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Medically Integrated Pharmacies, Oral Oncolytic Agents Grow in Importance During COVID-19

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Health care professionals have looked for innovative ways to work around many of the obstacles that the COVID-19 pandemic presents.

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As the most accessible member of the health care team, the pharmacist can give patients with cancer the information and support they need.
The Increasing Growth of Oral Oncolytic Agents Highlights Critical Role Oncology Pharmacists Play in Patient Care

WITH A SURGE in development of oral oncolytic agents for a variety of therapy targets, the support pharmacists can provide patients in areas such as oral oncolytic medication adherence has come to the fore. Considering that much of health care has shifted to being delivered and administered in patients’ homes during the COVID-19 pandemic, highlighting a variety of new setting-related topics is critical.

Patients with cancer have even greater need for a safe environment for delivery and administration of their health care than much of the rest of the population, bringing the role of oral oncolytic agents and oncology pharmacists to new heights within the field. Outside of their prominent role in the safe delivery of oncology care during the pandemic, oral oncolytic agents offer other advantages over parenteral treatment. They provide the opportunity for less invasive administration, prolonged drug exposure, and greater patient convenience.1

As early as May 2020, a survey of community practices in the United States showed that more than half of the oncologists/hematologists surveyed had shifted at least 10% of their patients from infusions to oral oncolytic agents.2 In October 2021, one can imagine this number has grown significantly. Consequently, this issue of Directions in Oncology Pharmacy® looks at the role of oral oncolytic drugs in the field today and provides information on what is to come in the drug pipeline.

In our cover story, on page 52, authors Mark Alwardt and Shereen Stutz, RPh, address the role of medically integrated dispensing (MID) pharmacies within a new paradigm of oncology care, focusing on the role of MIDs in the landscape of oral oncolytic agents. On page 25, author Jennifer Gershman, PharmD, CPh, provides an overview of the oral oncolytic pipeline for multiple myeloma, highlighting relevant data from the studies conducted to date for each oral oncolytic agent on the horizon.

Additionally, on page 36, we examine the role of home infusion within the oncology field today. With data demonstrating that home infusion remains a critical option for patients with cancer during the pandemic, the Preserving Patient Access to Home Infusion Act was introduced to the US Congress in August 2021. The bill focuses on ensuring the availability of home infusions for certain Medicare patients to support their ongoing care during the pandemic and beyond.

In this way, the impact of the pandemic on health care has been far reaching. Yet, the wake of this impact has left oncology pharmacists holding a pivotal role in this new paradigm. They are uniquely positioned to meet the needs of patients and ensure their safety, now and in the future. ■
From the Editor

THE COVID-19 PANDEMIC remains a monumental challenge and a devastating tragedy around the globe. Millions have been infected and the mortality rate has far exceeded initial projections. Many had hoped that with the introduction and widespread use of COVID-19 vaccines, we would see the pandemic end much sooner, but mutations of the virus have been able to circumvent our best solutions. In short, the pandemic may be with us for years.

It is generally recognized that to get the pandemic under control, 70% to 80% of the population must be immunized or, alternatively, be infected and recover. Unfortunately, we have fallen short of this immunization level in the United States. With the spread of variants and high levels of vaccine hesitancy among the public, we have not been able to meet our immunity goals.

As drug experts, oncology pharmacists have a critical role in educating patients, caregivers, and health care teams within their communities. Their role can affect not only the efficacy of advancements in our health care system but also the scope of health care progress in our country.

On the Front Lines of Care

With pharmacists on the front lines of community and institutional health care, they remain trusted sources of information, whether or not they are called out as such by media and lawmakers. Pharmacists have been and will be a strong presence in communities, providing crucial expertise during this crisis. Pharma-
cists can be found in hospitals, clinics, community pharmacies, long-term care, physician offices, and national and public health offices; all these settings have strong oncology components.

Although the human tragedy of COVID-19 has been vast, so have the efforts by oncology pharmacists to meet new challenges. The pandemic has forced us to adapt, and these adaptations have created a positive evolution of professional practice that, in most cases, will remain the new standard of care. Let’s explore a few of these adaptations in the oncology pharmacy space.

Virtual Health Care
Over the past year and a half, we have worked while using personal protective equipment, masks, plexiglass, computer monitors, and other measures to prevent the spread of COVID-19. This has required sacrificing the personal touch of patient care.

This necessary detachment has also forced us to adapt our methods of communicating with patients, serving as a catalyst for virtual technology adoption across the health care system. Virtual health—including telehealth, digital therapeutics, navigation of care, meeting platforms, and educational resources—is here to stay in one form or another.

Fortunately, oncology pharmacy had much of the technology already in place to allow for a shift to virtual communication. Oncology pharmacists were able to quickly move from the clinic to the home office or another remote location; likewise, patients have received care from oncology pharmacists within their homes or other relatively isolated environments.

With telehealth at their disposal, oncology pharmacists can provide initial drug education, work with patients and caregivers on establishing strong medication adherence, and make any other necessary treatment adjustments. The focus now is on scalability, sustainability, appropriate reimbursement, and optimizing the balance between in-person and remote health care. It is likely that shifts in these areas will not revert once the “new normal” standard of practice has been established.

Studies have indicated that the use of telehealth has exponentially expanded over the course of the pandemic. Patients and providers have become comfortable with consulting over the phone or over Zoom, Teams, or Skype.

Boards of pharmacy, payers, and other policy makers have seen the value of this shift toward virtual care and have supported these changes through new regulations and financing options. With the challenges imposed by the new COVID-19 variants, we have seen these policies kept in place, and they may become permanent.

Why Not Oncology Pharmacy?
Outside of health care, we see that the traditional Monday-through-Friday office commute has shifted to telecommuting or hybrid models, leading to the question: Why not oncology pharmacy? Given the risk profile of a typical immunocompromised oncology patient, it makes sense to implement this shift in the oncology pharmacy space as well.

Many of our oncology pharmacist colleagues have estimated that nearly half of oncology pharmacists are working remotely because of the pandemic. By using various platforms, oncology clinical pharmacists can be found doing their rounds remotely from an office location or their home. This requires working closely with colleagues and the entire medical team.

As we entered lockdowns, work elements such as order verification and chart reviews in the clinic and ambulatory settings shifted almost instantaneously. Rather than limit access to care, we have potentially expanded care through adapted use of technology. As a result, oncology pharmacists were able to take on greater responsibilities when interacting with patients and other medical disciplines on issues such as patient safety, satisfaction, and cohesiveness to overall oncology care.

Additionally, remote oncology pharmacists have been able to successfully shift their medication therapy management and medication reconciliation efforts to a virtual environment. Even the oncology infusion
pharmacists have been able to shift to performing their order verifications and completing their validation processes remotely, as well as checking the final administration of oncology infusions remotely via a photographic safety checking system.

Health care has historically been viewed as a locally managed process; through technology, many elements of patient care have been proven to be accessible remotely on a national scale. Post pandemic, we may see the emergence of a hybrid approach to patient care in oncology pharmacy. We will need the oncology pharmacist to be embedded with the overall oncology team to facilitate this, supporting oncologists and nurses directly.

Oncology pharmacists have demonstrated that follow-up and support can take place through technology, saving time and resources by expanding the scope of patient care. I see this as a reimbursable process through collaborative practice agreements made with providers and payers.

**Leveling the Quality of Care**

Although standardization and accreditation strive to provide relatively equivalent oncology care, no 2 settings can be totally alike. Additionally, it has been predicted that we will see a general decline in the number of oncologists and other oncology support personnel. With virtual health, we have an opportunity to expand care across traditional borders and institutions within the health care system.

Driven by the continued increase in the costs of cancer care, we have seen disparities in oncology care based on population groups and subgroups, income level, access to insurance and care settings, and proximity to clinical trials assessing novel treatments. Individuals affected by these disparities may experience decreased access to higher levels of oncology treatment, potentially leading to greater risk of financial challenges or poorer treatment outcomes.

These disparities have had greater attention and focus during the pandemic. Often, patients with less access to higher-quality cancer care are also at greater risk of acquiring SARS-CoV-2 due to their work or living environments. This exposure can also lead to a greater likelihood of hospitalization from COVID-19, resulting in a negative impact on cancer treatment outcomes.

Through the expanded use of virtual care, our profession can level patient access to higher-quality cancer care by closing disparities, improving access, and optimizing cancer care for all populations. With the recent move to expand access to broadband across the nation, more standardized oncology care is possible. A system in which patients would have broader access to their oncology pharmacist regardless of their location is foreseeable.

To make this future a reality, we must continue to make advancements in data sharing and set new standards in integrated health systems through electronic medical records. The pandemic has accelerated access to virtual care, but innovation coupled with adaptations to current methods of reimbursement and care access will need to rise to the occasion as well.

**Triumph Through Adversity**

The pandemic forced oncology pharmacy to make great shifts in practice, resulting in the need to further optimize the quality, care, and costs of oncology treatment. By bringing technology and innovative thinking to the fore, we have been able to significantly shift the paradigm of oncology care.
Overview of PARP Inhibitors in the Treatment of Ovarian Cancer

VERONA ABDELMESEH, PHARMD; BRITNY ROGALA, PHARMD, BCOP; AND JUSTIN LIAUW, PHARMD, BCOP

In the United States, ovarian cancer is the fifth-leading cause of cancer deaths among women and the leading cause of gynecological cancer deaths. Additionally, 10% to 15% of ovarian cancer cases nationwide are a result of germline or somatic BRCA mutations. With cognizance of tumor genetics, practice has shifted to include targeted agents in ovarian cancer treatment.

PARP enzymes are responsible for detecting and repairing single-stranded and double-stranded DNA breaks during cell replication. BRCA1/2 mutations hinder the homologous recombination repair pathway, and tumor cells utilize PARP enzymes to repair DNA. For this reason, these tumors are particularly sensitive to the mechanism of PARP inhibitors.

There are 3 PARP inhibitors that are FDA approved in multiple settings of ovarian cancer: olaparib (Lynparza; AstraZeneca), rucaparib (Rubraca; Clovis Oncology), and niraparib (Zejula; GlaxoSmithKline). However, there are points of note for each regarding pivotal trial results, safety profiles, and significant differences (Table 5-7).

**Olaparib**

Olaparib was the first PARP inhibitor approved in 2014 for patients with ovarian cancer with a germline BRCA mutation. Based on results of the phase 3 SOLO-2 trial (NCT01874353), it received approval in the maintenance setting following platinum-based therapy in recurrent ovarian cancer with an underlying BRCA mutation.

In the SOLO-2 trial, the median progression-free survival (PFS) in the olaparib arm was significantly longer than placebo at 19.1 vs 5.5 months (HR, 0.3; 95% CI, 0.22-0.41; P < .0001). Additionally, during a different phase 2 trial (NCT04858334), investigators evaluated olaparib regardless of BRCA mutation as a maintenance therapy in patients with partial response or complete response following platinum therapy, with the results showing that PFS remained longer in the olaparib arm (8.4 vs 4.8 months) vs the placebo arm (HR, 0.35; 95% CI, 0.25-0.49; P < .0001). Long-term follow-up also demonstrated an overall survival benefit regardless of BRCA mutation; FDA approval for this indication followed in 2019.

In the PAOLA-1 trial (NCT02477644), investigators combined olaparib and bevacizumab, a vascular endothelial growth factor receptor inhibitor also utilized in maintenance therapy. Patients received bevacizumab up front with platinum-based therapy and were randomized to bevacizumab with either olaparib or placebo.
During the PAOLA-1 trial, the greatest benefit was seen in patients with homologous recombination deficiency (HRD) including BRCA mutations, with a median PFS of 37.2 vs 17.7 months with placebo (HR, 0.43; 95% CI, 0.28-0.66). Subsequently, the combination obtained FDA approval as up-front maintenance in this corresponding setting.\(^5\)

The safety profile of olaparib is consistent across all trials.\(^5,8-11\) Among the common toxicities is myelosuppression, especially anemia, which occurs in 23% to 44% of patients. Fatigue develops in approximately 67% of patients; gastrointestinal toxicities, particularly nausea, are experienced in 45% to 77% of patients. One unique concern is pneumonitis, with an incidence in less than 1% of patients during trials.

**Rucaparib**

A second PARP inhibitor, rucaparib, was approved in 2016 with similar indications in ovarian cancer to olaparib.\(^6\) The ARIEL2 trial (NCT01891344) found a significant PFS benefit in patients with either a BRCA mutation or high loss of heterozygosity at a median PFS of 12.8 months vs 5.7 months, respectively, compared with 5.2 months in patients with low loss of heterozygosity (HR, 0.27; 95% CI 9.0-14.7; P < .0001).\(^12\)

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**TABLE. Comparative Review\(^5,7\)**

<table>
<thead>
<tr>
<th>FDA-approved ovarian cancer indications</th>
<th>Olaparib</th>
<th>Rucaparib</th>
<th>Niraparib</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Following ≥ 3 prior therapies with gBRCA&lt;sub&gt;m&lt;/sub&gt;</td>
<td></td>
<td></td>
<td>33 vs 12</td>
</tr>
<tr>
<td>2. Maintenance in recurrent PR/CR following platinum therapy with gBRCA&lt;sub&gt;m&lt;/sub&gt; or sBRCA&lt;sub&gt;m&lt;/sub&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. First line in PR/CR following platinum therapy with BRCA-mutated/genomic instability</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. First line in HRD-positive advanced ovarian cancer in combination with bevacizumab</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dosing</td>
<td>300 mg twice daily*</td>
<td>600 mg twice daily</td>
<td>300 mg daily, consider evening administration</td>
</tr>
<tr>
<td>Maintenance setting:</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>• &lt; 77 kg or &lt; 150K platelets: 200 mg daily</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• &gt; 77 kg or &gt; 150K platelets: 300 mg daily</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Preparations</td>
<td>100-mg tablet 150-mg tablet</td>
<td>200-mg tablet 250-mg tablet 300-mg tablet</td>
<td>100-mg capsule</td>
</tr>
<tr>
<td>Interactions requiring modification</td>
<td>Moderate/strong CYP3A inducers/inhibitors</td>
<td>Myelosuppressive agents</td>
<td></td>
</tr>
<tr>
<td>Common adverse effects</td>
<td>Elevated serum creatinine, nausea and vomiting, and fatigue</td>
<td>Neutropenia, thrombocytopenia, anemia, elevated serum creatinine, anemia and vomiting, and fatigue</td>
<td>Hypertension, nausea and vomiting, fatigue, and dose-limiting neutropenia, thrombocytopenia, or anemia</td>
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<tr>
<td>Notable adverse effect(s)</td>
<td>Pneumonitis</td>
<td>Elevated AST/ALT Elevated cholesterol</td>
<td>Hypertension Palpitations</td>
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<tr>
<td>Other indications</td>
<td>Prostate cancer Pancreatic cancer</td>
<td>Prostate cancer</td>
<td>N/A</td>
</tr>
</tbody>
</table>

ALT, alanine aminotransferase; AST, aspartate transaminase; CR, complete response; gBRCA<sub>m</sub>, germline BRCA-mutated; HRD, homologous repair deficient; PR, partial response; sBRCA<sub>m</sub>, somatic BRCA-mutated.

*400-mg capsule phased out of US market.
All PARP inhibitors may rarely cause secondary hematologic malignancies, with incidence varying between trial and agent.

After the submission of further positive results from the ARIEL3 trial (NCT01968213), rucaparib was approved for maintenance therapy following response to platinum-based therapy, with median PFS doubled compared with placebo at 10.8 months vs 5.4 months (HR, 0.36; 95% CI, 0.3-0.45; P < .0001). During clinical trials, rucaparib was found to have a similar adverse effect (AE) profile to olaparib. Anemia, fatigue, and nausea occurred at rates of 39%, 73%, and 76%, respectively. Additionally, dyspepsia and dysgeusia were more common with rucaparib than with olaparib. Drug-specific concerns for rucaparib included elevated liver enzymes (60%-70%) and increased cholesterol (40%-84%).

**Niraparib**

In 2017, the FDA approved niraparib for maintenance treatment of patients with recurrent epithelial ovarian cancer based on the results of the NOVA trial (NCT01847274). The study included patients with platinum-sensitive recurrent ovarian cancer with and without BRCA mutations, and niraparib was given to patients after their penultimate platinum regimen. During the NOVA trial, all cohorts benefited from niraparib therapy, with a PFS of 21 months in the BRCA-mutated group in contrast with 5.5 months with placebo (HR, 0.26; 95% CI, 0.17-0.41; P < .0001). Both patients with HRD and non-BRCA-carrying patients also benefited from maintenance niraparib.

In the PRIMA trial (NCT02655016), investigators assessed niraparib in the first-line maintenance setting for patients responding to platinum-based therapy regardless of biomarker status. PFS in the HRD population was 21.9 vs 10.4 months (HR, 0.43; 95% CI, 0.31-0.59, P < .0001) and 13.8 vs 8.2 months in the overall population (HR, 0.62; 95% CI, 0.50-0.76; P < .0001). To evaluate efficacy following relapse, investigators conducted a single-arm QUADRA trial (NCT02354586), which included heavily pretreated patients. The reported overall response rate was 28% in patients with HRD disease or a BRCA mutation (95% CI, 15.6-42.6; P = .00053).

Niraparib has a similar toxicity profile to other PARP inhibitors; however, it is associated with the highest rates of anemia (50%-64%), neutropenia (30%-42%), and thrombocytopenia (61%-66%). Additionally, body weight and baseline platelet count predict increased risk of thrombocytopenia in the first month of treatment. Nausea occurs in 57% to 74% of patients; fatigue is seen in 57% of patients. Drug-specific concerns include hypertension (20%) and palpitations (10%).

**Summary**

PARP inhibitors have expanded treatment options in ovarian cancer. Drugs in this class are well tolerated, and discontinuations due to AEs are rare. All PARP inhibitors may rarely cause secondary hematologic malignancies, with incidence varying between trial and agent. Activity against BRCA mutations make this class valuable against breast cancer tumors harboring similar mutations. Interest in olaparib and rucaparib in prostate and pancreatic cancer has increased due to the sensitivity of HRD pathways against proposed mechanisms in these cancers. There is another PARP inhibitor, veliparib, under investigation in ovarian cancer.
CAR T Cell–Associated CRS, Neurotoxicity

ALINA VARABYEVA, PHARMD; AND JORDAN PLESKOW, PHARMD

CHIMERIC ANTIGEN RECEPTOR (CAR) T-cell therapy is an exciting, rapidly progressing field in cancer immunology. During clinical trials, CAR T-cell therapy has shown unprecedented efficacy in the management of hematological malignancies and produced sustained tumor regressions in a majority of treated patients.1,2

CAR T and other adoptive cell therapies work by harnessing and boosting the natural capacity of the immune system to fight cancer.2 The technology used for this therapy involves genetically engineering T cells to express recombinant CARs that recognize specific antigens on the surface of cancer cells.

With antigen recognition on cancer cell surfaces, targeted and specific T-cell–mediated cytotoxicity is then triggered independent of major histocompatibility complex (MHC).2,3 This allows CAR T cells to overcome mechanisms of immune escape used by cancer cells, such as downregulation of MHC molecules. In addition to selective destruction of tumor cells, the natural development of CAR T memory cells allows for durable and sustained antitumor immunity, preventing tumor recurrence.2

CAR T-cell technology was born in the late 1980s, with the first design of chimeric T-cell receptors in 1989.2,4 Since then, several key discoveries were made to improve CAR T persistence, cytotoxicity, and resistance to tumor-induced immunosuppression and overcome manufacturing challenges.2

In 2017, the FDA approved the first 2 CAR T products: axicabtagene ciloleucel (Yescarta; Kite Pharma) and tisagenlecleucel (Kymriah; Novartis Pharmaceuticals) for the treatment of patients with relapsed or refractory leukemia and lymphoma. Brexucabtagene autoleucel (Tecartus; Kite Pharma) CAR T-cell therapy was approved by the FDA for adult patients with relapsed or refractory mantle cell lymphoma in July 2020. Most recently, in March 2021, idecabtagene vicleucel (Abecma; Bristol Myers Squibb) was approved for the treatment of relapsed or refractory multiple myeloma.

CAR T-cell therapy can cause potentially serious adverse events (AEs), including cytokine release syndrome (CRS) and neurotoxicity, ranging in severity from mild to life-threatening.5 The incidence and onset of CRS varied in clinical trials, with the incidence ranging from 35% to 100% and onset from 1 to 63 days depending on CAR construct, diagnosis, and various CRS grading systems.6,8 The symptoms may include high-grade fevers, myalgias, arthralgias, and rigors, whereas more severe, life-threatening manifestations include hypotension, vascular leak, cytopenias, coagulopathy, and multiorgan failure.1,5,6 Pathogenesis of CRS is thought to be associated with a high level of inflammatory cytokines released by the CAR T cells, other immune cells, and lysed target cells.5,6

During clinical trials, neurotoxicity was reported in up to 67% of patients; however, the incidence varied widely depending on the product, patient factors, and the grading scale used in the studies.5,7 Neurologic symptoms were most commonly observed as
CAR T therapy has revolutionized cancer treatment options, and ongoing research promises to solve many challenges associated with this technology.

occurring within 1 to 3 weeks after CAR T-cell infusion, although delayed presentation has been reported.6,7 The pathophysiology of neurotoxicity is linked to the high systemic concentrations of inflammatory cytokines affecting blood-brain barrier (BBB) permeability and infiltration of T cells into the central nervous system (CNS).6

Treatment algorithms for CRS and neurotoxicity vary depending on different CAR T-cell products and trials.6 Supportive care, evaluation to exclude other etiologies, and administration of antibiotics are recommended for mild CRS. Agents used to attenuate the immune response associated with CAR T-cell expansion include corticosteroids and cytokine-targeted therapies such as tocilizumab (Actemra; Genentech USA), siltuximab (Sylvant; EUSA Pharma), and anakinra (Kineret; Sobi).5-7

Because corticosteroids may theoretically adversely affect the efficacy of CAR T cells, tocilizumab, an anti–IL-6 receptor monoclonal antibody (mAb) approved by the FDA for the treatment of CAR T-cell therapy–associated CRS, is commonly the first choice after appropriate supportive care. However, neurologic toxicity has been observed with tocilizumab; this is hypothesized to be caused by the biochemical upsurges in IL-6 levels and inability of tocilizumab to cross BBB.5,7

Unlike tocilizumab, anti–IL-6 mAb siltuximab binds IL-6 directly and prevents binding of this inflammatory cytokine to soluble and membrane-bound receptors in the peripheral circulation, as well as in the CNS. Therefore, it is used in both the treatment of CRS resistant to first-line therapy and neurotoxicity; however, data supporting its use in neurotoxicity remain limited.

Another cytokine-targeted agent is the IL-1 receptor antagonist anakinra, which is used in treatment of refractory CRS and, with limited data, neurotoxicity as well. Supportive care and high-dose corticosteroids are the first-line treatment recommendations for CAR T cell–associated neurotoxicity, with seizure prophylaxis also recommended. Use of defibrotide is being investigated in this setting and as a potential addition to treatment with siltuximab and anakinra.

CAR T therapy has revolutionized cancer treatment options, and ongoing research promises to solve many challenges associated with this technology.1,2,9 For example, research efforts are working to make great strides in strategies to improve CAR T therapy efficacy and safety, as well as investigate novel CAR T-cell designs used in the treatment of cancers other than hematological malignancies, such as solid tumors.

REFERENCES
PROSTATE CANCER (PCA) accounts for 26% of new cancer cases—the most common cancer diagnosis in men—and 11% of all cancer-related deaths, making it the second most common cause. \(^1\) PCA diagnosis has a median age of 67 years. \(^2\) Nonmodifiable risk factors include age (55 years or older), race (due to the high relative incidence in Black men), and genetics (such as mutations in DNA repair genes like BRCA1/2 or PCA-specific risk genes like HOXB13). \(^3\)

However, the relative impact of modifiable risk factors, such as obesity and smoking cigarettes, remains controversial. \(^3\) Although 5α-reductase inhibitors, sele- nium, and vitamin E are among the agents explored for PCA prevention, outcomes have been mixed and none are FDA approved for this indication. \(^4-7\)

Most cases of PCA are detected at an early stage through prostate-specific antigen (PSA) testing and digital rectal examinations, with 70% of new diagnoses presenting localized disease and 5% with distant metastases. \(^2,8-10\) Although multiple screening recommendations do exist, most take into consideration age, life expectancy, and family history of any cancer. \(^8-10\)

Patients with early-stage PCA are often asymptomatic. \(^3\) Common symptoms, when present, include urinary hesitancy, incomplete voiding, and hematuria. \(^3\) Additionally, bone, lymph nodes, liver, and thorax are common sites of distant metastases. \(^3,11\)

PCA arises from excess activation of the androgen receptor (AR) signaling pathway. The serine protease gene PSA, produced by both normal and abnormal cells in the prostate gland, localizes to nuclei of androgen-stimulated PCA cells and impacts transcription and translation within the AR pathway; \(^3\) normal PSA values range from 0 to 4.0 ng/mL.

Elevated PSA is a component of diagnosis for PCA and is trended to monitor response to treatment and disease progression. However, PSA may also be elevated by non-PCA causes, such as benign prostatic hyperplasia, infections, trauma, and ejaculation. \(^3\)

The risk groups for PCA are based on factors such as PSA, Gleason grade (higher scores indicate abnormal cribriform gland formation), tumor size (TNM staging), and prostate biopsy or pelvic/abdominal imaging; however, both risk group and life expectancy lead to the determination of eligibility for less aggressive interventions. \(^12\) Definitive treatment for localized PCA includes active surveillance, external beam radiation therapy, brachytherapy, and radical prostatectomy. \(^3,12\)

One aim of systemic therapy in PCA is to reduce testosterone levels and receptor binding, which leads to dampening growth/proliferation of prostate basal/luminal cells. Castrate levels of testosterone (< 50 ng/dL) may be achieved surgically with bilateral orchiectomy, or medically with androgen deprivation therapy (ADT). \(^12,13\)

For lower-risk patients with longer life expectan- cies, ADT is utilized adjuvantly. \(^11\) In contrast, ADT is initial therapy—commonly with radiation—for unfavorable intermediate-risk, high-risk, and very high-risk localized PCA, as well as PCA with metastases to regional lymph nodes or distant sites. \(^12\)

ADT used for PCA treatment includes luteinizing hormone-releasing hormone (LHRH) agonists and antagonists. For advanced PCA, the FDA-approved LHRH agonists include goserelin and leuprolide. \(^14,15\)

Tumor flare (eg, hot flashes, bone pain) due to initial testosterone surge with agonists can be prevented in patients with bone metastases by administering a first-generation antiandrogen initially from 7 to 10 days prior to initiating LHRH agonists and continued through the end of LHRH agonist therapy. \(^16\) Notably, disease progression during tumor flare is unlikely. \(^17\)
Compared with agonists, LHRH antagonists result in more immediate decreases of testosterone; these agents are administered without an antiandrogen. Both intravenous (degarelix) and more recently, oral (relugolix) LHRH antagonists are FDA approved.

In the multinational, randomized, open-label, phase 3 HERO trial (NCT03085095), investigators compared relugolix and leuprolide acetate for the treatment of advanced PCa. Among the 622 patients receiving relugolix and 308 receiving leuprolide, 50.2% of patients had biochemical recurrence after definitive treatment. For sustained castration rate (cumulative probability of testosterone suppression to < 50 ng/dL from day 29 through 48 weeks), relugolix attained a rate of 96.7% (95% CI, 94.9-97.9), which was superior to leuprolide at 88.8% (95% CI, 86.4-91.8) based on the lower boundary of the 95% CI for the difference between the 2 arms.

The rate of testosterone suppression at less than 20 ng/dL on day 15 was also higher with relugolix (78.4% vs 1.0%). Testosterone at less than 20 ng/dL with ADT has been associated with improved survival and time to disease progression when compared with testosterone at less than 50 ng/dL.

During the trial, the most common adverse event (AE) was any-grade hot flash, with similar incidence between cohorts. Major cardiovascular events occurred among all patients at 2.9% for relugolix (95% CI, 1.7-4.5) and 6.2% for leuprolide (95% CI, 3.8-9.5); for patients with cardiovascular history, a cardiovascular event during treatment was 4.8 times more likely with leuprolide. For metastatic castrate-sensitive prostate cancer (CSPC), ADT may be combined with other therapies, including abiraterone (if high-risk CSPC) with or without radiation, docetaxel (if high-volume metastases and ADT-naive), apalutamide, and enzalutamide.

On average, medical castration is effective for 2 to 3 years before clinical, radiographic, or biochemical progression, despite castrate testosterone levels. At this point, the disease is termed castration-resistant PCa (CRPC). Because of diverse mechanisms of resistance, ADT should be continued throughout CRPC as tolerated to target those PCa cells that lack a means of evading AR-induced apoptosis.

For nonmetastatic CRPC, second-generation antiandrogens apalutamide, darolutamide, and enzalutamide may be combined with ADT. Differing toxicity profiles help drive treatment selection.

For metastatic CRPC (mCRPC), first-line options include abiraterone (conventional or micronized) or docetaxel. Cabazitaxel is an alternative for docetaxel, particularly if peripheral neuropathy is a concern. Cabazitaxel can be combined with carboplatin if disease is aggressive (eg, bulky disease or high lactate dehydrogenase) or characterized by unfavorable genomics (eg, TP53 or PTEN). Additionally, mitoxantrone is used in subsequent lines of therapy due to inferior overall survival (OS) vs docetaxel or cabazitaxel. Another first-line option for hormone therapy-naive mCRPC is enzalutamide alone or with ADT.

Therapies with more niche indications include radium-223, which is reserved for symptomatic mCRPC (bone metastases), and sipuleucel-T, which is limited to asymptomatic, indolent mCRPC, excluding visceral metastases.

For mCRPC progressed on hormone therapy and/or docetaxel, the PD-1 inhibitor pembrolizumab may be used for known deficient mismatch repair (dMMR) gene mutations or microsatellite instability-high (MSI-H) cancer cells. Non-dMMR or MSI-H populations are included in ongoing pembrolizumab studies as monotherapy or with enzalutamide, olaparib, and docetaxel.

The PARP inhibitor olaparib is FDA approved for mCRPC progressed on AR-directed therapy and known homologous recombination repair mutations. PROfound, a randomized, open-label, phase 3 trial (NCT02987543), demonstrated prolonged imaging-based median progression-free survival (mPFS) with olaparib (7.4 months for n = 162) vs choice of enzalutamide or abiraterone (3.6 months for n = 83; P < .001) in mCRPC with a deleterious germline/somatic alteration in BRCA1/2 or other DNA damage response and repair (DDR) gene. More mature data will be needed to finalize OS benefit of olaparib. Anemia was the most common AE at grade 3 or greater.

Rucaparib, in contrast, is FDA approved for mCRPC previously treated with both AR-directed and taxane therapies, and with known BRCA1/2 mutations (12% incidence in mCRPC). TRITON2, an international, open-label, phase 2 study (NCT02952534), found that...
rucaparib with concomitant LHRH agonist/antagonist or prior bilateral orchiectomy resulted in an overall response rate based on an independent radiology review of 43.5% (95% CI, 31.0%-56.7%) in 62 patients with a deleterious germline/somatic alteration in BRCA1/2 or other DDR gene and measurable disease.\textsuperscript{47} Additionally, PSA response rate was seen in 54.8% (95% CI, 45.2-64.1) of enrolled patients, including those without measurable disease. Anemia/decreased hemoglobin was the most common grade 3 or greater AE.

Prostate-specific membrane antigen (PSMA) expression is elevated in CRPC, making room for a radioligand in heavily pretreated mCRPC with PSMA positivity. The prospective, open-label, randomized, international, phase 3 VISION trial (NCT03511664) evaluated the impact of adding 177Lu-PSMA-617 to standard care in mCRPC previously treated with greater than or equal to 1 AR-pathway inhibitor and 1 to 2 taxanes, although FDA-approved chemotherapy, immunotherapy, and radium-223 were excluded.

During the VISION trial, investigators randomized 551 men to 177Lu-PSMA-617 and 280 to only standard of care.\textsuperscript{48} Primary end points of imaging-based mPFS (8.7 vs 3.4 months; \textit{P} < .001) and median OS (15.3 vs 11.3 months; \textit{P} < .001) were prolonged with addition of this radioligand, though in context of a high incidence of withdrawal in the control group. The most common AEs observed with the addition of 177Lu-PSMA-617 were all-grade and high-grade fatigue, dry mouth, nausea, and anemia.

Although ADT continues to be a cornerstone of PCa treatment, new therapeutics—a lone and with existing first-line agents—will need to be assessed for comparative safety and efficacy, as well as accessibility for patients. Additionally, preferred regimens may continue to shift as data emerge, particularly in the mCRPC setting. ■
A Variety of Multiple Myeloma Oral Oncolytic Drugs Are on the Horizon

WITH A VARIETY of multiple myeloma therapies in the pipeline, approximately 25% to 35% of new oncology therapies in development are oral medications. Oral oncolytic drugs offer advantages over parenteral treatment, including less invasive administration, patient convenience (eg, location and timing of administration), and prolonged drug exposure.

Ultimately, these factors are important in improving patients’ quality of life. Evidence demonstrates that pharmacists play a critical role in treating patients on multiple myeloma therapies, especially through a collaborative physician-pharmacist clinic that works to support oral oncolytic medication adherence. The multiple myeloma pipeline is continuously expanding, and pharmaceutical companies are involved in research and development for novel oral oncolytic drugs and therapies already approved for other cancer indications.

Multiple Myeloma Drug Pipeline

Venetoclax
Venetoclax (Venclexta; AbbVie) is an oral BCL2 inhibitor drug currently FDA approved to treat chronic lymphocytic leukemia (CLL), small lymphocytic leukemia (SLL), and acute myeloid leukemia. Additionally, venetoclax is being studied for the treatment of relapsed and refractory multiple myeloma and has shown promising results in patients positive for the t(11;14) translocation in phase 1/2 clinical studies.

However, the BELLINI phase 3 double-blind randomized trial (NCT02755597) interim results revealed an increased risk of death in patients receiving venetoclax compared with the control group. These results prompted the FDA to warn health care professionals of the risks of investigational use of venetoclax for multiple myeloma and to require that no new patients be enrolled in the BELLINI trial and other clinical studies. In patients with the t(11;14) translocation, mortality rates were lower, demonstrating that future studies should specifically focus on this patient population.

In the CANOVA (NCT03539744) phase 3 ongoing study, investigators are evaluating the safety and efficacy of venetoclax plus dexamethasone compared with pomalidomide plus dexamethasone in participants with t(11;14)-positive relapsed or refractory multiple myeloma.

Lisaftoclax
APG-2575 (lisaftoclax; Ascentage Pharma) is a novel oral BCL2 inhibitor being studied for several hematologic cancers including multiple myeloma. Additionally, the FDA has granted Orphan Drug Designation to lisaftoclax for the treatment of multiple myeloma. Lisaftoclax is being investigated in an ongoing phase 1b/2 clinical trial (NCT04942067) in combination with other therapies in patients with relapsed or refractory multiple myeloma.

Ibrutinib
Ibrutinib (Imbruvica; Pharmacyclics and Janssen) is a novel first-in-class once-daily Bruton tyrosine kinase inhibitor that is FDA approved for CLL/SLL, Waldenström macroglobulinemia, chronic graft-vs-host disease, mantle cell lymphoma, and marginal zone lymphoma.

Additionally, the safety and efficacy of ibrutinib were evaluated in a phase 1/2b study (NCT01962792) combined with carfilzomib/dexamethasone in patients with relapsed/refractory multiple myeloma. The study revealed that patients had an overall response rate of 71%, median progression-free survival of 7.4 months, and a median overall survival of 35.9 months. The most common grade 3 or greater hematologic treatment-emergent adverse events were anemia and thrombocytopenia.
Because the study enables multiple therapies to be evaluated at once, this has the potential to expand treatment to high-risk multiple myeloma patients.

**Myeloma-Developing Regimens Using Genomics (MyDRUG)**

The MyDRUG phase 1/2 study (NCT03732703) is an ongoing precision medicine clinical trial that aims to develop new multiple myeloma regimens based on individual patients’ genomics. Findings from the Multiple Myeloma Research Foundation CoMMpass study (NCT01454297) and the Multiple Myeloma Research Consortium Molecular Profiling Initiative revealed that genetic mutations can play a role in the disease, prompting the MyDRUG trial.

Additionally, this study includes high-risk multiple myeloma patients with 1 to 3 prior lines of therapy. During this trial, investigators assign patients to the appropriate therapy based on their pharmacogenomic profile along with a standard-of-care regimen that includes ixazomib, pomalidomide, and dexamethasone.

In this study, the oral oncolytic treatment options include investigational drugs and those approved for other cancers that have shown promise for multiple myeloma, such as abemaciclib (cyclin-dependent kinase mutations), enasidenib (isocitrate dehydrogenase mutations), cobimetinib (RAF/RAAS mutations), and venetoclax (chromosomal translocation t[11;14]).

Furthermore, investigators in the MyDRUG trial plan to enroll 228 patients into one of 8 treatment arms. Patients with a greater than 25% mutation to any of the genes being studied are eligible to be enrolled in one of these treatment arms. Because the study enables multiple therapies to be evaluated at once, this has the potential to expand treatment to high-risk multiple myeloma patients.

**REFERENCES**

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MULTIPLE MYELOMA is a cancer of plasma cells that is associated with low blood counts (eg, anemia, thrombocytopenia, and leukopenia), bone and calcium problems, infections, and renal dysfunction. According to the American Cancer Society, over 34,000 new multiple myeloma cases will be diagnosed and approximately 12,000 deaths are expected to occur in 2021.\(^2\)

Chimeric antigen receptor (CAR) T-cell therapy is an innovative treatment option for multiple myeloma, but these medications can be associated with serious adverse events (AEs).\(^2\) Pharmacists can play an integral role as part of a multidisciplinary team to treat patients with multiple myeloma.

**Multiple Myeloma Treatment Options and New Drug Approvals**

Treatment for multiple myeloma generally depends on cancer stage. For example, solitary plasmacytoma is a rare disorder similar to multiple myeloma that is typically treated with radiation therapy.\(^2\) Additionally, chemotherapy is used if multiple myeloma develops.

Patients with smoldering multiple myeloma generally do not require treatment in the early stages. Evidence suggests that treating patients with smoldering multiple myeloma with lenalidomide (Revlimid; Bristol Myers Squibb) and dexamethasone before symptoms develop can prolong survival.\(^2\)

**CAR T-cell Therapy**

Active (symptomatic) myeloma patients are typically treated with combination therapy consisting of 2 to 3 medications. CAR T-cell therapy is a type of immunotherapy that assists the body’s immune system in locating and attacking cancer cells. Idecabtagene vicleucel (Abecma; Bristol-Myers Squibb) is a CAR T-cell therapy that targets the B-cell maturation antigen protein; it received FDA approval on March 26, 2021.

The FDA approval of idecabtagene vicleucel was based on a multicenter study that showed 72% of patients partially or completely responded to treatment.\(^3,4\) Idecabtagene vicleucel is the first cell-based gene therapy to treat adult patients with relapsed or refractory multiple myeloma after at least 4 different types of treatment.\(^3\)

Idecabtagene vicleucel is administered as a single-dose intravenous (IV) infusion, and patients should receive premedication with acetaminophen and diphenhydramine 30 to 60 minutes before the infusion.\(^4\) Additionally, it carries a boxed warning for cytokine release...
syndrome (CRS), neurologic toxicities, and hemophagocytic lymphohistiocytosis/macrophage activation syndrome, which can be fatal.4

Idecabtagene vicleucel is only available through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) because of the risk of CRS and neurologic toxicities.4 Possible signs of CRS include fever, hypotension, tachycardia, chills, headache, fatigue, and low oxygen in the blood.4

Chemotherapy
Chemotherapy was once part of the main treatment for multiple myeloma, but it is now used less often because newer medications have become available.2 Examples of chemotherapy include cyclophosphamide (Cytoxan) and doxorubicin (Adriamycin).

Melphalan flufenamide (Pepaxto) was approved by the FDA on February 26, 2021, in combination with dexamethasone to treat adult patients with relapsed or refractory multiple myeloma.5 However, the postmarketing phase 3 OCEAN trial (NCT03151811) revealed an increased risk of death in patients receiving melphalan flufenamide.5,7

Additionally, the FDA required that the manufacturer suspend enrollment in the OCEAN trial and other ongoing melphalan flufenamide clinical studies.6 Patients who experienced clinical benefits from melphalan flufenamide could continue to receive treatment in the OCEAN trial, but they must be educated about the risks and sign a revised informed consent.6

Any AEs associated with melphalan flufenamide that are observed by pharmacists should be reported to the FDA’s MedWatch AE reporting program.6

Corticosteroids
Corticosteroids such as dexamethasone and prednisone can be used alone or in combination with other medications as part of a treatment regimen for multiple myeloma, and they can help decrease nausea and vomiting from chemotherapy.2 Common AEs associated with corticosteroids include high blood glucose, increased appetite and weight gain, insomnia, and behavioral changes.2

Immunomodulating Agents
These medications include thalidomide (Thalomid), lenalidomide, and pomalidomide (Pomalyst). Lenalidomide and pomalidomide are derivatives of thalidomide, and all the products carry a boxed warning regarding the risk of fetal toxicity and venous and arterial thromboembolism.2 Because of the risks associated with these medications, they are available through REMS.2

Thalidomide was previously used to treat morning sickness in pregnant women but was taken off the market because it was found to cause birth defects. In 2006, thalidomide was approved in combination with dexamethasone for the treatment of patients with newly diagnosed multiple myeloma.2

Proteasome Inhibitors and Histone Deacetylase Inhibitors
Proteasome inhibitors include bortezomib (Velcade), carfilzomib (Kyprolis), and ixazomib (Ninlaro),2 with common AEs such as nausea, vomiting, thrombocytopenia, and diarrhea. Ixazomib is the first and only oral proteasome inhibitor, the form of which may help to improve patient adherence.2

Panobinostat (Farydak) is an oral histone deacetylase (HDAC) inhibitor used in combination with bortezomib and dexamethasone for the treatment of patients with multiple myeloma who have received at least 2 prior regimens that include bortezomib and an immunomodulatory medication.8 Panobinostat carries a boxed warning for severe diarrhea and severe and fatal cardiac ischemic events. Patients should receive antidiarrheal medication at the onset of diarrhea, and panobinostat treatment should be interrupted for moderate diarrhea, occurring at 4 to 6 stools a day.8 Patients should receive an electrocardiogram and have blood work to monitor electrolytes at baseline and during treatment to assess for cardiac abnormalities.8
Monoclonal Antibodies, Antibody-Drug Conjugate, and Nuclear Export Inhibitor

Isatuximab (Sarclisa) is a monoclonal antibody IV infusion that received FDA approval on March 31, 2021 when used in combination with carfilzomib and dexamethasone for patients with relapsed or refractory multiple myeloma who have received 1 to 3 prior different types of therapies. Additionally, this marks the second approval for isatuximab for a multiple myeloma indication. Common AEs for isatuximab include respiratory tract infections, infusion-related reactions, fatigue, hypertension, diarrhea, pneumonia, shortness of breath, bronchitis, and cough.

Other monoclonal antibody treatment options available include daratumumab (Darzalex; Janssen Biotech) and elotuzumab (Empliciti; Bristol Myers Squibb). Additionally, belantamab mafodotin-blmf (Blenrep; GlaxoSmithKline) is an antibody-drug conjugate, whereas selinexor (Xpovio; Karyopharm Therapeutics) is an oral nuclear export inhibitor that works by blocking the XP01 protein.

Pharmacist’s Role in Treating Patients With Multiple Myeloma

Pharmacists can play an integral role as part of an interdisciplinary team to treat patients with multiple myeloma. Monitoring for AEs, educating patients about their drug regimens, and managing supportive therapies are important roles for pharmacists.

Outcomes for patients with multiple myeloma have improved with novel therapies that include immunomodulatory drugs, proteasome inhibitors, and monoclonal antibodies. Supportive care medications, such as oral anticoagulants, calcium and vitamin D supplements, and antivirals, are also typically needed to prevent disease and treatment-related complications, which can increase the pill burden and lead to adherence obstacles.

Evidence has demonstrated that collaborative pharmacist-physician multiple myeloma clinics can improve medication adherence. Pharmacists can provide medication therapy management services that include drug administration education, missed dose instructions, drug-drug and drug-food interactions, and necessary laboratory monitoring.

Additionally, pharmacists can play an active role in ensuring that patients with multiple myeloma receive COVID-19 vaccines. The National Comprehensive Cancer Network recently issued guidance that patients with hematologic malignancies, such as multiple myeloma, should be prioritized to receive a third COVID-19 vaccine dose as immunocompromised patients.
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The Home Infusion Setting Remains a Critical Option for Cancer Care During the Pandemic

New legislation is set to ensure the availability of home infusions for certain Medicare patients.

SKYLAR KENNEY, ASSISTANT EDITOR

The COVID-19 pandemic has put immunocompromised patients, including those immunosuppressed because of cancer or cancer treatment, at much greater risk of SARS-CoV-2 infection and serious complications than the general population.

Consideration of these risk factors can result in treatment delays for patients with cancer, due to the need to weigh the risks of not receiving treatment against possibly becoming infected with SARS-CoV-2.1

Additionally, the risks associated with treatment delay for patients have been further exacerbated by health care institutions being pushed to their limits during the pandemic, leading members of the National Home Infusion Association to recommend legislation ensuring access to home-based health care, including home infusion.2

In August 2021, the Preserving Patient Access to Home Infusion Act was introduced by Sens Mark Warner (D, Virginia) and Tim Scott (R, South Carolina) to assist Medicare patients in maintaining access to home infusion therapies requiring the use of an infusion pump.3

“Medicare’s home infusion therapy benefit provides increased access to care for patients with immune diseases, cancer, serious infections, heart failure, and other conditions that might otherwise force them to receive their care in a more expensive and less convenient hospital or nursing home setting,” said Warner in a prepared statement. “This legislation will ensure that patients in need of home infusion therapy can get the care they need in a more affordable and commonsense way.”3

The evidence available suggests home infusion is safe, effective, and cost saving for patients and providers.4-6 Interviews with clinicians and patients suggest that individuals favored outpatient or inpatient settings for cancer treatment if they had no previous experience with home treatment; however, physicians reported that they continued to have concerns about safety and increased burden for the clinical care team.7

Home infusion has also been shown to be not only safe and clinically effective, but also to improve patients’ quality of life and reduce health care costs. In a systematic review of articles relating to safety, clinical efficacy, quality of life and satisfaction, and/or costs of home infusion, investigators concluded that home infusion patients were no more likely to experience drug-related adverse events than patients who received infusions in a medical setting.3

Furthermore, clinical outcomes for patients were as good or better in the home infusion setting; as an example, home infusion patients with hemophilia had a 40% reduction in likelihood of hospitalization for bleeding complications.4

In a meta-analysis of available data, investigators found patients overwhelmingly preferred home infusion. Study participants reported significantly better physical and mental well-being in the home infusion setting, as well as reduced disruption of family life and personal responsibilities. Home infusion was also found to significantly lower costs for patients, with data demonstrating that study participants saved between $1928 and $2974 per treatment course.4

In another review of data on home infusions, investigators observed similar results, with studies showing a decrease in costs associated with home treatment vs hospital or in-clinic treatment. These cost savings were established from both health care payer and patient...
perspectives. The studies demonstrating cost savings were published from 1981 to 2018, establishing a long-standing, consistent benefit.5

Delivering chemotherapy at home has been determined to be feasible and safe, indicating that home infusion has potential as an alternative to outpatient clinic treatment. In a study of patients who had undergone radical surgery for colon cancer and who were eligible to receive adjuvant treatment with capecitabine and oxaliplatin, investigators randomized patients to receive either 4 treatments at home followed by 3 in an outpatient clinic, or 3 treatments in an outpatient clinic followed by 4 at home.6

During the study, the investigators found that treatment was safe and acceptable in all cases, and participants expressed feeling secure and preferring the reduction in transportation time and waiting time they experienced in the home infusion setting.6

With the pandemic creating treatment hesitancy and barriers to health care access,1,2 efforts like the Preserving Patient Access to Home Infusion Act can offer patients with cancer, as well as other high-risk populations, an opportunity to receive health care in an environment that is safe, comfortable, and less costly for patients and providers.4,6

Although biases may exist among some health care professionals regarding the delivery of cancer care outside a medical setting,7 the available evidence suggests that home infusion is safe and clinically effective, making it a valuable option for cancer care during the COVID-19 pandemic and beyond.4,5

REFERENCES
Antineoplastic Extravasation Prevention, Management

CHRISTINA BILLIAS, PHARMD, AND MEGAN MENON, PHARMD, BCOP

ALTHOUGH INFILTRATION CAN be defined as the inadvertent leakage of an irritant, extravasation is defined as the inadvertent leakage of a vesicant from the vein into surrounding tissue. During cancer treatment, extravasation is the accidental leakage of chemotherapy from the vein into surrounding tissue. Rates are not clearly defined and no centralized database of chemotherapy extravasation events exists, but some literature reports overall incidence as ranging from 0.1% to 6.5%. 

The damage potential from antineoplastic therapy extravasation ranges from mild toxicity, such as local pain and erythema, to severe toxicity including tissue necrosis. Because of the potential for severe tissue injury, it is imperative that preventive measures are taken and extravasation is identified and managed quickly.

Ensuring team members are educated about what causes extravasation, opportunities to prevent it, and how to respond when chemotherapy leakage occurs is critically important. There are a few concepts that pharmacists working in oncology need to know about extravasation involving commonly used chemotherapies.

Classification of Agents
Chemotherapy drugs are grouped according to their potential to cause tissue damage if extravasation occurs; agents may be classified as irritants or vesicants. Depending on the treatment being utilized, other categories such as nonvesicant, nonirritant, or irritant with vesicant-like properties may be used as well.

Classifications of antineoplastic drugs are not absolute. Chemotherapy agents may have characteristics of irritants and vesicants. Additionally, there are inconsistencies among antineoplastic agent classifications in the literature.

If extravasation of an irritant occurs, there is potential for burning, pain, and erythema. This is typically a temporary, local reaction without tissue necrosis. Vesicants have potential for burning, pain, and erythema, along with more severe, progressive damage including blister formation and tissue necrosis.

Vesicants can be further subclassified into DNA-binding and non–DNA-binding agents. DNA-binding vesicants remain bound to the DNA of dead cells and can be internalized by adjacent, healthy cells. This allows the agent to remain in the tissue, continuing to cause damage. The damage potential of DNA-binding vesicants is generally more severe, progressive, and permanent.

Non–DNA-binding vesicants are metabolized in the tissue and damage potential is generally mild to moderate, localized, and improves with time. Examples of DNA-binding vesicants are anthracyclines, whereas examples of non–DNA-binding vesicants are vinca alkaloids. Table 1 shows the European Society for Medical Oncology and European Oncology Nursing Society Clinical Practice Guideline classification of chemotherapy drugs.
**TABLE 1. Antineoplastic Agents Classification**

<table>
<thead>
<tr>
<th>Vesicant</th>
<th>Irritant</th>
<th>Nonvesicant</th>
</tr>
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<tbody>
<tr>
<td><strong>Anthracyclines</strong></td>
<td><strong>Topoisomerase inhibitors</strong></td>
<td><strong>Arsenic trioxide</strong></td>
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<tr>
<td>Doxorubicin</td>
<td>Etoposide</td>
<td>Asparaginase</td>
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<td>Daunorubicin</td>
<td>Tenoposide</td>
<td>Bleomycin</td>
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<td>Anthracyclines</td>
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<td>Cytarabine</td>
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<td><strong>Alkylating agents</strong></td>
<td><strong>Platinum compounds</strong></td>
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<td>Mechlorethamine</td>
<td>Carboplatin</td>
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<td>Bendamustine</td>
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<td>Interleukin 2</td>
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<td><strong>Antimetabolites</strong></td>
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<tr>
<td>Fluorouracil</td>
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<td><strong>Others</strong></td>
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<tr>
<td>Ixabepilone</td>
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</table>

**Risk Factors**

Identifying and acknowledging extravasation risk factors is essential to reducing risk. Risk factors may be classified as patient-related, procedure-related, or drug therapy-related, as noted in Table 1.1,2,5,8

**Prevention**

Implementation of prevention measures is key to minimizing risk of extravasation and potential consequences, with education on these measures remaining crucial for the medical staff and the patient. Medical staff should be trained in risk identification, appropriate vascular access, institute protocols, and extravasation prevention, identification, management, and documentation. Additionally, patients should be educated on extravasation risk and the need to promptly report any signs or symptoms of its occurrence.1,5,7

The vascular access site options include central or peripheral access, with central access being generally preferred for chemotherapy agents, especially those with more severe damage potential such as anthracyclines. A flexible cannula should be used, and large veins of the forearm are preferred when selecting a cannulation site for peripheral access.1

**Identification and Management**

The clinical presentation of an extravasation may present as a wide range of symptoms that are nonspecific, such as tingling, burning, discomfort, pain, swelling, erythema, and visible accumulation of fluid. Additionally, there may be a lack of blood return, resistance on the syringe plunger, or an interruption in the free flow of the drug infusion.1,5

If an extravasation of an antineoplastic agent is identified, general management principles are as follows:1

- Stop the infusion
- Disconnect tubing while leaving the cannula in place
- Without applying pressure, carefully aspirate as much drug as possible using a syringe
- Remove the cannula
- Assess the site and outline border of extravasation area with a pen
- Notify physician
- Initiate substance-specific measures
  - Thermal compresses
  - Antidotes, if applicable
- Elevate limb
- Documentation
- Follow-up
Dry, thermal compresses should be applied in 20-minute intervals 4 times a day for 1 to 2 days. There are some inconsistencies among thermal compress recommendations pending the resource utilized. However, most agents will require cold compresses for extravasation management. For extravasation of vinca alkaloids, warm compresses are universally recommended. Substance-specific antidotes should also be used as appropriate (Table 3). If dexrazoxane is being administered for anthracycline extravasation management, it must be started within 6 hours after extravasation. Additionally, cold compresses should be removed 15 minutes before and during dexrazoxane administration to maximize antidote delivery to the tissue.

The documentation of extravasation incidents should include the patient’s name, date and time of extravasation, name of extravasated drug and diluent used, signs and symptoms, IV access utilized, extravasation area, and management steps.

Best practice recommendations for documentation also include incorporating photographic documentation, because this can be helpful during follow-up. Patients should be instructed to monitor the area and report changes. Routine follow-up is recommended with more frequent monitoring within the first week post extravasation, followed by weekly review until symptoms are resolved.

**Surgical Intervention**

Surgical debridement may be necessary if patients experience unresolved tissue necrosis or pain lasting more than 10 days, full-thickness skin necrosis, and/or chronic ulcer. For severe tissue damage, it is recommended that surgical intervention be managed by a plastic surgeon. Necrotic tissue will be excised, followed by skin grafting and reconstruction if necessary.

Antineoplastic therapy extravasation is a serious event that has the potential for severe complications. Employing strategies and preventive interventions will help ensure extravasation incidents remain rare and that staff are prepared to respond promptly and appropriately.

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Improving Adherence to Oral Oncolytics

Multiple strategies can be used to create an individualized approach to therapies and removing barriers for patients with cancer.

KRISTEN COPPOCK, MA

THE USE OF oral oncolytics has become increasingly prevalent in cancer care with their use accelerated by the COVID-19 pandemic. Adherence to these medications, however, can be challenging for patients.

In a session of the virtual American Society of Health-System Pharmacists (ASHP) Specialty Pharmacy Conference, presenter Eve Segal, PharmD, BCOP, lead clinical pharmacist, University of Washington Medical Center/Seattle Cancer Care Alliance, discussed advantages of oral oncolytics as well as a need for pharmacists to understand barriers to adherence faced by patients who are prescribed these medications. Segal also offered strategies for improving adherence for patients taking these medications.

“Oral oncolytics really have solidified their place in cancer treatment. The oral route has many advantages in cancer management. In some cases, the oral route is actually preferred to other forms of medication,” Segal said during the ASHP session.

According to Segal, oral oncolytics offer more convenience and improved quality of life for patients than other forms of therapy. She noted less interference with work and social activities, avoiding painful injections and prolonged time with infusions, as well as allowing patients to take more ownership of their therapy with self-administration. Additionally, in some cases, patients taking oral oncolytics may experience prolonged drug exposure and may have access to a more effective delivery option.

Although adherence to medication leads to better control of the disease, rates of adherence vary widely. A review of literature showed that adherence rates with oral antineoplastic therapies range between 46% and 100%, with differences in study results based on patient sample, medication type, measure of assessment, adherence calculation, and when follow-up occurred. Segal said barriers exist that prevent many patients from taking their oral oncolytics. She cited common barriers:

- **Logistical**: cost, regimen complexity, adverse events, poor access to medication
- **Perceptual**: poor understanding, lack of belief in efficacy, lack of understanding for therapy’s purpose, inability to see benefits
- **Physical**: visual deficits, physical difficulties
- **Mental**: memory deficits, mental illness
- **Social**: poor communication with care team, language deficits, poor literacy, lack of support system, cultural or religious beliefs

Direct and indirect methods can help improve adherence. Although expensive and impractical, smart pill bottles and smart caps can assist many patients, for example. Self-reporting by patients, pill counts, and pharmacy claims data are examples of indirect support for adherence; however, these methods do not prove that a patient has taken a medication.

“Each method has its own advantages and disadvantages,” Segal said. “Keep in mind that there is no gold standard to assessing and evaluating adherence.”

By working with an oncology care team, pharmacists have opportunities to help improve care for patients with cancer who are taking oral oncolytic agents. Segal suggested using a combination of patient education and behavioral intervention, and
routinely following up with patients to combat nonadherence. These strategies may include informational handouts that use plain language; calendars or other visual reminders; reviewing the refill process and confirming that a patient understands it; ensuring a patient is scheduled for a follow-up visit to assess adherence and potential toxicities to treatments; discussing medication cost; use of pill boxes; and smartphone apps that remind patients to take their medications. Segal said a pharmacist’s approach should be customized to individual patients based on what works best for them.2

Overall, patient education is key, Segal said, noting that there is no clear, best way to educate patients, but the information provided should be consistent.2 “Patients should also know how to obtain their medication, the role of the specialty pharmacy, and [about] financial assistance,” she said. ■

REFERENCES
Medically Integrated Pharmacies, Oral Oncolytic Agents Grow in Importance During COVID-19

Mark Alwardt; and Sheeren Stutz, RPh

Despite efforts to diminish the effects of COVID-19 on care of patients with cancer, the pandemic still poses challenges to oncology care delivery. However, as practices have gained experience in this new environment, health care professionals have found innovative ways to work around many of the obstacles COVID-19 presents.

Last year’s lockdowns and restrictions dramatically affected in-office care, initially halting screenings and new patient consults while changing the way care could be delivered to existing patients. Eventually, practices identified and adopted strategies that reduced immunocompromised patients’ potential exposure to the virus. Ultimately, changes were made that brought medically integrated dispensing (MID) pharmacies and oral oncolytic agents to the forefront of patient treatment, along with technologies facilitating continuity of care.

Oral Therapies and MIDs Support Ongoing Care

Although care for new patients was basically on hold for several months, practices largely were able to continue caring for existing patients. As the pandemic progressed, oncologists altered treatment of patients undergoing therapy, selecting oral agents when possible in place of intravenous options, to minimize patient time in the clinic.

In May 2020, a survey of community practices throughout the United States was conducted by Healthcare Research & Analytics, the results of which showed that over half of the oncologists/hematologists had shifted at least 10% of their patients from infusions to oral oncolytic agents.1 Because the survey was taken just a few months into the pandemic, it is reasonable to assume the percentage is probably much higher now.

Although oral oncolytic agents do not require administration in the clinic like infusion therapy does, patients still must be closely monitored, and this is where MIDs played a key role. These in-office pharmacists took on increased responsibility in the care management paradigm as use of oral oncolytic agents increased drastically.

When this shift toward oral oncolytic agents occurred, MIDs stepped forward to perform vital functions such as comprehensively evaluating patient comorbid conditions, determining dosing schedules, managing toxicity and adverse effects (AEs), clearing insurance hurdles, and educating patients and the care team about new oncolytic

About the Author

Mark Alwardt is vice president of medically integrated dispensing for McKesson. Sheeren Stutz, RPh, is senior director of medically integrated dispensing for McKesson.
agents. Vigilance concerning any changes in these patient factors was required, and that responsibility fell more onto MIDs. MIDs were highly successful in their expanded role, especially in driving adherence. With all the turmoil and changes the pandemic caused, a decline in adherence might be expected. However, based on data from community practices supported by McKesson, patients had a higher adherence rate during that time frame than in the prior year.

This uptick in adherence demonstrated the value MIDs provide in effective patient treatment. It also revealed that there may have been increased patient awareness as to the importance of adherence, resulting in patients taking greater control and ownership of their treatment.

**Restriction Reductions Provided New Delivery Options**

In response to the pandemic, the nation’s largest pharmacy benefit managers (PBMs) lifted certain delivery restrictions. This enabled a different approach to care, allowing practices to customize how medications reach each patient. For practices within the US Oncology Network (the Network), an assessment was done to determine how each practice could best serve patients, which supported the development of new delivery models to minimize patient time in the facility, including advance fulfillment, coordinating a pickup date to coincide with an appointment, or having the patient wait outside while the prescription was prepared.

- **Curbside pickup**—MID staff delivered the prescription to the patient’s vehicle to complete point of sale and patient treatment activities.
- **Courier or delivery service**—The MID staff sent the prescription to the patient’s home via a local courier.
- **Biologics specialty pharmacy home delivery**—Express delivery through Biologics by McKesson was also available. Biologics was fully staffed to perform benefit investigations, obtain prior authorizations, secure patient funding, and offer medication counseling.

**Telemedicine Empowered Continuity of Care**

Another factor played a key role in providing ongoing care during the pandemic: telemedicine. Three federal stimulus packages addressing COVID-19 were enacted in March 2020 that expanded coverage of Medicare telemedicine services, resulting in the rapid adoption of telemedicine across the health care landscape.

The Centers for Medicare & Medicaid Services (CMS) previously required telemedicine recipients to have a prior established relationship with a provider; however, at the start of the pandemic, CMS allowed patients to be cared for remotely by new physicians, opening the door to new patient consultations, meeting a critical need in cancer care.

CMS also expanded telemedicine coverage to include many additional services, enabling virtual patient/oncologist consultations and follow-ups. These reimbursement regulations are quite complex and remain very fluid.

Telemedicine in oncology care is not new but its use was very limited before the pandemic. According to the Healthcare Research & Analytics survey, 8% of oncologists/hematologists used telemedicine services.
There is a strong likelihood telemedicine will remain available to patients.

prior to the pandemic, but by May 2020 when the survey was taken, that total jumped to 88%.1

During COVID-19, telemedicine took on an expanded role as it enabled social distancing, providing the mechanism for continuity of care. Although physicians could not see their patients in person, they could see them on video calls, allowing assessments to be conducted. Additionally, from an oral perspective, MIDs were able to use telemedicine to monitor patients and be proactive in managing toxicities and AEs, which enabled a high adherence rate among patients.2

All practices in the Network utilized telemedicine platforms to provide safe care during the pandemic, and the usage rate continues to be around 10% to 15%. From March 2020 through February 2021, more than 436,000 visits were performed virtually by providers in the Network.3 These included medical and radiation oncology, multiple surgical specialties, and other visit types such as genetics, palliative care, hospice, nutrition, AE management, and prechemotherapy counseling.1

Although patients can now visit clinics in person, there is a strong likelihood telemedicine will remain available to patients. In fact, the Healthcare Research & Analytics survey reported that 90% of the oncologist/hematologist respondents indicated they will continue to utilize telemedicine in their practices.1

Takeaways From the Pandemic

Much was learned over the past year about how to provide care to patients with cancer in the new COVID-19 environment. One important thing that came to the forefront was that MIDs are part of a robust system able to successfully treat existing cancer patients during the pandemic. Employing oral therapies, MIDs kept adherence high and supported quality care in multiple ways. The value of MIDs and oral therapies was clearly demonstrated throughout this period.

From the pandemic also emerged a new appreciation and role for telemedicine, which became the mechanism driving continuity of care. This innovative tool enabled patients with cancer to connect with their integrated health care teams to receive uninterrupted quality care safely in their homes. Post COVID-19, telemedicine will likely be more heavily utilized than before the pandemic, playing a key role in routine checkups and light reviews.

Finally, stakeholders that often contend with one another about site of care, pricing, or access took action that created a unique health care industry team effort—whether intentional or not—to keep quality care accessible to patients with cancer. From government and PBMs lifting restrictions to oncology practices being more flexible, all entities moved in the same direction to do what was necessary to ensure patients could still receive their treatments.

Not only did these efforts create a united front for meeting patient needs during the pandemic, they also provided a blueprint for how to meet future emergencies that may arise. Hopefully, COVID-19 will soon be in the rearview mirror, but either way, oncology stakeholders have identified new strategies to successfully serve patients during times of crisis.

REFERENCES


Advancements and Updates in the Treatment Options for CLL

Including insights from the 2020 ASH Annual Meeting & Exposition

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In this *Directions in Oncology Pharmacy*® Insights® series, experts discuss the advancements and updates in the management of chronic lymphocytic leukemia (CLL). Our panel of experts will discuss the updated data presented at ASH 2020 for the current treatment options with long-term data as well some new treatment plans being investigated and the impact on patient management.

*Meet the Experts:*

Katie Culos, PharmD, BCOP  
Adult Cellular Therapy Clinical Pharmacist  
Director, PGY-2 Oncology Pharmacy Residency  
Vanderbilt University Medical Center

Daniel Wojenski, PharmD, BCPS, BCOP  
Hematology/Oncology Practice Coordinator  
PGY-2 Oncology Pharmacy Residency Director  
Hematology/Oncology Clinical Pharmacist  
Northwestern Memorial Hospital

*Watch now: [https://tinyurl.com/y5jwpxng](https://tinyurl.com/y5jwpxng)*
PATIENTS WITH CANCER should not be overlooked in any pharmacy setting. These patients are in need of resources, help, and hope. They endure a grueling process of coping with their diagnosis, treatment, changes in treatment, and, in cases of recovery, the fear of recurrence. All these stages can affect patients emotionally and physically.

Patient GV, aged 65 years, has been in disbelief since receiving his diagnosis, and his wife has been overwhelmed with the diagnosis and the frequency of doctor visits. On top of this, GV had planned on retiring from work at the end of the year because his daughter and son-in-law are expecting a baby—GV has been really looking forward to being a grandparent.

GV confides in you that he feels very depressed and is upset the cancer was not caught earlier. Over a year ago, he started having symptoms and thought his persistent sore throat was due to COVID-19. He was tested for COVID-19 multiple times, and all tests came back negative.

Gradually, GV’s symptoms became more painful and uncomfortable, making it hard to eat solid food and to talk at times. Once COVID-19 precautions had been

lightened in GV’s area and he was fully vaccinated, he started making routine health care appointments again.

As he began to make these appointments, he noticed his gums were sore around his teeth where he had had dental work done in the past. His wife told him he had bad breath, which was unusual given his regular oral hygiene. The dentist was the first on his call list.

You sympathize with GV after hearing about his situation. You explain that you and his providers are always there to help and answer questions at each step of his illness. GV appreciates your listening and presents a new list of medications and his current laboratory data. He explains that he just left the clinic and that these are his most up-to-date documents.

You look through the papers and notice a medication reconciliation performed by the oncology clinic pharmacist. You review it against GV’s profile at your pharmacy and notice multiple changes.

As you conduct your review, you see the concern and confusion in GV’s face. Upon seeing this, you explain the concept of pharmacy brown bag and medication therapy management sessions and ask whether he would be interested. GV is relieved. He tells you he would like to receive this type of support and will bring his wife and his medications along with him for the session the following day to get your advice. You suggest GV visit around 2 PM; it’s a slower time in your pharmacy and will allow you to provide the best service and care possible.

Brown Bag Consult®
The next day, GV and his wife are waiting in your consultation area. Having done your homework, you
have filled GV’s new medications, reviewed discontinued medications, opened his medication profile, and accessed his laboratory data and medication reconciliation.

You compare what is in GV’s brown bag with your information:

- Atorvastatin 40 mg daily
- Metoprolol 50 mg twice daily
- Niacin as dietary supplement
- OTC Cepacol lozenge as needed
- OTC ibuprofen pm as needed
- OTC Chloraseptic spray as needed
- OTC omeprazole 20 mg daily
- OTC acetaminophen 500 mg as needed

Your updated pharmacy profile includes:

- Ondansetron ODT 4 mg as needed
- Atorvastatin 10 mg daily
- Atenolol 25 mg daily
- Lorazepam 0.5 mg as needed
- Duloxetine 30 mg once daily for one week, then 60 mg daily

During the consult, GV and his wife mention that they appreciate your time. Because his wife helps with GV’s medical care and general well-being, she shares some of her concerns with you.

She admits that GV is still smoking. He is not happy about his wife mentioning this and defensively says he is only smoking cigars. You explain the negative impact of smoking and offer help if and when he is ready to quit smoking. You also explain that smoking will not help his blood pressure or cancer diagnosis, so it may be time to prioritize trying to quit.

GV tries to change the subject and talks to you about eating. His throat hurts and the pain often prevents him from eating despite his strong appetite. He admits using many OTC sore throat medications, knowing they offer only temporary relief. Using them has almost become a bad habit, and GV feels dependent on them despite knowing that his cancer is causing the issue.

You acknowledge the OTC throat medications and suggest GV allow you to follow up about pain management options that may be more effective. GV has lost weight and wants to prevent a dramatic weight loss once he starts chemotherapy and radiation next week. You show him and his wife various protein shakes, ones that other patients have told you taste good, and recommend those for the time being.

You offer to help GV follow up with a nutrition expert so they can help his wife with a plan because she manages the household shopping and cooking. You also mention the new antinausea medication GV has been prescribed and describe how to use it under the tongue, which may help him increase his calorie intake. GV thinks this will be helpful because he has trouble swallowing a lot of pills.

You let GV know that once he starts chemotherapy, a lot may change very quickly as his body adjusts to new medications and fights the cancer. GV understands and tells you that his wife will update you if he needs further help.

You mention the new antidepressant and anxiety medications he has been prescribed. GV hates that he must take these but understands he will need help with his mood and spirit during the fight against his cancer. You encourage him to monitor how he feels and to stay positive as much as possible.

You mention that although you know it is hard, even small amounts of exercise can elevate his mood. Reading, stretching, and time with family can all be very helpful in bringing joy to his life, you add.

The goal of a brown bag session is to discover discrepancies. The information that comes out of the session can allow you to make a number of short-term and long-term suggestions, while also supporting improved communication between GV and his multiple providers. Overall, this may improve GV’s quality of life and reduce unnecessary doctor calls or visits.

GV is willing to have you act as a community liaison between him and his providers. The first step is to follow up with his providers to make them aware of your brown bag session discoveries and the suggestions you have regarding GV’s plan of care. Time will be your most challenging factor and you will need to find a way to incorporate these complex clinical opportunities into your workflow. Loyalty and patient satisfaction are priceless and worth the energy to help GV.

ABOUT THE AUTHOR
JILL DRURY, PHARM.D, BCOP, is a clinical pharmacy specialist in Chicago, Illinois, and Milwaukee, Wisconsin.
Evaluating Frontline and Maintenance Therapy in Acute Myeloid Leukemia

At the completion of this activity, the participant will be able to:

- Examine the most recent treatment updates and clinical data of emerging therapies in acute myeloid leukemia (AML)
- Explain how maintenance therapy is used as part of the AML treatment paradigm
- Apply strategies to manage older patients with AML in the COVID-19 environment

Introduction

Acute myeloid leukemia (AML) is a complex disease that has historically been managed with few therapeutic options, mainly intensive induction therapy consisting of cytarabine and an anthracycline (referred to as 7+3) followed by consolidation with a cytarabine-based regimen or low-intensity hypomethylating agents used as monotherapy (azacitidine or decitabine). In the past several years, targeted agents, combination regimens, and maintenance therapy have offered promising approaches but have also added complexities to a previously simple treatment algorithm. Pharmacists can play a key role in guiding oncologists in selection of regimens, medication access, and toxicity prevention and management.

AML is a disease characterized by a disruption in clonal hematopoiesis of myeloid cells in the bone marrow and peripheral blood. It is estimated that there will be approximately 20,000 new diagnoses of AML in the United States in 2021, accounting for roughly 11,400 deaths. Patient presentation ranges vastly from asymptomatic coincidental detection to multiorgan failure from anemia, tumor lysis syndrome (TLS), or infection. Most often, patients will report a period of fatigue and nonspecific symptoms prior to their diagnosis. AML can present de novo or can arise from a preexisting bone marrow disorder, myelodysplastic syndrome (MDS), or a myeloproliferative neoplasm (MPN). Cancer-inducing exposures, such as ionizing radiation, benzene, or chemotherapy used to treat other malignancies, can also cause secondary AML.

Cytogenetic and molecular mutations can be identified during the diagnosis of AML. Until recently, these mutations were used solely to define prognosis and goals of therapy, but they are now used to drive treatment decisions when targeted therapy is available. Prognosis is generally broken into 3 groups: favorable, intermediate, and poor. More information about prognosis can be found in TABLE 1.
When mutations in fms-like tyrosine kinase 3 (FLT3) or isocitrate dehydrogenase 1 and 2 (IDH1 and IDH2) are identified, patients may benefit from novel oral therapies targeting these mutations. Patients with certain cytogenetic mutations, including core binding factor mutations, may benefit from gemtuzumab ozogamicin-based combination regimens.

Mutations in p53, which are known to derive a poor prognosis across many malignancies, also present a potential target for unique therapies and regimens currently under investigation. Unlike the treatment of acute lymphoblastic leukemia, treatment of AML has historically not included a maintenance phase, nor has it been tailored by measurable residual disease (MRD) assessment. However, emerging data suggest both of these treatment strategies may derive superior long-term treatment options in AML. This article will review novel therapies and combination regimens used to treat AML, discuss the role of maintenance therapy and MRD testing in AML, and, finally, reflect on the impact of COVID-19 on treatment strategies in AML, particularly in older or less fit individuals.

### Evolving Therapeutic Approaches in AML: Focus on the Shifting Treatment Paradigm

When midostaurin was approved for the treatment of FLT3-positive AML in 2017 based on the results of the RATIFY study, it represented the first new FDA approval for AML in more than a decade. Subsequently, there has been a rapid influx of approvals for drugs with novel mechanisms that has changed the landscape of AML therapy. TABLE 2 provides an overview of oral FDA approvals for AML since 2017. These agents, particularly when used in combination regimens, are the subject of much ongoing investigation. Pharmacists should pay careful attention to dosing cycles, drug interactions and dose adjustments, and adverse effects of these oral agents in order to impact patient care. In addition, complex dosing strategies and regimens for these agents pose an opportunity for pharmacists to support and reinforce patient education and adherence.

### BCL-2 Targeted Therapy

Venetoclax is an oral BCL-2 inhibitor initially approved for the treatment of chronic lymphocytic leukemia, and it was subsequently approved for newly diagnosed AML in combination with either a hypomethylating agent or low-dose cytarabine. Venetoclax was studied in combination with hypomethylating agents in a phase 3 multicenter, randomized, double-blind, placebo-controlled trial.

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**TABLE 1. RISK STRATIFICATION AND PROGNOSIS***

<table>
<thead>
<tr>
<th>Risk</th>
<th>Mutations</th>
<th>Estimated 5-year overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytogenetic</td>
<td>t(8;21)(q22;q22): RUNX1-RUNX1T1 inv(16)(p13;q22) or t(16;16)(p13;q22): CBFBMYH11</td>
<td></td>
</tr>
<tr>
<td>Molecular</td>
<td>Mutated NPM1 without FLT3-ITD or with FLT3-ITD&lt;sup&gt;low&lt;/sup&gt; Biallelic mutated CEBPA</td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytogenetic</td>
<td>t(3;11)(p21.3;q23); MLL3-KMT2A Cytogenetic abnormalities not classified as favorable or adverse</td>
<td></td>
</tr>
<tr>
<td>Molecular</td>
<td>Mutated NPM1 and FLT3-ITD&lt;sup&gt;low&lt;/sup&gt; Wild-type NPM1 without FLT3-ITD or with FLT3-ITD&lt;sup&gt;low&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytogenetic</td>
<td>t(6;9)(p23;q34): DEK-NUP214 t(v;11)(v;q23): KMT2A rearranged t(3;22)(q341;q112): BCR-ABL1 2 (1.0) −7 −5 or del (5q) inv(3) or t(3;3) Complex karyotype Monosomal karyotype</td>
<td></td>
</tr>
<tr>
<td>Molecular</td>
<td>Wild-type NPM1 and FLT3-ITD&lt;sup&gt;low&lt;/sup&gt; Mutated RUNX1 Mutated ASXL1 Mutated TP53</td>
<td></td>
</tr>
</tbody>
</table>

ITD, internal tandem duplication.

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**STAR***

How have treatment options for elderly patients or patients unable to tolerate intensive chemotherapy evolved in recent years?

*S = Stop; T = Think; A = Assess; R = Review
<table>
<thead>
<tr>
<th>Agent Class</th>
<th>Dose</th>
<th>FDA-approved indication (approval date)</th>
<th>Trial design (n)</th>
<th>Study outcomes</th>
<th>Adverse effects (&gt;30% incidence and black box warnings)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azacitidine (Onureg) Hypomethylating agent</td>
<td>300 mg PO once daily Days 1-14 of 28-day cycle</td>
<td>Maintenance therapy following intensive induction chemotherapy in patients in CR but unable to complete intensive curative consolidation (2020)</td>
<td>QUAZAR AML-001: Phase 3, randomized, azacitidine vs placebo (n=472)</td>
<td>OS: 24.7 vs 14.8 months (P &lt; .001) PFS: 10.2 vs 4.8 months (P &lt; .001)</td>
<td>N/V, diarrhea, constipation, neutropenia</td>
</tr>
<tr>
<td>Enasidenib (Idhifa) IDH2 inhibitor</td>
<td>100 mg PO once daily</td>
<td>R/R AML with IDH2 mutation (2017)</td>
<td>Phase 1/2 open label, single arm in patients with R/R IDH2+ AML (n=239 total included in safety, 179 AML included in results)</td>
<td>ORR: 40.3% OS: 9.3 months, 17.9 months in CR EFS: 6.4 months DOR: 5.6 months Time to response: 1.9 months</td>
<td>N/V, diarrhea, decreased appetite, electrolyte imbalances, indirect hyperbilirubinemia, differentiation syndrome</td>
</tr>
<tr>
<td>Gilteritinib (Xospata) FLT3 inhibitor</td>
<td>120 mg PO once daily Use with caution with strong CYP 3A4 inhibitors</td>
<td>R/R FLT3 ITD+ AML (2018)</td>
<td>ADMIRAL: Phase 3, randomized 2:1 gilteritinib vs investigator choice salvage chemo (n=371)</td>
<td>OS: 9.3 vs 5.6 months (P = .0007) CR/CRi: 34% vs 15.3% (P = .0001) CR: 21.1% vs 10.5% (P = .016) EFS: 2.8 vs 0.7 months (P = .0830)</td>
<td>Swelling, fatigue, fever, muscle pain, rash, infection, diarrhea, renal toxicity, LFT elevation, SOB, electrolyte abnormalities</td>
</tr>
<tr>
<td>Glaegebig (Daurismo) Hedgehog inhibitor</td>
<td>100 mg PO once daily Use with caution with strong CYP3A4 inhibitors 200 mg once daily with moderate CYP3A4 inducers Use with strong CYP3A4 inducers contraindicated</td>
<td>Newly diagnosed AML in older or unfit patients in combination with LDAC (2018)</td>
<td>Phase 2, randomized 2:1 LDAC + glasdegib vs LDAC alone in newly diagnosed patients or patients unfit for intensive chemotherapy (n=132)</td>
<td>OS: 8.3 vs 4.9 months (P = .002) CR: 17% vs 2.3% (P &lt; .05)</td>
<td>Neutropenia, fatigue, N/V, edema, increased creatinine, muscle pain, electrolyte abnormalities, embryo-fetal toxicity</td>
</tr>
<tr>
<td>Ivosidenib (Tibsovo) IDH1 inhibitor</td>
<td>500 mg PO once daily 250 mg PO once daily when used with strong CYP3A4 inhibitors</td>
<td>R/R AML with IDH1 mutation (2018)</td>
<td>Newly diagnosed AML in older (age &gt;75) or unfit for intensive chemo (2019)</td>
<td>Phase 1 open label in patients with R/R IDH1+ AML (n=258 total included in safety, 179 AML included in results)</td>
<td>ORR: 41.6% OS: 8.8 months, mOS =18 months in CR EFS: not reported DOR: 6.5 months, 9.3 months in CR Time to response: 19 months</td>
</tr>
<tr>
<td>Midostaurin (Rydapt) FLT3 inhibitor</td>
<td>50 mg PO BID days 8-21 of each cycle Use with caution with strong CYP3A4 inhibitors</td>
<td>Newly diagnosed FLT3 ITD or TKD + AML (2017) Systemic mastocytosis (2017)</td>
<td>RATIFY: Phase 3, randomized, double-blind, placebo-controlled trial in patients aged 18-59 years with newly diagnosed FLT3+ AML compared with chemo alone (n=717)</td>
<td>CR: 58.9% vs 53.5% (P = .15) OS: 74.7 vs 25.6 months (P = .009) EFS: 8.2 vs 3.0 months (P = .002) DOR: 26.7 vs 15.5 months (P = .01)</td>
<td>Anemia, N/V, diarrhea, edema, fatigue, headache, hyperglycemia, rash, mucositis, muscle pain, bruising, LFT elevation, electrolyte abnormalities</td>
</tr>
<tr>
<td>Venetoclax (Venclexta) BCL2 inhibitor</td>
<td>400 mg PO once daily following 3-day dose increase (600 mg for LDAC) Reduce cycle intensity for profound/prolonged neutropenia 100 mg once daily with strong CYP3A4 inhibitor (70 mg with posaconazole)</td>
<td>Newly diagnosed AML in older or unfit patients in combination with LDAC or HMA (2018)</td>
<td>HMA (VIALE-A): Phase 3, randomized azacitidine + ven vs aza alone in newly diagnosed AML (n=431)</td>
<td>OS: 14.7 vs 9.6 months (P &lt; .001) CR/CRi: 66.4% vs 28.3% (P &lt; .001) CR: 36.7% vs 17.9% (P &lt; .001) OS: 8.4 vs 4.1 months (P = .04) CR/CRi: 48% vs 13%</td>
<td>Neutropenia, diarrhea, N/V</td>
</tr>
</tbody>
</table>

AML, acute myeloid leukemia; CMP, comprehensive metabolic panel; CR, complete response; CRi, complete remission with incomplete hematologic recovery; DOR, duration of response; EFS, event-free survival; HMA, hypomethylating agent; LDAC, low-dose cytarabine; LFT, liver function test; mOS, median overall survival; N/V, nausea/vomiting; OS, overall survival; PFS, progression-free survival; PRES, posterior reversible encephalopathy syndrome; R/R, relapsed/refractory; SOB, shortness of breath; TKD, tyrosine kinase domain; TLS, tumor lysis syndrome. *Black box warnings are indicated in bold.
trial comparing azacitidine alone with azacitidine plus venetoclax in patients with newly diagnosed AML who were older or unfit for intensive induction chemotherapy. Patients were randomized 2:1 to receive azacitidine 75 mg/m²/day for 7 days subcutaneously or intravenously (IV) with oral venetoclax or azacitidine plus oral placebo. Patients in the investigational arm received venetoclax 100 mg on day 1, 200 mg on day 2, and 400 mg on days 3 through 28 of a 28-day cycle. In subsequent cycles, patients received 400 mg daily throughout. CYP3A4 and PgP inhibitors were allowed but with dose modifications. For concomitant moderate CYP3A4 inhibitors or PgP inhibitors, venetoclax was reduced by 50%. For concomitant strong CYP3A4 inhibitors, venetoclax was reduced to 50 mg. On study, patients were admitted at least 1 day prior to starting venetoclax and for at least 24 hours after the last dose in the first cycle. Median patient age was 76 years, 75% had de novo AML while 25% had secondary AML; greater than half (55%) had a performance status of 0-1, and the majority (64%) had intermediate cytogenetics. Patients in the combination arm had a median overall survival (mOS) of 14.7 months versus 9.6 months in the placebo arm (P < .001), and patients achieved complete remission (CR) more than twice as often in the investigational arm (36.7% vs 17.9%; P < .001). Adverse effects (AEs) were common, with some occurring in 100% of treated patients in both arms. The most notable differences in AEs between the venetoclax and placebo arms were hematologic AEs: grade 3 or 4 hematologic effects occurred in 82% of patients in the venetoclax arm versus 68% of patients in the placebo arm. Patients in the venetoclax arm experienced more grade 3 or 4 neutropenia (42% vs 28%) and grade 3 or 4 febrile neutropenia (42% vs 19%). Dose interruptions and treatment reductions from 28 days to 21 days per cycle due to delayed hematologic recovery occurred in 53% of patients in the venetoclax arm versus 28% of patients in the placebo arm.

Similarly, venetoclax was studied in combination with low-dose cytarabine (LDAC) in a phase 3 randomized, placebo-controlled trial comparing cytarabine 20 mg/m² subcutaneous once daily on days 1 to 10 of a 28-day cycle with either oral venetoclax or placebo. Venetoclax was administered by mouth 100 mg on day 1, 200 mg on day 2, 400 mg on day 3, and 600 mg on day 4 and thereafter. CYP3A4 and PgP inhibitors were allowed but with dose modifications noted above. The mOS was 7.2 months in the venetoclax arm versus 4.1 months in the placebo arm (hazard ratio [HR], 0.7; CI, 0.52-1.07; P = .11). Patient demographics were similar to the previous study. Patients had a median age of 76 years; 66% had de novo AML and 34% had secondary AML; half had a performance status of 0-1 and 63% had intermediate cytogenetics. When controlling for baseline prognostic factors (de novo vs secondary AML, intermediate vs poor cytogenetic risk, ECOG < or ≥2, and age < or ≥75 years), the adjusted HR was 0.67 (P = .03). Patients in the venetoclax arm had higher response rates, with CR or complete remission with incomplete hematologic recovery (CRi) rates of 48% in the investigational arm versus 13% in the placebo arm. Consistent with these results, patients were more likely to experience an independence from red blood cell and platelet transfusions in the investigational arm (37% vs 16%).

Studies of venetoclax in the relapsed setting are less promising. In a retrospective observational study conducted in Spain of patients who received venetoclax with either a hypomethylating agent or LDAC, CR or CRi were only achieved in 10% of patients and mOS was 49 days after initiation of the venetoclax-based regimen in the salvage setting. However, some small cohorts have reported some success. In a single-center analysis of real-world outcomes, 25 patients with relapsed/refractory AML received venetoclax plus a hypomethylating agent (eg, azacitidine). The majority (52%) had poor risk disease. In this cohort, there was a CR + CRi rate of 32%, ORR of 52%, and median OS of 5.5 months. For the patients who achieved CR or CRi, the median OS was 21.6 months. Further research is needed to identify those patients who are most likely to benefit from venetoclax in the relapsed setting.

Although venetoclax has been approved in combination with agents that have colloquially been considered “low-intensity” therapies, these combination regimens are associated with significant AEs. Appropriate patient selection and careful monitoring are necessary for safe administration. There is much debate over timing, pace, and setting for venetoclax initiation. Some institutions initiate venetoclax simultaneously with a hypomethylating agent or LDAC, whereas others initiate venetoclax sequentially. Rationale for this may be multifactorial and could include concern for TLS in patients with a high disease burden, overlapping AEs in patients who are newly diagnosed, or medication access delays. Though the incidence of TLS in clinical trials is extremely low (0-1%), it has been reported that real-world TLS rates may be increased, and also heightened by drug interactions with triazole antifungal prophylaxis. Although low, there is a risk of TLS during venetoclax initiation, especially for patients on CYP3A4 inhibitors. Allopurinol prophylaxis should be initiated prior to and continued at least during the initial week of therapy. Pharmacists should also encourage adequate hydration during venetoclax initiation. Consistent with practice in clinical trials, some institutions admit patients to an inpatient service for venetoclax initiation, whereas others initiate therapy in an outpatient setting with close monitoring. Hospital-based reimbursement, patient preference, and hospital capacity concerns,
particularly during the COVID-19 pandemic, may be reasons to avoid hospitalization where treatment initiation may be done safely as an outpatient.

Routine antimicrobial prophylaxis in venetoclax-based regimens is controversial. Notably, triazole antifungals were prohibited in some clinical trials due to the known drug interactions of venetoclax with CYP3A4 inducers or inhibitors. The Infectious Diseases Society of America and American Society of Clinical Oncology joint statement on antimicrobial prophylaxis in cancer-related immunosuppression recommends patients at high risk for febrile neutropenia or profound, protracted neutropenia receive an oral triazole or a parenteral echinocandin during the period of expected neutropenia. In addition, an antimal triazole is recommended when the risk of invasive aspergillosis is greater than 6%. There were no reported cases of aspergillosis in the pivotal venetoclax trials, but venetoclax was associated with high rates of febrile neutropenia (32%-61%) and grade 3 or 4 neutropenia (17%-42%), which could warrant prophylaxis. A pharmacokinetic study evaluated the effect of posaconazole 300 mg on venetoclax doses 50 to 100 mg. Results of this study showed that, compared with venetoclax 400 mg alone, venetoclax 50 mg administered with posaconazole achieved 53% of $C_{\text{max}}$ and 76% of area under the curve (AUC); venetoclax 100 mg administered with posaconazole achieved 93% of $C_{\text{max}}$ and 155% of AUC. Based on this information, it is feasible to administer venetoclax 50 to 100 mg in combination with posaconazole. It is important to note, however, the prescribing information recommends a reduction in venetoclax dosing to 70 mg when combined with posaconazole.

**FLT3-Targeted Therapy**

Midostaurin was approved for use during induction and consolidation based on the results of the RATIFY study, which demonstrated an OS benefit when midostaurin was used in combination with 7+3 in patients with FLT3+ (internal tandem duplication [ITD] or tyrosine kinase domain [TKD]). Since then, midostaurin has also been studied in combination with hypomethylating agents. A phase 1 study (N = 17) of azacitidine 75 mg/m²/day IV days 1-7 followed by midostaurin 25 to 75 mg by mouth twice daily was conducted by Cooper and colleagues. In this study, 3 patients with FLT3+ AML experienced CR and 2 patients experienced a hematologic improvement from baseline. However, hospitalizations occurred in one-third of treatment cycles, usually due to infections. In addition, grade 3 and grade 4 neutropenia and thrombocytopenia occurred in 63% and 65% of treatment cycles, respectively, demonstrating a need for close monitoring and infection prevention.

Gilteritinib was the second FLT3 inhibitor to be FDA approved for AML. It was approved based on the ADMIRAL study, a phase 3 trial in which patients with FLT3+ ITD relapsed/refractory AML were randomized 2:1 to receive gilteritinib 120 mg by mouth once daily or investigator choice salvage chemotherapy. Prior therapies included anthracyclines (83.8%), stem cell transplant (19.9%), and prior FLT3 inhibitors (12.4%). Salvage regimens included mitoxantrone, etoposide, and cytarabine (MEC); fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin (FLAG-IDA); LDAC; or azacitidine. Patients enrolled were a median of 62 years of age, 60% had relapsed disease, and 40% had primary refractory disease. The majority of patients (73%) had intermediate cytogenetics. Patients who received gilteritinib had a longer OS compared with those who received salvage chemotherapy (9.3 months vs 5.6 months; $P < .001$). AEs leading to gilteritinib discontinuation occurred in 11% of patients, most commonly due to liver function test (LFT) elevations and pneumonia. Gilteritinib has also been studied in the upfront setting in combination with azacitidine. The LACEWING study was initiated to evaluate the use of gilteritinib plus azacitidine versus gilteritinib alone. In the primary safety analysis, the investigators reported a CR + CRi rate of 67%; however, the study was abandoned early when it did not meet its primary objective of OS. There are ongoing studies comparing gilteritinib and midostaurin in combination with intensive chemotherapy in the upfront setting. Quizartinib is another FLT3 inhibitor under investigation for monotherapy and combination regimens. It previously showed promising results as monotherapy in relapsed and refractory FLT3+ AML. More recently, it has been studied as part of a combination regimen with venetoclax and decitabine in patients with relapsed or refractory AML or newly diagnosed patients who were unfit for standard induction. In the relapsed/refractory cohort, CR rates were 69%; in newly diagnosed patients, 100% achieved CR. This represents a potential future combination that quizartinib obtain FDA approval in the United States. It had previously been denied by the FDA after the Oncology Drugs Advisory Committee sited marginal outcomes and increased cardiac toxicity.

Crenolanib has also been studied for relapsed/refractory FLT3 ITD and TKD+ AML. Among several other trials, it was studied in a phase 2 open-label study of crenolanib 200 mg/m² three times daily in 34 patients with relapsed AML. The median age was 61 years. Patients were heavily pretreated with a median number of prior therapies of 3.5; 62% had prior FLT3 inhibitor exposure. In the FLT3 inhibitor-naive group, the rate of CRi was 23% while the rate of CRi in the FLT3 inhibitor-exposed
group was only 5%. The median OS in the FLT3 inhibitor-naïve group was 55 weeks compared with just 13 weeks in the FLT3 inhibitor-exposed group. This study suggests sequencing of FLT3 inhibitors may not be feasible.

Pharmacists can play a role in management of AEs associated with FLT3-directed therapies. Midostaurin-induced nausea is common and can be difficult to manage. Scheduled prophy- lactic antiemetics and additional antiemetics should be consid- ered as needed for breakthrough nausea. Choice of antiemetic agent can be difficult due to the QT-prolonging nature of both midostaurin and gilteritinib. Differentiation syndrome will be discussed in more detail; however, it may also be a result of FLT3-directed therapies.\textsuperscript{8,41}

**iDH1/2-Targeted Therapy**

Enasidenib is an oral IDH2 inhibitor approved as monotherapy for patients with relapsed/refractory IDH2-mutated AML.\textsuperscript{6} Mutated IDH2 occurs in approximately 8% to 19% of patients with AML.\textsuperscript{6,42} Enasidenib was approved based on a phase 1/2 open-label, single-arm dose escalation study, which included 239 patients with myeloid malignancies, of which 176 had AML or MDS with excess blasts.\textsuperscript{43} Included patients were a median age of 67 years; 32% were primary refractory while 23% had relapsed after at least 2 prior regimens. The majority (64%) had intermediate cytogenetics and most (85%) had a performance status of 0-1. Patients received enasidenib 100 mg by mouth once daily and had an overall response rate of 40.3%, of which 19.3% achieved CR, with a median response onset of 1.9 months and duration of 5.8 months.\textsuperscript{43} Enasidenib has also been studied in newly diagnosed AML in a phase 1/2 study, which found an overall response rate lower than that in the relapsed patients of 30.8%, of which 18% achieved CR.\textsuperscript{15}

Ivosidenib is an oral IDH1 inhibitor approved as monotherapy for patients with newly diagnosed or relapsed/refractory AML.\textsuperscript{7} Similar to the approval of enasidenib, ivosidenib was approved initially in the relapsed/refractory setting based on a phase 1 open-label, single-arm dose escalation study that included 258 patients with myeloid malignancy, of which 179 had relapsed/refractory AML who received ivosidenib 500 mg by mouth once daily.\textsuperscript{21} Median age was 76 years; 66% of enrolled patients had de novo AML, while 34% had secondary AML. The median number of prior therapies was 2 (range, 1-6). A lower proportion (53%) of patients had intermediate-risk cytogenetics than previously discussed studies, and more patients (30%) had poor cytogenetics. Patients achieved CR + CRi in 30.4% of cases, CR in 21.6% of patients, and there was an overall response rate of 41.6%. Median onset of response was 2.7 months and median duration of response was 8.2 months.\textsuperscript{21} Conversely to the study of upfront enasidenib, when ivosidenib was studied in the upfront setting, it led to CR + CRi rates of 42.4% and CR rate of 30.3%.\textsuperscript{44}

Although only currently approved as single-agent therapies, IDH1/2 inhibitors are actively being studied in combination regimens. A phase 1/2 study of azacitidine with or without enasidenib in patients with IDH2+ AML was presented in 2019.\textsuperscript{42} Patients were randomized 2:1 to receive azacitidine 75 mg/m\textsuperscript{2} day subcutaneously for 7 days plus enasidenib 100 mg oral daily or azacitidine alone. CR rates were significantly higher in the combination arm (50% vs 12%; \textit{P} = .0002). Objective response rates were also numerically higher in the combination arm (68% vs 42%; \textit{P} = .0155). Not surprisingly, AEs were more common in the combination arm. Grade 3 or 4 neutropenia (34% vs 19%) and thrombocytopenia (34% vs 19%) occurred more commonly; differentiation syndrome occurred in 12% of patients in the combination arm versus 0 patients in the monotherapy arm.\textsuperscript{42}

In addition, both enasidenib and ivosidenib have recently been studied in combination with intensive chemotherapy in newly diagnosed AML.\textsuperscript{45} In a phase 1, multicenter, open-label study in patients with IDH1 or IDH2+ newly diagnosed AML, patients received either ivosidenib 500 mg by mouth once daily (if IDH1) or enasidenib 100 mg by mouth once daily (if IDH2) in combina- tion with cytarabine 200 mg/m\textsuperscript{2} continuous IV infusion for 7 days and either daunorubicin 60 mg/m\textsuperscript{2} IV or idarubicin 12 mg/m\textsuperscript{2} IV for 3 days. Patients achieved CR in 68% of cases in the ivosidenib arm and 55% of cases in the enasidenib arm and CR + CRi rates were 77% and 74%, respectively.\textsuperscript{45}

Theoretically, concomitant IDH inhibition and BCL inhibition may be synergistic.\textsuperscript{46} Therefore, a phase 1/2b study was under- taken to investigate the combination of venetoclax and ivosidenib with or without azacitidine.\textsuperscript{47} This ongoing proof-of-concept study had 3 cohorts in which 19 patients received ivosidenib 500 mg once daily days 15 and onward, either 400 mg (cohort 1 and 3) or 800 mg (cohort 2) of venetoclax on days 1 to 14 with or without azacitidine 75 mg/m\textsuperscript{2} days 1 to 7 (cohort 3) of a 28-day cycle. Overall, CR + CRi rates were 78% (cohort 1, 67%; cohort 2, 100%; cohort 3, 67%).\textsuperscript{47} This represents a promising future combination to offer to patients with IDH-mutated leukemia.

Pharmacists should pay particular attention to the differences in drug interactions, dose adjustments, and AE profiles between enasidenib and ivosidenib. Enasidenib inhibits UGT1A1 to compete with bilirubin for clearance, and therefore, elevated bilirubin is an expected outcome of enasidenib therapy; however, dose adjustments are only necessary for a sustained hyperbilirubinemia greater than 3 times the upper limit of normal.\textsuperscript{6} Ivosidenib is known to cause QTc interval prolongation, so the
Differentiation syndrome is common in acute promyelocytic leukemia (APL), but it has only recently been more clearly described in AML with the advent of novel oral therapies. When used as single agents, differentiation syndrome occurred in 6% to 19% of patients and had a median time to onset of 29 to 48 days, which is substantially longer than the typical onset in APL, which generally occurs within 10 to 14 days. Notably, when these agents were used in combination with intensive chemotherapy, rates of differentiation syndrome were low (2%-3%). It is important to quickly identify and intervene with corticosteroids when differentiation syndrome is suspected. Recommended starting doses for corticosteroids are consistent with differentiation syndrome in APL such as dexamethasone 10 mg every 12 hours for at least 3 days and resolution of symptoms. For low-grade symptoms, IDH-directed therapy can generally be maintained during differentiation syndrome; however, it may require treatment interruption for severe reactions.

**Hedgehog Inhibitors**

In 2018, glasdegib was approved in combination with LDAC for the treatment of AML in older patients or patients unfit for intensive chemotherapy. Glasdegib was studied in a phase 2, randomized, open-label, multicenter study comparing LDAC plus glasdegib with LDAC alone. Patients were stratified by cytogenetic risk, and 132 patients were randomized 2:1 to glasdegib 100 mg once daily with azacitidine 75 mg/m²/day days 1 to 7 of a 28-day cycle. Patients achieved CR + CRi in 37% of cases and CR in 17% of cases; median time to CR was 5.6 months. Toxicities were similar to those reported in the glasdegib + LDAC study and included nausea, constipation, diarrhea, and hematologic toxicities. A recent labeling update included dose adjustments for glasdegib when used in combination with CYP3A4 inducers. Pharmacists should pay careful attention to these interactions and note the recommended glasdegib dose increase to 200 mg when appropriate.

**Oral Hypomethylating Agents**

Historically, hypomethylating agents have had poor bioavailability due to gastrointestinal deactivation by cytidine deaminase (CDA). One method for overcoming this mechanism is combining hypomethylating agents with CDA inhibitors, as was accomplished with decitabine/cedazuridine, which was recently FDA approved for the treatment of MDS. Although not yet approved for AML, the ongoing phase 3 bioequivalence study does include patients with AML.

**Maintenance Therapy in AML**

Historically, maintenance therapy has not played a role in AML. Therapies such as interleukin-2 (IL-2) and interferon (INF) have been studied and have not demonstrated favorable outcomes. It could be argued that lack of access to MRD testing and targeted patient selection for such studies may have minimized any potential benefit in those historical cohorts. More recent attention on MRD and maintenance therapy has led to a renewed emphasis. Ultimately, the goal of maintenance therapy is to reduce risk of relapse and improve overall survival.

**Hypomethylating Agents**

Use of hypomethylating agents as maintenance therapy has historically yielded mixed results. In a phase 2 study by Cancer and Leukemia Group B (CALGB, now the Alliance) evaluating maintenance therapy in young (<60 years) adult patients (N = 134) following intensive induction and consolidation, patients received decitabine 20 mg/m²/day for 5 consecutive cycle days, which is substantially longer than the typical onset in APL, which generally occurs within 10 to 14 days.

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days every 6 weeks for 8 cycles.\textsuperscript{55} At a median follow-up of 56.7 months, 1-year and 3-year disease-free survival (DFS) were 79\% and 54\%, respectively, and 1-year and 3-year OS were 96\% and 68\%, respectively.\textsuperscript{55} These results were similar to historical comparisons performed by CALGB and represented no significant benefit compared with past studies without maintenance therapy. More recently, decitabine has also been evaluated for use in maintenance in a phase 3, randomized trial comparing an abridged decitabine regimen (20 mg/m\textsuperscript{2} IV for 3 days every 4 weeks for 1 year) to observation.\textsuperscript{56} OS was significantly improved in the decitabine arm compared with observation (HR, 0.69; \(P = .06\), prespecified \(\alpha \) 0.1). DFS was not significantly different between the groups.

In addition, a more recent analysis of azacitidine maintenance in older patients demonstrated an improvement in DFS.\textsuperscript{57} In this phase 3 study, older patients who achieved CR after at least 2 cycles of intensive chemotherapy were randomized 1:1 to receive either observation or azacitidine 50 mg/m\textsuperscript{2} subcutaneously on days 1-5 every 4 weeks for a maximum of 12 cycles. Of the 56 patients randomized to the azacitidine arm, 46 received at least 4 cycles and 35 received 12 cycles. Median DFS was significantly better in the investigational arm (15.9 months vs 10.3 months; \(P = .04\)); however, OS was not different. Notably, more than half of the patients in the observation arm were initiated on salvage therapy, though only 9 patients in the azacitidine arm were initiated on salvage therapy.\textsuperscript{57}

Given the mixed aforementioned results and logistical challenges of transporting patients for daily injections, it is reasonable that providers and patients may choose not to initiate maintenance therapy. Oral therapy may pose a more feasible option for maintenance therapy for patients. Oral azacitidine was approved in 2020 for maintenance therapy in the treatment of AML.\textsuperscript{17} Patients were included if they were 55 years or older and were in CR after intensive induction chemotherapy, but were not candidates for bone marrow transplant. Patients were randomized 1:1 to oral azacitidine 300 mg or placebo once daily for 14 days of a 28-day cycle. Median age was 68 years and more than 90\% of enrolled patients had a performance status of 0-1. The majority (89\%) had de novo AML; 85\% had intermediate cytogenetics. While the majority of patients had a good performance status, only 78\% of the included patients received any consolidation cycles. Also of note, 43\% of patients had MRD. Median OS and progression-free survival (PFS) were significantly improved in the investigational arm compared with placebo (24.7 months vs 14.8 months, \(P < .001\); 10.2 vs 4.8 months, \(P < .001\), respectively). Neutropenia was more common in the investigational arm (44\% vs 26\%); other hematologic AEs were similar between the groups. Gastrointestinal AEs were more common in the azacitidine arm, including nausea (65\% vs 24\%), vomiting (60\% vs 10\%), diarrhea (50\% vs 21\%), and constipation (39\% vs 24\%).\textsuperscript{17} Given the emetogenic potential, it is important for pharmacists to ensure the patient has appropriate antiemetic prophylaxis and rescue medications prescribed. It is recommended the patient take a prophylactic antiemetic prior to each dose of the first 2 cycles.\textsuperscript{16} The antiemetic can be discontinued if the patient tolerates therapy well. Oral azacitidine and parenteral azacitidine should not be interchanged at any time.\textsuperscript{16}

**FLT3 Inhibitors**

Midostaurin was evaluated for maintenance therapy as part of the RATIFY study.\textsuperscript{12} On study, patients who were in CR after induction and consolidation cycles went on to receive midostaurin 50 mg by mouth twice daily for 1 year. Of 360 patients in the midostaurin arm, 120 received maintenance and 69 received the full 12 cycles; the study was not designed to show the independent benefit of maintenance.\textsuperscript{12} Despite its inclusion in the study design, maintenance was not included in the FDA approval.\textsuperscript{9} There are ongoing clinical trials evaluating maintenance therapy with gilteritinib and quizartinib.\textsuperscript{58,59}

**Checkpoint Inhibitors**

Immune checkpoint inhibitors (ICIs) have been studied across the spectrum of oncologic malignancies but to date have not been approved for any AML indications. Recently, results of a pilot phase 2, single-arm, open-label study (\(N = 15\)) evaluating nivolumab maintenance in patients with high-risk AML (including secondary AML, high-risk cytogenetics, FLT3 ITD, or MRD+) receiving nivolumab 3 mg/kg every 2 weeks for 12 doses followed by every 4 weeks for 6 doses followed by every 12 weeks until disease progression, death, or intolerable AEs were published.\textsuperscript{60} Patients received a median of 6 cycles. At a median of 30.4 months of follow-up, the mOS had not been reached. Grade 3 or 4 immune-related adverse events (irAEs) occurred in 27\% of patients and generally subsided with high-dose steroids and dose interruptions. Although the PFS was similar to historical comparison, OS may be promising, especially for AML with high-risk features.\textsuperscript{60} There are also ongoing studies of pembrolizumab maintenance therapy in AML.\textsuperscript{61}

Maintenance therapy remains overall an elusive approach for AML, but an area of much ongoing research, including targeted therapy, immunotherapy, and cytotoxic chemotherapy. Addi-
### COUNSELING CORNER

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<thead>
<tr>
<th>Medication</th>
<th>Administration Details</th>
<th>Adverse Effects</th>
<th>Notes</th>
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<tbody>
<tr>
<td><strong>Azacitidine</strong>:</td>
<td>This medication is administered 300 mg (1 tablet) by mouth days 1 through 14 of a 28-day cycle.</td>
<td>• Adverse effects (AEs) include nausea or vomiting, diarrhea, constipation, and white blood cell lowering.</td>
<td>• Patients are asked to take antinausea medication prior to each dose for the first 2 cycles to prevent nausea and vomiting. If the patient does not experience nausea, this can be omitted after 2 cycles. • Oral azacitidine and parenteral azacitidine cannot be interchanged.</td>
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<tr>
<td><strong>Enasidenib</strong>:</td>
<td>This medication is administered 100 mg (1 tablet) by mouth once daily.</td>
<td>• AEs include differentiation syndrome and increase in liver enzymes.</td>
<td>o Differentiation syndrome occurs when white blood precursor cells mature into adult cells. This can cause rapid white blood cell elevation, weight gain, and difficulty breathing. If patients experience these symptoms, they should call their provider immediately.</td>
</tr>
<tr>
<td><strong>Gilteritinib</strong>:</td>
<td>This medication is administered 120 mg (3 tablets) by mouth once daily.</td>
<td>• AEs include muscle pain, increase in liver enzymes, neurologic toxicity, heart rhythm effects, and differentiation syndrome.</td>
<td>o Patients may receive heart rate and rhythm monitoring with an electrocardiogram (ECG) to check for AEs. • This medication has many drug interactions. Patients are encouraged to speak to their pharmacist or provider before starting a new medication.</td>
</tr>
<tr>
<td><strong>Glasdegib</strong>:</td>
<td>This medication is administered 100 mg (1 tablet) by mouth once daily in combination with subcutaneous therapy.</td>
<td>• AEs include muscle pain, heart rhythm effects, and kidney function worsening.</td>
<td>o Patients may receive heart rate and rhythm monitoring with an ECG to check for AEs.</td>
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<tr>
<td><strong>Ivosidenib</strong>:</td>
<td>This medication is administered 500 mg (2 tablets) by mouth once daily.</td>
<td>• AEs include heart rhythm effects and differentiation syndrome.</td>
<td>o Differentiation syndrome occurs when white blood precursor cells mature into adult cells. This can cause rapid white blood cell elevation, weight gain, and difficulty breathing. If patients experience these symptoms, they should call their provider immediately. o Patients may receive heart rate and rhythm monitoring with an ECG to check for AEs. • This medication has many drug interactions. Patients are encouraged to speak to their pharmacist or provider before starting a new medication.</td>
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<tr>
<td><strong>Midostaurin</strong>:</td>
<td>This medication is administered 50 mg (2 tablets) by mouth twice daily days 8 through 21 of each chemotherapy cycle.</td>
<td>• AEs include rash, nausea or vomiting, heart rhythm effects, and blood count lowering.</td>
<td>o Patients are asked to take antinausea medication prior to each dose to prevent nausea and vomiting. o Patients may receive heart rate and rhythm monitoring with an ECG to check for AEs. • This medication has many drug interactions. Patients are encouraged to speak to their pharmacist or provider before starting a new medication. • This medication can be associated with a distinct odor. It is recommended to open the blister packaging a few minutes before taking the medication if the smell induces nausea.</td>
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<tr>
<td><strong>Venetoclax</strong>:</td>
<td>This medication is administered 400 to 600 mg (4-6 tablets) by mouth once daily in combination with intravenous or subcutaneous chemotherapy.</td>
<td>• AEs include nausea or vomiting, diarrhea, white blood cell lowering, or tumor lysis syndrome (TLS).</td>
<td>o TLS is a rapid killing of cancer cells, which may cause organ damage if the patient is not properly hydrated. Patients are asked to take allopurinol and stay well hydrated for several days before and during the initial weeks of therapy for prevention. o Patients “ramp up” to the target daily dose over 3 to 4 days. • This medication has many drug interactions. Patients are encouraged to speak to their pharmacist or provider before starting a new medication. For all of these medications, doses may be reduced due to response, AEs, or drug interactions. Additionally, medication will usually be dispensed by a specialty or mail-order pharmacy. When the prescription is received, it should be stored in a cool, dark place. After touching the medication, hands should be washed to prevent drug exposure to others. This medication should be taken at the same time every day. If a dose is missed, the dose is to be skipped, and therapy is to be resumed the next day. These medications should not be crushed, split, or chewed.</td>
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**STAR**

How has COVID-19 impacted care of patients with hematologic malignancies including AML?

**Considerations for Older Patients During the COVID-19 Pandemic**

Despite advances, novel treatment approaches, and ongoing research in AML, challenges remain in treating older patients with AML. The majority of patients who are diagnosed with AML are older, with 75% older than 55 years and 60% older than 65 years.2 Despite this majority, providers may be hesitant to treat older patients with currently available therapies. In 2020, the American Society of Hematology published a guideline for the management of older patients with newly diagnosed AML.62 This guideline advocates for older patients to receive active antileukemic therapy over best supportive care. Furthermore, it promotes intensive therapy over less-intensive options when patients are fit for such therapies. Many patients may not be fit for such intensive therapies due to comorbidities or patient preference. Many lesser-intense options are now available in this setting, in both monotherapy and combination regimens. At this time, the guidelines recommend monotherapy LDAC or hypomethylating regimens over combination regimens for patients not fit for intensive therapy and note that the recommendations are subject to change with forthcoming phase 3 data of combination regimens with glasdegib and venetoclax.63 Many of the phase 3 randomized studies evaluating these combination regimens were published after the guidelines and demonstrated survival advantages, so it is reasonable to suspect this recommendation may be amended to include combination regimens in the future. Nevertheless, caution must be taken when initiating older patients on complex regimens, particularly those who have comorbidities that may exacerbate AEs or lead to drug interactions.

Older patients have also been particularly vulnerable to SARS-CoV-2 and, therefore, exercising caution and other practical considerations became necessary for treating older patients with AML during the COVID-19 pandemic. One way in which providers have attempted to reduce health care and infectious exposures during the pandemic was to consider oral therapies over IV therapies where appropriate.65

Furthermore, a reduction in access to stem cell transplants and blood products has changed treatment decisions for patients with AML during the pandemic.64 Travel restrictions limited stem cell donors from providing blood or marrow donations, and patients who were eligible and in need of transplant may not have had access. In this setting, recent maintenance therapy data should be reviewed for options where transplant may be unavailable. Patients who were eligible for transplant were ultimately not included in the QUAZAR-AML001 oral azacitidine study for obvious ethical reasons; however, in the setting of limited access to transplant, it has been recommended after careful individualized consideration of risks versus benefits.17,65

Some researchers have looked specifically at the impact of COVID-19 on patients with AML. In one early series of COVID-19 in patients with hematologic malignancies, 101 patients were identified, of which ten had AML. Overall, 7 patients had modifications of their leukemia treatment, including dose reductions, cycle delays, or drug discontinuations. Half of the patients ultimately succumbed to the virus. Access to vaccination and better understanding of COVID-19 disease management has led to a reduction in mortality rates, but it is still important for providers to be diligent. Some therapies that have been used as potential anti–COVID-19 agents, such as hydroxychloroquine, azithromycin, and chloroquine, also have unique drug interactions and overlapping toxicity profiles to AML-directed therapies; additional caution must be taken, particularly with QT-prolonging agents.66

Ultimately, many lessons can be learned from the pandemic that will translate beyond this period. In addition to the quickness with which health care providers and pharmacists adjusted treatment algorithms, regimens, monitoring, and supportive care to preserve resources and reduce exposures, there were many practical lessons as well. In particular, there are many opportunities for virtual patient care, such as counseling, toxicity management, and adherence support, all of which can be provided by pharmacists remotely.67

**Conclusion**

After decades of stagnant treatment algorithms in AML, much has changed since 2017. With new drug approvals and regimens come new complications and obstacles. Armed with the right tools, pharmacists are poised to support oncologists and patients through navigating complex schedules, unique AE profiles, significant drug interactions, and adherence barriers. Finally, it must be noted that novel therapies are only advantageous if the patients are able to obtain them. Pharmacists can also play key roles in medication access and helping to mitigate financial toxicities to AML therapy.
Interactive Patient Simulation

This portion of the activity is unique and interactive, as it simulates real patient cases. Access the simulation at www.pharmacytimes.org/go/frontline-AML

ADDITIONAL RESOURCES

American Society of Hematology. COVID-19 and Acute Myeloid Leukemia: Frequently Asked Questions
Reville PK, Kadia TM. Maintenance therapy in AML. Front Oncol. 2021;10(3255).

REFERENCES

22. DiNardo CD, Jonas BA, Pallavarkat V, et al. Azacitidine and venetoclax in previously untreated...


INSTRUCTIONS FOR EARNING CREDIT

Begin the activity by reading the content in its entirety. Go to www.pharmacytimes.org/go/frontline-AML to access the online version of this activity. Click “Proceed,” then complete the online pretest. Once completed, click “Next” until reaching the activity posttest. After successful completion of the online interactive patient simulation, posttest, and activity evaluation, your credit will be uploaded into CPE Monitor. You must complete these steps before the activity expires in order to receive your credit. You may view your credit within 48 hours at www.mypcemonitor.net.

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POSTTEST QUESTIONS

1. Differentiation syndrome is a known adverse effect of:
   A. FLT3 inhibitors, and usually occurs about 2 weeks into therapy
   B. IDH1 and IDH2 inhibitors, and usually occurs in the first 24 to 48 hours of therapy
   C. IDH1 and IDH2 inhibitors, and usually occurs about 1 to 2 months into therapy
   D. Venetoclax in acute myeloid leukemia (AML) and patients should be assessed for level of risk in the first 24 to 48 hours of therapy

2. Which patient is the most appropriate candidate for azacitidine maintenance therapy?
   A. A 45-year-old with relapsed/refractory AML who just completed gemtuzumab ozogamicin therapy
   B. A 51-year-old with core binding factor AML who is in complete remission after induction chemotherapy and is scheduled for bone marrow transplant following one cycle of consolidation high-dose cytarabine
   C. A 67-year-old who completed induction chemotherapy and has 38% residual blasts on his bone marrow biopsy following induction
   D. A 60-year-old who has completed induction chemotherapy and is in remission, but is debilitated from his induction and is not a candidate for transplant

3. When starting a patient on azacitidine maintenance therapy, which of the following should be emphasized during an initial counseling session?
   A. Oral azacitidine is known to cause nausea. Patients should be instructed to take a prophylactic antiemetic before each dose for the first 2 cycles.
   B. Oral azacitidine is given every day indefinitely with no breaks in therapy unless advised by physician.
   C. Oral azacitidine is known to cause differentiation syndrome. The patient should be educated on signs and symptoms and management strategies.
   D. Oral azacitidine is known to have drug interactions with CYP3A4 inducers. If an inducer is started, the dose should be increased to 600 mg once daily.

4. Use this case for questions 4 and 5.
   HP is a 71-year-old man started on azacitidine and venetoclax for newly diagnosed AML. Which of the following would be most appropriate to recommend for the management and prevention of tumor lysis syndrome?
   A. Hospital admission is indicated for therapy initiation and each venetoclax dose increase.
   B. Venetoclax dosing is 20 mg by mouth for the first week, 50 mg for the second week, 100 mg for the third week, 200 mg for the fourth week, then 400 mg for the fifth week and thereafter.
   C. Allopurinol is recommended for 3 days before starting venetoclax and for the first week of therapy. Patients should drink plenty of water while increasing doses.
   D. The patient has no risk of tumor lysis syndrome and does not need to take any precautions.

5. After 2 cycles, HP has prolonged profound neutropenia and his physician is worried about opportunistic infections. The team decides to initiate him on posaconazole prophylaxis. Which of the following should be recommended with his venetoclax dose?
   A. Posaconazole does not pose a drug interaction with venetoclax. No adjustment is needed.
   B. Posaconazole poses a significant drug interaction; the dose of venetoclax should be reduced to no more than 100 mg.
   C. While posaconazole does pose a drug interaction, no dose adjustments are needed as long as the patient continues to tolerate therapy.
   D. Posaconazole is a contraindicated combination with venetoclax. A different antifungal agent should be initiated.
6. Which statement is most accurate about oral hypomethylating agents?
   A. Oral decitabine and oral azacitidine have good bioavailability and can be used interchangeably with the parenteral counterparts.
   B. Oral decitabine is approved for AML and can be interchanged with parenteral decitabine within a single cycle.
   C. Oral azacitidine cannot be interchanged with parenteral azacitidine, and the products have different indications.
   D. Oral decitabine and oral azacitidine are both approved for maintenance therapy for AML and are recommended in patients who achieve a complete response after induction but are not candidates for intensive therapy.

7. A patient on low-dose cytarabine and glasdegib is admitted for recurrent methicillin-sensitive Staphylococcus aureus bacteremia and is placed on a 6-week course of nafcillin. Nafcillin is a moderate CYP3A4 inducer. What additional therapeutic changes do you recommend?
   A. Glasdegib dose should be reduced to 50 mg once daily.
   B. Glasdegib dose should be increased to 200 mg once daily.
   C. Glasdegib requires no changes for a moderate CYP3A4 inducer.
   D. Treatment with glasdegib is contraindicated.

8. Which statement is most accurate about recommended treatment modalities for older patients with AML?
   A. Older patients should not be offered intensive therapy, as the risk of morbidity outweighs any potential benefit.
   B. Patients older than 55 years were excluded from the azacitidine and venetoclax study by DiNardo and colleagues and therefore this regimen cannot be applied to them.
   C. Oncologists should recommend antileukemic therapy instead of best supportive care, even in older patients.
   D. Patients should always be offered a hypomethylating agent in the first-line setting, even when targeted therapy exists.

9. Which of the following recommendations is most appropriate to support the care of older patients with AML during the COVID-19 pandemic?
   A. Delay of intensive induction therapy
   B. Empiric dose reductions to limit neutropenia
   C. Monthly COVID-19 testing during neutropenia
   D. Prophylactic antimicrobials for prolonged neutropenia

10. What is true about IDH-directed therapy in AML?
    A. Ivosidenib is an IDH2 inhibitor approved only for relapsed/refractory AML.
    B. Ivosidenib is an IDH1 inhibitor approved for newly diagnosed and relapsed/refractory AML.
    C. Enasidenib is an IDH1 inhibitor approved only for relapsed/refractory AML.
    D. Enasidenib is an IDH2 inhibitor approved for newly diagnosed and relapsed/refractory AML.
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