened by an increasing realization that neither oncologists nor healthcare systems are remotely prepared for this rapidly expanding cohort of OPC survivors. Their unique needs and problems have yet to be objectively defined and quantified.

Relationship Between Survival and Long-Term Toxicity in HPV-Associated OPC

Survivorship care after OPC treatment is a growing challenge in terms of the numbers of patients affected, the negative impact on quality of life (QOL), and the potential burden on the healthcare system. The rapidly growing number of OPC survivors who are living long enough to develop delayed adverse effects related to their past OPC treatment[1,2,8]

Vlad C. Sandulache, MD, PhD, has disclosed no relevant financial relationships.

includes many patients in whom toxicities can be truly debilitating,[9,10] generating significant unmet needs.

Tumor and Treatment Toxicity

Although HPV-associated OPC demonstrates excellent response to conventional chemoradiotherapy (CRT), this finding cannot be interpreted to mean that reducing treatment intensity is safe for patients with this disease. Prospective trials have now demonstrated that neither replacing or eliminating conventional chemotherapy, nor significantly reducing radiation doses, can be considered safe at this time.[11-15] As a result, a patient with newly diagnosed HPV-associated OPC in 2025, and potentially even 2030, is likely to receive the same treatment as patients who were treated in the late 2010s.[14]

Three decades ago, the chronic effects of tumor and treatment were largely limited to a small cohort of survivors; however, today they affect more patients.[1,2,7] Chronic xerostomia, dysphagia, trismus, radiation fibrosis, and osteoradionecrosis (ORN) now confront tens of thousands of OPC survivors; over the coming decades, these treatment effects have the potential to affect millions of patients.[16-22]

While most acute toxicities resolve within several months of completing CRT, late CRT sequelae tend to be dynamic and can progress silently over many years.[16,23] Adverse effects vary widely, with many toxicities (eg, dysphagia, ORN) being particularly debilitating. Many of these effects occur in a radiation dose–dependent fashion, but radiation dose does not fully predict late toxicities, pointing to a role for other, yet unidentified contributing factors.[24,25]

Dysphagia in Survivors of OPC

About two-thirds of survivors of head and neck cancer (HNC) who seek follow-up care 5 years after treatment report dysphagia and at least partial dependence on a feeding tube.[26] The incidence of dysphagia increases proportionately with higher radiation doses delivered to the pharyngeal constrictors and supraglottic larynx.[18] Dysphagia can severely reduce QOL years after treatment, necessitating substantial changes in diet and social behavior among OPC survivors. Often, patients are forced to choose between chronic malnutrition or starvation and feeding tube dependence.[27] Loss of a normal oral diet is frequently one of the most affected QOL measures for OPC survivors.[28]

In addition to effects on QOL, dysphagia can have life-threatening consequences. In a recent systematic review and meta-analysis, life-threatening aspiration occurred after >24 months at a reported incidence ranging from 3% to nearly 35%. Although a reduction in radiation dose to the pharyngeal constrictors can reduce chronic dysphagia,[27] whether this can be done safely in most OPC patients, particularly those with bulky primary tumors, remains unclear.

Osteoradionecrosis (ORN) in Survivors of OPC

ORN is one of the most potentially serious complications of CRT and may not manifest for years after treatment. Its median time of onset after radiotherapy is 8 years in patients with OPC.[24] Bone injury and impaired healing of the alveolar mucosa are signs of ORN, which occurs in ~7% of patients receiving intensity-modulated radiation therapy for OPC.[17] ORN is accompanied by pain, difficulties with chewing, exacerbation of concomitant dysphagia and, in the advanced stage—gross cosmetic deformity secondary to mandibular or maxillary fracture and/or decay.[29] Despite the severity of this complication, we are just beginning to understand why ORN develops in a subset of patients. Although ORN is generally more common in patients with advanced-stage OPC who receive higher doses of radiation to a larger overall bone volume,[17,19,24,30] comprehensive translational research efforts focused on ORN (as well as other late toxicities of OPC treatment) are still in their infancy.

Unmet Needs in Predicting and Evaluating Late Toxicities

Predicting which patients will experience long-term treatment toxicities or which types of late toxicities they may develop is not yet possible. Whereas increased data collection and prognostic models can help inform healthcare systems as to expected frequencies of toxicity, they are unlikely to be prognostic at the individual patient level. As such, there is a critical need for individualized biomarker strategies that can predict one's risk of toxicity and identify normal tissue shifts in biology and function early in the process to initiate interventions before significant deterioration. Adding to the complexity of predicting late toxicities is the lack of standardization in instruments used to categorize them. Examples of tools that may be used to categorize dysphagia include the Common Terminology Criteria for Adverse Events v4.0 grading scale, the Radiation Therapy Oncology Group grading system, and the European Organization for Research and Treatment of Cancer Performance Status Scale for Head and Neck Cancer.[20] The MD Anderson Symptom Inventory for head and neck cancer may also be used to catalog dysphagia and other common symptoms of HNC, as well as treatment-related concerns.[31] Magnetic resonance imaging-based techniques coupled with machine learning approaches represent emerging tools that may have a role in identifying early radiation-induced bone changes that can facilitate early detection of ORN.[32,33] Although conventional and newer tools can be used to generate objective metrics of treatment-related toxicity, consistent and appropriate deployment across the entire cohort of OPC survivors in the United States remains a distant goal.

Calibrating Treatment Intensity to Disease Intensity

Given the risk of severe and potentially life-threatening consequences of radiation-based treatment, there is a large unmet need to better calibrate treatment intensity to the intensity of HPV-associated OPC.[14,34] In light of the good prognosis of the disease in most patients, recent efforts have focused on identifying ways to de-escalate treatment intensity while preserving the good outcomes known to be possible for patients with HPV-associated OPC. Improving tolerability and limiting the risk of late effects of radiation-based treatment is especially important with the aging population of HPV-associated OPC survivors, who would also be expected to have unrelated comorbidities.[1]

Various modes of de-escalation have been studied, including adding surgery to CRT, reducing radiation dose, and modifying systemic therapy regimens. Most of these efforts have largely failed to identify a safe regimen for treatment de-escalation that applies to a majority or even a significant plurality of patients with OPC.[14,35,36] Although CheckMate 141 and KEYNOTE-048 garnered excitement when immune checkpoint inhibitors (ICIs) significantly prolonged overall survival and had a more favorable safety profile than standard systemic therapy in recurrent and metastatic OPC,[11,37,38] adding definitive frontline avelumab to CRT failed to prolong progression-free survival versus CRT alone in the phase 3 JAVELIN Head and Neck 100 trial.[13] Combined with additional recent trial data, these findings make it unlikely that an ICI-based regimen will provide previously unavailable de-escalation options for patients with OPC in the near future.

Considering continued de-escalation efforts, it is important to remember that survival is not uniform among all patients with HPV-associated OPC. For example, patients with HPV-associated OPC and a history of current or prior heavy tobacco use have not experienced the same dramatic prolongation in overall survival as their nonsmoking counterparts.[36] Patients with recurrent disease also face a dismal prognosis, with failure rates of about 70% with salvage treatment with surgery, re-irradiation, or systemic therapy.[38-41] Therefore, de-escalation may not be appropriate in all patients, but identifying which patients are at risk of overtreatment is not straightforward. Better risk stratification of patients may provide part of the solution but will require rigorous testing and long-term follow-up to establish.

Discussion

There is an urgent need to carefully consider how to manage long-term survivors of HPV-associated OPC. With ever-increasing numbers of patients who are living years beyond their OPC treatment, continual reevaluation of treatment strategies in certain subsets of patients and making concerted efforts to identify and manage late toxicities early is paramount. Yet there remains a critical gap in knowledge due to insufficient metrics for both toxicity intensity and the frequency of debilitating, life-threatening toxicity. Unfortunately, the lack of tools available combined with the mismatch in disease intensity with treatment intensity likely results in excessive treatment-induced toxicity for many patients.

In the absence of clear evidence about which treatment strategy to use for individual patients, clinicians are tasked with making therapeutic choices without being fully able to predict outcomes. Patient preference is important to consider, but these conversations can be complicated. How does one talk to a patient about their willingness to risk a cancer recurrence and potentially risk late toxicities when the clinician does not know whether that individual patient will develop late toxicities, or know how severe they will be? It is a trade-off between QOL (ie, possible feeding tube dependence) and survival—yet the magnitude of the effect on QOL remains impossible to predict at present for the individual patient.

Moreover, the needs of individual OPC survivors vary. A cross-sectional study performed at Princess Margaret Cancer Centre found that 61% of the 158 participants had unmet needs related to their cancer survivorship.[42] Meeting the needs of survivors may require the development of better screening instruments that can manage various complications early and effectively. Continuing to follow OPC survivors with a multidisciplinary team would most certainly be beneficial and has been reported to improve QOL.[43] Continual Speech Pathology management and therapy from the time of diagnosis into the survivorship phase of care has been suggested as one way to improve functional outcomes.[44] Given that coordinating long-term care teams is logistically challenging, well-planned research is warranted to equip these teams to provide OPC survivors with the care they need. These efforts will be particularly important considering the large number of survivors who will need this type of care in the coming decades. The time to start is now well past.

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Progress in Ovarian Cancer: Discovery of Fallopian Tube Involvement

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The field of ovarian cancer has experienced a paradigm shift; ovarian cancer is now known to most often arise from the fallopian tubes.[1] The ovaries can act as a magnet for tumor cells that may originate elsewhere in the body. Moreover, it has been found that relatively simple risk-reducing interventions may virtually eliminate progression to invasive disease in the ovaries.[1] These types of discoveries—and others—are igniting new research into novel approaches to improving outcomes for patients with ovarian cancer.

Incidence and Mortality

By 2040, the number of women diagnosed with ovarian cancer annually worldwide is expected to increase by 100% in low Human Development Index (HDI) countries, and by 19-28% in high HDI countries.[2] The causes of this increasing incidence are likely to be multifactorial, including both hereditary and modifiable risk factors.[3] In addition to increasing population size, the growing prevalence of obesity, estrogen exposures, and nulliparity are particularly pertinent as potential causes of the rising incidence of ovarian cancer in younger women. The number of ovarian cancer-related deaths is also projected to rise from about 200,000 to nearly 314,000 annually, an increase of over 50% from 2020.[2,4] Although outcomes in developed regions and nations continue to improve somewhat, 5-year survival rates range from 36% to 46%.[5] These outcomes are nevertheless dismal when compared with 5-year survival rates from other cancer types, such as breast cancer, which are approaching 90%.[6]

These types of discoveries—and others—are igniting new research into novel approaches to improving outcomes for patients with ovarian cancer.

Principal Histotypes

The principal histotypes in ovarian cancer are epithelial in origin and include high-grade serous carcinoma, clear-cell carcinoma, endometrioid carcinoma, low-grade serous carcinoma, and mucinous carcinoma. Other rarer types are nonepithelial, ie, arising from stromal or germ cell lines.[7] Incidence rates appear to be affected over time by trends such as birth rates, use of combination oral contraceptives, and menopausal hormone therapy.[8]

Figure 1 shows that most ovarian cancers—approximately 70%—are high-grade serous carcinoma, although in Asian countries clear cell and endometrioid carcinomas comprise a higher proportion.[9]

Into the Fallopian Tube

One of the most salient and dramatic discoveries of the last 2 decades has been the finding that high-grade, clear-cell, and endometrioid tumors appear to arise from tissues not normally present in the ovary.[1] As a result of risk-reducing efforts to prevent serous cancers in women with genetic predisposition to develop ovarian cancer (ie, those with *BRCA1* or *BRCA2* mutations), it became increasingly clear that many early cancers arose in the fallopian tube,[10-12] with the distal portion—the fimbria—as the most common site of origin.[13-16]

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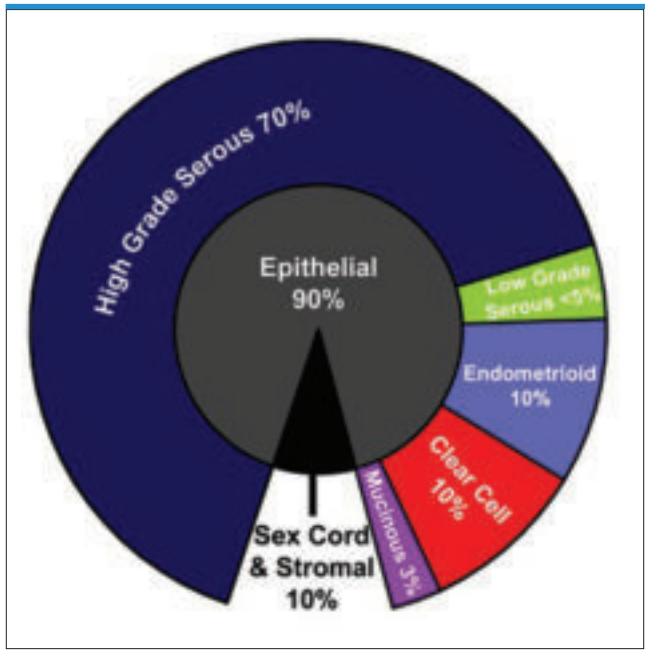
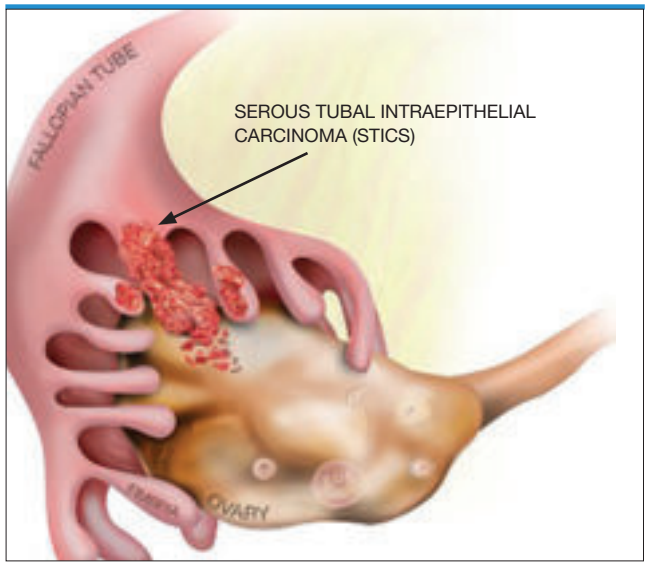
FIGURE 1. Major Histotypes in Ovarian Cancer



Most ovarian cancers are epithelial carcinomas. High-grade serous carcinoma is the most common, whereas the other subtypes represent 10% or fewer cases each.[9]

FIGURE 2. Serous Tubal Intraepithelial Carcinomas



Lesions that develop in the fallopian tube fimbria, called serous tubal intraepithelial carcinomas (STICs), have been identified as precursors of ovarian cancer.

Figure 2 depicts the female reproductive tract, including the location of the fimbria compared with the ovaries. Moreover, lesions observed in the fallopian tube fimbria—serous tubal intraepithelial carcinomas (STICs)—were identified as precursors of ovarian cancer, with a window of 7 years between development of STIC and the beginning of an ovarian cancer.[14,16]

Early Detection

Early, localized ovarian cancer is asymptomatic; by the time a patient presents with symptoms, even with nonspecific abdominal complaints, the disease is almost invariably advanced. The concept of early detection has improved both the rate of cancer diagnoses and outcomes for some malignancies, such as cervical, colorectal, breast, and lung cancers,[17] but this strategy is yet to be effectively applied in ovarian cancer. A large, population-based study, for instance, yielded negative results when multimodal screening (using both measurement of CA125 blood levels and transvaginal ultrasound imaging) failed to improve survival, even though such screening was able to detect lower stage disease.[18] Emerging technologies, such as liquid biopsies and uterine lavage, which seek to detect potential biomarkers (new types of blood tests) of ovarian cancer at an early stage and closer to the site of tumor origin, are being investigated and refined but are not yet ready for clinical use, particularly at the population level for screening.[19]

Risk-Reducing Interventions

Use of oral contraceptives has been associated with a significant reduction in risk for ovarian cancer, but the potential risks (eg, increased risk for breast cancer, increased risk for venous thromboembolism) preclude its universal recommendation.[20-22] Simple removal of the fallopian tube, salpingectomy, was proposed as a potential intervention to "intercept" the progression of a STIC to cancer. Researchers recently compared simple salpingectomy with salpingo-oophorectomy as a risk-reduction procedure in carriers of *BRCA 1/2* pathogenic variants after they had completed childbearing.[23]

These investigators proposed that later removal of the ovaries would delay menopause and would contribute to fewer/less severe symptoms, such as hot flashes, disturbed sleep, and sexual issues, as well as maintain or improve overall quality of life. The hypothesis was supported by results, which showed that patients had better menopause-related quality of life after salpingectomy than after salpingo-oophorectomy, regardless of the use of hormone replacement therapy.[23] The oncologic safety of this approach was subsequently demonstrated by other studies that showed a significantly lower incidence of ovarian cancers in women who had undergone opportunistic salpingectomy.[22,24,25]

An international prospective trial, TUBA-WISPII, is now underway to test the hypothesis that postponement of oophorectomy after salpingectomy is non-inferior to standard salpingo-oophorectomy in terms of ovarian cancer risk for patients at high-risk.[26]

Treatment

First-Line Therapy

Currently, there are no durable curative therapies for ovarian cancer once advanced disease has been diagnosed.

Surgery plus platinum-based chemotherapy. Most patients, even those diagnosed with advanced disease, are treated initially with debulking surgery, ideally by a gynecologic oncologist, and adjuvant chemotherapy. Most ovarian carcinomas are initially platinum-sensitive, but resistance and disease recurrence are almost inevitable. According to the National Comprehensive Cancer Network (NCCN) guidelines for ovarian cancer,[27] preferred chemotherapy regimens include paclitaxel and carboplatin with or without bevacizumab, docetaxel and carboplatin, or carboplatin and liposomal doxorubicin. Numerous other regimens, combinations, and agents are included in the guidelines to help providers customize treatment plans.

Neoadjuvant vs adjuvant regimens. Neoadjuvant chemotherapy has been used for other malignancies to gauge sensitivity to systemic treatments and to improve surgical margins.[28] Thus far, though, outcomes in ovarian cancer have been similar whether patients were given neoadjuvant or adjuvant treatment in the perioperative period. Individualizing these decisions based on ability to surgically resect, patient age, tumor histology, disease stage, and performance status is recommended.[29]

Intraperitoneal chemotherapy. Other approaches have been explored to reduce risk for micrometastases after surgery. Hyperthermic intraperitoneal chemotherapy,[32] for instance, administered immediately after cytoreductive surgery was studied as a technique that might prevent some of the risks and adverse effects associated with intraperitoneal chemotherapy.[31] Results showed some improvement in progression-free survival and overall survival in a subgroup of patients who underwent interval cytoreductive surgery after neoadjuvant therapy, but no differences were observed for the larger population with advanced epithelial ovarian cancer. Adverse reactions to intraperitoneal chemotherapy were also observed.

Angiogenesis inhibition. Tumors need energy and oxygen to grow. Angiogenesis is the process of new blood vessel formation that provides the tumor with nutrients. Blocking angiogenesis can thwart tumor growth and improve patient outcomes. Bevacizumab is an antiangiogenic agent that has been extensively studied for 2 decades for many cancers including ovarian carcinoma. The NCCN guidelines note that bevacizumab may be considered as part of a first-line regimen with platinum agents, as maintenance in patients with wild-type or unknown *BRCA* mutation status and a good response to first-line therapy, or in combination with a poly (ADP-ribose) polymerase (PARP) inhibitor in eligible patients.[27]

PARP inhibitors. Approximately half of all high-grade serous ovarian carcinomas exhibit some defect in the ability to repair DNA damage using the homologous recombination (HR) pathway. These tumors include those with mutations in the *BRCA1, BRCA2,* and other HR genes. Defects in HR make tumors more dependent on back-up DNA repair systems, including the activity of PARP. PARP inhibitors were developed to specifically target HR-deficient tumors. To date, 3 PARP inhibitors have been approved for use in ovarian cancer—olaparib, rucaparib, and niraparib. Their use has expanded from later-line use in patients with *BRCA1/2*-mutated tumors to include frontline maintenance regimens for women with high-grade serous and high-grade endometrioid carcinomas, as well as women with recurrent disease.[32] Numerous clinical trials are ongoing to develop next-generation PARP inhibitors and to explore their efficacy in combination with chemotherapy and other targeted agents.

Resistance and Disease Progression: Second-Line and Subsequent Treatment

A number of second-line and subsequent systemic treatment regimens may be considered when primary platinum-based chemotherapy and/or maintenance are no longer effective.[33,34] As emphasized by the NCCN, a clinical trial is always an appropriate option, depending on eligibility, and sometimes a second cytoreductive surgery[35,36] may be considered for patients who experience radiographic and/or clinical relapse after a long disease-free interval (6+ months). Each line of treatment is associated with progressively lower response rates and shorter durations of response. According to the NCCN guidelines, as patient performance status decreases and the toxicities of each line of therapy accumulate, assessment for palliative care should be considered and discussed.[27]

Investigational Approaches

With the high mortality rate associated with ovarian cancer, the challenges of detecting the disease at its early stages, and the lack of therapies that can significantly extend progression-free and overall survival in patients with advanced disease, many investigators are focused on novel treatment approaches. Preclinical observations, for instance, showing synergy

between ataxia telangiectasia and RAD3-related (ATR) kinase inhibitors and PARP inhibitors led researchers to initiate a phase 2 study of olaparib plus ceralasertib (an ATR inhibitor) in patients with recurrent, platinum-resistant epithelial ovarian cancer.[37] No objective responses were noted, but some signals of activity were seen among patients with *BRCA1* mutations.

Due to success in other malignancies, immunotherapy is also being explored. Although some promising signals were reported at 6 months when nivolumab, a PD-1 (programmed cell death protein 1) inhibitor, and ipilimumab, a cytotoxic T-lymphocyte-associated antigen 4 antibody, were combined to treat patients with platinum-resistant epithelial ovarian cancer; final results are not yet available.[38]

Ovarian cancer is sometimes characterized as immunologically "cold." This description means that immune cells, especially T cells, are not able to enter the tumor and destroy the cancer cells. It also means that these tumors are not as responsive to immune-based treatments. Therefore, some researchers are examining novel alternative immunotherapy strategies, such as chimeric antigen receptor T-cell (CAR-T) therapy.[39] When a CAR T-cell encounters a tumor antigen, the CAR T-cell becomes activated. Activated CAR T-cells multiply, signal to other immune cells, and ultimately kill the tumor cells. Although CAR T-cell therapy has been tremendously successful in hematologic malignancies, to date, the benefits in solid tumors have been modest.[39] However, there is significant enthusiasm for novel tumor antigens that can be targeted by CAR-T therapy, including mesothelin, folate receptor, Claudin-6, B7-H3, B7-H4, HER2, CD47, and L1-CAM, among others.[40]

Other investigational strategies include a p53 vaccine that would enhance the patient's immunologic response to abnormal proteins produced by a mutated *p53* gene, which is the most common finding in ovarian tumors.

Although researchers are investigating many approaches to treating advanced ovarian cancer, one strategy that has been pursued in other cancer settings—development of antibody-drug conjugates (ADCs)[41]—has seen promising results. In the late fall of 2022, the US Food and Drug Administration granted accelerated approval for mirvetuximab soravtansine-gynx for use in patients with a specific type of type of tumor (folate receptor alpha [FRα]-positive) when platinum resistance emerges.[42] A companion diagnostic assay was also approved for selecting patients with FRα-positive disease. Several other clinical trials are investigating the efficacy of targeting other ovarian tumor antigens using the ADC approach. These targets include NaPi2b, mesothelin, B7-H4, Claudin-6, and Trop-2.[43,44]

Progress to Come

Progress in ovarian cancer will be made through a multipronged approach that includes interventions that may proactively "intercept" the development of cancer (eg, salpingectomy for women planning to have other simple gynecologic procedures after childbearing is complete). Although prophylactic surgeries are often undertaken by individuals at high risk for ovarian cancer because of genetic findings, such as *BRCA1/2* abnormalities, even women with normal risk may consider when planning tubal ligation, removing their tubes, and other routine procedures. A substantial number of malignant tumors, and associated morbidity and mortality, may be thwarted as a result. The question of whether to treat when a STIC is detected remains to be answered.

The search for better methods of early detection continues, as local therapies for early-stage disease are invariably more effective than treatments in the advanced and/or metastatic setting.

Finally, as with certain other malignancies, even in the advanced setting, effective, often targeted, treatments can significantly prolong both progression-free and overall survival, transforming an often-lethal disease into a chronic one that allows patients to enjoy a better life expectancy with good quality of life.

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An Evolving Understanding of Adenosquamous Carcinoma of the Lung

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Adenosquamous carcinoma (ASC) of the lung is a rare, biphasic type of non-small cell lung cancer (NSCLC) that accounts for 2% to 4% of all lung cancers.[1] According to the World Health Organization (WHO) classification, the composition of ASC includes both adenocarcinoma (AC) and squamous cell carcinoma (SCC) histologies, with each subtype comprising at least 10% of the tumor.[2] As with other lung cancers, the average age at ASC diagnosis is about 70 years of age, it affects more men than women, and most patients are current or former smokers.[3,4] Despite these similarities, mounting evidence suggests that the molecular and genomic features of ASC are unique and they remain poorly understood.[5-8]

Perhaps owing to the distinct genomics of these tumors, ASC of the lung is reported to be relatively aggressive compared to typical AC and SCC tumors. Studies indicate that ASCs at diagnosis have higher rates of lymph node invasion, metastasize rapidly, and carry a generally poor prognosis. Accordingly, the overall survival (OS) of patients with these tumors is relatively short compared to other NSCLC subtypes.[2,3,8-10] In a 2022 population-based study of the SEER database, 5-year post-surgical survival rates for early stage cancers were reportedly 65% for ASC vs 69% for SCC P=0.003 and 77% for AC P<0.001.[3] While it is clear that underlying biology driving ASC differs from more typical NSCLC subtypes, there is a lack of effective treatment options specific to ASC and a paucity of clinical research available to support therapeutic decisions for patients with ASC histology. Current management of NSCLC is based primarily on the stage of the tumor, and clinical features of the patient. In a more personalized era of targeted treatments, tumor histology is used only to predict presence of actionable mutations in adenocarcinomas.[7,8] However, optimal treatment strategies for ASC remains a significant unmet need in lung cancer.

Diagnosis: Complex but Critically Important

Given the mixed histologies that characterize ASC of the lung, intratumoral heterogeneity often hinders and may delay diagnosis. Studies suggest that ASC is misdiagnosed as AC or SCC in at least half of biopsies prior to surgical pathology confirming an ASC diagnosis.[11] In one retrospective study, nearly all ASC cases (98%) were either misdiagnosed or undiagnosed preoperatively.[12] What's more is that different types of biopsy samples may yield different results. One case report of a patient eventually diagnosed with ASC described 3 different results on workup: SCC on bronchial lavage and bronchial biopsy, AC on immunohistochemistry, and NSCLC undifferentiated on pleural effusion cytology.[13] While a diagnosis can be made using biopsy and cytology samples, a definitive diagnosis may require larger samples (ie, several core biopsies or complete surgical resections) to fully evaluate all components of the tumor lesion.

Comprehensively evaluating entire tumor specimens can aid in further characterization ASC of the lung. ASCs may be sub-classified according to the proportions of AC and SCC histology components present. Tumors with either AC or SCC components comprising at least 60% of the tumor are referred

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to as AC- or SCC-predominant ASC, respectively. Those with a more even split of AC and SCC histologies (40% to 60% of each) are referred to as structure-balanced ASC and have been reported to have a better prognosis than either of the more imbalanced subtypes.[9,14]

Adding to the complexity of diagnosing ASC of the lung is its unclear histologic origin and the transitional nature of these tumors over time. Some studies have pointed to possible precursor lesions, including AC with squamous metaplasia, collision tumor, and high-grade mucoepidermoid tumors.[15] Reports have also shown that the molecular and histological features of the primary tumor can differ from that of metastases/recurrences.[16,17] In one case report, a patient with a resected ASC harboring an epidermal growth factor receptor *(EGFR)*-sensitizing mutation recurred several months later as SCC in the brain with the same *EGFR* mutation. A later recurrence in the lung was diagnosed as an AC and had the same *EGFR* mutation.[16] In this example, if only the SCC component had been diagnosed, molecular testing would likely have never been ordered and the potentially actionable *EGFR* mutation would have been left undetected. Therefore, careful and accurate diagnosis of ASC is critically important in guiding testing for driver mutations, as well as in informing treatment choices in ASC.

Genomics

Studies indicate that ASC of the lung exhibits genomic features of both AC and SCC, with standard immunohistochemical profiles represented in each component. As expected, TTF1 positivity is common in the AC component while p63 and CK5/6 are expressed in the SCC component.[18] However, evidence also indicates that ASC of the lung is a distinct entity rather than being a simple hybrid of AC and SCC histologies. That is, despite the seemingly dichotomous nature of ASC, this type of tumor is thought to have unique molecular and genomic features that have not yet been fully identified.[5-8]

While the genomics of AC and SCC of the lung have been well studied, the inherent intratumoral heterogeneity that defines ASC, together with its relative rarity, complicates its analysis. There is a paucity of data available, but several groups have conducted molecular testing to better understand the genotype of ASC and potentially discover predictors about prognosis and treatment. To date, most studies on ASC lung samples have been small, and while some groups have reported overlapping results, other findings contrast with one another. In one of the most recent and comprehensive studies published on the topic, Wang et al. used next generation sequencing (NGS) to identify a wide range of somatic mutations in 124 Chinese patients with ASC of the lung, including *TP53* (66.9%), *CDKN2A* (21%), *TERT* (21%), and *LRP1B* (18.5%).[6] Importantly, they found high rates of *EGFR* mutations (54.8%), of which 45.6% were EGFR 19del, 38.2% were EGFR L858R and 29.4% were EGFR amplifications. Notably, not all studies have found such a strikingly increased rate of EGFR mutations in ASC versus AC of the lung.[19] Other actionable mutations were found in the analysis by Wang and colleagues, including *ALK* and ROS1 fusions. Regarding known predictors of immunogenicity in these tumors, a subset of patients were associated with high tumor mutational burden (TMB), which was correlated with mutations in *ARID2, BRCA1*, and *KEAP1*. Immunohistochemical analyses demonstrated half of patients were positive for PD-L1 (≥1% tumor proportion score [TPS]).[6] Interestingly, another study showed that PD-L1 expression in ASC differed between SCC (30% to 40%) and AC (11% to 15%) components.[20]

Actionable mutation rates (ie, EGFR, ALK) in AC are known to vary between Asian and White patients, a finding that seems to be similar in ASC of the lung as well, although it is less clear given the limited sample size of ASC studies. Vassella et al. performed NGS and fluorescence in situ hybridization (FISH) on ASC samples from 16 White patients and found that 30% had *EGFR* mutations, while Tochigi et al reported an *EGFR* mutation rate of 13% in a study of 23 Western patients.[5,12,21] In their analysis, Vassella and colleagues also found a high rate of mutations in the PI3K pathway (25%), but no *KRAS* mutations, which are the most common molecular driver in typical AC (30%), and thus supporting the notion that ASC has its own molecular genomic profile, distinct from AC or SCC.[5,21] Also of interest in this study was the finding that classifier miR-205 expression was intermediate between that of classical AC and SCC, suggesting that ASC of the lung may alternatively represent a transitional stage between these tumor types rather than an unrelated entity.[5] These findings, along with others that have been reported on the genomic landscape of ASC, have advanced our understanding of the underlying biology of this malignancy, but also highlight the unmet need for more research to improve our ability to personalize treatment for ASCs.

Treatment

Owing to the heterogeneity of ASC of the lung, as well as its complex and incompletely characterized genomic landscape, treating patients with these tumors is challenging. In general, stage-based treatment approaches are used to manage ASC. The current treatment paradigm of all NSCLC has dramatically changed in recent years, with increasing incorporation of targeted treatments and immunotherapies across all stages and histologic types. Considering ASCs are composed of glandular cell components, they can contain substantial levels of relevant actionable driver mutations as described above. Therefore, if ASC is diagnosed or if a SCC has a glandular component,

molecular testing is recommended and supported by guidelines, even on surgical specimens where EGFR may be targeted as adjuvant treatment.[23] However, while targeting actionable mutations and the PD1/PDL1 axis has been studied extensively in AC and SCC in all stages, the impact of these markers in ASC is unknown because patients with this histologic subtype are frequently excluded from clinical trials.

For patients with ASC and actionable mutations, EGFR inhibitors have been perhaps the best studied targeted therapies. EGFR inhibitors have yielded responses in ASC, but benefit has been highly variable in small case series and generally inferior to outcomes in patients with AC alone.[19] Ongoing clinical trials are aiming to better understand the effects of EGFR inhibitors in ASC. As one example, first-line almonertinib is being compared to paclitaxel/carboplatin in the phase 2 ARISE clinical trial, which is specifically enrolling patients with *EGFR* mutation-positive locally advanced or metastatic pulmonary ASC (Clinicaltrials.gov NCT04354961). Most other reported studies are case studies or retrospective in nature. Given that outcomes are usually reported from single patients or a group of only a few patients, contradictory findings are not uncommon. For example, crizotinib, a multi-kinase inhibitor approved for the treatment of advanced or metastatic *ALK*-positive and *ROS1*-positive NSCLC, was reported to have clinical response in an ASC in a patient with recurrent *ALK*-positive disease which lasted for just over one year.[24] However, the response to second-line crizotinib in a case report of female non-smoking patient with *ROS1*-positive ASC was only 4 months.[25] Newer, more specific kinase inhibitors are currently in clinical practice and trials of *ALK* and *ROS1* NSCLCs; however, their efficacy is ASC remains unclear.

In the absence of driver mutations, the optimal choice of chemotherapy (often given with immunotherapy) for neo-/adjuvant therapy or for metastatic disease has not yet been identified. While the AC component might typically be treated with pemetrexed plus a platinum agent, the SCC component may be better treated with taxane plus a platinum agent.[23] Especially in cases where neither histologic subtype is predominant, it can be difficult to decide which combination may be suitable for an individual patient. Whether the relative proportion of AC and SCC components affect treatment outcomes is not yet known. Outcomes of pemetrexed-based chemotherapy have been reported in a case study of 2 patients with relapsed disease harboring *ALK* and R*OS1* mutations, pemetrexed alone or as part of a combination regimen (with pembrolizumab and carboplatin) was able to maintain stable disease for at least a year.[26]

While immune checkpoint inhibitors, either as monotherapy or in combination with chemotherapy, are currently recommended for patients with NSCLC23, few studies have reported outcomes of patients with ASC specifically. One recent real-world analysis by Li et al. evaluated the effect of immunotherapy in 46 patients with ASC, of which 18 (39%) did not contain actionable driver mutations and 18 (39%) had unknown mutational status.[27] In this study, 28% of the overall cohort responded to checkpoint inhibitors, the median progression-free survival was 6 months, and the median OS was 24.7 months. Notably, similar efficacy was observed in the 20 patients receiving immunotherapy monotherapy vs 26 patients who received combination immunotherapy plus chemotherapy.[27] Among 4 patients with EGFR mutations, 2 received immunotherapy monotherapy and progressed immediately compared to the other 2 receiving combination immunotherapy with chemotherapy achieving disease control and improved OS (18 months).

As exemplified by the select few cases summarized above, conventional treatments used in NSCLC have achieved only modest responses in ASC, most with a shorter response duration. The lack of specific treatment strategies for ASC, based on understanding of underlying tumor biology, limits optimal treatment outcomes for this increasingly common diagnosis. Novel therapies are sorely needed. A consensus should be developed to either study novel treatments specifically in this subtype or allow for incorporate of ASCs into future NSCLC clinical trials.

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Gastrointestinal Stromal Tumor: Reflecting on 2 Decades of Clinical Advancements

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Gastrointestinal stromal tumor (GIST) was recognized as a distinct tumor type in the late 1990s.[1] Advances in treatment have expanded since the 2001 US Food and Drug Administration (FDA) approval of imatinib, the first tyrosine kinase inhibitor (TKI).[2] In 2023, there are now 5 FDA-approved agents for GIST, and 4 additional agents have been approved (tumor agnostic) for patients whose cancer harbors specific genomic alterations (neurotrophic tyrosine receptor kinase *[NTRK]* fusions[3,4] or *BRAF V600E* mutations[5]). According to the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology, several other drugs (ie, in addition to those specifically approved for GIST) are listed as "useful in certain circumstances."[6]

Since the early 2000s, new discoveries about GIST genomics have contributed to better, more targeted treatments. Some genomic mutations have been linked to specific gut regions,[7] which may further help guide therapy as well.

GIST: What Is It, Who Gets It, and How Is It Diagnosed?

What, How Many, Where?

Even though GIST is considered rare—representing less than 1% of gastrointestinal tumors[8]—it is the most common sarcoma, which is a family of mesenchymal neoplasms. GISTs are thought to arise from the interstitial cells of Cajal, or the pacemaker cells of the gut that control peristalsis. In the United States, the incidence of GIST is roughly 4,000 to 6,000 new cases diagnosed per year, with most cases found in the stomach (60%) or small intestine (35%). Other gut regions in which GISTs may be identified include the rectum and esophagus.[8]

Although asymptomatic tumors are often discovered incidentally, GISTs that originate in the stomach—the most common primary tumor site—may present with nonspecific subjective symptoms such as pain, nausea, loss of appetite, early satiety, or bloating.[9] Symptoms may vary according to tumor location (eg, stomach vs rectum vs esophagus), size, and pattern of growth. More objective signs could include anemia related to gastrointestinal bleeding, weight loss, or a palpable mass.[9]

Who?

Most cases of GIST occur in patients later in life, with a median age of 64 years at diagnosis. A slight predominance of men has been noted, along with African American and Asian individuals affected somewhat more frequently than White or Hispanic populations.[10]

GIST is rare in children and adolescents, and the symptoms and pathology differ from those in most adults.[9] Previously age was considered a determining factor in the differences in GIST, with cases in children classified as "pediatric-type" GIST or "wild-type" GIST. These cases generally present in the stomach, are more likely to include lymph node involvement, and can also spread to the liver and abdominal lining. Importantly, they are usually not

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Owns stock in Personalis

associated with the tyrosine-protein kinase *(KIT)* or platelet-derived growth factor receptor alpha *(PDGFRA)* gene mutations found in most adults.[9] About 80% of these cases have hereditary mutations of the succinate dehydrogenase (SDH) enzyme complex. Because some adult cases of GIST share the distinct characteristics found in most pediatric cases, distinguishing them based on age, rather than on the specific genetic characteristics of the tumor, is unwarranted.[9]

How?

When GIST is suspected or when symptoms mandate further investigation, coordination among colleagues in imaging, gastroenterology, pathology, surgery, and oncology is critical for accurate diagnosis, staging, and treatment. Abdominal imaging may be ordered using modalities such ultrasound, computed tomography, magnetic resonance imaging, and, occasionally, positron emission tomography.[11] Endoscopic ultrasound is useful to identify and biopsy lesions in the stomach or rectum, as these tumors arise below the lining of the stomach or rectum. GIST diagnosis can be confirmed by biopsy during endoscopic ultrasound, which is the preferred approach, or by percutaneous biopsy when endoscopic biopsy is not feasible or safe.[11]

According to the European Society for Medical Oncology (ESMO) and European Reference Group for Rare Adult Solid Cancers (EURACAN) Clinical Practice Guidelines, the "standard approach to tumors ≥2 cm in size is excision, because they are associated with a higher risk of progression if confirmed as GIST. If there is an abdominal nodule not amenable to endoscopic assessment, laparoscopic or laparotomic excision is the standard approach."[11]

Genetic Mutations

A diagnosis of GIST is made based on the combination of the clinical scenario, the tumor's anatomic location, immunohistochemistry patterns, and molecular features.[12]

Research has shown that genetic mutations in the *KIT, PDGFRA*, or *SDH* genes are present in most cases of GIST (70-80%,[13] 10%,[12] and less than 10% of cases[12,14] respectively) and their presence can be used for diagnosis. A growing number of rarer mutations have also been discovered,[13] meaning that gene-based diagnosis of GIST is becoming increasingly sensitive. In addition, antigens on the surface of cancer cells can help classify them as GIST. For example, researchers have discovered that most GIST cells have the marker CD117, the protein product of the *KIT* gene that is commonly mutated in GIST, on their surfaces. A different marker, DOG1 (ie, **D**iscovered **O**n **G**IST 1), is also present on the vast majority of GISTs, but not unanimously overlapping with CD117. A tumor that is positive for both CD117 and DOG1 has a high probability (>97%) of being GIST.[15]

Next-generation sequencing (NGS) is considered the best tool for determining both germline and somatic mutations in patients with GIST, and NGS is recommended by both the NCCN[6] and the ESMO[11] for individualizing systemic therapy. Despite these recommendations, most patients do not undergo genetic testing, both in the United States[16] and internationally.[17] Several barriers to genetic testing have been cited, predominately inadequate tissue and high cost. However, a study demonstrated that costs of up to $3,730 for genetic testing were ultimately cost-effective for tailoring therapy with first-line imatinib for patients with newly diagnosed metastatic GIST.[18] Moreover, genetic testing also should be strongly considered for patients with nonmetastatic disease in whom systemic therapy is being considered.

Increasing evidence has emerged that gastric GIST mutations are related to tumor location within the gastrointestinal tract (**Figure**).[7] The anatomic location of the GIST may provide clues for clinical decision-making and may guide selective confirmatory genomic testing when access to testing is limited.

Treatment of GIST

Surgery

Surgery remains the main treatment for localized GIST, especially if the tumor is discovered at an early stage. Unfortunately, up to a quarter of patients present with metastatic disease at diagnosis. The goal of surgery is to resect the tumor with histologically negative margins. Every effort should be made to avoid rupturing the tumor capsule during resection. Studies have shown that laparoscopic resection is feasible and safe for gastric GISTs and is less invasive than traditional open surgery, with similar oncological outcomes.[19]

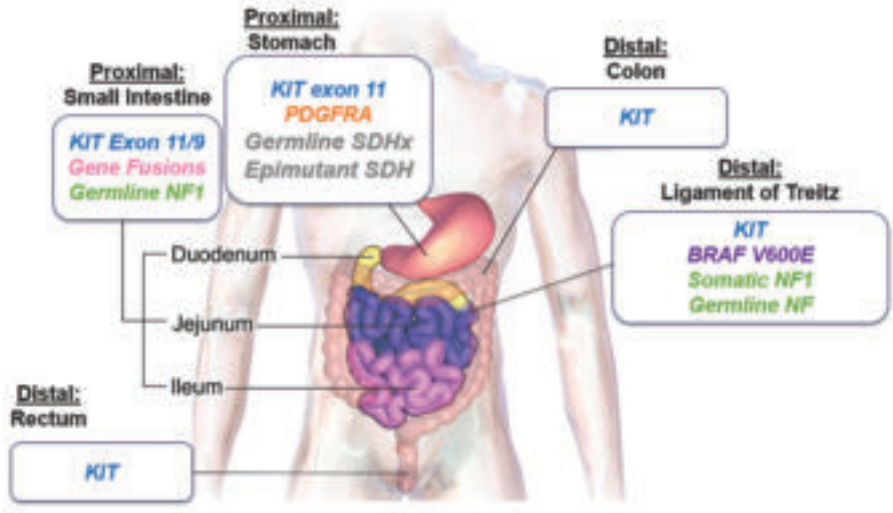
Debulking surgery is sometimes considered for patients with metastatic disease, especially for patients who demonstrate sensitivity to TKI and whose disease has not yet progressed.[20,21] Other interventions, such as microwave ablation or transhepatic arterial embolization, are sometimes used to control hepatic metastases.

Systemic Therapies

Whether systemic therapy is being considered in the neoadjuvant (preoperative), adjuvant (postoperative), or advanced disease setting, mutations in GIST determine the likelihood of treatment success. Both NCCN[6] and ESMO[11] strongly encourage use of mutational analyses and genetic testing for patients with GIST before systemic therapy is initiated.

In some cases of locally advanced GIST, tumors may be situated in particularly challenging anatomic locations

FIGURE. Mutations Correlate With Gut Locations



Proximal gastric GISTs are overwhelmingly KIT exon 11 mutant, whereas distal stomach tumors display non-*KIT* genomic diversity (*PDGFRA*, as well as germline [or inherited] SDHx mutant and SDHC epimutations). In contrast, tumors that arise in the small intestine (eg, duodenum, jejunum, and ileum) are associated with gene fusions and germline *NF1*, as well as mutations in *KIT* exons 11 and 9. Colon and rectal tumors are likely to be *KIT*-related, whereas those found in the duodenal-jejunal flexure (also called the ligament of Treitz) correlate with rarer mutations, such as *BRAF V600E* and somatic (nonhereditary *NF1*) in addition to germline NF, as well as *KIT*.

(eg, esophagus, duodenum, rectum) or may require a highly morbid, multivisceral resection. In such situations, neoadjuvant treatment with imatinib,[22,23] if deemed appropriate per mutational profiling, should be considered.

Patients who are determined to be at high risk for recurrence after surgery, based on tumor size, mitotic index determined by pathologist review of dividing cells, tumor location, and tumor rupture,[24] may be eligible for adjuvant treatment with imatinib. Although the ideal duration of adjuvant therapy is not yet known, the current standard is at least 3 years,[25] but many practitioners advocate for lifelong therapy.

Imatinib. Because chemotherapy was ineffective against GIST, prognosis was dismal for patients diagnosed with advanced disease before the approval of imatinib[2] in the early 2000s. A selective TKI, imatinib targets the KIT and PDGFRA receptor kinases, and most patients experience clinical benefit,[26] at least initially. Unfortunately, many tumors eventually develop resistance, and discontinuation of imatinib is associated with a risk for disease progression.[27]

Sunitinib. The emergence of resistance to imatinib spurred the search for second-line agents that might be useful after disease progression. Another TKI, sunitinib, which has both antitumor and antiangiogenic activity, was approved in 2006 for management of advanced imatinib-resistant GIST.[28] Knowledge of a tumor's driver mutation(s)[29] can help optimize use of sunitinib.

Regorafenib. In 2013, the FDA approved regorafenib, another TKI, as a third-line agent for patients with advanced GIST that is refractory to imatinib and sunitinib.[30] Regorafenib exerts its activity against multiple targets, including *VEGFR1-3, TIE2* (ie, antiangiogenic activity), *PDGFR-β, FGFR* (ie, stromal targets), and *KIT, RET,* and *RAF* (ie, oncogenic targets). As with other TKIs, common adverse effects associated with regorafenib treatment include hypertension, hand-foot skin reaction, rash, diarrhea, and fatigue.

Larotrectinib/entrectinib. The FDA approved larotrectinib[31] (2018) and entrectinib[32] (2019) as the first tumor-agnostic agents, whose use is based on the presence of a specific genomic alteration, in this case *NTRK*. If a tumor, including a GIST, harbors a specific, albeit rare, gene fusion, it may be considered for treatment with one of these small-molecule *TRK* family inhibitors. Although these agents are not specifically indicated for GIST, some subjects enrolled in the trials had GIST harboring the target *NTRK* gene fusion and their tumors responded to treatment.

Ripretinib. FDA-approved in 2020,[33] ripretinib is a novel TKI indicated for adult patients with advanced GIST who have received prior treatment with 3 or more kinase inhibitors, including imatinib. A phase 3 trial demonstrated improved progression-free and overall survival when ripretinib was compared with placebo in patients who had disease progression after treatment with imatinib, sunitinib, or regorafenib.[34] Ripretinib is now being investigated in the second-line setting in selected patients with *KIT* mutations.

Avapritinib. Cases of GIST with *PDGFRA D842V*-mutant tumors often demonstrate primary resistance to imatinib and sunitinib. In 2020, avapritinib, a selective TKI that targets both *KIT* and *PDGFRA*, was approved[35] for treatment of patients with unresectable or metastatic GIST harboring a *PDGFRA* exon 18 mutation, including *D842V* mutations. However, it is noteworthy that many of the non-*D842V* mutations in *PDGFRA* respond to imatinib.

Dabrafenib/trametinib. In 2022, the FDA issued an approval for treatment based on a driver mutation rather than tumor type. Acknowledging that a *BRAF* mutation—specifically a *V600E* mutation—appears to be a critical target in several cancers, the FDA granted accelerated approval for the use of dabrafenib plus trametinib in adults and children 6 years of age and older with unresectable or metastatic solid tumors with *BRAF V600E* mutation who have progressed following prior treatment and have no satisfactory alternative treatment options.[36]

Researchers have studied additional TKIs in the setting of unresectable, metastatic disease due to the varied genomic landscape of GIST. The NCCN Guidelines include evidence of some benefit for agents such as dasatinib, cabozantinib, everolimus (plus a TKI), nilotinib, pazopanib, and sorafenib "in certain circumstances."[6]

The Future of GIST

The most critical step toward optimal treatment decision-making when a patient has been diagnosed with GIST is identification of physicians with expertise in the care of patients with GIST. With increasing knowledge of genomic variations in GIST, patient care has become less prescripted and much more personalized. To that end, determination of the tumor's genetic mutational profile is critical to guiding treatment. Although factors such as cost, availability/accessibility, and insufficient tissue continue to represent substantial obstacles, pursing this information may be the most important way that clinicians can advocate for their patients. Moreover, now that the anatomic location of GIST has been linked to specific driver mutations, the ability to select and refine treatments may improve significantly.

Likewise, in view of the increasing complexity and multidisciplinary management of patients with GIST, efficient coordination is paramount among surgical and medical oncologists, as well as radiologists, gastroenterologists, and pathologists.

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Progress in Treating Testicular Cancer

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Approximately 1% of adult neoplasms and 5% of all urologic cancers are testicular cancer (TC).[1] In the United States, 9190 new cases have been estimated for 2023.[1] Testicular germ cell tumors (GCTs) comprise 90% to 95% of all TCs and are grouped into seminomas, nonseminomatous GCTs (NSGCTs), and mixed histology GCTs.[1] NSGCTs tend to be more aggressive and are more common in younger men (15-40 years old), whereas seminomas are slower growing and generally develop later in a patient's life.[2,3]

Mortality from TC has been decreasing since the 1970s due to cisplatin-based chemotherapy regimens[2,3]; TC is among the most curable of solid neoplasms, with a 5-year relative survival rate of 95%.[2-4] Thus, the focus of research has shifted from optimizing treatments for improved survival to decreasing treatment-related, long-term adverse events (AEs).[5]

New Modifications in Risk Assessment and Prognostication

The widely accepted risk stratification model in use today was first developed in 1997 by the International Germ Cell Cancer Collaborative Group (IGCCCG) after studying data on patients with seminoma and NSGCTs.[6] The original classification categorized metastatic NSGCTs as having good, intermediate, or poor prognosis based on levels of alpha-fetoprotein (AFP), human chorionic gonadotropin (hCG), lactate dehydrogenase (LDH), and the presence of nonpulmonary visceral metastases (NPVM). Primary mediastinal NSGCTs were classified as having poor prognosis regardless of the other factors.[6] Metastatic seminoma GCTs were categorized as having good or intermediate prognosis based on the occurrence of brain, liver, or bone metastasis.[7]

Using contemporary data from more than 12,000 patients with metastatic GCTs who received either cisplatin or etoposide, the IGCCCG model was updated in 2021. For seminoma GCTs, 5-year progression-free survival (PFS) and 5-year overall survival (OS) were extended for both good and intermediate prognostic groups.[7] LDH remained the most significant prognostic factor for determining good prognosis however, patients with LDH above 2.5× upper limit of normal (ULN) before chemotherapy had worse survival probabilities than patients with LDH at 2.5× ULN or lower. The survival probabilities for patients with otherwise good prognosis with LDH of more than 2.5× ULN were like those for patients with intermediate prognosis.[7] Thus, using LDH of more than 2.5× ULN has revealed a subgroup with significantly worse outcomes within the "good" prognostic group.[7,8]

For NSGCTs, 5-year PFS rates did not differ from the original IGCCCG for good and intermediate prognostic groups; however, the 2021 update revealed an improved PFS for the poor prognostic group. The 2021 update also demonstrated that 5-year OS rates improved for each group, and further confirmed that the 2 most important prognostic factors for NSGCT were the presence of NPVM and the presence of a mediastinal primary tumor. The update added 2 new adverse prognostic variables: age and metastases. Risk of progression increases 25% with every decade-of-life increase, and 66% with the presence of lung metastases. The LDH groups were reduced to a single cutoff at 2.5× ULN for NSGCTs.[8]

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Primary and Subsequent Treatments for TC

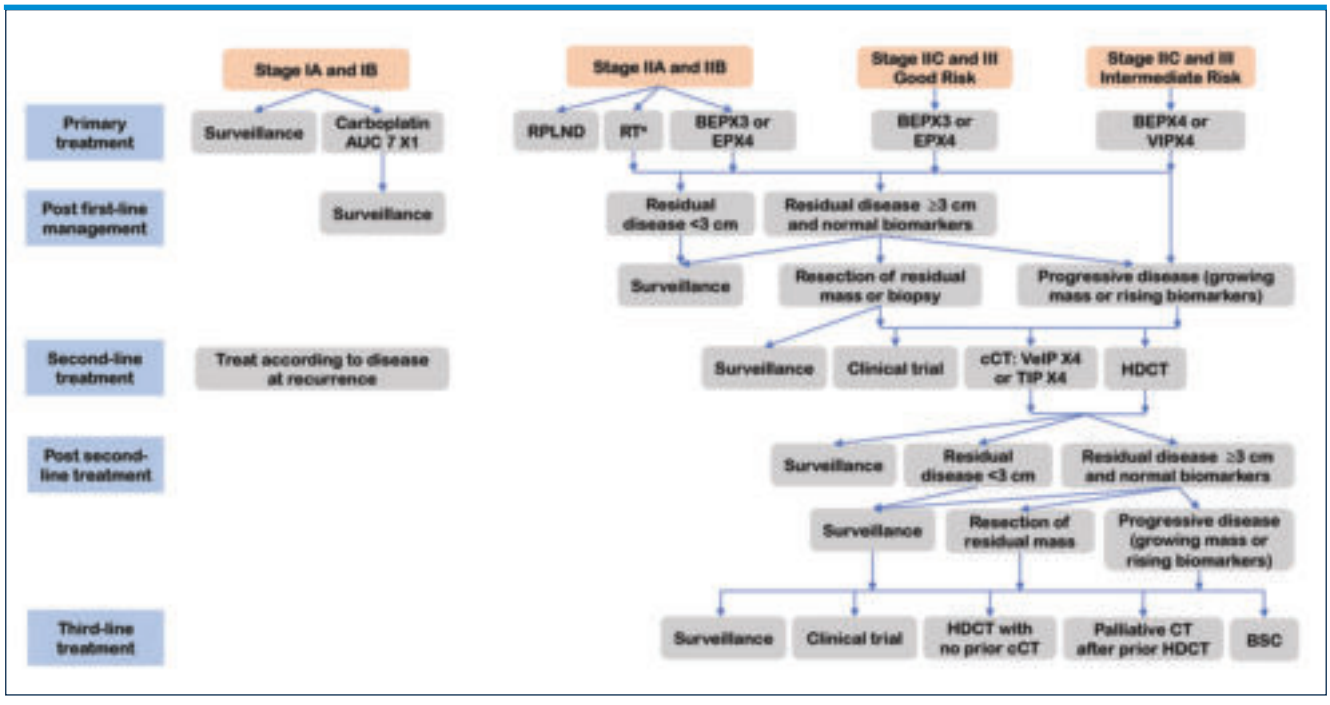
Guideline-directed first-line and subsequent treatments for seminomas and NSGCTs have been developed by several organizations, including the National Comprehensive Cancer Network, IGCCCG, and the American Urological Association (see **Figure 1** and **2**). An analysis of the most used treatments was performed using the National Cancer Database.[2] Most patients underwent orchiectomy without chemotherapy or radiation for both stage I seminomas (78%) and NSGCTs (57%). For stage II and III seminomas, most patients underwent surgery with chemotherapy (66% and 68%, respectively). Nearly half of patients with stage II NSGCTs were treated with surgery and chemotherapy (49%), and a third were treated with retroperitoneal lymph node dissection (RPLND) in addition to surgery and chemotherapy. Surgery with chemotherapy was used for 55% of stage III NSGCTs; other treatments included surgery combined with chemotherapy and RPLND (19%), and chemotherapy with or without radiation (20%).[2] However, nearly 30% of patients with TC do not receive guideline-directed therapy, including inappropriate imaging and overtreatment; and nonguideline–directed therapy has been independently associated with risk of relapse.[12,13]

TC Survivorship

The trend of improved OS after treatment for metastatic GCTs highlights a need to focus on survivorship. The 10-year survival rate for TC post-treatment is 95%.[14] Latest estimates suggest there are more than 300,000 TC survivors in the United States,[2] accounting for approximately 4% of all US male cancer survivors.[14] With longer-term survival, however, comes the risk for long-term complications from cancer treatments. For example, circulating platinum has been detected in the plasma of men up to 28 years after undergoing cisplatin-based chemotherapy for TC.[15] Increasing levels of residual serum platinum have also been shown to correlate with severity of neurotoxicity between 5 and 20 years after treatment.[16]

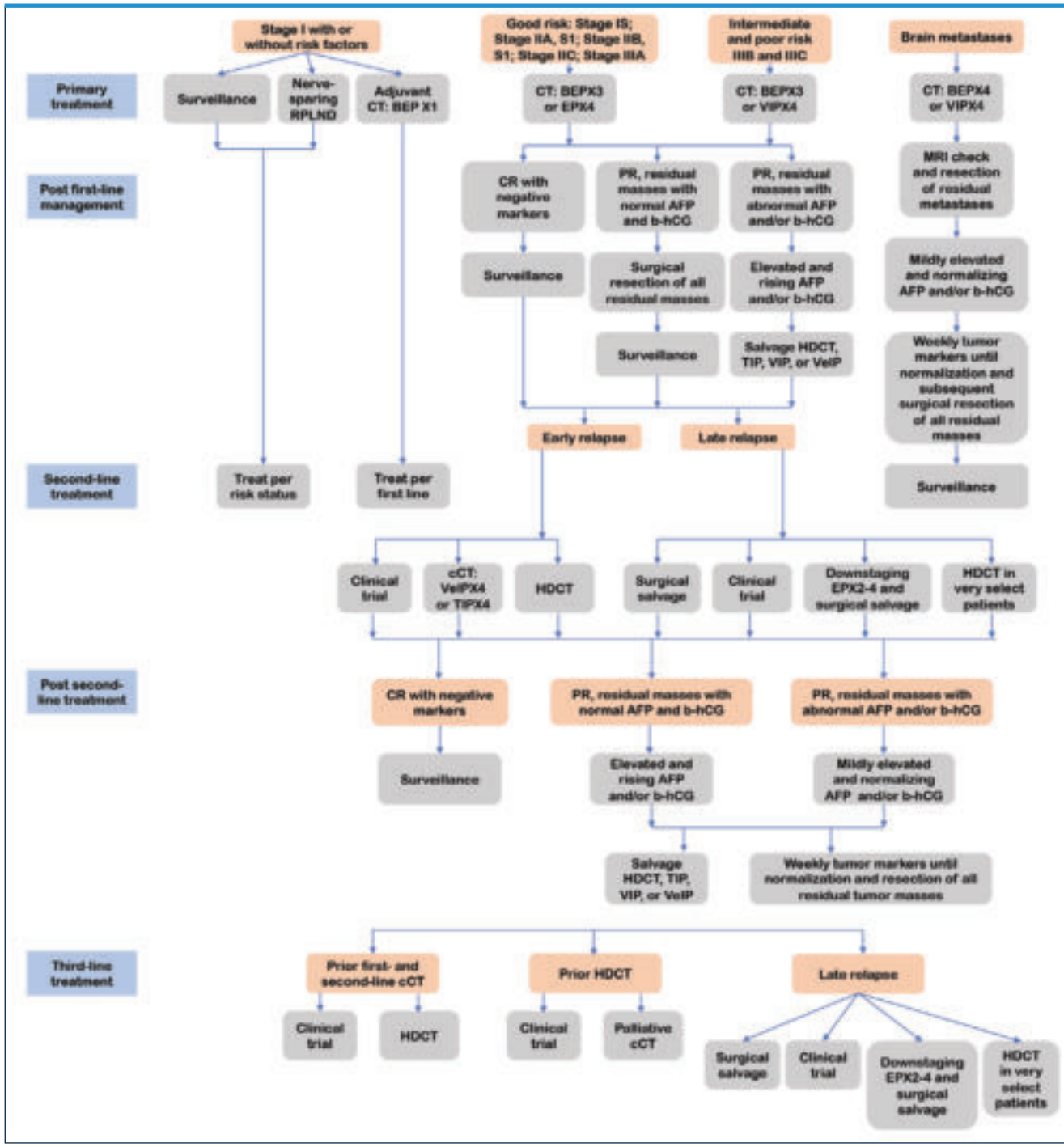
A significant concern with cancer treatment is the development of second malignant neoplasms (SMNs).[14,17] The relative risk of the development of SMNs depends on whether

FIGURE 1. First-line and Subsequent Treatment of Seminomas[3,6-11]



Abbreviations: AUC, area under the curve; BEP, bleomycin, etoposide, cisplatin; BSC, best supportive care; CT, chemotherapy; cCT, conventional chemotherapy, EP, etoposide, cisplatin; HDCT, high-dose chemotherapy; RPLND, retroperitoneal lymph node dissection; RT, radiation; TIP, paclitaxel, ifosfamide, cisplatin; VeIP, vinblastine, ifosfamide, cisplatin; VIP, etoposide, ifosfamide, cisplatin.
[a]This recommendation has been weaker in recent years

FIGURE 2. First-line and Subsequent Treatment of Non-Seminomas[3,6-11]



Abbreviations: AUC, area under the curve; AFP, alpha fetoprotein; b-hCG, beta-human chorionic gonadotropin; BEP, bleomycin, etoposide, cisplatin; BSC, best supportive care; CT, chemotherapy; cCT, conventional chemotherapy, EP, etoposide, cisplatin; HDCT, high-dose chemotherapy; RPLND, retroperitoneal lymph node dissection; RT, radiation; TIP, paclitaxel, ifosfamide, cisplatin; VeIP, vinblastine, ifosfamide, cisplatin; VIP, etoposide, ifosfamide, cisplatin.

radiation therapy or chemotherapy, or both, was used as the primary treatment. Patients who received either radiation therapy or chemotherapy are at increased risk for leukemia and solid cancers, including gastrointestinal cancers. For patients treated with cisplatin, a significant dose-response relationship between cumulative dose and leukemic risk has been reported.[14]

Other concerns are increased non-TC mortality and SMN mortality. Hellesnes et al examined cause-specific, non-TC mortality using a population-based cohort in Norway.[18] They determined that the overall 25-year, non-TC mortality risk was 13.7% (95% CI, 12.5-14.9) for patients who previously had TC vs 11.3% for patients who never had TC. The highest mortality rates were reported for patients who had radiation (19%) or platinum-based chemotherapy plus radiation (18.4%); the lowest mortality rate was reported for patients who had received platinum-based chemotherapy only (9.5%). Patients with the highest non-TC mortality risk were fewer than 20 years post-cancer diagnosis. Non-TC mortality excess ranged from 23% to 40% for patients with a prior TC diagnosis, and a significant 1.43- to 3.24-fold increase in SMN mortality emerged after treatment with platinum-based chemotherapy or radiation therapy, or both.[19] Awareness of the increased premature mortality risk is crucial for both TC survivors and their care providers.[18]

Quality of life for TC survivors appears to be affected by the presence of long-term treatment-related AEs.[18] The relative risk of developing cardiovascular disease increases after treatment with chemotherapy. Raynaud phenomenon resulting from bleomycin-induced vascular damage developed within 4 to 12 months after chemotherapy for 18.7% to 39% of TC survivors.[14,19] Bleomycin may also cause pulmonary toxicity. Pulmonary surgery, tobacco use of ≥ 20 pack-years, and a cumulative cisplatin dose of > 850 mg are risk factors for late bleomycin-associated pulmonary toxicity.[14]

Other late-developing toxicities resulting from cisplatin treatment include ototoxicity, neurotoxicity, nephrotoxicity, chronic fatigue, and hypogonadism.[14,19] Nearly 1 in 5 North American survivors treated with cisplatin reported severe-to-profound hearing loss within a median of 4.3 years. The extent of hearing loss has been directly associated with the increase in cumulative cisplatin dose. Peripheral neurotoxicity after cisplatin-based chemotherapy is reported to be as high as 40%.[14] Chronic cancer-related fatigue can range from 15% to 27%, and has been associated with peripheral neuropathy, low testosterone levels, low physical activity, anxiety, and depression. Post-treatment hypogonadism ranges from 11% to 16%.[14,17,20,21]

Psychosocial issues are also of concern. Mild-to-moderate psychological distress with diagnosis and survivorship has been reported.[17] Anxiety and depression are higher in TC survivors than in the general population. Variables associated with clinically significant anxiety include younger age and shorter time from diagnosis; whereas feeling helpless/hopeless, having less social support, having a higher number of physical symptoms, and having children are factors associated with higher levels of depression. A moderate-to-high level of fear of recurrence has also been reported.[17]

Recent Clinical Trials in Stage II Disease

Stage II disease has been the focus of current research to reduce treatment-related toxicities and limit longer-term complications. While few phase 3 clinical trials are ongoing (see **Table**), the results of several phase 2 trials have been reported recently.[22-24]

PRIMETEST was a single-arm, single-center, phase 2 study examining the efficacy and surgical safety of primary RPLND for stage II disease.[22] Participants underwent either open or robot-assisted unilateral RPLND for stage IIA or B seminoma. No adjuvant treatment was permitted. Of the 33 participants, 9 presented initially with clinical stage II disease (27%) and 24 (73%) had recurrence during active surveillance. Five of the 24 had 1 cycle of carboplatin prior to progressing to stage II. With a median follow-up of 32 months, the study did not meet its primary endpoint of PFS at 36 months. After 32 months, 10 recurrences (30%) were detected, yielding a PFS rate of 70%. All 10 patients with recurrence received chemotherapy and were alive without evidence of disease at the time of publication. This study demonstrates that RPLND may be appropriate for select patients; however, criteria for selecting patients to receive only RPLND need to be clearly defined.[22]

The SEMS (surgery in early metastatic seminoma) trial was a single-arm, international, phase 2 study of RPLND as first-line treatment for early metastatic seminoma with isolated retroperitoneal lymphadenopathy between 1 and 3 cm (stage II).[23] With a median follow-up of 24 months, OS was 100% and 2-year recurrence-free survival was 87%. Recurrence rate was 18% (10 recurrences) with a median time to recurrence of 8 months. Short-term complications occurred in 7 patients (13%), and no patients reported long-term complications. The authors suggested that RPLND is a therapeutic option for first-line treatment in early metastatic seminoma.[23]

SAKK 01/10 was a single-arm, international, phase 2 study examining the de-escalation of treatment to potentially avoid toxic effects for patients with either stage IIA or stage IIB seminoma.[24] Treatment included carboplatin (area under the curve [AUC] 7 mg/mL/min) followed 3 weeks later with involved-node radiotherapy (30 Gy in 15 fractions for stage IIA and 36 Gy in 18 fractions for stage IIB). The study did not meet

TABLE. Ongoing Interventional Phase 3 Clinical Trials Involving Testicular Cancer

Official study title/NCT number	Status	Interventions	Anticipated completion date
A randomized phase III study comparing one course of adjuvant bleomycin, etoposide and cisplatin (BEP) and one course of carboplatin AUC7 in clinical stage I seminomatous testicular cancer (SWENOTECA-ABC) NCT02341989	Recruiting	BEP vs carboplatin	December 2035
A randomized phase III trial comparing conventional-dose chemotherapy using paclitaxel, ifosfamide, and cisplatin (TIP) with high-dose chemotherapy using mobilizing paclitaxel plus ifosfamide followed by high-dose carboplatin and etoposide (TI-CE) as first salvage treatment in relapsed or refractory germ cell tumors NCT02375204	Recruiting	TIP vs TI-CE	June 2024
A phase III randomized, double-blind, placebo-controlled, cross-over study to evaluate olanzapine combined with fosaprepitant, ondansetron, and dexamethasone for preventing nausea and vomiting in patients with testicular cancer receiving 5-day cisplatin combination chemotherapy NCT05244577	Recruiting	Olanzapine tablets plus fosaprepitant, ondansetron, and dexamethasone vs placebo plus fosaprepitant, ondansetron, and dexamethasone	March 2024
A risk-adapted strategy of the use of dose-dense chemotherapy in patients with poor-prognosis disseminated non-seminomatous germ cell tumors NCT00104676	Active, not recruiting	BEP ×3 vs dose-dense sequential cisplatin, etoposide, bleomycin, paclitaxel, oxaliplatin, and ifosfamide	August 2023

Abbreviations: AUC7, area under the curve of 7 mg/mL/min; BEP, bleomycin, etoposide, cisplatin; TI-CE, paclitaxel, ifosfamide-carboplatin, etoposide; TIP, paclitaxel, ifosfamide, cisplatin.

its primary endpoint of PFS of 95% at 3 years. Grade ≥ 3 treatment-related AEs (TRAEs) included neutropenia (4%), thrombocytopenia (3%), and vomiting (1%). No treatment-related deaths and no late TRAEs were reported. One case of transient creatinine increase was reported as a serious AE, and second primary tumors were reported in 4 participants. Although the primary endpoint was not met, long-term AEs continue to be recorded for potentially up to 20 years. The favorable efficacy and toxicity profile observed in the de-escalation combination treatment warrants further study.[24]

Emerging Trends and Future Directions for TC Treatment

Although the outlook for most newly diagnosed patients with TC is promising, especially for those diagnosed with early-stage disease and good prognosis advanced disease, treatment challenges remain. Between 10% and 20% of patients will have a relapse of TC after initially achieving a complete remission. Most patients will have a relapse within 2 years of initial treatment, but a small subgroup will have a relapse more than 5 years after therapy. Most recurrences occur in the retroperitoneum and lungs and require definitive therapy using chemotherapy and surgical resection.[21]

Patients with platinum-refractory disease may still achieve long-term remission with salvage therapy of surgery, conventional-dose chemotherapy, or high-dose chemotherapy with autologous stem cell transplantation; however, these treatments will fail for some patients, resulting in poor prognosis. Targeted therapy for TC has not produced meaningful benefits for this population with refractory disease, and the optimal treatment for this group of patients with TC remains to be determined.[21]

Although current guidelines recommend determining the levels of AFP, hCG, and LDH for clinical staging, treatment monitoring, and follow-up, limitations exist with their usage.[9] The assays for these markers have low sensitivity and lack specificity; about half of all GCTs express only 1 of the

3 biomarkers, and seminomas lack AFP expression.[7,25,26] Further research is needed on LDH. An emerging group of patients with LDH below 2.5× ULN may be candidates for de-escalation strategies to reduce treatment burden, while inferior outcomes remain for patients with either good prognosis seminoma and elevated LDH, or intermediate prognosis seminoma.[7]

Other biomarkers, such as miRNA371a-3p and PD-L1, are being investigated; miRNA371a-3p has been shown to have prognostic significance. The results of this assay can be informative for both seminomas and NSGCTs.[26] However, the protocol for quantification and implementation still needs to be determined.[27]

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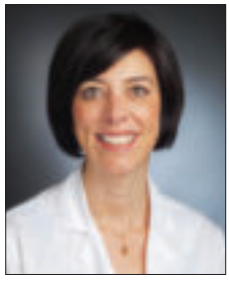
Strategies to Improve Long-Term Outcomes in Younger Patients With Hodgkin Lymphoma



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The current treatments for classical Hodgkin lymphoma (cHL) in adolescents and young adults (AYA) are associated with high rates of remission but may lead to treatment-related complications years later. These problems, such as organ damage and secondary malignancies that arise long after otherwise effective treatment, are a threat to long-term outcomes. This threat is seen especially in the AYA population because of their longer life expectancy. Concerns such as cardiovascular effects and second cancers in the AYA population are paramount, emphasizing the importance of identifying safer regimens for these individuals. Initiatives to incorporate risk-adapted treatment regimens and novel therapies with a lower risk of late-occurring complications are being actively pursued. This review highlights the potential of several of these initiatives for AYA patients.

Background

Hodgkin lymphoma occurs in fewer than 9,000 individuals in the United States each year,[1] but it is one of the most common types of cancer in AYAs.[2] For the purposes of cHL, AYA is typically defined as an age range of 18 to 39 years, which covers the first of 2 bimodal peaks in incidence but stops short of the second.[3,4] The first of these peaks occurs between the ages of 15 and 34 years, while the second begins at about age 55.[5] Children younger than 15 years of age can also develop Hodgkin lymphoma, but it is less common.[6]

In AYAs and in adults, more than 90% of patients with Hodgkin lymphoma have cHL.[7] Most AYAs present with the nodular sclerosis subtype, but cHL is managed differently in pediatric patients versus in adult centers.[8,9] Evidence suggests that the specific risks of common treatment protocols, although similar, are not the same in AYAs as in adults.[10,11] Even though the literature evaluating the presentation and management of AYA cHL has been growing since 2005, when the AYA Oncology Progress Review Group called for AYAs to be recognized as a distinct group, clinical trials specific to AYA cHL remain limited.[9]

Major Hodgkin lymphoma guidelines only partially address AYAs as a distinct group. In guidelines issued by the National Cancer Institute, the differences in clinical presentation of AYAs are described for young children, AYAs, and older adults, but there are no treatment recommendations specific to AYAs.[12] Guidelines from the EuroNet Paediatric Hodgkin Lymphoma Group offer recommendations for relapsed and refractory Hodgkin lymphoma, but do not differentiate between children and adolescents.[13] The National Comprehensive Cancer Network (NCCN) provides separate treatment recommendations for patients 18 years or younger and those who are older than 18.[14,15] For Hodgkin lymphoma, AYA is not addressed as a separate category even though the NCCN has provided general guidelines for treatment of malignancies in AYA.[16]

First-line therapies are effective in children, AYAs, and adults. Survival rates at 5 years have increased steadily, approaching or exceeding 90% across age groups even for patients with unfavorable risk characteristics.[17] This success has

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permitted greater focus on developing strategies that preserve efficacy with lower acute and long-term risks.

Risk-Adapted Therapies

While the potential for new and novel therapies to reduce the risk of long-term toxicities continues to be explored, adjusting existing regimens to reduce these risks has proven to be a viable strategy. This adjustment is a standard of care in the pediatric setting based on results from such studies as German GPOH-HD95, which suggested that doses of radiotherapy, a major contributor to late toxicities,[18] can be omitted in patients with a complete response after chemotherapy.[11] This pediatric trial contained both younger children and adolescents, but subsequent secondary analyses looking specifically at AYAs in this and other trials have suggested that efficacy is similarly preserved with risk-adapted strategies.[9]

However, due to AYA patients with cHL being treated using both pediatric and adult approaches, the persistent debate about optimal therapies in this age group complicates the effort to define a well-accepted strategy for risk adjustment. While risk-adapted strategies that rely on interim positron emission tomography (PET) to calibrate treatment intensity are now being used routinely across age stratifications, other initiatives are creating additional opportunities to gauge the impact on late effects in AYAs. These include strategies to improve collaboration across groups of trialists and data generated by observational cohorts, which can evaluate late effects not captured in time-limited clinical trials.

Among recent data supporting risk-adjusted therapy, the toxicity outcomes from a multicenter trial of PET-guided intensive treatment in patients with newly diagnosed advanced cHL were presented at the 2022 annual meeting of the American Society of Hematology.[19] This phase 3 trial enrolled patients younger than 60 years, 79% of whom were younger than 45 years. Building on previous evidence that PET guidance improves the safety of eBEACOPP (escalated doses of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone), nearly 1,500 patients were randomized to this strategy or to PET-guided BrECADD, a modified eBEACOPP in which the antibody conjugate brentuximab vedotin (BV) was substituted for bleomycin. For an adjudicated endpoint of treatment-related morbidity, the experimental BrECAAD regimen reduced the risk by nearly 30% (hazard ratio [HR] 0.72). It is unclear whether this strategy will be used in the United States, where trials have been built on ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) rather than BEACOPP.

Efficacy data from this trial are not yet available, and these data will be important. There is concern that PET-directed therapy might result in lower toxicity at a cost of reduced rates of disease control. It is possible that the serious consequences of late toxicities—including infertility, compromised cardiovascular function, secondary cancers, and other organ damage—might need to be balanced against some loss of efficacy.

Novel Targeted Therapies

The goal of reducing late toxicities of cHL therapy in AYAs is also likely to be advanced by novel therapies. Research endeavors include a multicenter collaboration between US and Canadian investigators that is exploring the combination of nivolumab (a checkpoint inhibitor) plus BV.[20] The trial recently completed accrual and includes both adult and pediatric patients. If novel agents prove effective for improving efficacy while reducing the risk of late complications in AYAs, they are expected to have a profound effect on clinical practice.

Arguably, the era of targeted and novel therapies in cHL was initiated more than 10 years ago with the introduction of BV for the treatment of advanced disease in older adults.[21] BV was moved into the front line for patients 18 years of age or older with advanced cHL in a trial that compared the standard of ABVD to the same drugs with BV substituted for bleomycin.[22] In this study, the BV-containing regimen was associated with a significantly improved progression-free survival (PFS) (P = .04) and a lower rate of adverse events, including pulmonary toxicity (1% vs 3%) after 2 years of follow-up.

A similar study recently associated a BV-containing regimen with even greater efficacy in pediatric high-risk cHL.[23] In this multicenter study with 600 treatment-naïve patients ranging in age from 2 to 21 years, the standard pediatric regimen of doxorubicin, bleomycin, vincristine, etoposide, prednisone, and cyclophosphamide was compared to the same regimen with BV substituted for bleomycin. With event-free survival as the primary endpoint, the experimental regimen was associated with a nearly 60% reduction in the risk of an adverse event or death (HR 0.41). However, no substantial differences were noted in toxicity after a follow-up of 42 months. It not yet clear whether the elimination of bleomycin will translate into less late toxicity, such as pulmonary or cardiovascular morbidity.

In the era of targeted therapies, the experience with BV has been a step toward more effective treatments using novel mechanisms of action to improve outcomes when used in the first-line treatment of patients with high-risk disease. Historically, many regimens and treatments that have demonstrated efficacy in relapsed and refractory cHL have found their way into the first-line setting. This trend might also be true of the checkpoint inhibitors, which have been tested extensively in relapsed/refractory cHL. In AYA patients with cHL, the rationale for these treatments might not only include a poor predicted response to current regimens, but a reduced risk of late toxicities

if long-term follow-up demonstrates these treatments reduce late complications, such as secondary malignancies, which are associated with standard strategies, particularly those that include radiotherapy.

If targeted therapies do preserve efficacy and reduce risk of late complications, strategies to individualize therapy will remain relevant. Many of the emerging targeted therapies involve challenging and costly treatment protocols that demand selective application. Efforts to develop simpler and more precise biomarkers might streamline this task. Of promising developments in this area, cell-free DNA (cfDNA) appears to be near routine clinical application. A small study of cfDNA conducted in 121 patients found that minimal residual disease assessment by repeat cfDNA sequencing predicted response and PFS when performed as early as a week after treatment initiation.[24] If larger studies confirm accuracy, this biomarker strategy might prove simpler and more convenient than PET imaging.

Summary

In the treatment of hematologic malignancies, cHL is widely regarded as a success story with high rates of extended survival among children, AYAs, and older adults. This level of success does not obviate the need for even more effective treatments, and also permits more attention to be directed to reducing the risk of late toxicities. For the AYA population, which represents a large group with cHL, the current directions of clinical research offer the promise of imminent changes in how the disease is controlled and a reduction in treatment-related late morbidity and mortality.

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Targeted Therapies in Younger and Older Patients With Mantle Cell Lymphoma

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For the first-line treatment of mantle cell lymphoma (MCL), high-dose chemotherapy and autologous stem cell transplantation (ASCT) have been reserved for relatively young and fit patients. Better-tolerated regimens have provided a preferable ratio of risk to benefit for less fit patients, even if the remissions associated with these combinations are less durable. Recent studies with targeted therapies are now challenging the premise that optimal control of MCL is obtained only by regimens that are difficult to tolerate. The relevance of these studies to specific case examples in this review demonstrates the potential of newer therapies across several MCL phenotypes.

Background

Of the approximately 80,000 individuals diagnosed annually in the United States with a non-Hodgkin lymphoma (NHL), MCL accounts for an estimated 5%.[1,2] At the time of diagnosis, most of these patients have advanced disease. The diagnosis of MCL is made based on characteristic immunophenotype and the presence of (11;14)(q13;q32) translocation resulting in overexpression of cyclin D1.[3,4] Long-term survival has been observed in a small proportion of patients with MCL, but this disease is generally considered incurable.[5]

Except for the approximately 10% of patients with MCL who present with asymptomatic indolent disease, for whom a watch-and-wait approach is generally used,[6] there are 2 types of treatment strategies. One is applied to people who are fit and relatively young. In these cases, intensive chemotherapy with or without ASCT has been the dominant approach. In patients who are poor candidates for the toxicities associated with aggressive treatment, less intensive approaches are applied. These strategies include not only better-tolerated combinations of cytotoxic chemotherapies, but also various combinations that involve immunomodulators or small molecule enzyme inhibitors. Although less toxic, these regimens are active, often achieving a complete response (CR) and an extended progression-free survival (PFS).[3]

Currently, "chemotherapy-free" therapies, a term that is sometimes used to identify drug combinations with modest or no cytotoxic effects, though inaccurate, are not preferred for first-line therapy in any group in the NCCN guidelines.

These 2 pathways of MCL treatment are reflected in guidelines from the National Comprehensive Cancer Network (NCCN), which describe separate first-line algorithms for stage I and stage II non-bulky disease and stage II bulky and advanced stage disease.[7] For stage II bulky or advanced stage disease, separate pathways are described for indolent, TP53-mutated, and TP53 wild-type MCL and are further divided into pathways for those who are candidates for ASCT and those who are not.

Currently, "chemotherapy-free" therapies, a term that is sometimes used to identify drug combinations with

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modest or no cytotoxic effects, though inaccurate, are not preferred for first-line therapy in any group in the NCCN guidelines. However, immunomodulators, such as lenalidomide and targeted therapies, such as Bruton tyrosine kinase inhibitors (BTKis) are being actively tested in the front-line setting with promising results. Practical approaches to the application of these agents are described in trials presented or published in the last year, including TRIANGLE and SHINE.[10,11]

Rethinking Front-Line MCL Therapy in the Young and Fit

Case Study

A 52-year-old man with a history of smoking presented with shortness of breath and general fatigue. The medical history included no major chronic diseases. The patient, who was referred after a routine examination, reported a recent decrease in body weight of unknown cause. Enlargement of inguinal, axillary, and submaxillary lymph nodes on examination along with laboratory abnormalities, such as anemia, and elevated lymphoid cells in the peripheral blood, raised suspicion of a lymphoproliferative disorder. A diagnosis of MCL was reached based on characteristic lymphoid cell morphology and immunotyping positive for CCND1 on lymph node biopsy. Ki-67 was 50% with wild-type TP53 on next-generation sequencing. The disease was characterized as stage III with intermediate risk MIPI (Mantle Cell Lymphoma International Prognostic Index).

For this presentation, one NCCN-guideline recommendation is a cytarabine-containing intensive chemotherapy regimen with rituximab followed by ASCT with maintenance rituximab in patients who are fit for transplant,[7] but the recent data from the multicenter open-label TRIANGLE study has challenged this paradigm.[10]

In TRIANGLE, 870 treatment-naïve patients younger than age 65 (median age 57 years) were randomized to 1 of 3 study arms.[10] In the control arm, patients received the standard-of-care induction with intensive chemoimmunotherapy (CIT) with ASCT consolidation (CIT + ASCT). In 1 of 2 experimental arms, patients received CIT + ibrutinib followed by ASCT consolidation and 2 years of ibrutinib maintenance (CIT + I + ASCT). In the other experimental arm, patients received CIT + ibrutinib followed by 2 years of ibrutinib maintenance with ASCT omitted (CIT + I). Rituximab maintenance as a single dose administered every 2 months for up to 3 years was permitted in all arms.

Most (87%) of the patients in TRIANGLE had stage IV disease and most (85%) had low- or intermediate-risk MIPI. The primary endpoint was failure-free survival (FFS). Rates of FFS at 3 years were 72% for the CIT+ ASCT arm, 88% for the CIT + I + ASCT arm, and 86% for the CIT + I arm. Overall survival (OS) at 3 years, during which time the trial was amended to permit rituximab maintenance in all 3 study arms, numerically favored ibrutinib arms (92% for CIT + I and 91% for CIT + I + ASCT), over chemotherapy alone (86% for CIT + ASCT).

The TRIANGLE trial does not yet establish a new standard for the types of patients enrolled, but it does show clearly that the use of ibrutinib with CIT was not inferior to the standard intensive approach integrating ASCT, and most types of adverse events occurred with less frequency in the ibrutinib-only arm.

There are numerous questions to pose and a broader understanding of applicability to be gained as more follow-up of this study and other studies utilizing targeted therapies, including other BTK inhibitors, provide more data. Of particular interest is whether the presence of minimal residual disease (MRD) and the prognostic implications of MRD are affected by the use of a BTKi and/or ASCT. The E4151 and E4181 clinical trials may collectively provide greater insight here.[12,13]

Rethinking Front-Line MCL Therapy in Older Patients

Case Study

A 74-year-old man with a history of cardiovascular disease, including a prior ST-elevated myocardial infarction, presents with nonspecific symptoms, including night sweats, intermittent fevers, and fatigue. Despite his symptoms, he continues to work 3 days per week and participates in a weekly game of doubles tennis. Axillary swelling leads him to seek medical attention. Imaging demonstrates diffuse lymphadenopathy. An axillary lymph node biopsy confirms a diagnosis of MCL with FISH (fluorescence in situ hybridization) positive for t(11;14). He is of intermediate risk on MIPI scoring.

Due to his age and concurrent heart disease, he is not a candidate for aggressive chemotherapy and ASCT. Less aggressive therapies including bendamustine plus rituximab (BR),[14,15] lenalidomide plus rituximab (RR),[8] and rituximab, bendamustine, and cytarabine (R-BAC) are discussed with this patient.[16]

Based on STiL data and BRIGHT studies, BR has become a widely used regimen.[14,15] However, attempts are being made to improve upon the BR backbone with the addition of BTK inhibitors.[11] In SHINE, BR plus ibrutinib further improved PFS relative to BR alone. SHINE was a 2-arm study, which was restricted to patients 65 years of age or older (median age 71 years); 523 previously untreated patients with good performance status and acceptable organ function were randomized to BR or BR plus ibrutinib. Most patients had intermediate- (~48%) or high- (~34%) risk MIPI. More than 90% had advanced stage disease.

Of patients in whom the TP53 mutation status was established, only about 10% were positive.

In the arm receiving BR alone, the median PFS was 52.9 months. With the addition of 560 mg once-daily ibrutinib to 6 cycles of BR followed by maintenance rituximab and continued ibrutinib, the median PFS, which was the primary endpoint, climbed to a median of 80.6 months. BR plus ibrutinib was associated with a 41% reduction in the hazard ratio (HR) for progression or death (HR 0.75; *P*=.01). When stratified by risk factors, the advantage of BR plus ibrutinib was particularly pronounced in patients with intermediate-risk, (although not high-risk) nonmutated TP53, and less bulky disease.[11]

There was no significant effect of the addition of ibrutinib on OS at the last analysis, but the longer PFS was achieved with only a modest increase in adverse events (AEs). For AEs of grade 3 or higher, the AE rates for BR plus ibrutinib and BR alone were 81.5% and 77.3%, respectively. Rates of cytopenias, including grade 3 or higher, were similar in the 2 arms. Rash and gastrointestinal AEs, such as diarrhea, nausea, and abdominal pain, occurred more frequently among patients who received ibrutinib.[11]

Without an OS advantage, the SHINE trial does not establish a new standard of care, particularly given that it was voluntarily revoked from the market for the treatment of MCL. However, results are likely to accelerate interest in evaluating other targeted therapies, in combination with other relatively well-tolerated treatments. In patients with MCL unfit for ASCT, there is interest in pursuing other BTK inhibitors, particularly with ibrutinib being revoked as an indication for MCL. including the newer noncovalent pirtobrutinib, which was recently approved for MCL in the relapsed/refractory setting,[17] and bispecific T-cell engagers (BiTEs) such as glofitamab.[18]

Rethinking Front-Line in TP53-Mutated MCL

Case Study

A previously healthy 62-year-old woman who presents with rapidly progressing lymphadenopathy and constitutional symptoms is diagnosed with MCL that has multiple adverse features. She has a Ki-67 level higher than 30%, a TP53 mutation, and blastoid morphology.[19]

The NCCN guidelines strongly recommend a clinical trial for patients with a TP53 mutation.[7] Despite various high-intensity combinations to control disease in these patients, the 2017 pooled analysis demonstrated that most patients with TP53 mutations have a poor or no response to chemotherapy with a high side effect burden.[19] In particular, such patients derive little benefit from high-intensity chemotherapy using ASCT.[19]

Nonetheless, for TP53-mutated MCL, several regimens have demonstrated activity. Most of these have used highly targeted therapies that offer the potential for low relative rates of toxicity. Two "chemotherapy-free" combinations involving venetoclax, the CD20-targeted obinutuzumab, and BTK inhibitors have completed phase 2 trials with promising results.[20,21] In a study evaluating the BOVen regimen (the second-generation BTK inhibitor zanubrutinib, obinutuzumab, and venetoclax) as time-limited therapy in TP53-mutated patients, 89% of patients achieved MRD at 26 months of follow-up.[20]

Several novel therapies being tested in the relapsed/refractory setting have generated interest for evaluation in front-line clinical studies. These strategies include the BiTE glofitamab,[18] the antibody-drug conjugate zilovertamab vedotin,[22] and the chimeric antigen receptor (CAR) T-cell therapy brexucabtagene autoleucel (brexu-cel).[23] Brexu-cel is already approved in relapsed/refractory MCL.[23] Given the poor response to available treatments seen in patients with TP53 mutations, these novel therapies have the potential to improve outcomes in this population of high unmet need.

Summary

Durable remissions of MCL can be achieved with aggressive combinations of chemotherapy, but recent studies suggest a momentum away from cytotoxic drugs toward therapies with more targeted effects. In at least some patient populations, these therapies can rival the degree and duration of disease control achieved with less well-tolerated treatment. If ongoing trials corroborate the long-term efficacy and safety of these approaches, these therapies may represent an important evolution in MCL management.

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Advances in Management of Relapsed/Refractory Hairy Cell Leukemia

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Hairy cell leukemia (HCL) is an indolent, low-grade B-cell lymphoid malignancy that typically presents with fatigue, pancytopenia, and splenomegaly.[1,2] It is a rare disease, with an estimated 1,200 new cases of HCL diagnosed annually in the United States.[1] Demographically, HCL is a disease of older adults (median age at diagnosis, 58 years), and is more commonly found in men than women and in White individuals compared with other ethnic or racial backgrounds.[3,4] Environmental or occupational exposure to toxic substances, pesticides, ionizing radiation, and petroleum products may be linked to increased risk for HCL development.[1,4]

Pathophysiology

HCL develops from activated, mature memory B-cells that, in most cases, have the acquired mutation in *BRAF V600E*, which is present in 80% to 90% of patients with classic HCL.[1,3,5] *BRAF* is an integral part of the RAS-BRAF-MEK-ERK cellular pathway that transmits growth factor signals from the cell surface to the nucleus to regulate cell growth and proliferation.[6] Mutated *BRAF V600E* continuously activates *BRAF* kinase and downstream signaling, resulting in enhanced HCL cell survival and unchecked proliferation.[3]

Variant HCL (HCLv) is a separate, more virulent disease that lacks *BRAF V600E* mutation and CD25 expression on flow cytometry.[1,7-9] Patients with HCLv have a worse prognosis and poor responses to front-line purine analogs, and a higher proportion of these patients carry the unmutated immunoglobulin heavy chain variable (*IGHV*) gene (54% vs 17% in HCL).[1,10,11] About 30% to 50% have wild-type *BRAF* and activating mutations in *MAP2K1*, which encodes aberrant *MEK* downstream of *BRAF*.[10,12]

Most patients with HCL have somatic mutations in the *IGHV* gene.[3,13,14] Patients with unmutated *IGHV4-34* and wild-type *BRAF* have an aggressive form of the disease, even if the HCL cells express CD25 as in classic HCL.[1,15] HCL in patients with unmutated *IGHV* is often refractory to purine analogs and these patients have poor prognosis and rapid progression.[16] Other identified mutations include *CDKN1B* in HCL and *MAP2K1* and *CCNC3* in HCLv.[2]

Signs and Symptoms

In many cases, HCL is asymptomatic, and diagnosed when pancytopenia, monocytopenia, and leukopenia are discovered on unrelated blood work.[2,3,11] Monocytopenia is a specific presentation of HCL, but not HCLv.[11] Typical systemic symptoms include unexplained weight loss and extreme fatigue (80%).[1,3] Other symptoms can include fever, recurrent infections, night sweats, splenomegaly and related pain or abdominal fullness, hepatomegaly, and bleeding or bruising due to thrombocytopenia.[1,3] Splenomegaly is associated with advanced disease.[11]

Up to 30% of patients may present with autoimmune disorders such as vasculitis or psoriasis. Although skin involvement is rare with HCL, 10% to 12% of patients will have dermatologic symptoms either due to recurrent infection or autoimmune reactions.[1,2] Skin reactions include localized or generalized

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maculopapular rash, pyoderma gangrenosum (which may be severe), and recurrent bacterial or viral skin infections.[17]

Diagnosis

After complete history and physical examination, a diagnosis of HCL is usually made based on flow cytometry for immunophenotyping and molecular testing for *BRAF V600E* (**Table 1**).[2,17]

Disease-related fibrosis may impede bone marrow aspiration, and trephine biopsy should be done to make the diagnosis.[11] On morphologic examination, HCL cells are small- to medium-sized, with round, oval, or indented, well-defined nuclei. Cytoplasm is pale blue, and cells have small cytoplasmic projections (**Figure 1**).[2,18]

On flow cytometry, HCL is positive for B-cell antigens (CD19, CD20, CD22), as well as antigens specific to the disease (CD11c, CD25, CD103, CD123), and by immunohistochemistry (IHC) for cyclin D1 and annexin-A1. CD20, CD123, and CD200 are bright in HCL. The presence of T-cell marker CD103 on B-cells indicates HCL.[1-3] HCLv, in contrast, is positive for CD11c and CD103, but usually negative for CD25, CD123, and annexin-A1.[2,19]

BRAF V600E mutation can be identified using droplet digital polymerase chain reaction (PCR), next-generation molecular sequencing, or IHC with a VE1 stain.[3,11] IHC for CD20, annexin-1, and VE1 establish the diagnosis, but also are useful in determining the extent to which leukemic cells have infiltrated bone marrow.[11]

Differential diagnosis of HCL includes HCL variants, splenic marginal zone lymphoma, and splenic diffuse red pulp small B-cell lymphoma.[7,11]

Indications for Treatment and Criteria for Response

Over time, about 90% of patients with HCL will require treatment. However, not all such patients will require urgent or immediate treatment, and some can be managed with observation and close monitoring.[1,11] The indications for initiating treatment generally are systemic symptoms and significant pancytopenia (**Table 2**).[2,11]

The optimal response with treatment of HCL is complete response (CR) without minimal residual disease (MRD-free), which minimizes the risk for relapse.[1,11] Hematologic and molecular response is assessed using peripheral blood samples;

TABLE 1. Essential Tests for HCL Diagnosis[2,11]

- **Workup**
  - History and physical examination
  - Assess for presence of splenomegaly, hepatomegaly, peripheral lymphadenopathy
  - Performance status
  - Peripheral blood smear
  - CBC with differential
  - Metabolic panel with focus on renal function, LDH
  - Assess for HBV/HCV before starting treatment
- Bone marrow biopsy ± aspirate
- Morphologic examination of peripheral blood or bone marrow: Wright's stain
- Immunohistochemistry (IHC) or flow cytometry for CD19, CD20, CD5, CD10, CD11c, CD22, CD25, CD103, CD123, cyclin D1, CD200, annexin-A1
- Molecular testing for *IGHV4-34* rearrangement and *BRAF* V600E

Abbreviations: CBC, complete blood count; CD, cluster of differentiation; HBV, hepatitis B virus; HCL, hairy cell leukemia; HCV, hepatitis C virus; LDH, lactate dehydrogenase.

FIGURE 1. Typical Appearance of Hairy Cell Leukemia.

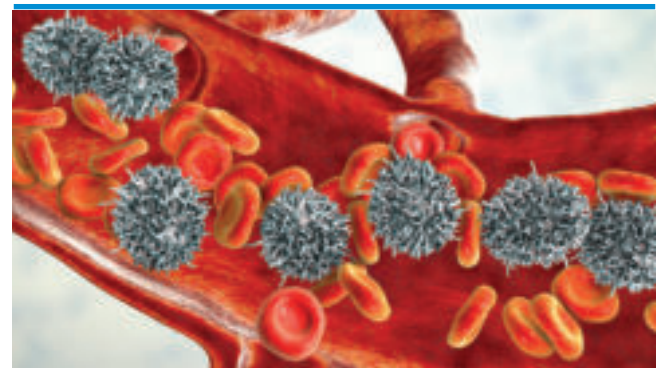

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TABLE 2. Indications for Treatment of HCL[2,11]

Systemic symptoms	
• Weight loss >10% in < 6 months • Excessive fatigue	
Hematologic parameters	
○ Hb	10-11 g/dL
○ Platelets	<100,000/mcL
○ ANC	<1000/mcL
Lymph nodes	> 2 cm in short axis
Symptomatic splenomegaly or hepatomegaly	
Progressive lymphocytosis/ lymphadenopathy	

Abbreviations: ANC, absolute neutrophil count; Hb, hemoglobin; HCL, hairy cell leukemia.

physical examination, ultrasound, computed tomography, or magnetic resonance imaging is used to determine response in lymph nodes, spleen, or liver.[1] MRD-free is defined by the absence of HCL cells by the chosen method (IHC, flow cytometry, or PCR).[20] Bone marrow aspirate flow cytometry is the most sensitive standard test for MRD detection.[1] **Table 3** summarizes response criteria for HCL.[2,11]

Initial Treatment of HCL

The purine nucleoside analogs (PNAs) cladribine (± rituximab) and pentostatin are widely recommended for initial treatment.[1,2,11] As monotherapy, cladribine and pentostatin are considered similarly effective, with CR in 70% to 90% of patients and durations of response > 10 years.[1] Adding the anti-CD20 monoclonal antibody rituximab in 8 weekly doses starting the first day of front-line cladribine (CDAR) improves remission, MRD-free rates, and duration of response (94% MRD-free at 96 months), with minimal added toxicity.[21] Rituximab is often added 4 weeks after cladribine, which offers more convenience, an equally high CR rate of 100%, and a 76% MRD-free rate at 3 months.[11] Bone marrow biopsy should be delayed for 4 to 6 months to allow a full response to develop with cladribine.[1,11]

Daily (intravenous or subcutaneous) and weekly cladribine are equally safe and effective.[2,11] Pentostatin is administered intravenously every 2 weeks for 3 to 6 months, allowing time for hematologic recovery between doses.[1,11] Patient factors to consider when choosing treatment include baseline neutropenia, patient preference, and comorbidities.

Toxicities of PNAs include neutropenia and fever, which typically occur during the first month of treatment and are more frequent in patients with baseline severe neutropenia; T-cell recovery may take years.[1] CDAR is associated with higher transient thrombocytopenia, but faster platelet and neutrophil recovery at 4 weeks than cladribine alone.[21] Both therapies are immunosuppressive. Patients should be evaluated for existing infection and watched for new infections during treatment. Control of active infection prior to treatment initiation is required.[11,23]

Patients with confirmed *BRAF V600E* mutation are candidates for vemurafenib if they are unable to tolerate a PNA, have an active infection, or would like effective vaccinations.[2,23-25]

Treatment at Relapse

At suspected HCL relapse, patients should be evaluated to determine whether cytopenia is due to recurrent disease or lingering effects from prior treatment. Use of successive flow cytometry over time can clarify whether symptoms are related to disease and need interventional treatment, or will resolve with additional time.[1]

Patients who have an HCL relapse after initial therapy with cladribine or pentostatin may be candidates for re-treatment with the same or alternate PNA plus rituximab.[2] Rituximab monotherapy has been used for patients unable to tolerate PNA but yields CR rates as low as 13%.[26] Repeated courses of PNA therapy yield lower rates and durations of response with each course.[1,2]

For patients with primary refractory disease (less than CR with initial therapy) or relapse within 2 years of initial therapy, treatment with the *BRAF V600E* inhibitor

TABLE 3. Response Criteria for HCL[2,11]

CR	• Hb >11 g/dL • Platelets: >100,000/mcL • ANC: >1500/mcL • Regression of splenomegaly, absence of morphologic signs of HCL in peripheral blood and bone marrow
CR with/without MRD	In patients who achieve CR, flow cytometry/IHC/PCR to detect residual disease
PR	• Peripheral blood count as in CR • ≥ 50% improvement in organomegaly and bone marrow infiltration
SD	Not meeting criteria for CR or PR
PD	25% increase in organomegaly or peripheral blood counts
Relapse	• Morphologic: reappearance of HCL in peripheral blood or bone marrow • Hematologic: blood counts below criteria for CR/PR

Abbreviations: ANC, absolute neutrophil count; CR, complete response; Hb, hemoglobin; HCL, hairy cell leukemia; MRD, minimal residual disease; PD, progressive disease; PR, partial response; SD, stable disease.

vemurafenib off-label, with or without rituximab, is an option.[2,5] In HCL, vemurafenib for patients with relapsed or refractory disease achieved CR in 35% and 42% in 2 small trials (N = 54). Relapse-free survival among people with CR was 19 months in 1 of the trials.[27] Vemurafenib plus rituximab achieved CR in 87% of patients with relapsed or refractory HCL, and an MRD-free CR rate of 57%. Among patients with CR, 85% were relapse-free at a median follow-up of 34 months.[5] Treatment with vemurafenib is not myelotoxic—an advantage for HCL patients. Adverse effects with vemurafenib are often manageable with dose reductions, if needed. A specific concern with vemurafenib is the potential development of secondary skin cancers.[5,27,28]

Novel Targeted Options and Recommended Use

Promising alternatives for patients with relapsed or refractory HCL include combined *BRAF* and *MEK* inhibitors and the Bruton tyrosine kinase (BTK) inhibitor ibrutinib. The concept of *BRAF/MEK* inhibition was validated in studies with *BRAF*-mutated melanoma, in which dabrafenib plus trametinib (the *MEK* inhibitor) improved overall survival (OS) with less toxicity and better quality of life than vemurafenib.[1,29] In a phase 2 trial in HCL, dabrafenib monotherapy demonstrated an overall response rate (ORR) of 80%, including 30% CR.[30] In a subsequent phase 2 trial, dabrafenib combined with trametinib was evaluated in refractory or late relapsed HCL. Among 55 enrolled patients, objective response rate was 89%, including 65.5% CR. Nine of 36 patients with CR were MRD-free. Among responding patients, duration of response was 97.7% at 24 months.[31] The most common grade ≥ 3 toxicities were hyperglycemia, pyrexia, neutropenia, and pneumonia. Secondary skin cancers were seen in about 5% of patients.[31]

BRAF/MEK inhibitor combinations in HCL offer effective therapy with less myelosuppression than PNAs, making them useful for patients with or at risk for infection.[23] Their use in HCL is off-label, as they currently are approved for treatment of *BRAF*-mutated melanoma and some other tumors.[32] A study of encorafenib (a *BRAF* inhibitor) combined with binimetinib (a *MEK* inhibitor) is ongoing (**Table 4**).[32]

Ibrutinib interrupts B-cell receptor signaling to stop tumor cell growth. In a phase 2 trial, patients with relapsed or refractory HCL or HCLv were treated with once-daily oral ibrutinib. Best ORR was 54% (19% CR; 3% MRD-free). Despite the low CR rate, 3-year progression-free survival with ibrutinib was 73% and OS was 85%. Treatment was well tolerated; cytopenia (including 22% grade ≥ 3 thrombocytopenia and neutropenia) and diarrhea were frequent toxicities.[33]

Moxetumomab pasudotox is a novel CD22-targeted antibody fused with protein toxin that interrupts protein synthesis in tumor cells.[1] As treatment, it was studied in a phase 3 trial of relapsed HCL in heavily pretreated patients, and achieved a CR rate of 41%, including 36% durable CR.[34] Although FDA-approved for relapsed or refractory HCL, the drug is being discontinued due to business decisions, not safety or efficacy concerns.[2] It is notable that many types of B-cell lymphoma also express CD22.[35]

Enrollment in a clinical trial to study possible treatment advances is recommended by the National Comprehensive Cancer Network (NCCN) at first and subsequent relapses of HCL for appropriate patients.[2]

Figure 2 summarizes an approach to treatment choice and sequencing for patients with HCL.

Supportive Care

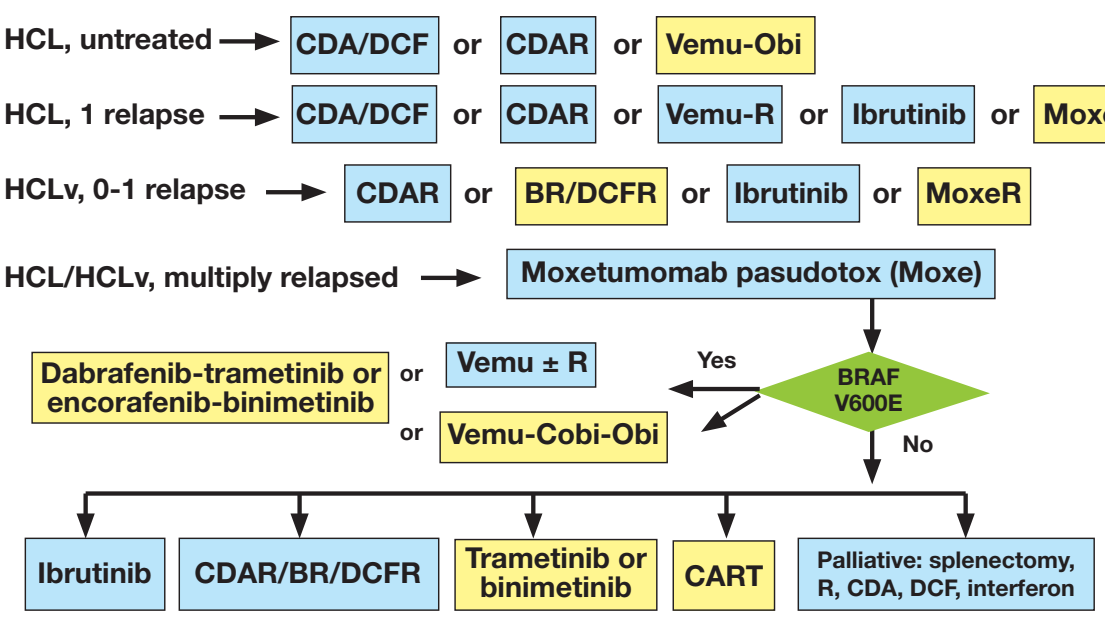
Patients being treated for HCL should have supportive care to manage adverse effects of their disease. Such care includes prophylaxis against herpes virus if CD4+ T cells < 200 cells/μL and other prophylactic vaccinations to hepatitis B virus, COVID-19 and Influenza. Patients with neutropenia may require broad-spectrum antibacterial prophylaxis or neutrophil growth factors if neutropenic fever develops. Blood product support is recommended if needed.[2] Assessment of anti-COVID-19 antibodies is recommended to optimize immunity, particularly prior to beginning anti-CD20 antibody therapy like rituximab.[23]

TABLE 4. Currently Recruiting Clinical Trials Specifically for HCL

Low-dose vemurafenib + rituximab for *BRAF*-mutated relapsed HCL (NCT05388123)
Binimetinib R/R HCL/HCLv without *BRAF V600E* (NCT04322383)
Encorafenib + binimetinib *BRAF*-mutated R/R HCL (NCT04324112)
Anti-CD22 CAR T-cell therapy (phase 1): relapsed HCL/HCLv (NCT04815356)
Cladribine and rituximab for once-relapsed HCL (NCT00923013)
Investigation of COVID-19 immunity in HCL/HCLv (NCT04362865)

Abbreviations: CAR, chimeric antigen receptor; CD, cluster of differentiation; CR, complete response; HCL, hairy cell leukemia; HCLv, HCL variant; R/R, relapsed/refractory.

FIGURE 2. Standard & Investigational Treatment of HCL/HCLv[36]



Abbreviations: CART, chimeric antigen receptor T-cell; CDA, cladribine; DCF, pentostatin; Cobi, cobimetinib; HCL, hairy cell leukemia; HCLv, hairy cell leukemia variant; Moxe, moxetumomab pasudotox; Obi, obinutuzumab; R, rituximab; Vemu, vemurafenib. Options currently or recently tested in clinical trials are in yellow.

Unmet Needs

Despite improvements in response and survival with newer therapies, not all patients with HCL benefit from these advances. Unmet needs are finding optimal treatment for patients with HCLv, despite some success with *MEK* inhibitors, and for patients with *BRAF* mutations other than *V600E*, who have few options beyond PNAs and rituximab.

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Treatment Needs of Older Adults With Newly Diagnosed Acute Myeloid Leukemia

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Defining "Unfit" for Intensive Chemotherapy

Within the last 40 years, younger fit patients have benefited from intensive chemotherapy regimens for acute myeloid leukemia (AML) with improved survival, and the possibility of long-term disease-free survival (DFS) ("cure").[1] Older patients are often considered too unfit for standard curative treatment with intensive induction chemotherapy followed by consolidation chemotherapy, allogeneic hematopoietic cell transplantation (allo-HCT), or both.[2-4] Higher induction mortality and poor overall survival (OS) are associated with worse performance status, organ impairment, significant comorbidities, and declining cognitive function, all of which are more common with advancing age. Although the suggested criteria for determining unfitness have not been validated (**Table 1**), they can provide guidance in clinical practice.[2-5]

The National Comprehensive Cancer Network (NCCN) panel recommends the consideration of a patient's performance status and comorbid conditions in addition to their age to determine a patient's fitness for intensive induction therapy.[6] Adverse disease features should also be considered, because disease biology may make intensive chemotherapy futile or inappropriate. For example, the mutational driver tumor protein p53 (TP53) appears at a higher frequency in older adults than younger adults and is associated with dismal outcomes even with intensive chemotherapy. Likewise, the spliceosome and chromatin modifier gene mutations are more common in older patients with AML and confer a worse OS with intensive therapy.[6,7] Older unfit patients faced a difficult decision: proceed with intensive therapy with some possibility of long-term survival but risk of early mortality and significant toxicity, or opt for supportive care

TABLE 1. Criteria to Define Unfitness for Intensive Chemotherapy to Treat AML[5]

- Age ≥ 75 years
- Congestive heart failure or documented cardiomyopathy with an ejection fraction ≤ 50%
- Documented pulmonary disease with DLCO ≤ 65% or FEV1 ≤ 65%, or dyspnea at rest or requiring oxygen, or any pleural neoplasm or uncontrolled lung neoplasm
- Age > 60 years, plus any of the following: Receiving dialysis, or having uncontrolled renal carcinoma, liver cirrhosis (Child B or C), documented liver disease with marked elevation of transaminases (43x normal values), any biliary tree carcinoma or uncontrolled liver carcinoma, or acute viral hepatitis
- Active infection resistant to anti-infective therapy
- Current mental illness requiring psychiatric hospitalization, institutionalization, or intensive outpatient management, or current cognitive status that produces dependence not controlled by the caregiver
- ECOG performance status ≥ 3 not related to leukemia
- Any other comorbidity deemed incompatible with conventional intensive chemotherapy by the physician

Abbreviations: DLCO, diffusing capacity of the lungs for carbon monoxide; ECOG, Eastern Cooperative Oncology Group; FEV1, forced expiratory volume in 1 s.

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and palliative chemotherapy, such as the hypomethylating agents (HMAs) or low-dose cytarabine, with much shorter survival.

Guidelines for Treating Older Unfit Patients

Evidence-based guidelines for managing older adults with newly diagnosed AML were developed by the American Society of Hematology in 2020; however, these guidelines were released prior to the results of several clinical trials involving older patients with AML (**Table 2**).[8] In 2022, the European LeukemiaNet (ELN) recommendations were updated to include new therapeutic agents that target specific mutations in genes such as tyrosine kinase 3 (*FLT3*), isocitrate dehydrogenase 1 (*IDH1*), isocitrate dehydrogenase 2 (*IDH2*), and B-cell lymphoma 2 (*BCL2*). Given the important effects of genetic aberrations on disease phenotype, treatment options, and outcomes, screening for genetic aberrations at diagnosis is now essential.[9]

The potential for clonal evolution leading to new actionable targets that were not present at diagnosis highlights the importance of reevaluation of genetic aberrations throughout clinical progression. Actionable targets can include mutations in *IDH1/IDH2, FLT3*-internal tandem duplication or *FLT3* tyrosine kinase domain.[9]

Treatment Landscape

Since 2018, several therapeutic agents have been added to the treatment armamentarium that can induce longer term complete remission (CR) for older unfit patients with newly diagnosed AML (**Table 2**).[4]

Management of Primary AML With Less Intensive Induction Therapy

VIALE-A established a new standard of care for older unfit patients by demonstrating the benefit of adding the BCL2 inhibitor venetoclax (VEN) to azacitidine (AZA).[2] VIALE-A demonstrated that the rate of CR plus CR with partial hematologic recovery (CRi) was 65% for VEN plus AZA and 18% for AZA. Most remissions

TABLE 2. Treatment Landscape for Older Unfit Patients[a-d]

Patient population	Clinical trial: Treatment arms	Median OS, months[a]
Induction Therapy		
AML without actionable mutations	VIALE-A (phase 3): VEN + AZA vs AZA	14.7 vs 9.6[2]
AML without actionable mutations	VIALE-C (phase 3): VEN + LDAC vs LDAC	Failed to meet primary end point[10] Post hoc analysis: 8.4 vs 4.1
CD33-positive AML	EORTC-GIMEMA AML-19 (phase 2/3): Gemtuzumab ozogamicin vs BSC	4.9 vs 3.6[11]
AML or high-risk MDS	NCT01546038 (phase 2): Glasdegib + LDAC vs LDAC	8.8 vs 4.9[4,12]
IDH1 mutated	AGILE (phase 3): Ivosidenib + AZA vs AZA	24 vs 7.9[13]
FLT3 mutated	NCT02752035 (phase 3): Gilteritinib + AZA vs AZA	Failed to meet primary end point[14]
Maintenance		
First CR after intensive therapy	QUAZAR AML-001 (phase 3): CC-486 (oral AZA) vs placebo	24.7 vs 14.8[15]
Relapsed/Refractory		
FLT3-mutated AML (prior anthracycline)	ADMIRAL (phase 3): Gilteritinib vs chemotherapy	9.3 vs 5.6[4,16]
IDH2-mutated AML	NCT01915498 (phase 1/2): Enasidenib	9.3[4]
IDH1-mutated AML	NCT02074839 (phase 1): Ivosidenib	8.2[4]

Abbreviations: AML, acute myeloid leukemia; AZA, azacitidine; BSC, best supportive care; CR, complete response; LDAC, low-dose cytarabine; MDS, myelodysplastic syndrome; OS, overall survival; sAML, secondary acute myeloid leukemia; VEN, venetoclax.
[a]*P*<.05 unless otherwise noted.
[b]BEAT is an umbrella trial targeting various mutations. Participants are randomized based on the results of the genomic screening within 7 days of diagnosis. The feasibility of delaying treatment until the karyotype and genetic profile are complete has been demonstrated.[7]
[c]Repeat mutational profiling at time of relapse.[4]
[d]Patients were enrolled regardless of their *TP53* mutational status.[17]

in the AZA/VEN arm occurred rapidly in the first 2 cycles. The median survival improved from 9.6 months with AZA to 14.7 months with AZA/VEN. An improvement in survival with VEN and low-dose cytarabine also emerged in a 6-month post hoc analysis of the VIALE-C trial.[10] Various other trials examining targeted therapies on specific mutations have provided mixed results in the front-line setting.[13,14,18] It is important to note that a recent systematic review found that 12% to 25% of patients who were unfit for intensive therapy were successfully bridged to HCT.[19]

Management of Postremission Response

Patients with a longer duration of first remission have demonstrated better survival outcomes.[15] Two trials have examined postremission therapy in the setting of prior intensive therapy. HOVON97 enrolled older patients who achieved CR/CRi after 2 cycles of intensive therapy to receive either AZA postremission or no further treatment. The proportion of patients with DFS at 12 months was greater in the AZA maintenance group than in the observation group (64% vs 42%), but significant DFS improvement did not translate into improved OS.[20] QUAZAR AML-001 demonstrated that OS was longer for older patients receiving maintenance therapy with CC-486 (a non-bioequivalent oral formulation of AZA) vs placebo (24.7 vs 14.8 months).[15] CC-486 was FDA-approved for maintenance therapy after intensive induction with or without consolidation in patients who are not candidates for allo-HCT. However, limited evidence exists specifically for postremission therapy in unfit patients who have received less intensive therapy. Continuation of the lower intensive therapy is recommended until disease progression.[6] No data are available to support the use of oral AZA therapy alone for maintenance of remission following HMA/VEN-induced remissions.

Management of Relapsed and Refractory AML

Nearly 50% of patients with AML experience relapse and up to 40% may be refractory.[19] Importantly, patients who were considered fit for intensive therapy may not remain so with relapsed or refractory AML (r/rAML), so patients should be evaluated for fitness for an intensive salvage regimen. Similar to assessing fitness for induction therapy, no standard definition of fitness exists for r/rAML.[19]

Disease control is the goal for patients with r/rAML who are unfit for intensive salvage therapy; however, treatment options remain limited and prognosis is poor.[19] Depending on the patient's cytogenetic profile, management can include HMA with or without VEN, glasdegib with LDAC, gilteritinib, ivosidenib or enasidenib, or gemtuzumab ozogamicin.[9] Only a few studies have been published involving the r/rAML population not eligible for intensive salvage regimen, and guidelines are needed for this population.[19] Thus, the ELN recommends that clinical trial enrollment be considered for patients with r/rAML.[9]

Management of Secondary AML or High-risk AML

Compared with de novo AML, both secondary AML (sAML) and therapy-related AML (tAML) have been associated with inferior outcomes. Factors that influence poor outcomes can include older age, comorbidities, persistent malignant disease or relapse of primary malignancy, treatment-induced depletion of hematopoietic reserves and/or prolonged myelosuppression, and genetic abnormalities, such as TP53 mutations.[21]

CPX-351 is a dual drug that contains cytarabine and daunorubicin.[9,22] An open-label study (NCT01696084) compared CPX-351 with conventional cytarabine and daunorubicin (induction and consolidation therapy) in older patients (aged 60-75 years) with newly diagnosed high-risk/sAML who were considered fit for intensive therapy. The OS for CPX-351 was longer (9.56 vs 5.95 months) and the safety profiles were similar between the treatment groups.[23] Patients achieving CR/CRi received up to 2 cycles of consolidation with CPX-351. An exploratory analysis of this subgroup revealed median OS was longer with CPX-351 consolidation (25.43 vs 8.53 months).[22] Patients with TP53 mutations had poor treatment outcomes regardless of treatment arm, whereas patients with sAML-type mutations including spliceosome and chromatin modifier genes had longer OS with CPX-351 therapy.[24] The 5-year results of this trial indicate that the survival benefit of CPX-351 was maintained.[25] However, data from a retrospective review involving 136 patients with either sAML or AML with myelodysplasia-related changes revealed no difference in survival outcomes between patients treated with either HMA/VEN or CPX-351.[26]

Case Study: Elderly Woman With Newly Diagnosed AML

In 2018, Ms. W, age 69 years, was diagnosed with seropositive, nonerosive rheumatoid arthritis; she began methotrexate 17.5 mg per week split dosing in conjunction with oral folic acid 2 mg/d with varying doses based on symptoms. Her comorbidities included recurrent episodes of diverticulitis, hypertension, hypothyroidism, obstructive sleep apnea, and gastrointestinal reflux disease. On February 4, 2021, her methotrexate was increased to 20 mg and required intermittent prednisone tapers for flares. In November 2021, a blood test revealed she had a decreased white blood cell (WBC) count at 1.8 K/µL, and her methotrexate dose was decreased to 15 mg weekly. Despite the dose reduction, she had grade 3 neutropenia and anemia (WBC: 0.7 K/µL; HGB:10.5 g/dL) with a normal platelet count (PLT: 165,000/µL). Methotrexate was discontinued and leucovorin was initiated. She then had only modest improvement in her lab values and peripheral blood blasts.

On March 17, 2022, she underwent a bone marrow biopsy and aspirate, which resulted in a diagnosis of AML. She had 55% blasts in a 90% cellular bone marrow with mild reticulin fibrosis and numerous circulating blasts. She was classified as having AML without maturation (FAB AML-M1). Flow cytometry detected a phenotypically abnormal population with CD45 expression and side scatter/forward scatter features of small-to-medium sized blasts, accounting for 23% of total cells. The chromosome analysis demonstrated a normal female karyotype in all 19 available metaphases. Polymerase chain reaction analysis was negative for *FLT3-ITD*, *FLT3*-TKD, and *NPM1* mutations and positive for an *IDH1* R132C missense mutation. The myeloid gene panel identified only a single pathogenic variant, *IDH1* R132C (variant allele frequency [VAF] 21.2%), and a variant of unknown significance DNMT3A A575P (VAF 25.7%).

Noting that she does not have favorable risk features, we discussed treatment options. Although she is a candidate for curative therapy, the patient was not interested in pursuing allo-HCT. Her history of diverticulitis is concerning for tolerating intensive chemotherapy. In addition, her immunosuppressive therapy increases her risk for opportunistic infections. Based on the available data from the AGILE and VIALE studies and associated potential adverse reactions, she opted for starting treatment with AZA and IVO.

On March 31, 2022, she began receiving AZA 75 mg/m^2 intravenous (IV) once daily days 1-7 and oral IVO 500 mg once daily continuously. She has received 12 cycles and has not needed transfusion. She has not had febrile neutropenia or symptoms of differentiation syndrome. On March 24, 2023, she underwent laparoscopic cholecystectomy, because an ultrasound revealed cholelithiasis, abnormal gallbladder wall thickening, and pericholecystic fluid. She was discharged home the following day and is continuing with AZA/ivosidenib.

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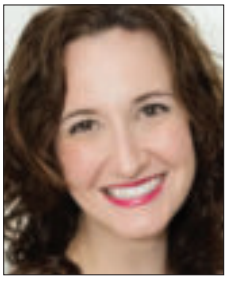
Progress in Management of Advanced Acute Lymphocytic Leukemia in Children



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Acute lymphocytic leukemia (ALL) is a heterogeneous malignancy that may develop from B or T lymphocytes (B-ALL, T-ALL) and affects patients of all ages.[1] In the United States, an estimated 6,540 new cases are diagnosed each year—including 3,100 in individuals aged < 20 years—and approximately 1,390 deaths annually.[2,3] It is the most encountered cancer in patients aged < 20 years, and generally carries a good prognosis; almost all younger patients achieve remission with current therapies. Five-year overall survival (OS) is 90% in patients aged < 15 years, 75% in patients aged 15-19 years, and 61% in adolescent/young adult patients (which generally includes patients up to age 39).[2,4,5] In contrast, only about 30% of adults with ALL achieve remission with current therapies.[1]

Incidence peaks in children aged 1-4 years, decreasing thereafter. Cases are highest among Native American/Alaskan Native and Hispanic children, and higher in White than Black children.[4] ALL is seen more in patients with certain inherited conditions, including Down syndrome, ataxia telangiectasia, neurofibromatosis type 1, and Bloom syndrome.[1]

Treatment advances have improved remission rates and outcomes for patients. However, relapse is still a leading cause of death for patients of all ages.[6] Prompt diagnosis and care are important to optimize outcomes, as treatment delay is associated with poorer survival.[7]

Pathophysiology

In ALL, abnormal, immature lymphocytes and progenitor B cells/T cells proliferate uncontrollably and eventually replace healthy cells in bone marrow and the lymphatic system. The loss of healthy cells leads to classic symptoms of cytopenia, splenomegaly, and hepatomegaly.[1] B cells and T cells are descended from lymphoid stem cells (and are transformed by germline or somatic mutation into pathogenic cells, leading to symptom development and bone marrow dysfunction. Most pediatric patients have extensive bone marrow involvement at diagnosis, with > 25% blast cells in marrow (defined as M3 disease).[4]

Presentation

Patients usually present with signs and symptoms that are related to disease-associated anemia, thrombocytopenia, or neutropenia; these signs and symptoms may include fatigue or weakness, pale skin, bleeding or bruising easily, fever or infection, joint or extremity pain, B-cell symptoms such as night sweats or unintentional weight loss, and splenomegaly or hepatomegaly. Central nervous system (CNS) symptoms can include stroke-like symptoms due to leukemic cell invasion of CNS vasculature or neuropathies related to increased intracranial pressure. Sometimes, children may present with no symptoms other than joint or extremity pain.[1,3,8]

Classification

ALL is classified by whether it derives from B-cell or T-cell progenitor cells and, within these, by typical genetic alterations (**Table 1**).[3,9-15] Some cytogenetics are associated with risk assessment as well. Well-identified B-ALL subtypes include Philadelphia (Ph) chromosome-positive, hyper- and hypodiploidy, and *KMT2A* rearranged, while newer classifications include Ph-like ALL and B-lymphoblastic leukemia with *iAMP21*. Provisional T-ALL subtypes include early T-cell

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TABLE 1. Common Genetic Alterations in ALL[3,9-15]

Alteration	Cytogenetic risk group	Frequency	
		Adult	Pediatric
B-ALL only			
Hyperdiploidy Double trisomy of chromosomes 4 and 10	Good risk Good risk	7%	25%
Hypodiploidy	Poor risk	2%	1%
Ph-positive/*BCR-ABL1*	Poor risk	25%	2%-4%
ETV6/RUNX1 fusion	Good risk	2%	22%
KMT2A rearrangement	Poor risk	10%	8%
TCF3/PBX1	N/A	3%	6%
c-MYC	N/A	4%	2%
BCR-ABL1-like (Ph-like)	Poor risk	10%-30%	15%
RUNX1 (B-ALL with *iAMP21*)	Poor risk	—	2%
IKZF1/IKAROS	Poor risk	25%-35%	12%-17%
T-ALL only			
NOTCH1/FBXW7 mutation	Good risk	~60%	55%
CRLF2 overexpression	Poor risk	N/A	N/A
Biallelic TCRλ deletion	Poor risk, poor response to induction therapy	N/A	N/A
PTEN	Poor risk	N/A	20%
TAL1	N/A	12%	7%
HOX11	N/A	8%	1%
HOX11L2	N/A	1%	3%

hyperdiploidy: 51-65 chromosomal alterations; hypodiploidy: <44 chromosomal alterations.

Abbreviations: ALL, acute lymphocytic leukemia; B-ALL, B-acute lymphoblastic leukemia; iAMP21, intrachromosomal amplification of chromosome 21; N/A, not available; Ph, Philadelphia chromosome; T-ALL, T-cell acute lymphoblastic leukemia; TCRλ, T-cell receptor gamma.

precursor lymphoblastic leukemia and natural killer cell lymphoblastic leukemia.[3]

B-cell lineage is present in 88% of pediatric and 75%-80% of adult disease. T-ALL is found in about 12% of pediatric patients and 25% of adults.[3,8] Familial syndromes associated with ALL are present in about 4% of pediatric patients, including autosomal dominant germline mutations in *RUNX1* (T-cell ALL), *ETV6* (B-ALL), PAX5 (B-ALL), *IKZF1* (B-ALL and T-ALL), and *TP53* (low-hypodiploid ALL).[3] If a known-familial genotype is identified, families should be referred for genetic counseling and further testing if needed. If germline mutation is suspected, early identification is important; hereditary ALL can influence treatment choice and use of allogeneic transplantation or radiation.[3]

A third classification crucial to guiding treatment is Ph-positive vs Ph-negative or Ph-like, the latter strongly associated with abnormal B-cell development due to deletions in related genes.[3,16] About 3% to 5% of pediatric patients and 25% of adults have Ph-positive ALL.[17] The remission failure rate among pediatric patients treated with chemotherapy was 11% in one study, vs 2%-3% among patients with Ph-negative ALL.[10]

Diagnosis and Risk Stratification

Diagnosis is based on presentation and molecular features, requiring demonstration of ≥ 20% lymphoblasts in bone marrow biopsy or aspirate or ≥ 1,000 circulating lymphoblasts/mL in peripheral blood. Testing can include immunophenotyping using flow cytometry, molecular characterization of baseline leukemic clone, morphology using hematoxylin and eosin staining and Wright/Giemsa staining, and karyotyping.[1,3] CNS involvement is assessed using a lumbar spinal tap.[1]

Risk stratification is based on molecular features (eg, high- and low-risk mutations, **Table 1**),[3,9-15] which are assessed using fluorescence in-situ hybridization, broad-panel next-generation sequencing, and reverse-transcriptase polymerase chain reaction of bone marrow or peripheral blood.[3] Other risk factors include age, CNS involvement, white blood cell (WBC) count, and response to initial induction or consolidation therapy.[3]

Pediatric patients are assigned standard or high risk based on factors identified by the Children's Oncology Group and National Comprehensive Cancer Network (NCCN). Patients aged 1 to < 10 years with WBC < 50 × 109/L are considered standard risk, and all others are considered high risk. Patients with ALL before age 1 have very high risk. All pediatric patients with T-ALL are considered high risk.[3] Ph-positive, Ph-like, hypoploidy, failure to achieve remission with induction, and extramedullary disease are high-risk factors as well, whereas hyperploidy and certain mutations convey low risk.[3]

Newer treatment strategies for initial ALL diagnosis include targeted therapies. One goal of targeted therapy is avoidance of long-term toxicity, leading to improved survival outcomes. Well-studied targeted therapies include the tyrosine kinase inhibitors used in first-line and subsequent treatment of Ph-positive ALL.[3]

Treatment Options in Relapsed/Refractory ALL

The initial treatment goal is complete remission (CR) defined as minimal residual disease (MRD) < 0.01% on flow cytometry (**Table 2**).[3] Prognosis is dependent on time and location of relapse. Early relapse (< 18 months from diagnosis) predicts poor survival. Relapse in bone marrow is associated with poorer prognosis than relapse in CNS.[11-18] Where possible, consolidation with allogeneic hematopoietic cell transplantation improves survival for patients with early relapse.[6] Three approaches have advanced treatment options for relapsed/refractory (R/R) B-ALL, all based around common cell markers seen in B-ALL.

The CD22-directed antibody-drug conjugate inotuzumab ozogamicin is approved for adults with R/R B-ALL. In clinical trials, a higher percentage of patients had results below the MRD threshold, and longer progression-free survival and OS compared with standard care.[19,20]

Blinatumomab is a bispecific T-cell engager that binds to CD19 on the surface of B-ALL cells and to CD3 on T cells to trigger apoptosis.[21] It was first approved for R/R ALL in adults or children, and is also now approved for treatment in remission with MRD ≥ 0.1%. Patients must demonstrate CD19-positive disease to qualify.[15-22] For R/R ALL, blinatumomab improves OS and CR rates compared with standard chemotherapy.[23]

TABLE 2. Response Criteria in ALL[3]

Response	Definition
Complete remission (CR)	When measuring MRD by flow cytometry, CR is defined by MRD negativity rather than blast percentage by morphology: **B-ALL** MRD positive: ≥ 0.01% detectable leukemia cells by flow cytometry MRD negative: < 0.01% detectable leukemia cells by flow cytometry **T-ALL** MRD positive: ≥ 0.1% detectable leukemia cells by flow cytometry MRD negative: < 0.1% detectable leukemia cells by flow cytometry
CR partial hematologic recovery (CRh)	CR except: platelets ≥ 50,000/μL and ANC ≥ 500/μL
CR incomplete hematologic recovery (CRi)	CR except without either platelet or ANC recovery
Refractory disease	Failure to achieve CR at end of induction in B-ALL, or at end of consolidation in T-ALL
Progressive disease (PD)	Circulating leukemic blasts or ≥ 25% increase in bone marrow or circulating blasts or Development of extramedullary disease
Relapsed disease	Return of detectable disease after CR: Threshold of disease detection depends on modality of testing

Abbreviations: ANC, absolute neutrophil count; B-ALL, B-acute lymphoblastic leukemia; CR, complete remission; MRD, minimal residual disease; T-ALL, T-cell acute lymphoblastic leukemia.

The use of CAR T-cell therapies has expanded greatly with increasing knowledge about their efficacy and safety. In R/R ALL, tisagenlecleucel (tisa-gen) is approved for treatment of patients aged ≤ 25 years, and brexucabtagene autoleucel (brexu-cel) is approved for treatment of adults.[3,24,25] Patients undergoing the CAR T-cell process have apheresis to collect T cells, which are then manufactured before being reinfused into the patient. Depending on local capabilities, the time between T-cell harvest and reinfusion can extend to weeks.[3,26,27] Cytoreduction with CAR T-cell therapy can allow previously ineligible patients (due to bulky disease) to undergo transplant. Patients treated in key clinical trials with tisa-gen or brexu-cel achieved high overall remission rates and improved event-free survival and OS rates compared with historical experience.[25,28,29] Important toxicities with CAR T-cell therapy are cytokine release syndrome (CRS) and neurotoxicity, which can develop rapidly. NCCN recommends hospitalizing patients at the first sign of either adverse event. Patients can be managed with tocilizumab or steroids for low-grade CRS or steroids for neurotoxicity. The Society for Immunotherapy of Cancer, American Society of Clinical Oncology, and NCCN have guidelines on management of toxicities related to CAR T-cell therapy as well as management of symptoms and other adverse effects of CRS.[5,23,24]

Programs also incorporate telemedicine for symptom monitoring and follow-up.[32-34] Centers providing CAR T-cell therapy must have a certified Risk Evaluation and Mitigation Strategy (REMS), which ensures adherence to specific guidelines for administration, adverse event management, and patient education.[35,36] Overcoming technical, social, and financial barriers to CAR T-cell therapy is an ongoing challenge of great interest.[37]

R/R T-Cell Precursor ALL

Patients with R/R T-ALL have poor prognosis, partly due to limited treatment options. Nelarabine, a nucleoside analog, is the only approved treatment for R/R T-ALL, but has increasingly been used in first-line therapy added to multiagent chemotherapy as a consolidation and maintenance approach to pediatric disease.[3,38,39] Four-year DSF in pediatric patients with newly diagnosed T-ALL undergoing treatment incorporating nelarabine was 88.9%.[39] Treatment is associated with grade ≥ 3 neurotoxicity in > 10% of patients, and can include CNS toxicity as well as neuropathy.[3]

In a recently completed phase 2 trial (NCT03384654), daratumumab was added to standard chemotherapy (vincristine, prednisone, PEG-asparaginase, doxorubicin) for R/R T-ALL in pediatric (ages 1-17 years) and young adult patients (age ≥ 18 years).[40] Among 24 pediatric patients, CR was 41.7% and overall response rate (ORR; ORR = CR + CRi) was 83% after 1 cycle of treatment. Ten (41.7%) pediatric patients achieved MRD-negative status as well. ORR was 60% in the 5 older patients. All

TABLE 3. Recommended Therapy for R/R ALL[3]

Ph-positive B-ALL	Ph-negative B-ALL	T-ALL
TKI ± chemotherapy	Blinatumomab (preferred)	Nelarabine ± etoposide and cyclophosphamide (preferred)
TKI ± corticosteroid	Inotuzumab ozogamicin (preferred)	Bortezomib + chemotherapy
Blinatumomab ± TKI	Tisagenlecleucel (preferred) • Age <26 years • Refractory disease • ≥2 relapses and failure of 2 TKIs	Daratumumab
Inotuzumab ozogamicin ± TKI	Brexucabtagene autoleucel (preferred)	High-dose cytarabine
Tisagenlecleucel • Age <26 years • Refractory disease • ≥2 relapses and failure of 2 TKIs	Inotuzumab ozogamicin + hyperCVAD ± blinatumomab	Mitoxantrone, etoposide, cytarabine
Brexucabtagene autoleucel • Relapse after therapy that included TKI(s)	Multiagent chemotherapy	Venetoclax + chemotherapy

Abbreviations: ALL, acute lymphocytic leukemia; B-ALL, B-acute lymphoblastic leukemia; hyperCVAD, cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate, and cytarabine; R/R, relapsed/refractory; Ph, Philadelphia chromosome; T-ALL, T-cell acute lymphoblastic leukemia; TKI, tyrosine kinase inhibitor (eg, dasatinib, imatinib, ponatinib, nilotinib, bosutinib).

pediatric patients had at least 1 grade ≥ 3 toxicity, but none of the adverse events led to discontinuation.[40]

Success in achieving MRD-negative responses in patients treated for R/R ALL has increased interest in using targeted therapies for newly diagnosed patients. Recommended treatment approaches are summarized in **Table 3**.[3]

Long-Term Follow-Up and Survivorship

A study of > 500 pediatric patients followed for an average 23 years reassuringly found low prevalence of adverse outcomes related to disease or treatment. Major adverse outcomes such as death due to late relapse; secondary malignancy; or development of osteoporosis, cataracts, and diminished functional status were infrequent.[41] Most prevalent were growth effects (short stature or growth hormone insufficiency), likely related to certain treatment approaches.[41] Guidelines for long-term follow-up of pediatric patients are available from the Children's Oncology Group.[42]

A 2017 systematic review concluded that the quality of life for survivors is diminished upon treatment, and persistently over time for some patients.[43] In contrast, a 2022 comparison of long-term survivors (median 20.5 years since diagnosis) of pediatric ALL with healthy controls found that survivors had better quality of life in some domains, including general health, vitality, and mental health.[44] Smaller percentages of survivors rated themselves happiest about sleep quality, absence of pain, and physical abilities.[44]

As therapy patterns and options evolve, continued follow-up is important to ensure patients derive optimal benefit from treatment and post-treatment life.

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