COVER STORY
Facilitating Access to Oncology Medication
JUSTIN LINDHORST, MBA

DRUG PATHWAYS
Targeting the Untargetable: Novel Agents in Acute Myeloid Leukemia
JORDAN TABISH, PHARMD; ASHLEY CHEN, PHARMD; AND IVAN HUANG, PHARMD, BCOP

EVOLVING THERAPIES
The Changing Landscape of Relapsed/Refractory Chronic Lymphocytic Leukemia Treatment
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Facilitating Access to Oncology Medication
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Research has shown that prompt access to cancer treatment can improve patients’ health outcomes, quality of life, and survivability, yet time to treatment initiation for patients with newly diagnosed cancer is increasing.

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EVOLVING THERAPIES

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Patient Access in Oncology: An Increasingly Complex Landscape

Following the tragedies of the COVID-19 pandemic, a light has been shined on the divide between those who have access to health care resources and those who do not, as access to quality care has directly affected patient outcomes during the public health crisis.

Additionally, underserved populations with limited access to medical care continue to be disproportionately impacted by certain cancers, even as more oncologic therapies become available to treat these conditions.

It is vital to address the impact social determinants of health (SDOH) have on a patient’s ability not only to initiate a therapy that will provide them with a real opportunity to fight the disease, but also to continue to progress on that therapy.

In this issue of Directions in Oncology Pharmacy®, we take a look at a few of the resources available to support patients’ ability to access quality cancer care, as well as provide an overview of some of the current efforts to advance the goal of providing equitable access to cancer care for all patients.

In our cover story, on page 68, author Justin Lindhorst, MBA, discusses the impact of financial toxicity on treatment outcomes for patients with cancer, as well as the role of SDOH on time to treatment initiation for patients with a new cancer diagnosis.

On page 14, author Dea Belazi, PharmD, MPH, addresses how the availability of groundbreaking gene therapies is driving change toward the development of alternative payment models, progressing the role of specialty pharmacy benefit management in bringing about this shift.

For patients who may need the aid of financial counselors, these health care professionals now have at their disposal technologies that proactively search for financial assistance for patients. On page 58, authors Brenda Bernard, MSN, RN, OCN, and Srulik Dvorsky explain how the use of this technology can improve health outcomes, save time, and achieve cost savings for pharmacies, hospitals, and practices.

Additionally, on page 54, we look at a study from the Community Oncology Alliance that shows how a lack of oncology drug pricing transparency can contribute to a lack of access to oncology care for patients. For the 340B program in particular, several flaws in the current structure of the program could be resolved through transparent hospital drug pricing that could shed light on these issues.

With these strides toward health care equity, each effort to establish change should not be forgotten when considering the great distance left still to travel. Instead, highlighting these efforts can remind us of the important work still before us.

Mike Hennessy Jr
PRESIDENT & CEO
The Road to Optimal Oncology Patient Outcomes Is Paved By Oncology Pharmacists

Oncology pharmacists play a significant role in clinical pathways.

Dan Steiber, RPh, Directions in Oncology Pharmacy® Editor-in-Chief

All patient treatment journeys should begin with a plan; in cancer therapy, that plan is called the clinical pathway. Oncology pharmacists play an instrumental role in these clinical pathways and often are the primary member of cancer care teams providing patients with assurance that they are on the right treatment plan.

The American Society of Clinical Oncology (ASCO) defines clinical pathways as “detailed, evidence-based treatment protocols for delivering cancer care to patients with specific disease types and stages.” Additionally, ASCO goes on to note that, when properly designed and implemented, these clinical pathways can act as a tool for improving care quality and reducing costs.

Within oncology teams, there is an ongoing debate regarding drug savings vs evidence-based care. Further adding to the debate is the increasing role of managed care in the clinical pathway decision-making process.

When navigating this drug treatment process, highly trained oncology pharmacists, whether
board certified oncology pharmacists or specialized pharmacists working in oncology settings, are well positioned to guide oncology teams. In light of this, further exploration of the oncology pharmacist’s role in clinical pathway management can provide more evidence to support this position on care teams.

The Debate: Savings vs Support
It is no secret that health care costs are dramatically increasing and there is an overall shift toward a value-based health care delivery system. As a result, we have seen a significant increase in clinical pathways in oncology.

As of this year, there are an estimated 60 individual health insurance plans in the United States that are implementing oncology pathways, and more than 170 million individuals are covered by those plans and are potentially being treated under a plan-sponsored pathway.

In the community setting, both oncologists and oncology pharmacists have found treatment pathways essential when providing care for patients with different types of cancers. Clinical pathways serve as guides for these experts so they can select the optimal therapy based on the diagnosis.

Over the past couple of years, there has been an increasing influence from managed care on oncology treatment, principally driven by newly approved higher-cost cancer products and therapies hitting the market. The debate within oncology teams that has emerged is one around the pathway’s development, which has been principally driven by improving care and outcomes; however, when cost becomes the primary point of the selection process, patients may suffer.

The question then becomes one of balance: the improvement of patient care in balance with cost of care. As always, obtaining the best clinical outcome must be the overriding priority. But, in most cases, the patient will make the ultimate decision about what treatment they want before therapy is implemented.

In addition to facilitating the drug selection process, the clinical pathway often becomes an education tool by which the oncology pharmacist can assist the patient in learning about adverse effects, toxicity, efficacy, and treatment burden. The most accepted clinical pathways have embedded elements of the patient’s perspective and facilitate the patient’s ability to have ultimate authority in final treatment decision-making. In this way, clinical pathways exist primarily to achieve the highest evidence-based level of oncology care.

What Is the Right Path?
Given the acceptance of clinical pathways, several players have emerged in the field, requiring the clinical oncology team to be called on to consider the different options available. The decisions are often driven by assessing a quality pathway and finding the most currently accepted oncology treatment for a given cancer based on the patient’s diagnosis.

A significant challenge for oncology teams that has emerged as a result of payer influence is managing multiple pathways and potentially providing patients, even within a single practice, varying care depending on their insurance. Most oncology pharmacists and oncologists are uncomfortable with having different treatment pathways and standards of care based on pure economics.

The “gold standard” of treatment pathways is generally acknowledged to be those pathways established by the National Comprehensive Cancer Network (NCCN). NCCN guidelines are often updated and considered contemporary vs those driven by payers, which often have longer review cycles, thus making them potentially out of date.

Over the past decade in specialty pharmacy, oncology products have come into play as over 50% of the total drug spend. Today’s clinical guidelines often recommend a high-cost targeted therapy or immunotherapy because they offer the best efficacy and lowest toxicity. However, the concern arises around payers influencing the product selection process, as the motive of cost savings is often not the oncology team’s preferred direction.

For example, several oncology drugs have been developed, such as tyrosine kinase inhibitors (TKIs) for the treatment of chronic myeloid leukemia (CML). Although hematopoietic stem cell transplantation remains the only curative option for CML therapy, oral TKIs...
have transformed CML from a progressive disease with a high mortality rate into a chronic condition with dramatically reduced mortality rates. However, TKIs are costly therapies and, often, the choice of pursuing TKIs meets resistance in the payer community.

As approvals continue to provide more options for oncology teams to consider, we should anticipate this debate to continue and strengthen, thus allowing payers to leverage 1 therapy over another.

The Patient and Oncology Team’s View of the Role of Oncology Pharmacists

Given the perspective of Directions in Oncology Pharmacy® principally being that of oncology pharmacists, it is important to note that patients’ and fellow oncology team members’ perspectives are also important for oncology pharmacists to consider when approaching the management of clinical pathways.

There is a strong general consensus, supported by a number of studies, that the role of the clinical pharmacist in enhancing patient-reported adherence rates is significant and validated by medication ratio rates. However, it remains unclear whether patient perceptions of the clinical pharmacist’s role in managing clinical pathways align with the findings of this research.

In a recent study, investigators asked patients whether they felt the clinical pharmacist plays an instrumental role in their oncology care—and the results were impressive. Of the patients surveyed, 87.5% stated that they believed the clinical pharmacist plays a critical role in their care.

When patients were asked about their overall satisfaction with their oncology pharmacy care, the results were equally impressive. Patients said that they were 100% satisfied with the role of the clinical pharmacist in their pharmaceutical care. Some important additional takeaways from this survey included:

• having an onsite specialty pharmacy as a part of the clinic or hospital providing patient care facil-

tated greater clinical interaction with oncology patients than was possible at external pharmacies;  
• real-time access to medical records greatly assisted exchanges and education when making informed and patient-engaged clinical pathway decisions;  
• clinical pharmacists’ involvement resulted in higher patient satisfaction ratings and an enhanced overall relationship with the oncology team; and  
• high patient satisfaction ratings coincided with higher adherence to oral chemotherapy medications.

The Future Is Now

As clinical pathways continue to evolve, so will the oncology pharmacist’s role. We should anticipate that we will continue to see new and innovative therapies rise in price, creating more pressure from payers to manage costs.

Many of the new, innovative therapies will be for cancers that were more challenging to treat previously; however, we are seeing replacement or updated therapies for existing treatments emerge as well. These updated therapies often create opportunities for managed care to influence product selection either through a formulary, step edit, treatment pathway, or like mechanism. For example, biosimilars are creating these opportunities in today’s market.

All oncology pharmacists have a responsibility to play a role in the rational and ethical use of therapies and the clinical application of product selection and management, whether their decisions are driven by a clinical pathway or by their professional judgment. Oncology pharmacists have before them the opportunity to spearhead initiatives that promote safe, effective, and cost-efficient medication use, allowing them to lead the efforts of patient and interprofessional education.

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The Changing Landscape of Relapsed/Refractory Chronic Lymphocytic Leukemia Treatment

Treatment approaches have changed significantly over the past several years.

ALANA HIPPENSTEELE, SENIOR EDITOR

The landscape of relapsed or refractory (R/R) chronic lymphocytic leukemia (CLL) has changed significantly over the past several years, explained Jennifer Brown, MD, PhD, director of the CLL Center at Dana-Farber Cancer Institute and professor of medicine at Harvard Medical School, during a session at the Society of Hematologic Oncology (SOHO) 2021 Annual Meeting.

For example, patients relapsing after minimal therapy are now considered to be essentially like frontline, which is a significant shift in practice, Brown explained. Most of the data demonstrating this shift in practice pertain to patients relapsing after chemoimmunotherapy with targeted agents. For these patients relapsing after being previously treated with targeted agents, there is not yet enough data available regarding an efficacious approach to their care.

Brown noted that she generally divides patients with R/R CLL into the following categories: patients exposed to Bruton tyrosine kinase (BTK) inhibitors (BTKi), patients relapsing after venetoclax, and patients relapsing after BTKi and B-cell lymphoma-2 (BCL2) inhibitors.

“In terms of patients exposed to BTKi, in data from Ohio State, the most common reason for discontinuation was adverse events (AEs), and then over the long term, progression was the other main reason for discontinuation,” Brown said during the session.

In the study from Ohio State, investigators assessed toxicities and outcomes from ibrutinib-treated patients. The results showed that the most common AEs that led to discontinuation of therapy in patients with frontline CLL were arthralgia (42%), atrial fibrillation (25%), and rash (17%). For patients with R/R CLL, the most common AEs were atrial fibrillation (12%), infection (11%), pneumonitis (10%), bleeding (9%), and diarrhea (7%).

“Unfortunately, this does result in a reduced progression-free survival compared to what we’ve seen in patients who stay on therapy in randomized trials,” Brown said during the session. “Those who come off for AEs have a better prognosis than those who progress and can still respond to other kinase inhibitors, such as phosphoinositide 3-kinases (PI3Ks) kinase inhibitors. However, in these real-world data, the best outcomes were with venetoclax.”

In addition to PI3Ks kinase inhibitors, data have demonstrated that patients who stop ibrutinib or another BTK inhibitor for an intolerance can respond with a relatively low rate of recurrence to acalabrutinib and zanubrutinib, which demonstrates these are viable options for patients who stop BTKi because of AEs.

Additionally, patients who have stopped BTKi are at an increased risk of progression, Brown explained. Progression among these patients is most commonly due to mutations in BTK, with a subset of patients also having a mutation in phospholipase C gamma 2.

“We now have data that similar mechanisms of resistance with mutations of C481 in BTK apply to acalabrutinib, in data from Ohio State, and also zanubrutinib, in data from Australia. Our only prospective data specifically in this population are from a trial of venetoclax, in which the overall response rate [ORR] was 65%, which is really quite good,” Brown said during the session.

However, Brown noted that the complete response rate of 9% and the undetectable minimal residual disease (uMRD) of 42% are both lower than expected.
Patients who have stopped BTKi are at an increased risk of progression. Specifically, progressing after BTKi is associated with a lower response rate to venetoclax in combined analyses of outcomes.

To manage this lower response rate to venetoclax, some groups have responded by adding PI3Ks to venetoclax. In a study assessing umbralisib, ublituximab, and venetoclax, half the patients were R/R prior to BTKi, and the ORR to umbralisib and ublituximab in the first 3 cycles was 64% in patients with R/R CLL, Brown explained.

“This is rather encouraging,” Brown said during the session. “And then, of course, venetoclax was added, with very high rates of uMRD. Our study of duvelisib and venetoclax had similar results. So, there are opportunities for combinations in this space that can potentially enhance the efficacy of venetoclax.”

REFERENCE


Advancements and Updates in the Treatment Options for CLL

Including insights from the 2020 ASH Annual Meeting & Exposition

Now available on PharmacyTimes.com!

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:

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Director, PGY-2 Oncology Pharmacy Residency
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Hematology/Oncology Clinical Pharmacist
Northwestern Memorial Hospital

Watch now: https://tinyurl.com/y5jwpnxg
Genes Therapies Are not simply another new class of specialty drugs to treat symptoms of a given disease, but instead aim to cure by correcting the underlying genetic abnormalities causing the disease. As some of the nation’s leading pharmaceutical and biotech giants ramp up product development and commercialization, what was once a futuristic concept has become a reality.

With more than 900 investigational new drug applications for ongoing clinical studies of gene therapy products under way and the FDA predicting approval of 10 to 20 gene therapies a year, the availability of these groundbreaking drugs is becoming an emerging driver of change in alternative payment models, ushering in a growing role for specialty pharmacy benefit management (SPBM).

In their role within specialty pharmacy, specialty-focused pharmaceutical management companies can help reduce prescription drug costs, engage patients to make better health decisions, and maximize the use of their benefits while supporting health care providers through evidence-based care.

A Pharmacy Trend Ramps Up
Gene therapy, a type of highly targeted treatment that uses genetic material with the goal of changing a disease’s course, presents new and potentially life-altering options for patients. But the costs can be staggering. A new spinal muscular atrophy gene therapy, onasemnogene abeparvovec-xioi (Zolgensma; Novartis), far and away leads the list with its one-time price of $2.12 million. Another near the top is the first approved one-time DNA-altering gene therapy voretigene neparvovec-rzyl (Luxturna; Spark Therapeutics), which cures an inherited retinal disease that leads to blindness; its price tag: $850,000.

As diagnosis rates for rare disease rise, the drug pipeline continues to grow and advance through clinical trials. National Institutes of Health estimates that there are about 7000 rare diseases that affect approximately 25 million to 30 million Americans—and many have no approved therapies.

The 1-gene group of rare genetic disorders being studied for gene therapies includes the following:

- Cystic fibrosis is a disorder caused by CFTR gene mutation that makes the body unable to produce a specific protein essential for free-flowing mucus. Because of the lack of protein production, a thick sticky mucus builds up in the lining of the lungs.

- Duchenne muscular dystrophy (DMD) is a result of the mutation of the DMD gene, which is necessary for producing a protein responsible for muscle development.

- Gaucher disease is caused by a single gene, GBA1, that can have many mutations. The different types of the disease break down into 2 categories: those that do not affect the nervous system (type 1) and those that do (types 2 and 3).

- Hemophilia A and B are caused by a mutation in either the F8 or F9 genes. With the presence of this mutation, a person with hemophilia is missing an important element needed for their blood to clot after an injury.
Sanfilippo syndrome (mucopolysaccharidosis type III) is caused by a nonfunctional or missing SGSH gene, which produces an enzyme that’s essential for processing sugar molecules. This causes a buildup in different areas of the body, especially the brain, leading to neurological and developmental issues.

Spinal muscular atrophy is caused by a missing or nonfunctional SMN1 gene, which is responsible for a protein that connects certain nerves, or motor neurons, to muscles, supporting their functioning. Over time, these motor neurons die, and the muscles required for walking, talking, eating, and breathing eventually cease to function.

**Next-Generation Payment Models**

Although million-dollar gene therapies are promising, the possibility exists that they won’t work. Unlike other products, refunds for these therapies are not authorized. Furthermore, simply repackaging existing services or negotiating value-based contracting based on predefined outcome measures may not suffice.

However, new alternative payment models may make costly human gene therapies financially feasible for stakeholders. This benefits the manufacturers as well, as they have high market expectations for the increased use of these exciting new interventions that give patients and providers expanded therapeutic choices.

Long-awaited, timely solutions that go beyond the traditional pharma-payer/pharmacy benefit manager (PBM) framework to enable affordability could help payers manage the extraordinary costs of novel products. Currently, innovative programs are being designed to help make gene therapies and other specialty drugs more affordable. The goal of these alternative financing models is to assist in the management of value-based relationships between manufacturers and payers, including price monitoring and tracking trends for high-cost therapies.

Because of their efforts, SPBM programs have been successful in reducing costs for specialty and high-cost therapies, including emerging gene therapies. In fact, a suite of financial and insurance products is likely to become the industry standard for how high-cost medical care is delivered and paid for.

By treating each situation individually to maximize the outcome for patients and payers, SPBMs can help make emerging therapies not only more affordable but also more accessible, while increasing the quality of care.

Additionally, specialty-focused care improves patient adherence to their treatment plans, supports patient safety, and helps patients afford lower-cost pharmacy plans that offer convenient access and extra discounts at certain pharmacies.

**Finding the Right SPBM Partner**

An effective SPBM partner can help to ensure that a patient is getting the right therapy at the right time and the right treatment plan with the least amount of waste. Additionally, by identifying the most cost-effective route possible for the highest quality of care, the right SPBM partner can also offer benefit to other stakeholders within specialty pharmacy as well, such as to payers, pharma/biotech, and providers.

An effective SPBM partner should offer the following:

- Proper inventory and assay management to ensure that dispensed therapies compare reasonably with what’s prescribed and that the patient is receiving the appropriate number of doses
- Verification services for how much product the individual has available to determine how many more doses are needed each month so that the patient is always covered
- The ability to serve as a hybrid of traditional and innovative approaches that focus on specific populations that have an acute or chronic condition
- Education opportunities for individuals and caregivers regarding programs available, allowing them to feel more empowered after diagnosis and referral
- Personalized approach to enable a preferred formulary, evidence-based clinical policy bulletins and pathways, step therapy, lab, and other clinical assessments

Effective SPBM partners should also foster ongoing positive patient outcomes through persistence, adherence, compliance, and timely collaborative patient management. These professional teams can measure and track program effectiveness and validate savings and opportunities for continuous improvement and best practice outcomes.

Additionally, the most effective SPBM partners support cost containment, making them an obvious choice for innovative financing programs. These SPBM partners deliver value for patients, payers, and manufacturers, offering specialty pharmacy and infusion network options that specialize in data, analytics, and cost modeling, as well as real-time front-end prescription triage to ensure that patients get the right care at the right time.

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NSCLC cancer (NSCLC) is a collection of different entities with 3 major subtypes (Figure 1). Advancements in genomic and mutational analysis show that up to 60% of adenocarcinomas and up to 50% to 80% of squamous cell carcinomas (SCC) have a known oncogenic driver mutation (Figure 2, 3). These driver mutations ultimately lead to uncontrolled growth, proliferation, and survival; they also serve as potential targets for therapeutics.

Adenocarcinoma by far has seen the most progress, with targeted agents proving useful against the various driver mutations that can be found in the histology of these cancers. Additionally, immune checkpoint inhibitors have proven useful for the treatment of SCLC and NSCLC.

Historical Perspective on NSCLC Treatment
In NSCLC, the historical treatments have been platinum-based doublets. The typical 5-year survival for patients with metastatic NSCLC receiving only chemotherapy is approximately 6%, based on extended analysis of the KEYNOTE-001 (NCT01295827) phase 1 study, whereas the 5-year survival rate for those eligible for immunotherapies or targeted therapy ranges from 15% to 50%, depending on the biomarker. Furthermore, it is important to know that the initial response rates, median progression-free survival (PFS), and median overall survival (OS) that are associated with first-line platinum doublet therapies are around 15% to 32%, 3 to 5 months, and 9 to 12 months, respectively.

In the second-line or subsequent-line setting, pemetrexed (Alimta; Eli Lilly & Company) and docetaxel (Taxotere; Sanofi) generated overall response rates (ORRs) of 9.1% and 8.8%, respectively, in clinical trials. Median PFS was 2.9 months for each drug, whereas median OS was around 8 months for both.

Therapeutic Pathways With Drugs in NSCLC

**Sensitizing EGFR Mutations**
EGFR mutations are most common in nonsmokers or former light smokers with adenocarcinoma histology. The 2 most common EGFR gene mutations are deletions in exon 19 in 45% of patients and a point mutation in exon 21 (L858R) in 40%. Current drugs in use include osimertinib (Tagrisso; AstraZeneca), which is the current standard of care for first-line treatment; dacotinib (Vizimpro; Pfizer); afatinib (Gilotrif; Boehringer Ingelheim); erlotinib (Tarceva; Genentech); and gefitinib (Iressa; AstraZeneca).

Additionally, use of osimertinib has recently moved to the adjuvant setting for stage IB-IIIA NSCLCs that have a sensitizing EGFR mutation. Tumors with EGFR mutations do not respond to immune checkpoint inhibitors (ICIs) except for the atezolizumab (Tecentriq; Genentech) quadruplet regimen.

**EGFR Exon 20 Insertion Mutations**
EGFR exon 20 insertion mutations account for 4% to 10% of EGFR mutations seen. Until now, patients with EGFR exon 20 mutations have had poor outcomes when treated with available EGFR tyrosine kinase inhibitors (TKIs). Amivantamab is a bispecific antibody directed against MET receptors and EGFR and was studied in those who progressed on or following platinum-based chemotherapy. In the phase 1 CHRYSALIS study (NCT02609776), amivantamab elicited an ORR of 40% (3.7% were complete responses and 36.3% were partial responses). Immature data for median OS and PFS have been shown to be 22.8 months and 8.3 months, respectively.

**ALK Rearrangements**
ALK fusions are the result of a rearrangement of the ALK gene, which codes for a tyrosine kinase, and another gene product—most commonly EML4. Their resulting fusion product is a constitutively
active kinase that increases cellular proliferation and survival. Two Tumors with ALK mutations do not respond to ICIs. Current drugs include alectinib (Alecensa; Genentech), the standard of care for first-line treatment; brigatinib (Alunbrig; Takeda Oncology); ceritinib (Zykadia; Novartis); crizotinib (Xalkori; Pfizer); and lorlatinib (Lorbrena; Pfizer).

ROS1 Rearrangements
The ROS1 tyrosine kinase is very similar to ALK in molecular function. ROS1 tends to occur more frequently in those who are negative for EGFR mutations, KRAS mutations, and ALK gene fusions. Response to ICIs is truncated with ORRs at 17%. Current drugs include crizotinib, a preferred first-line treatment; ceritinib; entrectinib (Rozlytrek; Genentech), a preferred first-line treatment; and lorlatinib, which is reserved for second-line treatment.

BRAF V600E Mutations
BRAF is a serine/threonine kinase that is part of the MAP/ERK kinase pathway. Mutations of the BRAF gene are associated with more aggressive tumor histology and a poorer prognosis. Patients with BRAF mutations respond to ICIs at a rate of 24%. Current targeted agents for these mutations include dabrafenib (Tafinlar; Novartis) plus trametinib (Mekinist; Novartis), which is preferred; or vemurafenib (Zelboraf; Genentech) monotherapy.

NTRK1/2/3 Gene Fusions
NTRK genes encode for 3 TRK proteins (TRKA, TRKB, and TRKC) that play an important role in cellular growth, differentiation, and apoptosis of peripheral and central nervous system neurons. NTRK fusions occur in NSCLC at a rate between 0.2% and 4%. It is unknown whether there are ethnic-related or social behavior-related predilections for NTRK mutations. Current therapies include larotrectinib (Vitrakvi; Bayer) and entrectinib.

MET exon 14 (METex14) Skipping Mutations
METex14 skipping mutations are found in approximately 3% of NSCLC cases and are found more often in females, patients 70 years or older, nonsmokers, and in patients with pulmonary sarcomatoid carcinoma. METex14 skipping mutations are associated with poor prognosis and, unlike KRAS and BRAF mutations, response to immunotherapy is truncated to ORRs of 16% to 17%. Current guideline-recommended agents include capmatinib (Tabrecta; Novartis), tepotinib (Tepmetko; EMD Serono), and crizotinib. Additionally, the investigational drug savolitinib (AZD6094; AstraZeneca) is a selective MET inhibitor that is being studied.
**RET Rearrangements**

RET rearrangements occur when the gene that codes for RET fuses with other genes, leading to a fusion RET protein that is overexpressed and increases cellular proliferation. RET fusions are oncogenic drivers in 1% to 2% of NSCLC diagnoses.

Immunotherapy response is minimal with responses of 6%. The current agents that can be used include selpercatinib (Retevmo; Eli Lilly and Company), a preferred treatment; pralsetinib (Gavreto; Blueprint Medicines and Genentech), a preferred treatment; and cabozantinib and vandetanib (Caprelsa; Sanofi Genzyme).

**PD-1/PD-L1 Axis**

ICIs that target PD-1/PD-L1 axis work by reversing tumor-mediated inactivation of T cells and improving immune antitumor response. Classwise, PD-1 receptor inhibitors include nivolumab (Opdivo;...
Lung cancer therapeutics are numerous and varied and depend on the histologic subtype that is being treated.

Bristol Myers Squibb), pembrolizumab (Keytruda; Merck), and more recently cemiplimab (Libtayo; Regeneron Pharmaceuticals and Sanofi Genzyme), whereas atezolizumab and durvalumab (Imfinzi; AstraZeneca) inhibit PD-L1.

ICIs are typically used in patients negative for driver mutations and have essentially eliminated the need to use chemotherapy by itself in the first-line setting, except in cases where contraindications to immunotherapy exist. At present, all first-line regimens for NSCLC in this setting include ICIs. Additionally, when PD-L1 expression is 50% or more, pembrolizumab, atezolizumab, or cemiplimab can be used as monotherapy.

HER2 Mutations
HER2 (or ERBB2) differs from EGFR (ERBB1) in that it does not have an endogenous ligand. It promotes oncogenesis through heterodimerization with other members of the ERBB family that then activate various kinase pathways (Figure 4'). Despite a rough start with other anti-HER2 agents, TDM-1 or ado-trastuzumab emtansine and trastuzumab deruxtecan have shown much higher ORRs.

KRAS
KRAS is a G protein with GTPase activity and is a part of the MAP/ERK pathway; point mutations in the KRAS gene commonly occur at codon 12. KRAS mutations confer shorter survival and predict nonresponsiveness to EGFR TKIs. Additionally, KRAS mutations do not appear to affect chemotherapeutic efficacy and, contrary to many of the other driver mutations, they seem to respond to immunotherapy.

Despite years of research on the subject, attempts at inhibiting KRAS met with failure. However, more recently, hope has been restored due to presented data from a phase 2 trial (NCT03600883) of sotorasib (Lumakras; Amgen), a TKI that inhibits the KRAS G12C mutation by binding to KRAS in its inactive GDP state. The KRAS G12C mutation occurs in approximately 13% of patients with NSCLC, and therefore accounts for roughly half of all KRAS mutations.

KRAS G12C occurs in approximately 13% of patients with NSCLC, and therefore accounts for roughly half of all KRAS mutations.

Hot on the heels of sotorasib is adagrasib (MRTX849), another KRAS G12C kinase inhibitor. It differs from sotorasib in that it exhibits a much longer half-life of 24 hours compared with 5 hours for sotorasib, which is important because KRAS G12C is regenerated every 24 to 48 hours.

Conclusion
Lung cancer therapeutics are numerous and varied and depend on the histologic subtype that is being treated. The molecular pathways of SCLC and SCC NSCLC are still being researched, whereas adenocarcinoma by far has had the most innovation with the discovery of different driver mutations that support oncogenesis but also serve as a therapeutic target. There is still more research to be completed, but advancement seems probable, even if made only 1 step at a time.
Targeting the Untargetable: Novel Agents in Acute Myeloid Leukemia

Pharmacists have an important role in the optimization of AML therapies.

JORDAN TABISH, PHARMD; ASHLEY CHEN, PHARMD; AND IVAN HUANG, PHARMD, BCOP

Acutely Myeloid Leukemia (AML) is the most common acute adult leukemia with an estimated 20,000 new cases annually in the United States and a median age at diagnosis of 68 to 71 years.¹ With a complex pathophysiology, AML’s genetic mutations can cause accelerated growth and impaired differentiation in hematopoietic stem cells, leading to accumulation of immature myeloid cells. Over time, immature myeloid cells make up a progressively greater portion of the marrow, leading to impaired hematopoiesis and development of AML’s hallmark symptoms.²

Diagnosis of AML can be made based on detection of certain chromosomal abnormalities or by presence of 20% or greater immature myeloid cells in the peripheral blood or bone marrow.² Upon diagnosis of AML, prognostic factors such as physiologic age, functional status, and cytogenetics guide the selection of initial treatment.

Younger individuals with few comorbidities typically receive anthracycline and cytarabine containing chemotherapeutic regimens aimed at producing a deep and durable remission. Older patients unfit for intensive induction will alternatively be offered lower intensity induction therapy, most commonly a hypomethylating agent with or without venetoclax.¹,²

Despite significant advances over the past decades, overall prognosis remains poor because of a high rate of disease relapse. The 5-year overall survival (OS) in patients with favorable-risk disease is 34% to 65% and drops to 2% to 14% in those with poor risk.²,³ To more effectively combat such an aggressive disease, the AML treatment landscape has drastically changed in recent years with the introduction of targeted agents; however, many genetic and molecular abnormalities detected in AML remain without any targeted pharmacotherapy options.

Molecular Targets

Innovative research in AML has been focused on developing pharmaceutical agents to target specific molecular abnormalities, also known as driver mutations.³ Current FDA-approved targeted agents include midostaurin and gilteritinib for FLT3 mutations and gemtuzumab ozogamicin for CD33-positive leukemic blasts.

Around 30% of newly diagnosed AML expresses a mutated form of FLT3, a transmembrane ligand-activated receptor tyrosine kinase. FLT3 is normally present on hematopoietic stem cells and promotes cell survival, differentiation,
and proliferation.\(^4\) Midostaurin is a multitargeted FLT3 kinase inhibitor and has been shown to improve OS when added to standard AML induction chemotherapy in patients with FLT3 mutations.\(^5\) Gilteritinib is another multitargeted FLT3 kinase inhibitor; however, its approval is for relapsed or refractory (R/R) AML.\(^6\)

Additionally, over 80% of patients with AML express CD33 on their leukemic cells.\(^7\) A CD33-targeted monoclonal antibody conjugate, gemtuzumab ozogamicin works by binding to leukemic cells expressing CD33, which is internalized by the cell, and then releases cytotoxic calicheamicin, leading to apoptosis.

However, initial studies with a single high dose of gemtuzumab ozogamicin demonstrated an unacceptable risk of sinusoidal obstruction syndrome,\(^8\) leading to its momentary removal from the market. A more recent study with lower, fractionated dosing has since demonstrated benefit in adding it to intensive induction chemotherapy in patients with favorable risk disease without excessive hepatotoxicity, leading to the incorporation of this agent as a first-line therapeutic in clinical guidelines.\(^1,9\)

Although these therapies have improved treatment outcomes for patients with AML, there are numerous molecular abnormalities that confer a poor prognosis with no available targeted therapies (Table 1).\(^10\)

The treatment of R/R AML also remains a substantial challenge as current treatment options are limited in their ability to produce durable response without excessive toxicity. Encouragingly, there are numerous novel targeted agents currently under investigation that may further change the treatment landscape of AML.\(^10\)

**Pipeline Drugs: Existing Molecular Targets**

In the pipeline currently, quizartinib is a once-daily oral multitargeted tyrosine kinase inhibitor with activity against mutant FLT3. In a phase 3 study among patients with R/R AML, quizartinib was compared against salvage chemotherapy and was found to be associated with significantly improved OS, with median OS of 6.2 months, compared with 4.7 months with salvage chemotherapy.

In an exploratory analysis, composite complete response (CRc) was observed in 48% of patients receiving quizartinib, compared with 27% of patients receiving traditional chemotherapy. In the quizartinib arm, the response was more durable with a CRc median duration of 12.1 weeks vs 5 weeks for traditional chemotherapy. Consequently, a greater percentage of patients in the quizartinib arm were able to proceed to hematopoietic stem cell transplant (32% vs 11%). Toxicities of quizartinib include QT interval prolongation, nausea, hepatotoxicity, and myelosuppression.\(^11\)

Currently, quizartinib is currently being studied in newly diagnosed AML as an addition to induction and consolidation therapy.\(^12\) Quizartinib could be an alternative to midostaurin and gilteritinib in the newly diagnosed and R/R settings, respectively.

Another therapy in the pipeline is AMG330, which is a bispecific T-cell engager (BiTE) which redirects T lymphocytes expressing CD3 to target and attack CD33-expressing cells. AMG330 is currently undergoing a phase 1 study investigation in patients with R/R AML. Preliminary results have demonstrated response in 8 of 42 evaluable patients, with 3 exhibiting a complete response (CR).

It is important to take into account that this is a dose-finding study and a substantial number of non-responding patients may have been treated with
doses lower than what will be recommended in the phase 2 study. Overall, it is too early to speculate the role AMG330 may play in AML therapy, but the observation of complete responses in the phase 1 study is encouraging. If eventually approved, AMG330 would be the first BiTE indicated for treatment of AML.

Pipeline Drugs: Novel Molecular Targets
In the pipeline currently, devimistat (CPI-613) is an intravenously administered inhibitor of the ketoglutarate dehydrogenase (KGDH) and pyruvate dehydrogenase (PDH) complexes in the mitochondrial tricarboxylic acid cycle of leukemic cells, which results in decreased oxygen consumption and sensitization of leukemic cells to chemotherapy. In a phase 1 trial, devimistat was combined with high-dose cytarabine and mitoxantrone for treatment of patients with R/R AML. CR or CR with incomplete hematologic recovery was observed in 50% of patients and efficacy was similar in a subgroup of patients aged greater than 60 years. Notable nonhematologic toxicities of grade 3 or greater included hyperglycemia, hypokalemia, hypophosphatemia, transaminase elevation, QT interval prolongation, and diarrhea. Devimistat is currently being evaluated to improve response rates in older patients with R/R AML, which is a historically challenging population to treat.

Also in the pipeline, magrolimab is a CD47-targeted monoclonal antibody that blocks CD47 cell interactions with its ligand on macrophages, leading to phagocytic elimination of cancer cells. CD47 expression is upregulated in leukemic cells and functions as a macrophage checkpoint, providing an inhibitory signal that allows for tumor cell evasion of immune destruction by macrophages.

Additionally, a phase 1b trial of magrolimab in combination with azacitidine in patients with newly diagnosed AML unfit for intensive chemotherapy with predominantly poor risk cytogenetics (65% with \( TP53 \) mutations) showed promising results. During the trial, overall response was achieved in 65% of patients, with 44% achieving CR. The objective response (OR) in patients with \( TP53 \) mutations was 71%, with 48% achieving a CR. Since \( TP53 \) mutations are associated with inferior response and survival, magrolimab may be an attractive therapeutic option for this patient population.

Also in the pipeline, APR-246 (Eprenetapopt) is an intravenous agent that restores transcriptional activity of mutant \( TP53 \), a tumor suppressor gene, leading to apoptosis of leukemic cells with mutant \( TP53 \). \( TP53 \) mutations are detected in 10% to 20% of patients with AML and are associated with a poor prognosis, with median OS ranging from 6 to 8 months.

APR-246 was evaluated in combination with azacitidine in a phase 1b/2 study in 55 adult patients (median age, 66 years) with newly diagnosed AML, myelodysplastic syndrome (MDS), or chronic myelomonocytic leukemia with \( TP53 \) mutation. Median OS was 10.8 months in the AML population with CR in 36%. During the study, APR-246 was well tolerated with most grade 3 or greater toxicities being hematologic in nature. APR-246 is being further evaluated in an ongoing randomized, phase 3 study in patients with MDS. Should this trial yield positive results, future randomized controlled studies in patients with AML may be warranted to investigate its role in patients with a \( TP53 \) mutation.

Also in the pipeline, onvansertib is an oral serine-threonine kinase inhibitor that inhibits PLK-1. PLK-1 is highly expressed in leukemic cells and plays a role in centrosome maturation, spindle formation, and cytokinesis during mitosis. Inhibition of this process results in mitotic arrest and leukemic cell death.

Onvansertib is currently being investigated in combination with low-dose cytarabine or decitabine in a phase 1b/2 study of patients with R/R AML. Of

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| Summary of Drugs in the Pipeline |

- **Induction Therapy**
  - **Eprenetapopt** (p53 reactivator): Phase 2
  - **Magrolimab** (CD47 monoclonal antibody): Phase 3

- **Relapsed or Refractory AML**
  - **AMG330** (CD3-CD33 BiTE): Phase 1
  - **Onvansertib** (PLK-1 inhibitor): Phase 2
  - **Devimistat** (KGDH and PDH complex inhibitor): Phase 3

- **Induction and Relapsed or Refractory AML**
  - **Quizartinib** (FLT3 kinase inhibitor): Phase 3
the 30 evaluable patients at the interim assessment, only 4 achieved OR. However, response was significantly associated with translationally controlled tumor protein biomarker positivity, indicating leukemic cell reliance on PLK-1–mediated pathways of survival.

Nonhematologic AEs of grade 3 or greater thus far include stomatitis and elevated bilirubin. Results have yet to be reported, but onvansertib could be a compelling option for AML with high PLK-1 expression.19

Targeted therapies continue to play a vital role in changing the landscape of AML treatment. Numerous investigational therapies in the pipeline for AML with novel mechanisms of action have so far demonstrated encouraging results in various populations of patients with AML. As these novel agents enter the market and further complicate treatment decisions, pharmacists will play an important role in optimizing therapies for patients with AML.

REFERENCES

**DURING A PANEL** discussion on treatment approaches in the management of Hodgkin lymphoma for *Pharmacy Times*, experts reviewed the efficacy and safety of the recommended treatment regimens and discussed which treatment strategy they would recommend for their patients.

During the discussion, the panelists addressed the results of the RATHL trial (NCT00678327), which found that giving patients a PET scan following 2 cycles of chemotherapy with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) could determine whether bleomycin—part of the ABVD regimen known to cause long-term lung damage—can be removed from the regimen of patients who are responding well to treatment.

According to the study results, removing bleomycin and continuing with doxorubicin, vinblastine, and dacarbazine (AVD) for these patients is equally effective and safer than ABVD.\

“Clearly everyone knows bleomycin can cause lung toxicity—it’s unpredictable,” said Andrew Whiteley, MD, of Texas Oncology. “It could be a young healthy person in that bimodal distribution of Hodgkin lymphoma, where you’re treating a 20- to 30-year-old, and they’re not a smoker—they’ve got healthy lungs—and all of a sudden they’ve got a cough, fever, and then they’re in the ICU. And a small percentage of people—thankfully a small percentage of people—actually die of bleomycin-induced lung toxicity.”

The panel also discussed the results of the ECHELON-1 trial (NCT01712490), an open-label, multicenter, randomized phase 3 trial involving patients with previously untreated stage III or IV classic Hodgkin lymphoma. The study investigators found that using brentuximab vedotin (Adcertis; Seagen) in combination with AVD therapy had superior efficacy to ABVD in the treatment of patients with advanced-stage Hodgkin lymphoma.\

Whiteley, the updated 5-year results of the study make an even stronger case for removing bleomycin from the treatment regimen for Hodgkin lymphoma.

“The way I look at it, if I have a patient in front of me, unless they have a contraindication to Adcertis—which would basically be some sort of severe neuropathy to start out with—then I personally favor Adcertis AVD over ABVD because there’s a randomized, phase 3, large trial that showed a benefit—and a potentially increasing benefit at 5 years compared to the 2 year,” Whiteley said.

Whiteley also discussed the bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) treatment regimen.

The reason why, in America, we don’t use BEACOPP—even before the Adcertis ECHELON-1 data came out—is because of the amount of toxicity, the level of infertility, and the secondary malignancies in particular,” Whiteley said.

During the discussion, Ryan Haumschild, PharmD, MS, MBA, director of pharmacy services at Emory Healthcare, agreed with Whiteley’s assessment of BEACOPP as a therapy to avoid for the majority of patients.

“We’re starting to adapt more to assessing quality of life and patient-reported outcomes, and looking at the treatment of a patient more holistically and not just at clinical data,” Haumschild said. “Because if the patient can’t sustain treatment, what good is it having the best therapy if they’re not going to be able to handle it?”

**REFERENCES**

Society of Hematologic Oncology (SOHO) 2021 Annual Meeting

Balancing Toxicity, Tolerability, Efficacy Is Essential for CAR T-Cell Therapies in Indolent B-Cell Lymphoma

As CAR T-cell therapies show promise, clinicians must weigh toxicity and tolerability almost as strongly as efficacy.

AISLNN ANTRIM, ASSOCIATE EDITOR

AS VARIOUS chimeric antigen receptor (CAR) T-cell therapies show promise for the treatment of follicular lymphoma and marginal zone lymphoma (MZL), clinicians must weigh toxicity and tolerability almost as strongly as efficacy because patients can live years with these diseases, according to a presentation at the Society of Hematologic Oncology (SOHO) 2021 Annual Meeting.

During the session, presenter Caron A. Jacobson, MD, MMSc, medical director of the Immune Effector Cell Therapy Program at the Dana-Farber Cancer Institute, reviewed results from the ZUMA-5 (NCT03105336) and ELARA (NCT03568461) clinical trials, both of which have found encouraging data with CAR T-cell therapies. ZUMA-5 is a phase 2 clinical trial investigating axicabtagene ciloleucel for the treatment of relapsed or refractory indolent B-cell non-Hodgkin lymphoma (NHL), whereas the ELARA trial is investigating tisagenlecleucel in relapsed or refractory follicular lymphoma.

Jacobson said the ZUMA-5 trial enrolled 124 patients with follicular lymphoma and 22 with MZL, all of whom are considered high risk. Significantly, 55% of participants experienced progression of disease within 24 months of their first anti-CD20 monoclonal antibody-containing therapy (POD24) and most patients were in the third-line treatment setting.

After patients received treatment with axicabtagene ciloleucel, researchers found a 92% overall response rate (ORR) and a 78% complete response rate (CRR). The median time to first response was 1 month. Furthermore, among 25 patients with follicular lymphoma who originally had a partial response, 52% subsequently converted to a complete response after a median of 2.2 months.

The median duration of response, progression-free survival (PFS), and overall survival (OS) rates have not yet been reached for patients with follicular lymphoma, and 78% of patients with follicular lymphoma are maintaining their response. Jacobson noted that the duration of response data for patients with MZL are immature.

Among patients with POD24 status, Jacobson said researchers saw a lower CRR and shorter duration of response and PFS rates, but this was most notably in the MZL cohort, which had a 58% complete response rate and 11.1-month duration of response rate.

The safety profile for axicabtagene ciloleucel is favorable, Jacobson said, with only 9% of patients experiencing grade 3 or higher cytokine release syndrome (CRS). The most common CRS symptoms of any grade were pyrexia (96%) and hypotension (41%), and the most common neurologic events of any grade were tremor (52%) and confused state (40%).

Patients in the ZUMA-5 trial were allowed to be re-treated if their response lasted at least 3 months, with 13 patients being retreated in total. Among these patients, researchers found a 100% response rate and a 58% 12-month estimated PFS, as well as a similar safety profile and peak cytokine profile at the first infusion. »
Jacobson next turned to a discussion about the ELARA trial, which is investigating the use of tisagenlecleucel in relapsed or refractory follicular lymphoma. During the phase 2, single-arm, multi-center, open-label trial, investigators enrolled 94 participants. According to the presentation, the CRR was 66% with an ORR of 86% and a median follow-up of 11 months. A high proportion of patients were maintaining response at the data cutoff point and the median PFS and OS were not reached.

Jacobson also noted improvements in the toxicity profile compared with studies of diffuse large B-cell lymphoma, with 47 patients experiencing CRS, 9 of whom were grade 3 or higher. The median time to onset for CRS was 4 days.

Based on these findings and other ongoing research, Jacobson said CD19 CAR T cells have shown activity across B-cell NHL histologies and can lead to a high rate of durable remissions in indolent B-cell lymphoma. Toxicity for these patients appears to be the same or better than in aggressive B-cell NHL. Longer follow-up is needed to determine whether the responses seen in the ZUMA-5 and ELARA trials have the potential to represent cures for these historically incurable diseases.

REFERENCE

Updates in Sequencing Treatment for Early Multiple Myeloma Relapse
Optimal sequencing in multiple myeloma has changed, with new guidelines modeled after more current treatment regimens.

JILL MURPHY, ASSOCIATE EDITOR

THE FUTURE LANDSCAPE of multiple myeloma (MM) depends on the type of relapse, as each combination therapy can be specific to a certain set of patients, according to a presentation at the Society of Hematologic Oncology (SOHO) 2021 Annual Meeting.

Optimal sequencing in MM has changed from those outlined in the older EU guidelines, explained Maria-Victoria Mateos, MD, PhD, of the University Hospital of Salamanca-IBSAL in Salamanca, Spain, during the SOHO presentation. The new guidelines for relapsed/refractory MM (RRMM) are modeled around CD38-based and non-CD38-based regimens.

“The new response criteria are applicable to all patients,” Mateos said during the session.

Mateos further detailed different studies that analyzed treatments using carfilzomib, dexamethasone, and daratumumab vs carfilzomib and dexamethasone; isatuximab plus carfilzomib-dex in patients with RRMM; and daratumumab plus carfilzomib (Kyprolis) and dexamethasone in lenalidomide-refractory patients with multiple myeloma.

While examining all of the options, the best way to pick between the different combinations is by the duration of treatment with lenalidomide, comorbidities, and lifestyle of the patient, according to Mateos.

“Optimal sequencing treatment is at relapse, when the majority of patients receive lenalidomide as a part of first-line therapy and progress while on lenalidomide,” Mateos said during the session.

Even with the new guidelines in place, Mateos still feels that new combinations are needed for this population of patients, as many of the treatments are selected after the patient is exposed to proteasome inhibitors, immunomodulatory imide agents, and anti-CD38 during the first and second line of therapy. Further, new options are emerging for early relapses.

 “[Pomalidomide, bortezomib, and dexamethasone] is the most solid combination from my point of view for these patients,” Mateos said. “Selinexor dexamethasone is also showing promise.”

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Marginal Zone Lymphoma: Subtypes, Treatments, the Role of the Pharmacist

Although marginal zone lymphoma is relatively rare, it contains a broad spectrum of conditions under it that require an individualized treatment selection process.

Marginal Zone Lymphoma (MZL)—a low-grade, B-cell, non-Hodgkin lymphoma—is relatively rare, explained a panel of experts during an Insights series video discussion for Pharmacy Times.

The disease arises from a marginal zone of the lymph nodes, spleen, or mucosa-associated lymphoid tissue (MALT), and accounts for around 10% of non-Hodgkin lymphoma cases.

“Nodal MZL is even rarer,” said Amitkumar Mehta, MD, during the Insights discussion. “About 4000 cases of nodal MZL happen every year. The main pathophysiology of MZL is chronic antigen stimulation and that can happen for a variety of reasons.”

When describing the pathophysiology of MZL, Mehta noted the role of chronic antigen stimulation; in external MZL, Helicobacter pylori can cause chronic antigen stimulation in a condition known as H pylori gastritis.

“The other important part that I want to emphasize is hepatitis C,” Mehta said. “It is seen in about one-quarter to one-third of patients with MZL associated...”
with hepatitis C infection. So that is one of the tests that we would definitely conduct in all the patients apart from other regular tests for lymphomas.”

When asked to review the differences between MZL and other B-cell disorders, Javier Munoz, MD, MS, FACP, highlighted the broad spectrum of conditions under the MZL umbrella.

“It is not 1 disease but many. MZL represents a group of lymphomas that have historically been classified together, but truly are different,” Munoz said. “Some of these external lymphomas grow from epithelial cells in the stomach or in the periorcular area; hence, they can remain localized in that area for a long time.”

Additionally, Munoz noted that since the clinical manifestations of MZL can be powerful, it is important to remain cautious and not give a blank check for treatment recommendations.

“Treatment needs to be individualized so that patients with localized disease could potentially receive localized treatments like radiation,” Munoz said.

The panel also reviewed patient management and explained that frequently, active surveillance is required. Patients are monitored for symptoms and treatment criteria before therapy is selected in order to avoid accidental diagnosis and mistreatment. According to Mehta, only around 15% to 20% of MZL patients have symptoms, so it is critical to make sure patients have not been misdiagnosed.

“For early stage, there is a potential for cure,” Mehta said. “You could achieve that by giving radiation. You’re to always have a risk-benefit in that situation, but it depends on the site where you’re going to radiate. If it is auxiliary lymph node, definitely you can radiate and you can have patients cured with low-grade lymphoma. For advanced stage, again, following the same guidelines, if they meet the indications for treatment, that’s when you jump in and do systemic therapy.”

The panelists also highlighted the potential for B-cell depletion therapies, which are frequently powerful treatments for the disease. According to Bhavesh Shah, RPh, BCOP, following 4 doses of rituximab, patients can still be in remission from MZL 7 years after treatment. In terms of maintenance therapy, Mehta also highlighted the importance of considering the subtype of MZL when selecting a therapy.

“Whether this is nodal vs mucosa-associated MZL or splenic MZL, all would have a different goal of therapy. Amongst this, I feel that advanced stage nodal marginal lymphomas are the ones that are going to give you trouble. The others, they have relatively better outcomes.” Mehta said. “For low-grade lymphomas, maintenance therapy definitely improves progression-free survival, but the impact on overall survival we have not seen yet. I think that applies to MZL also.”

Mehta also commented on the impact of the COVID-19 pandemic on treatment options for these patients, explaining that when putting patients on maintenance therapy, there are 2 specific disadvantages to consider during the pandemic.

“One, they have to come more frequently to the clinic to get the infusion. That’s why they’re at relatively high risk of catching COVID-19; hospitals are the main source,” Mehta said. “The second, which is important, is chronic B-cell depletion. That leads to hypogammaglobulinemia, which puts them at a high risk of infections in general. Pneumonia and sinus infections are most common, and they also have a high risk of catching COVID-19 in this situation.”

Mehta explained further that several small, short-term studies were recently conducted that showed patients with lymphoma on maintenance therapy have been shown to not have as strong an immune response to vaccination against COVID-19 compared to other patients. These study results highlight the need to proceed with caution when approaching therapy selection, as requiring patients to return to the hospital for treatment during the pandemic, even for patients on maintenance therapy, continues to put patients at an increased risk for COVID-19 exposure.

MZL Treatment Selection Guidelines
Reviewing the National Comprehensive Cancer Network (NCCN) treatment guidelines for MZL, Shah commented on the impact these guidelines can have on current practice, stating that certain institutions directly place NCCN guidelines into their electronic medical record.

The panelists agreed that while these guidelines have considerable impact on treatment selection and payer coverage, it’s important to treat them first and foremost as recommendations.

“NCCN guidelines are not gospel, but it’s extremely helpful for us to validate some of these therapies. To recommend the second-line therapy, first, we need to
know which was the first-line therapy,” Munoz said. “This is important as we tend to lump together multiple indolent lymphomas in the same bucket. The BRIGHT study included follicular lymphoma, MZL, even mantle cell lymphoma, which most of us consider an aggressive lymphoma, not an indolent one.”

As a result, there are a number of NCCN-recommended treatments for MZL, including bendamustine plus rituximab, bendamustine plus obinutuzumab, R-CVP, R-CHOP, R-squared (lenalidomide plus rituximab), BTK inhibitors, and PI3 kinase inhibitors.

“So we have a plethora of options, which is a good problem to have,” Munoz said. “Now, how do we choose? Again, it depends on the first-line therapy, the duration of response to that first-line therapy, performance status comorbidities, patient preference, age. I personally look for excuses not to prescribe chemotherapy, so I’m grateful to have nonchemotherapy options in second-line therapy.”

The panel also emphasized the important role pharmacists play in managing toxicities and drug interactions for patients with MZL. As patients with this disease are expected to undertake long-term therapies with increased risks of toxicity, having the direct involvement of a pharmacist is crucial to ensure patients receive the appropriate treatment.

“My nurse and our pharmacist are critical team members. They are my right hand; they help me to review concomitant medications, make sure I’m not missing any possible interactions, particularly proton pump inhibitors,” Munoz said. “As you know, that is important when it comes to acalabrutinib. And I always follow the algorithms, or the recommendations regarding dose reductions or dose interruptions, and we make these decisions as a team including the patient, keeping the patient front and center when it comes to his or her symptoms.”

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Self-Management Support in Cancer Care
The cancer care system lags in comparison to other chronic health conditions in this key area.

JUSTIN LINDHORST, MBA

We have entered an unprecedented era of treatment advancements, novel therapies, and improved survivorship for patients with cancer. Despite these rapid and ongoing advances, the cancer care system lags in comparison to other chronic health conditions around a key component of successful care—self-management support (SMS).¹

Literature identifies several reasons for cancer SMS trailing other conditions, which includes the complexity of cancer and the historically paternalistic treatment paradigm for cancer care. For the latter, this structure centers treatment as an acute occurrence in which providers maintain primary responsibility for disease management through directives to the patient.¹⁺² Furthermore, many cancer clinicians often do not have the time or additional coaching skills required to effectively train patients in successful self-management.²

For oncology pharmacists, these factors present an opportunity to aid health care professionals (HCPs) in advancing SMS as a critical component of quality cancer care. Specifically, oncology pharmacists are well placed to assist in promoting positive self-management support for patients with chronic illness and cancer.

Self-Management and Chronic Illness
Self-management for patients with chronic illness has been defined as the process through which individuals can actively cope with their chronic disease in the context of their daily lives.³ Clinical research has shown that self-management can be an effective tool to improve patient outcomes for a range of chronic conditions, such as asthma, diabetes, and arthritis.⁴

Self-management interventions can help engage patients to actively participate in their daily care. These interventions go beyond simply providing information or education, as they additionally help patients learn to employ psychosocial skills and actively engage in their own care.⁵ Patients engaged in SMS experience better health outcomes including quality of life (QOL) measures, such as mood and feelings of wellbeing.⁶

SMS has also been shown to reduce emergency room visits and overall costs for patients with chronic health conditions.⁷ As the US health care system pivots to a value-based model of care, self-management support for patients with chronic illness has become a strategic priority. A wide body of research demonstrates the efficacy of self-management in meeting a triple aim for health care reform: better health, better health care, and better value.⁸

Self-Management and Cancer
In 2005, the Institute of Medicine laid out 6 phases in the cancer care continuum. The phases include prevention, early detection, diagnosis, treatment, survivorship, and end-of-life-care.⁴

However, self-management in the continuum of cancer care has been found to be lagging when compared to SMS for other chronic conditions.¹

This lag has changed in recent years as cancer is increasingly treated as a chronic health condition in which patients, their families, and caregivers participate in the development and execution of personalized cancer care.

Additionally, a growing body of research is demonstrating the efficacy of SMS across the cancer care continuum. One literature review identified a range of positive outcomes attributed to SMS interventions including higher levels of self-care, self-help, and psychosocial adjustment; significant reduction in fatigue, pain, and nausea; decrease in pain intensity scores; fewer hospitalizations; and increased survivorship.²
Patients with cancer value working with a pharmacist.

Promoting Self-Management for Patients With Cancer

Patients with cancer value working with a pharmacist. Recent polling from Gallup shows Americans’ trust in the pharmacy profession is the highest it has been in a decade. Working in conjunction with HCPs, the oncology pharmacist has a unique opportunity to leverage that trust to engage patients and deploy SMS interventions that can impact health outcomes and QOL.

Patients value seeing the humanistic qualities of their health care providers and want to be engaged in shared decision making around their own care. For this engagement to occur, the importance of the patient-provider relationship cannot be understated. Research shows that strong patient-provider relationships can impact patient ability to cope, adherence, QOL, and positive beliefs regarding impact of therapy.

Pharmacists typically participate in the cancer continuum of care during a critical juncture—treatment. Often the first opportunity the pharmacy team has to deploy SMS interventions is around medication access. Under pharmacist supervision, referral and intake specialists provide the resources and support to help patients navigate a fragmented, often confusing health care environment. Specifically, this can include addressing the financial challenges associated with cancer treatment.

“Open communication and patience are key. Patients are understandably overwhelmed when it comes to coordinating access to their cancer treatment,” said Amanda Hasenei, a referral specialist at BioMatrix Specialty Pharmacy. “We acknowledge their emotion and develop goals around their concerns. We use our expertise to help break down barriers to care while actively involving the patient and caregiver wherever possible, so they are better prepared to anticipate and resolve future issues.”

Additionally, oncology-focused pharmacists can deploy medication therapy management (MTM) to help patients navigate the course of their cancer treatment. Embedding SMS interventions as part of the MTM process can help lead to positive health outcomes around key aspects of treatment, including adverse events, treatment adherence, and QOL.

“Successful SMS is about communication, education, empowerment, and ongoing follow-up throughout the patient journey,” said Royce Burrrus, MBA, RPh, FASCP, corporate director of clinical services for BioMatrix Specialty Pharmacy. “Providing the right resources and support can help patients effectively manage adverse events, tolerate therapy, and avoid unscheduled higher levels of care.”

There has never been a greater need to promote positive self-management skills for patients with cancer. A shortage of oncology medical professionals, new treatments, longer survivorship, polypharmacy, and site-of-care shifting to the outpatient setting underscores the importance of helping patients develop strong self-management capabilities.

“Effective SMS means fostering collaboration between patient and other health stakeholders including the oncologist,” said Kionna Oleru, PharmD, pharmacy manager at BioMatrix Specialty Pharmacy. “Empowering and assisting patients to overcome the fragmentation that occurs in our health care system helps to alleviate some of the challenges associated with cancer treatment.”

Currently, there are numerous SMS resources, frameworks, and implementation strategies outlined for chronic health conditions in current academic literature. Specialty pharmacies serving patients with cancer should identify opportunities to incorporate SMS throughout the patient journey as a key component of quality, value-based care.

Visit PharmacyTimes.com for references.
WITH HOME INFUSION providers experiencing increased demand since the start of the COVID-19 pandemic, pharmacists have had to utilize new technology to coordinate care, communicate with team members, and practice and deliver a higher quality of service.

Modern technology is crucial to the provision of home infusions, according to Vincent Thompson, founder of Thompson Solutions, an Ohio-based consulting company serving home infusion pharmacies. After 32 years in the home infusion space, Thompson said, he has seen reliance on technology increase significantly. For pharmacies, this involves clinical documentation, reimbursement, billing, and tracking of dispensing, inventory, lot numbers, and more.

Although Thompson said he has not seen a significant shift in the features and functions of technology used in home infusions, he said there have been incremental changes. For example, he explained home infusion providers have been utilizing electronic charting for 20 years, so virtual applications had already existed pre-pandemic, but were adapted as needs changed.

“I think that the industry has been more ahead of the curve than a lot of health care,” Thompson said.

Although many home infusion providers were moving toward digital processes before the pandemic, the last 2 years accelerated this progress further. In a recent survey, 228 home infusion providers gave data on their use of technology between April 2021 and June 2021. According to the report, 99% of respondents increased their use of technology and data solutions since the start of the pandemic, including technology for electronic medical records, intake management, care coordination, and reporting and analytics. The use of this technology is also a significant factor in cost savings, with 30% of survey respondents saying technology saves them between $1000 and $5000 per month due to improved efficiency. Software platforms enable this efficiency in several ways, explained Sean Hill, senior account executive of AlayaCare. Home infusion appointments can be lengthy, he said, and although nurses might check vitals regularly, they can spend up to 8 hours sitting with the patient. New software allows the nurses to complete documentation electronically at the point of care, in addition to accessing necessary information at any time during the appointment.

Thompson said improving efficiency is a major goal in the home infusion market because providers want to improve automation and reduce touchpoints, especially during the pandemic. He added that many technology products used by home infusion providers allow more effective communication between departments, because, although hospitals and home health have had interoperable platforms for decades, home infusions have been largely separated, much like retail pharmacies. Now, novel platforms are pushing for more connection between different team members—such as specialty pharmacists in the office, nurses in the field, and prescribers. This greater level of technological connectivity also translates into better communication with patients via emails or texts rather than phone calls.

In addition to accelerating the adoption of new technology, the pandemic created a need for expanding access to contact-free health care. Cassandra Redmond, PharmD, MBA, director of pharmacy operations for Penn Home Infusion Therapy with
Penn Medicine, explained that although technology has allowed contact-free care in certain respects, there are still areas in which it has not been possible.

“Many of the platform engineers were looking at how to provide services and engage patients in a contact-free manner,” Redmond said. “Obviously, there are certain areas [in which] that thought process may work—delivery, waste pickup, order transmission. However, there are still things like lab draws, medication administration, and dressing changes that require hands-on, in-person nursing care.”

Redmond added that she has seen exponential growth of home infusion care in the ambulatory marketplace over the last 10 years, with drug safety and stability, ease of administration, potential adverse effects, and compounding requirements used as guiding principles to determine whether they can be administered at home. The growing number of therapies and the desire for patients to receive care at home has enabled a massive expansion of the market.

“This growth and shift in care has provided a basis for software companies to keep up with the ever-changing needs of home infusion providers and patients,” Redmond said. “Many have upgraded platforms that have been around for decades. Others have created entirely new platforms that are nothing like their predecessors, whereas others decided to join forces and resources to create competitive products in the market space that can handle all aspects of home infusion.”

With a growing market and opportunities to collaborate with nurses, physicians, and other health care professionals, pharmacists are perfectly positioned to work in the home infusion space. Thompson said pharmacists are frequently able to act as “true clinicians” in home infusion care, making therapeutic recommendations and performing more clinical functions than pharmacists working in traditional hospital or retail settings, as well as coordinating care, compounding medications, overseeing the delivery of treatments, and following up with patients.
BLADDER CANCER IS one of the most commonly occurring cancers, usually forming from the urothelial cells lining the inside of the bladder.\(^1\) Stretching from 2 inches to more than 6 inches in length, the bladder has the capacity to hold approximately 16 to 24 oz of urine (400-600 mL), with the urge to urinate often occurring when the bladder is approximately one-fourth full.\(^2\) During urination, urine initially moves from the kidneys to the bladder through ureters, which are 2 tubes connecting each organ. The urine then passes through the urethra.\(^3\)

Although bladder cancer usually starts from the urothelial cells inside the bladder, those cells are also found in the kidneys and ureters, meaning cancer can develop in these areas as well. Usually, bladder cancer can be detected during the initial stages; however, following treatment, bladder cancer has a high rate of recurrence. Considering this risk, routine checks are recommended for patients who experienced successful treatment outcomes.\(^1\)

Symptoms of bladder cancer can include blood in the urine, or hematuria, which makes urine bright red. Additional symptoms may include frequent urination, which may be painful, and severe, persistent back pain.\(^1\)

Each year in the United States, approximately 55,000 men and 17,000 women are given a bladder cancer diagnosis, with approximately 12,000 men and 4600 women subsequently dying from the disease.\(^4\) However, in 2021, the number of new diagnoses for bladder cancer reached approximately 83,000 patients. With this increase, it is estimated that approximately 2.4% of the US population will receive a bladder cancer diagnosis at some point in their lives.\(^5\)

Although it is the sixth most common cause of cancer, bladder cancer risk increases with age and is more common among men than women.\(^3\) Upon diagnosis, the 5-year relative survival rate for patients is approximately 77%.\(^5\)

There are 3 main types of bladder cancer: urothelial carcinoma, squamous cell carcinoma, and adenocarcinoma. Squamous cell carcinoma is rare, especially in the United States, and is usually caused by long-term infections. Such infections tend to occur in parts of the world where parasitic infections, such as schistosomiasis, are more frequent.\(^1\)

Additionally, adenocarcinoma is even more rare than squamous cell carcinoma. Adenocarcinoma occurs in the mucus-secreting glands of the bladder.\(^1\)

Risk factors for bladder cancer include smoking, older age, male gender, and exposure to chemicals such as arsenic, manufactured dyes, textiles, and paint, as well as certain chemicals within rubber and leather products. Bladder cancer can also be caused by prior cancer treatments such as cyclophosphamide, as well as by radiation treatments to the pelvis.\(^1\)

Patients with a family history of bladder cancer involving parents, »
Patients should be continuously monitored and evaluated for cancer regrowth.

siblings, or close relatives face increased risk as well. For squamous cell bladder cancer, chronic bladder inflammation from repeated urinary infections and inflammations (cystitis) can also increase risk.¹

Diagnostics for bladder cancer can be conducted in several ways, including cystoscopy, transurethral resection of the bladder tumor (TURBT), urine cytology, or imaging tests. In cystoscopy, a scope is placed inside the bladder for examination; however, during this process, TURBT can also be conducted within the bladder by removing a sample tissue of the organ for testing.¹ For less invasive approaches, bladder cancer diagnosis can be conducted through urine cytology—which entails the examination of a urine sample—or through imaging tests such as CT, which provides images of the structure of the bladder and potential cancer.¹

After a diagnosis of bladder cancer, specialists can order further tests, such as CT scan, MRI, positron emission tomography imaging, bone scan, and chest x-ray. Based on the results, the specialists can then assign a cancer stage to the disease, which can range from 0 to IV. The lowest stage indicates a cancer confined to the inner layers of the bladder; the highest indicates that the cancer has spread to lymph nodes or surrounding organs.¹

Bladder cancer can also be classified by grade based on the appearance of the cancerous cells under a microscope. For this classification, a low grade indicates that cells are closer in appearance to normal cells, which grow slowly. A high-grade bladder cancer appears abnormal; this type of bladder cancer grows more aggressively than the low-grade tumor and may be more likely to spread to the muscular wall of the bladder and other organs.¹

The treatment options available for bladder cancer include chemotherapy, radiation therapy, immunotherapy, targeted therapy, and surgery, with the surgery option including TURBT and cystectomy. During the operation, the surgeon creates a new bladder after cystectomy, termed neobladder reconstruction.¹

During the reconstruction process, a new bladder is made from the intestines; following this, the ileal conduit technique is used, entailing the creation of a tube from a piece of the intestine that runs from the ureters and drains urine from the kidneys to outside the body. Next, the surgeon creates a continent urinary reservoir, which is another type of small pouch that holds urine for patients.¹

Chemotherapy is another treatment option for patients with bladder cancer, with options including intravesical or systemic chemotherapy. For the intravesical option, the chemotherapy drug is placed inside the bladder; BCG is the most common intravesical immunotherapy used for treating early-stage bladder cancer.⁵

For systemic chemotherapy, the medication is given either orally or intravenously. Specifically, when given with radiation, common chemotherapy drugs used are cisplatin, cisplatin plus fluorouracil (5-FU), or mitomycin with 5-FU. When chemotherapy is used without radiation, the common drugs are gemcitabine and cisplatin; a combination of methotrexate, vinblastine, doxorubicin, and cisplatin; a combination of cisplatin, methotrexate, and vinblastine; or gemcitabine and paclitaxel.⁶

If too many adverse effects (AEs) occur with a combination treatment, single therapies can be used instead. Common AEs that may be observed from these chemotherapy drugs may include nausea and vomiting, loss of appetite, hair loss, mouth sores, diarrhea, constipation, increased risk of infections, easily bleeding or bruising, and fatigue.⁶

Additional treatment options for patients with bladder cancer are PD-1 and PD-L1 inhibitors. PD-L1, a cell protein that helps the immune system defend itself, can be targeted with atezolizumab (Tecentriq; Genentech USA) and avelumab (Bavencio; EMD Serono). Alternatively, nivolumab (Opdivo; Bristol Myers Squibb Company) and pembrolizumab (Keytruda; Merck & Co) target PD-1,
which is a protein on specific immune T cells that keep the cells from attacking other cells in the body.\(^6\)

Enfortumab vedotin (Padcev; Astellas Pharma US) is an antibody-drug conjugate containing an anti–Nectin-4 antibody attached to a chemotherapy drug. This drug is used for patients with bladder cancer who have already been treated with a platinum chemotherapy drug, such as cisplatin, and immunotherapy, such as PD-1 or PD-L1 inhibitors.\(^6\)

An additional antibody-drug conjugate option is sacituzumab (Trodelvy; Gilead Sciences), which attaches to the Trop-2 protein on the bladder cancer cells and brings the chemotherapy directly to them. This option is usually used for advanced bladder cancer that has already been treated with a platinum chemotherapy drug and immunotherapy options. It is infused into the vein once a week for approximately 2 weeks, followed by a week off.\(^6\)

Radiation is another option and works by destroying the cancer itself. This option is often used as either a primary treatment when surgery is not an option or when the patient wishes not to pursue surgery.\(^6\)

Targeted drug therapies are also available for bladder cancer treatment, with those that target fibroblast growth factor receptor being the most common, such as erdafitinib (Balversa; Janssen Biotech), which can be used to treat locally advanced or metastatic bladder cancer that is growing despite chemotherapy; erdafitinib is taken orally as tablets once a day.\(^6\)

For patients with bladder cancer, the best option may include more than 1 of these treatments. Depending on the patient status and the cancer growth, a specialist may decide to pursue medication; otherwise, the best method available may be radical cystectomy, which entails removal of the entire bladder.\(^5\)

Regardless of the therapy options and approaches taken during cancer treatment, patients should be continuously monitored and evaluated for cancer regrowth because of the high rate of recurrence following successful bladder cancer treatment.\(^7\) Based on the data available, continuous follow-ups have been demonstrated to support an approximate 5-year survival in 77% of patients with bladder cancer.\(^5\)

### REFERENCES
Representation in Oncology Drug Trials Impacts Patient Health
The FDA looks to address a lack of diversity in cancer drug trials.

SKYLAR KENNEY, ASSISTANT EDITOR

In clinical trials evaluating the effects of cancer drugs on patient populations, there has been a long-standing, consistent lack of diversity that is representative of the US patient populations likely to receive the treatment.\(^1,3\) Additionally, landmark oncology trials frequently fail to report the racial diversity of their patient populations, with one study finding that only 33% of the trials reviewed over a 14-year period reported on ethnicity,\(^1\) and a second finding that trials leading to FDA oncology drug approvals reported race only 63% of the time between 2008 and 2018.\(^2\)

When race and ethnicity are reported, Black and Hispanic patients are consistently underrepresented when compared with the burden of cancer incidence faced by these populations, and investigators have observed that recruitment of members of racial minority groups in cancer clinical trials has decreased over time.\(^1,2\)

The Importance of Diversity and Representation in Drug Trials
In an interview with *Pharmacy Times®,* Lola Fashoyin-Aje, MD, MPH, associate director of the Science & Policy to Address Disparities program at the FDA’s Oncology Center of Excellence (OCE), discussed the importance of promoting inclusion of members of racial and ethnic minority groups in cancer drug development, and the potential impact of that lack of adequate representation on patient health.\(^3\)

“The whole goal of representation is to be able to generate data that reflect the variability in the study population,” Fashoyin-Aje said. “Things like race and ethnicity, they’re not really biological constructs; they’re sociopolitical constructs. However, they tend to track with certain ancestry, which can sometimes reflect certain genetic or genomic factors that contribute to a drug’s effect or its safety.”\(^3\)

A homogeneous patient population during clinical trials testing drugs, Fashoyin-Aje explained, can result in a study that fails to appropriately account for differences among the patient population that will ultimately receive these treatments. Because the purpose of a clinical trial is to study the effects of a drug on patients in a controlled environment, failing to properly include minority groups in a study leaves potentially critical health interactions unexamined.\(^3\)

Sources, Influences, and Potential Solutions
Several sources contribute to this lack of diversity, and other factors involving the structural ecosystem, patient level, and drug development exacerbate the problem further. Although efficient drug development can result in patients receiving treatment faster, decisions made in the interest of speed can make the problem worse if they are not thoughtfully deployed.

Fashoyin-Aje noted that an emphasis on speed during clinical trials can result in smaller patient populations, which decreases the likelihood of appropriately representing each subgroup.\(^3\)

“Probably the largest factors have to do with not having a plan that is thought about in terms of how we’re going to enroll these underrepresented subgroups in the trial at the outset and how we can address the barriers that may preclude their enrollment or make it difficult for them to enroll,” Fashoyin-Aje said.\(^3\)
According to Fashoyin-Aje, the problem is also partially rooted in how these trials are designed around the toxicity of the drugs in use. Investigators and trial sponsors are likely to select trial participants who have very few comorbidities in the interest of producing data that will allow for a greater level of ease and clarity during analysis. For the investigators, choosing patients free of medical conditions that could interact with and alter the effect of the drug makes it easier to study the baseline effects of the medication.

However, this can also result in the exclusion of populations that, because of social determinants of health, have a higher rate of the comorbid conditions the investigators are avoiding when selecting the trial population.

“The downside to that is that you’re studying the trial in a population that does not reflect who will be receiving the drug once it’s approved, so one has to be very thoughtful at the outset—particularly in the design phase—to ensure that we are enrolling a diverse population for the cancer trials,” Fashoyin-Aje said.

Currently, the FDA’s OCE is attempting to counteract this lack of diversity in trial populations. The FDA has issued guidance on how to collect and present data on diverse populations that represent subgroups based on sex, age, race, and ethnicity. Guidance has also been issued for how to enhance diversity of drug trial populations, and the OCE has taken action on this issue.

“Our efforts are focusing on the engagement of stakeholders who really have a stake in representation,” Fashoyin-Aje said. “This includes our patients, our providers, professional organizations, and so many [others]. Engaging with them to provide transparency regarding what we’re seeing in terms of diversity can then help inform their policies and their research programs, but also vice versa.”

The Future of Diversity in Cancer Drug Trials

Fashoyin-Aje is hopeful that ongoing recognition of the lack of diversity as an obstacle to accurate data in clinical trials will lead to sustained remedies. She also explained that she hopes perfectionism will not thwart efforts to ensure inclusivity in clinical research. Although work toward change may be imperfect and incomplete, each step forward reduces the impact that a lack of representation can have on patients’ health, Fashoyin-Aje noted.

“I think what we saw with the COVID-19 pandemic was that it was a catalyst for broader and greater awareness of the need to address disparities and to ensure that there is appropriate representation of all subgroups in clinical research,” Fashoyin-Aje said. “My hope is that those efforts are going to be sustained, and that we continue to learn and refine strategies to promote inclusion and representation, but also to start to understand how that actually adds value to the research that we’re conducting. I think that that’s something that’s not well articulated. We tend to focus on the fact that there is not enough, but we don’t focus so much on when there is appropriate representation, how it adds value to the research.”

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Lack of Transparency in 340B Program Leads to Lack of Access for Patients

More transparent drug pricing could improve patient care.

AISLINN ANTRIM, ASSOCIATE EDITOR

Pricing transparency has become an increasingly discussed issue in health care spending, with the United States spending 17.7% of its gross domestic product (GDP) on health care compared with similarly developed countries, which spend no more than 12%, according to a report from the Community Oncology Alliance (COA).

Such transparency is especially important with regard to the 340B Drug Pricing Program, which is designed to ensure access to comprehensive services for eligible patients who might otherwise be unable to receive adequate care as a result of high drug prices. Created in 1992, the program requires manufacturers to provide eligible hospitals with discounts on outpatient drugs. According to the COA report, although estimates of the discounts vary, the minimum discount is 23.1% and the average is 34.7%.

Eligibility criteria for 340B hospitals has also evolved, and the largest group of participants is now disproportionate share hospitals (DSHs), which represent 40% of all United States hospitals and were responsible for 78% of drugs purchased under the 340B program in 2015.

Despite the program’s intentions, the report noted that critics have pointed out several flaws, including a lack of oversight and accountability, aggressive attempts by hospitals to leverage their 340B status, the direction of discounts to the institution and not the patient, and a competitive disadvantage for community physicians. According to the COA report, more transparent hospital pricing could shed light on several of these problems.

In order to understand these concerns and develop a standardized price data set across all hospitals, analysts from COA selected 59 oncology treatment and supportive drugs based on a list of highest dollar expenditure for Medicare Part B drugs in 2019, as well as lower expenditure drugs sharing the same active ingredient. They also used a list of 1087 acute care 340B DSH hospitals, 890 of which had a price transparency file on their website.

Using these data, the researchers analyzed whether the hospitals attempted to comply with new transparency regulations from the US Department of Health and Human Services, which took effect January 1, 2021. If any data relevant to the new regulations were found in the file, the hospital was considered as “attempting to comply.” Notably, only 327 of the hospitals in the 340B program attempted to comply with the new regulations, according to the report.

Investigators then searched the files of these 327 hospitals and noted that some hospitals do not include drugs in the transparency file for several reasons, including the separate management of the organization of the files or the choice by some hospitals to eliminate certain drugs because of drug markup.
controversies and 340B drug discounts. Additionally, if the file mentioned any of the 3 most common oncology drugs—pembrolizumab, rituximab, or pegfilgrastim—they were considered to include drugs in the file. After this search, the researchers found that just 233 hospitals out of the 1087 340B hospitals included drug prices in the file.

Finally, the report said the investigators realized that some hospitals had not included data on individual negotiated payers, which is required by the new transparency law. Instead, they included only data on cash price, minimum, maximum, and chargemaster prices.

Just 123 hospitals included the individual plan names, which allowed them to be used to create the standardized price data set. The majority of these, however, did not provide well-organized and easy-to-understand data sets, according to the report. Instead, much of these data were “snapshots” from internal systems, according to the COA report. They included data that were unrelated to pricing, multiple entries for the same products, and cost modifiers, and the coding was inconsistent and reflected internal terminology that was difficult to understand.

Notably, the report found that the drug amount associated with the negotiated price was often unclear. Because the analysts’ goal was to create a standardized data set, they removed unreasonable data points and addressed duplicate entries, such as different dosages listed separately. The resulting database contains 52,180 data points across the 123 hospitals used for the analysis.

In addition to creating the standardized price data set, the report emphasized several recommendations to improve reporting data around hospital price transparency. “The best solution, in our view, is for [the Centers for Medicare & Medicaid Services (CMS)] to create a database that it will own and manage,” the report said. “Hospitals, rather than publishing their own files, would upload the data to the CMS database based on the provided [Healthcare Common Procedure Coding System (HCPCS)] code and unit size.”

In addition to this far-reaching and structural recommendation, the authors also suggested amendments to CMS requirements in order to enforce more price transparency. First, they recommended a centralized data location to ensure easy access to files, rather than having hospitals post files only on their websites.

Second, the data qualification process should be strengthened, according to the report. A file should be readable and should have a standard format with the required minimum of data. Reviewing this data would encourage hospital compliance and would improve clarity about which hospitals provide the required data and which do not.

Another recommendation to improve data clarity is to report only negotiated price data instead of having what the report authors termed a “database dump” approach; no other data should be included.

Data standardization should also be improved, including a requirement to report products and services with their associated HCPCS codes and unit sizes. Product descriptions should be unique, and a single cell should be used for each data attribute, since the authors said they often saw a single cell describing the product, amount, health plan, and site of care. According to the report, hospitals should also use a standard nomenclature to indicate whether drugs are for inpatient or outpatient use and for which line of service.

Finally, the report urged CMS to require specific data schema. Although the current requirements define which information should be published, they do not specify the X-Y organization, order of the data presented, headers, terminology, or naming convention, which makes it much more challenging to aggregate and compare the data from different hospitals.

In addition to helping industry companies achieve price transparency, the authors concluded that these changes are also essential for patients attempting to compare prices across several hospitals. Based on their findings of the current system, the authors said patients would be entirely unable to obtain and compare the cost of oncology drugs between local hospitals specific to their health plan, thereby limiting their ability to locate and access affordable care.
CINV is one of the most distressing and feared adverse effects (AEs) that patients can experience while receiving chemotherapy. In addition to adversely impacting patients’ quality of life, CINV can lead to treatment delays, dose reductions, and potentially compromised treatment outcomes.

Types of CINV
CINV is classified into 5 types: acute, delayed, breakthrough, refractory, and anticipatory. Acute CINV and delayed CINV correlate with time parameters, as acute CINV occurs within 24 hours of the initial administration of chemotherapy, and delayed CINV occurs after 24 hours and may persist for as long as 7 days after antineoplastic therapy administration.

However, not all CINV is classified by time of occurrence, as anticipatory CINV is understood as a conditioned response to a prior experience of CINV, while breakthrough CINV is nausea and/or vomiting that occurs despite the use of appropriate prophylaxis. Additionally, refractory CINV is defined as nausea and/or vomiting that continues to occur in subsequent chemotherapy cycles.

Pathophysiology of CINV
CINV is a complex process that involves communication between several neurotransmitters and their receptors, which can be triggered by chemotherapy administration. Known as the main mediator of acute emesis, serotonin (5-HT3) is transmitted via a peripheral pathway mechanism that originates in the gastrointestinal tract. The neurotransmitter called substance P, which binds to the neurokinin-1 (NK-1) receptors in the central nervous system, is thought to be predominantly involved in delayed CINV via the central pathway. Dopamine, histamine, and acetylcholine are also involved and may serve as additional targets for antiemetic therapies.

Antiemetic Strategies and Principles
The goal of antiemesis therapy is to prevent CINV by using an appropriately designed antiemetic prophylaxis regimen. When clinicians are deciding on an antiemetic regimen, the emetogenic potential of chemotherapy is the most important treatment-related factor for prevention of CINV.

In addition, there are patient-specific risk factors that may affect the development of CINV and should be considered when selecting antiemetic agents.
Staying up to date on the current guidelines and clinical trial data is critical for oncology care providers.

Patient risk factors include age, gender, prior CINV, anxiety, alcohol intake history, and history of motion sickness. Equally important, type of CINV, comorbidities and contraindications, patient adherence, and cost should also be considered, further complicating antiemetic regimen selection. To address these challenges during the selection process, there are several updated guidelines available to help clinicians design individualized antiemetic prophylaxis and treatment.

Pharmacologic Therapy

To maximize antiemetic control, agents of different mechanisms of action are combined. Corticosteroids, 5-HT3 receptor antagonists (5-HT3 RA), and NK-1 receptor antagonists (NK-1 RA) are the main pharmacologic classes of medications that serve as the backbone of antiemetic regimens.

Development of 5-HT3 RAs—such as ondansetron, granisetron, and dolasetron—has revolutionized CINV management by preventing up to 80% of acute nausea. Furthermore, the addition of a second-generation 5-HT3 RA known as palonosetron has been shown to also provide improved delayed antiemetic prophylaxis by action of a longer half-life.

NK-1 RAs such as aprepitant, fosaprepitant, neupitant, and rolapitant have enhanced our ability to prevent delayed CINV. Olanzapine, a second-generation antipsychotic, is an effective addition to both prevention and treatment of CINV owing to its mechanism of action, which targets serotonin, dopamine, adrenergic, and histamine receptors.

Additionally, benzodiazepines’ place in therapy is mostly in the prevention of anticipatory CINV, but also in breakthrough and refractory settings. Dopamine antagonists, anticholinergics, antihistamines, and cannabinoids are also useful in managing breakthrough or refractory CINV.

Antiemesis Guideline Updates

The current guidelines on antiemesis that are used in clinical practice come from the National Comprehensive Cancer Network (NCCN), the American Society of Clinical Oncology (ASCO), and the Multinational Association of Supportive Care in Cancer (MASCC).

The most recent update was published by NCCN in March 2021, with one key update in the option of a lower, 5-mg dose of olanzapine for CINV prophylaxis with high or moderate emetic risk of chemotherapy regimens. This was a change from a previously recommended dose of 10 mg, as new data have found that a lower dose is efficacious. The guidelines now recommend a 5- to 10-mg range, but the lower dose may help alleviate some of the AEs of olanzapine, such as sedation in older patients.

In the update, several clinical pearls were added, including recommendation for morning administration of dexamethasone to minimize insomnia, and olanzapine evening administration to mitigate sedation. Also recommended is a short-term only administration of metoclopramide to minimize the risk of tardive dyskinesia. MASCC antiemetic guidelines are currently under revision.

The 2020 edition of ASCO’s antiemetics guideline update also included the option of a lower, 5-mg dose of olanzapine. Based on newer data, ASCO recommends the addition of olanzapine to the antiemetic prophylaxis regimen in the setting of hematopoietic stem cell transplantation.

Additionally, ASCO addressed in the guideline a common question asked in clinical practice regarding the omission of dexamethasone, explaining that no clinical evidence exists to support omission of dexamethasone from antiemetic regimens when checkpoint inhibitors are used in combination with chemotherapy.

Prevention of CINV is the most important goal of antiemetic therapy; it ensures patients can complete their chemotherapy regimens while maintaining their quality of life. For this reason, staying up to date on the current guidelines and clinical trial data is critical for oncology care providers so that they can design the best possible CINV prevention and treatment strategies.

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Technology Can Help Navigate Financial Assistance Programs in Specialty Care

BRENDA BERNARD, MSN, RN, OCN; SRULIK DVORSKY

ACCESSING FINANCIAL ASSISTANCE programs (FAPs) is a challenge for even the most skilled financial counselor or navigator. The goal of the financial counselor is to identify available funding for patient care in a timely manner, but the sheer number of resources and variables involved results in a long, tedious process. There’s a lot at stake, from jeopardized outcomes and financial hardship on the part of the patient to the risk of bad debt write-offs for the pharmacy, hospital, or specialty practice.

Fortunately, technological solutions have been developed to help financial counselors navigate and manage these complexities. These systems are capable of using technology, data, and predictive analytics to identify financially at-risk patients and match them with an array of FAP resources—from biopharma manufacturers’ copay assistance or replacement drug programs to foundations and governmental resources that can help with transportation or living expenses. These systems have been developed to proactively prevent financial roadblocks early in a patient’s medical journey before the first drug is dispensed.

When financial roadblocks occur during a patient’s treatment process, they can result in significant setbacks for the patient’s care. A 2018 study found that 32% of cancer patients with between $100 and $500 in out-of-pocket drug costs did not fill their prescriptions, while 50% of patients facing $2000 or more in out-of-pocket costs also left their prescriptions unfilled. Additionally, the investigators noted that about 1 in 8 cancer patients faces more than $2000 in out-of-pocket drug costs.

An array of trends, such as the rise in high-deductible health plans with steep out-of-pocket costs for patients, an increase in high-priced specialty medications, and greater financial instability during the pandemic, have made the job of the financial counselor more critical than ever. Effective counseling not only helps patients get on treatment and stay the course, but also supports the financial viability of the organizations involved in patient treatment and care.

Having a Plan Matters

For costly therapies that treat conditions such as multiple sclerosis, chronic obstructive pulmonary disease, and cancer, financial counselors can help establish a process for getting as much assistance as possible to patients in need, even before they know they need it.

For example, a 2017 study revealed that access to drug assistance programs increased medication adherence by over 60%. However, the key to the success of these assistance programs is early intervention, which allows for the preservation of patient access to care while controlling bad debt write-offs through the improvement of patient collections and funding resources.

Tackling FAP Challenges With Automated Technology

With so many different FAP resources available, each with its own set of qualifying criteria, it can be a time-consuming process...
to find the right assistance for the right patient. The sheer complexity of the playing field means that health systems or large practices may have multiple financial counselors as full-time employees.

Automated technology can simplify the workflow to help the health care entity bring the focus back to what it does best: providing quality patient care. Automated technology can help facilitate this process on several levels:

- **Identify funding sources quickly**
  One of the biggest challenges is simply knowing what FAP resources are available for patients and whether they meet eligibility requirements. Automatically leveraging available patient data alongside a vast array of FAP data is an efficient way to match patients with financial assistance programs in real time. For instance, some technological platforms can generate a short list of programs that are currently open for enrollment and for which the patient is eligible so the counselor doesn’t need to sift through hundreds or even thousands of programs to find the right fit.

- **Help patients proactively**
  Technology should use predictive analytics to estimate out-of-pocket expenses on a per-patient basis, enabling a workflow that is proactive rather than reactive. Instead of scrambling to find FAP resources for a patient who is already facing financial hardship, financial counselors can use technology at the start of the care journey to stay ahead of the curve and address patient concerns before they arise.

- **Reduce manual workload**
  Without technology, financial counselors must often resort to a manual search process with tracking sheets, spreadsheets, or folders for each patient. Data ingestion and patient eligibility should be automatic, so the system pulls from existing demographic information to prepopulate FAP applications. This type of software makes it easier to track applications, follow up when needed, and prevent anything from falling through the cracks when securing funds.

- **Centralize workflows**
  Alongside financial counselors, some organizations have social workers or community health workers assisting with each case, helping find travel assistance, gas assistance, and perhaps even social support for patients. Bringing these needs together in 1 platform is important so that all staff involved can quickly discover patient-eligible resources to help with everything from transportation costs to nutrition requirements.

**Patient-Centered Care**

Supportive technology allows for a 360-degree approach to patient care while helping to ensure that patients receive their medication in a timely manner and have necessary resources in place to stay adherent. It also contributes to the financial viability of the health care entity involved in providing that treatment and care to the patient.

With the time and cost savings that such technology affords, financial counselors can help more patients in less time than manual processes allow. Health care entities can reduce their risk of write-offs and bad debt from prescription abandonment, and patients can get a better, more efficient and perhaps even more compassionate experience that alleviates their financial burdens and anxieties, while obtaining their medications when they need them to support their best chance for positive health outcomes.

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Breaking the Bank: Financial Toxicity in Cancer Care

The increasing economic burden of treatment may impact patient outcomes.

Allison P. Golbach, PharmD, BCPS; Scott A. Soefje, PharmD, MBA, BCOP, FCCP, FHOPA

The American Cancer Society estimates there will be nearly 1.9 million new cancer diagnoses in 2021. As the global cancer burden continues to grow, the expected number of patients receiving chemotherapy will increase from 9.8 million to 15 million per year over the next 2 decades. These patients will face the stress, anxiety, and uncertainty that comes with not only a cancer diagnosis, but also, increasingly, how to afford their cancer treatments.

Globally, the market for cancer drugs will grow from $164 billion in 2020 to an estimated $269 billion by 2025. Spending on cancer drugs in the US reached $71 billion in 2020, and Medicare estimates that one-third of all their cancer expenditures are for cancer drugs. By 2030, the total cost of cancer care in the US will approach $250 billion.

For these reasons, the question of why health care costs so much remains a pertinent issue to address. Many factors contribute to the increasing cost of care, including a growing and aging population, changes in disease prevalence or incidence, increased service utilization, and an increase in service prices. A recent study investigating the causes of increases in US health care cost found that a primary driver of cost was the increase in service price and intensity (Table 1). The US has service utilization rates comparable to the rates of other countries but spends almost twice as much on those services.

Although there is no formal definition, financial toxicity is a term used to describe problems that patients have related to the cost of their medical care. Financial toxicity is the unintended, yet often predictable, consequence and adverse effect of the financial burden experienced by patients because of their treatment.

The financial burdens of health care are increasing across various fields but are particularly prominent in cancer care. Although many factors contribute to the increasing cost of oncology care (Box), in the past, hospitalizations were the driving factor of excessive costs. Today, however, there is a shift in cancer care practice to the increasingly expensive chemotherapy and biologics that patients are receiving.

Prevalence of different measures of financial toxicity tend to vary because many studies only measure 1 aspect of

About the Authors

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financial hardships, are limited to single institutions or specific geographic locations, or are focused on selected samples of cancer survivors. Factors that have been shown to affect financial toxicity include high out-of-pocket costs, loss of productivity, asset depletion, medical debt, and the anxiety associated with financial distress.9

The financial burden of medical care, especially cancer care, deeply affects patients. In 2018, US patients paid $5.6 billion out of pocket for cancer treatments, which can pose a significant financial burden on these patients and their families.10 A 2013 study of Medicare beneficiaries found that almost 50% of patients with cancer spent 10% of their income out of pocket and that 28% spent 20% of their income.11 A Kaiser Family Foundation and Los Angeles Times survey found that 20% of patients with cancer have been contacted by collection agencies due to medical debt and that 9% reported filing for bankruptcy.12 With these available data, it is not surprising that the leading cause of bankruptcy in the US is medical debt.13 As the average cost of cancer care continues to skyrocket and the out-of-pocket demands increase, patients face the effects of this financial toxicity.

Cancer survivors also have added financial burdens. In 2019, there was an estimated 17 million cancer survivors in the US, and the number of survivors will continue to grow over the next 10 years. In a study examining cancer survivors from 2008 to 2010, cancer survivors had annual out-of-pocket expenses of $1107 compared to noncancer patients’ out-of-pocket expenses of $617 annually.14 In a more recent analysis of the 2011 to 2016 Medicare Expenditure Panel Survey, investigators found that annual out-of-pocket expenses for cancer survivors was $1000 versus $622 for a matched cohort.15,16

Patients with cancer also have a significant issue with loss of productivity. Overall, employed patients with cancer miss 22.3 more workdays than those without cancer.17 The probability that patients with cancer are employed decreases 9% within 3 years of receiving a diagnosis and does not improve in the fourth and fifth years if patients are still alive.9

In a study examining data from 2008 to 2011, the annual per capita productivity loss was measured at $3719 for male and $4033 for female cancer survivors compared with noncancer patients at $2260 and $2703, respectively. Additionally, employment disability accounted for 75% of this loss of productivity, with one-third of cancer survivors reporting that they experienced work limitations and a decreased ability outside of work to do daily activities. Furthermore, employed cancer survivors reported that cancer interfered with physical tasks (25%) and mental tasks (14%) required by their job.18

### Risk Factors for Financial Toxicity for Cancer Patients

Factors leading to an increased risk of financial toxicity can be broken down into defined categories, including socioeconomic, insurance related, disease related, treatment related, and end-of-life care (Figure).9

#### Demographic factors

Race and socioeconomic status are strong indicators for overall health care disparities and have strong correlation with disparities in cancer outcomes, including survival and increased risk of financial toxicity.19 Non-White race, Hispanic ethnicity, and female gender are associated with a significant risk of financial distress.20 Household factors such as the wage-earner status of

| Table 1. Factors Associated with Increased Health Care Costs in the United States1 |
|-------------------------|-------------------------|
| Disease prevalence/incidence | (-2.4%) |
| Population aging | 11.6% |
| Population growth | 23.1% |
| Service utilization | 2.5% |
| Service price and intensity | 50.0% |

| Box. Factors Related to the Cost of Medical Care6 |
|-------------------------|-------------------------|
| Appointments | Travel costs |
| Procedures | Treatments |
| Laboratory testing | Chemotherapy |
| Imaging | Biologics |
| Hospitalization | Supportive medications |
| Time away from work | Radiation |
the patient, especially if the patient is the primary wage earner in the household, the income of other household members, the pre-illness debt load, and the total household assets all influence the ultimate monetary impact of the cancer diagnosis and treatment. Employment status is also a risk factor that can change throughout the course of the cancer due to the increased risk of loss of productivity and unemployment. Lastly, age is a significant indicator of financial toxicity, with younger patients with cancer being more affected than older patients with cancer. Younger patients have a lack of savings and assets with associated lower incomes because they are often just starting careers and have competing financial obligations, such as children and student loan debt. The younger patient lacks the safety-net protection of Medicare coverage and may have a high-deductible health plan that forces a significant out-of-pocket expense, be underinsured, or have no health insurance at all. Thus, financial hardship was twice as frequent in patients aged 18 to 54 as compared to those patients older than 65 years.

Insurance-coverage issues
Health insurance status is a significant predictor of financial toxicity. A lack of health insurance and high-deductible plans increase risk for financial toxicity significantly. This is, again, especially true for younger patients. Patients without health insurance are more likely to experience financial burdens than those with health insurance and even those with partial insurance. Additionally, Medicaid patients have a higher financial burden versus patients with Medicare, supplemental, and commercial insurance.

Disease-related factors
The type of cancer can also contribute to risk of financial toxicity; however, no single tumor type, stage, or histology is a predictor on its own. However, tumors that are in advanced stages, have a poor prognosis, are recurrent, or require multiple hospital admissions put patients at higher risk of financial toxicity.

Treatment-related factors
Those patients getting chemotherapy and/or radiotherapy tend to have greater financial hardship; this hardship increases further among patient populations with underlying comorbidities who are undergoing chemotherapy and/or radiotherapy. With the cost of cancer drugs routinely exceeding $10,000 per month, the median monthly cost of cancer drugs far exceeds the median monthly household income. Thus, patients

FIGURE. ETIOLOGY AND RISK FACTORS FOR FINANCIAL TOXICITY IN CANCER CARE

- Health status, assets, debt, income, employment status
- Cancer type, stage, prognosis
- Treatment choices
- Nonmedical costs
- Medical costs
- Medical insurance
- Financial strain, distress, bankruptcy
- Financial consequences
- Health outcomes
- Time
- Pre-illness
- Cancer-related costs
- Financial consequences
- Health outcomes
receiving chemotherapy are more likely to experience financial toxicity than patients receiving only radiation or surgery.

Additionally, the greater duration of therapy, such as the growing trend of maintenance immunotherapy, and an increased intensity of therapy, are associated with increased financial burden, especially in tumors requiring chronic long-term therapies, such as multiple myeloma or chronic myelogenous leukemia. In this way, the financial burden does seem to continue when the time from treatment increases; however, few studies are currently investigating this issue in detail.

### Measuring Financial Toxicity

The definition of financial toxicity varies in the literature; therefore, the ability to objectively measure financial toxicity has been a significant challenge. For this reason, most current published studies measure financial toxicity using self-developed questionnaires.

To help standardize the measurement of financial toxicity, the COmprehensive Score for financial Toxicity (COST score) was developed in 2014 and later validated in patients with cancer in the United States. The COST score is a patient-reported outcome measure based on an 11-item questionnaire, including 1 item on financial spending, 2 items on financial resources, and 8 items focusing on the psychosocial response to patients' financial situation. Each statement is scored on a Likert scale, which comprises the patient’s COST score. Lower COST values show the patient subjectively feels a higher sense of financial toxicity.

Although this a validated questionnaire, it has yet to be widely adopted in financial toxicity literature, so objectively measuring the extent of financial toxicity continues to be a challenge.
**Effects of Financial Toxicity**

Literature exploring financial toxicity and its impact on patients is ever growing. To date, many negative outcomes have been associated with financial toxicity, such as symptom burden, survival, quality of life, access to treatment, adherence to therapy, care satisfaction, financial debt, and impacts on caregivers.

In a systematic review published in 2019, the association between financial toxicity and perceived symptom burden was investigated further (Table 2). Articles were screened for inclusion based on if they were available on Medline, Embase, or CINAHL and published between 2000 and 2018.

A total of 9 articles were included in the qualitative synthesis, which encompassed more than 11,000 cancer survivors. The articles included were heterogeneous in their assessment of financial toxicity, making it difficult to form strong conclusions. Of the 8 articles that evaluated psychological symptoms associated with financial toxicity, 6 of them reported a positive correlation, with increased sense of financial toxicity associated with an increased symptom burden.

In the analysis, the primary psychological symptoms assessed included depression, anxiety, stress, fear of cancer recurrence, spiritual suffering, and overall psychological symptoms. The association between financial toxicity and physical symptoms was less clearly defined by the studies because 2 of the 3 studies reported inconsistent results. This systematic review underlined the need for future studies to further elucidate the relationship between financial toxicity and symptom burden for patients, as well as the need for more consistent and objective methods for evaluating financial toxicity in studies.

A different study aimed the investigation on the relationship between severe financial toxicity and health outcomes. The authors included patients aged 21 years and older with cancer (excluding nonmelanoma skin cancers) within the period between January 1, 1995, and December 31, 2009. Data for the analysis were collected from the Western Washington Surveillance, Epidemiology, and End Results cancer registry and federal bankruptcy record to show the cumulative risk of filing bankruptcy after cancer diagnosis. The mortality risk was also compared between those who filed for bankruptcy and those who did not.

The study included 231,596 patients who had received a cancer diagnosis, and 4728 of those patients filed for bankruptcy. When assessed, those who filed for bankruptcy were more likely to be younger, female, non-White, have local or regional disease at diagnosis, and have received previous treatment for the malignancy.

A propensity score matched sample was assessed to better compare outcomes for those who did versus did not file for bankruptcy. Baseline variables for the matched sample included sex (male, 54%), race (White, 86%), marital status (married, 60%), urban/rural residence (urban, 91%), income level based on home zip code, year of diagnosis, age, cancer stage (59%, local), and initial treatment modality. The worst outcomes were for patients with lung cancer who filed for bankruptcy. Additionally, mortality rates among patients with breast, lung, colorectal, or prostate cancer who filed for bankruptcy were significantly higher than those who did not file for bankruptcy.

The investigators concluded that there is a consistent positive association between filing for bankruptcy and earlier mortality after cancer diagnosis. However, they also noted that more studies need to be completed to understand the causality between bankruptcy and increased mortality in patients with cancer.

The relationship between financial toxicity and patient-reported quality of life is another area of interest. A study used data from the 2010 National Health Interview Survey, the largest source of health information for US households, and analyzed it using a
**TABLE 3. CHOOSING WISELY: LOW-VALUE SERVICES IN CANCER CARE**

<table>
<thead>
<tr>
<th>American Society of Clinical Oncology</th>
<th>American Society for Radiation Oncology</th>
<th>Commission on Cancer</th>
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</thead>
</table>
| Do not use cancer-directed therapy in patients with the following:  
  • Low PS (ECOG PS 3 or 4)  
  • No benefit from prior evidence-based interventions  
  • Not eligible for clinical trials  
  • No strong evidence supporting additional therapy | Do not initiate whole breast radiotherapy as part of breast conservation therapy in early stage breast cancer without considering shorter treatment schedules | Do not perform surgery to remove a breast lump for suspicious findings unless needle biopsy cannot be done |
| No PET, CT, or radionuclide bone scans for staging of early stage prostate cancer at low risk for metastasis | Do not initiate management of low-risk prostate cancer without discussing active surveillance | Do not initiate surveillance testing after cancer treatment without providing the patient with a survivorship care plan |
| No PET, CT, or radionuclide bone scans for staging of early-stage breast cancer | Do not use extended fractionation schemes for palliation of bone metastases | Do not use surgery as the initial treatment without considering neoadjuvant systemic and/or radiation therapy when there is evidence it is effective in improving local cancer control, QoL, or survival |
| Do not do surveillance testing (biomarkers) or imaging (PET, CT, or radionuclide bone scans) for asymptomatic patients with breast cancer treated with curative intent | Do not routinely recommend proton beam therapy for prostate cancer outside of a clinical trial | Do not perform major abdominal surgery or thoracic surgery with a standard protocol for pain control and pneumonia prevention |
| Do not use white cell growth factors unless the febrile neutropenia risk is expected to be >20% | Do not routinely use IMRT to deliver whole breast radiotherapy for breast conservation | Do not initiate cancer treatment without defining the extent of the cancer and discussing the intent of treatment |
| Do not use high emetogenic antinausea treatments for patients on low or moderate risk emetogenic chemotherapy | Do not recommend radiation following hysterectomy for endometrial cancer in low-risk disease. | |
| Do not use combination chemotherapy for metastatic breast cancer instead of 1 drug unless patient needs rapid response to relieve tumor symptoms | Do not routinely offer radiation therapy for patients who have NSCLC negative margins N0-1 disease | Do not initiate noncurative intent radiation therapy without defining the goal of treatment and considering palliative care therapy |
| Avoid PET or PET-CT as part of routine follow-up in asymptomatic patients who have finished initial treatment unless there is high-level evidence from the scan that will alter outcomes | Do not initiate noncurative intent radiation therapy without defining the goal of treatment and considering palliative care therapy | |
| Do not routinely perform PSA screening for prostate cancer in men with no symptoms of the disease | Do not routinely recommend follow-up mammography more often than annually following radiotherapy for breast conservation | |
| Do not use targeted therapy unless the patient’s tumor has the specific biomarker or there is evidence for use | Do not routinely add adjuvant whole-brain radiotherapy to stereotactic radiosurgery for limited brain metastases | |

PS, performance status; ECOG, Eastern Cooperative Oncology Group; PET, positron emission tomography; CT, computed tomography; PSA, prostate-specific antigen; IMRT, intensity modulated radiation therapy; NSCLC, non—small cell lung cancer; N0-1, American Joint Committee on Cancer Staging System node status of 0 or 1; QoL, quality of life.
multivariable regression model to assess the relationship between financial concerns and quality of life.29

The data used in the study included survey responses from 2151 adult cancer survivors. If the interview participant reported they had received a cancer diagnosis at some point in their lives, they were asked, “To what degree has cancer caused financial problems to you and your family?” They then selected a response from a list of choices that included: “a lot,” “some,” “a little,” or “not at all.” These answers were then evaluated for correlation with other sociodemographic factors.

In the bivariable analysis, patients who reported a lot of financial burden were less likely to have Medicare as their primary insurance and more likely to be female, younger than 61 years, and non-White; have less than 4 years of college education; and have a total combined household income of $35,000. In the multivariable analysis, self-reported quality of life was inversely correlated with the degree to which cancer caused financial problems. Patients who reported a lot of financial toxicity were 4 times less likely to report quality of life as good or better.

Other independent risk factors for quality of life included age, education, insurance status, and total combined family income. Overall, this study concluded that financial burden is common among cancer patients and is associated with decreased quality of life.

Solutions
No prospective studies have systematically evaluated the effects of interventions designed to reduce financial distress in patients with cancer. However, one 4-step approach has been proposed:8

1. Acknowledge and understand the problem.
2. Engage stakeholders.
3. Foster communication.
4. Implement solutions that are different for each patient and for different sites within the health system.

Addressing the problem
The first step to addressing financial toxicity is recognizing that the patient is experiencing financial distress, which can be assessed through the use of validated tools that allow universal screening and early triage for such patients. Universal screening of patients’ financial concerns, triaging potential financial issues, and examining the available financial assistance resources can be a valuable first step.30

Engaging stakeholders
Clinicians have been major advocates of controlling costs for patients, and more than 75% of physicians believe it is their responsibility to discuss the cost of care with patients.31

However, major steps in helping to reduce the use of low-value services as outlined by the American Society of Clinical Oncology, American Society for Radiation Oncology, and Commission on Cancer (Table 3) through the Choosing Wisely campaign have not met with provider adoption.32 One study found that the use of low-value services has decreased slightly or even occasionally increased.33 These findings demonstrate that there is still reluctance to address some practice issues that could affect financial toxicity and that providers still report difficulty when talking to patients about low-value services and when they are not needed for care.32 Cancer care providers must become stewards of health care dollars and help their patients navigate the financial toxicity that is increasingly occurring.

Foster communication
As has been shown, financial toxicity leads to increased mortality, decreased quality of life, rationing or skipping care, and bankruptcy; therefore, the cost of therapy must be considered as an essential part of the overall discussion around the provision of care.

However, providers are concerned about the additional time needed for these types of discussions, as well as their overall lack of expertise in discussing and providing potential solutions to cost issues related to cancer care. Additionally, patients may be concerned that sharing personal information regarding their experience of financial toxicity could lead to their not being given the best possible care available; furthermore, other patients may not understand or be prepared for the magnitude of the cost of therapy.

For these reasons, financial counseling and the use of financial navigators should be made available, with the cost of therapy and expected outcomes discussed with the patient before therapy is started.34 Patients should also be encouraged to ask and discuss financial issues they are having with their care provider.
Financial counseling and the use of financial navigators should be made available, with the cost of therapy and expected outcomes discussed with the patient before therapy is started.

In a Mayo Clinic study, more than 500 recordings of health care conversations between physicians and patients were analyzed to study whether the cost of an impending course of cancer treatment was discussed. The results showed that fewer than one-third of patients questioned the cost of the proposed cancer treatment. Of those conversations, approximately 60% of physicians acknowledged that there could be a potential financial issue for the patients. Other studies have confirmed that less than one-third of patients with cancer have engaged in financial discussions with their health care providers; however, most patients report positive attitudes about having these cost-related discussions.

Although physicians have said they believe that financial discussions about therapy are their responsibility, less than 30% feel comfortable discussing costs, and when such discussions do occur, the duration of the cost discussion may be limited. In one observational study, cost discussions occurred in 22% of visits and were initiated by the physician slightly less than 60% of the time, with cost-reduction strategies mentioned only 38% of the time. These results help to demonstrate that there is still a significant need for patients and clinicians to pursue and navigate discussions regarding financial issues associated with care, as well as methods to alleviate the issues that are causing patients financial distress.

Individualize solutions

Furthermore, a solution to financial toxicity will not be a “one size fits all” strategy. Each patient has unique challenges, and each institution has unique barriers and opportunities. For this reason, addressing the financial toxicity of each patient will likely take a concerted effort on the part of the institution to recognize the problem, communicate with the patient, determine the patient’s unique needs, and then develop a tailored program to help meet those needs.

In this way, communication with patients that leads to shared decision-making around care plans can allow oncology care providers to cohesively provide stewardship of the health costs for cancer care to patients. Additionally, oncology care providers can develop a strategy of creating a financial care plan to go alongside the cancer treatment plan.

Conclusions

Financial toxicity is an increasing problem in cancer care. With cancer costs continuing to increase, the effects of this toxicity are coming into greater focus. Still, at the present, there is no clear and simple solution in sight.

One potential model to address patients’ financial toxicity proposes that we maximize value when we maximize clinical, humanistic, and economic outcomes. As we develop new therapies, we must recognize that not all these therapies bring added value to the patient. Small improvements in progression-free survival may not truly offer the benefit we expect when we consider the enormous cost some therapies now demand. As we incorporate the financial distress caused by the excessive cost of cancer care, the value equation begins to change.

In cancer care, we are mostly focused on the clinical outcomes. Although we may, as a field, be progressing in our understanding and appreciation of the humanistic outcomes of the care we provide, it is time that we also turn our attention to the economic outcomes that patients experience under our care in order to maximize the value of that care and minimize patients’ financial toxicity in support of the best possible patient health outcomes.

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Facilitating Access to Oncology Medication
Timely access to cancer treatment improves patient outcomes.

A growing body of research supports the importance of timely access to cancer treatment because patients who obtain prompt care have been found to have better outcomes, including improved quality of life and increased survivability. Though the impact of timely access to care is well documented, time to treatment initiation (TTI) for patients with newly diagnosed cancer in the United States is increasing. A recent study found TTI for all cancers increased by 38% during a 9-year observation period. In order to understand the factors leading to this increase, it is important to assess the social determinants of health (SDOH) influencing access to oncology medications, how they affect TTI, and the role of oncology-focused specialty pharmacies in facilitating timely access to prescribed therapy.

SDOH Influencing Medication Access
The fastest-growing population group in the United States is those aged 85 years and over, with the 85-plus age group projected to reach 19 million individuals by 2060. An aging population will increase demand for cancer-related services. As demand increases, shortages of medical oncologists will challenge our health system. Projections indicate a 40% growth rate in oncologists will be required to meet this growing demand, yet the current growth rate is only 5%.

In 2020, the FDA approved a record 19 new cancer drugs. Looking ahead, 65% of new drug approvals over the next several years will target cancer or rare disease. A recent report analyzed the challenges faced by developed countries regarding access to oncology medicines and found uncertainty around clinical benefits, products with multiple indications, and pricing challenges for therapies used in combination with other treatments were impeding sustainable access to oncology medications.

The cost of cancer treatment is increasing. The US spent $200.7 billion on cancer in 2020, and that cost is projected to reach $245.6 billion by 2030. As costs rise, patient cost-sharing has increased. In a recent analysis of US specialty pharmacy trends, payers listed “increased cost-sharing” as a leading strategy across both commercial and Medicare patients. Recent research shows the average out-of-pocket costs for cancer treatment has increased by more than 15%.

Impact on TTI
Record growth in the number of specialty drugs treating cancer has created unique challenges for the...
A significant **challenge** impeding medication access for oncology patients is **financial toxicity**.

Public and private health plans who pay for treatment. Payers incorporate utilization management (UM) strategies to determine whether prescribed therapy is medically necessary and appropriate. Common UM strategies used by payers include prior authorization requirements, drug formularies, step therapy, and specialty drug tiers. However, UM can ultimately limit the access patients have to novel therapeutics even years after their FDA approval.

A recent survey found 1 in 3 patients experienced a delay in their care due to UM. According to the American Medical Association, 94% of physicians report the prior authorization (PA) process leads to delays in necessary care. Although the need for UM is generally understood, a growing coalition of health care organizations are advocating to reform UM strategies.

Oncologists are faced with increased demand for quality care, arduous administrative tasks, and an ongoing shortage of health care workers, yet physicians and their staff spend an average of 2 full business days each week completing PA requirements.

Amanda Hasenei is a referral specialist for BioMatrix Specialty Pharmacy, and her primary responsibilities include assisting providers and patients with initiating and maintaining access to therapy. “Prescribers are forced to navigate an increasingly complex landscape of burdensome administrative requirements while juggling dose changes, refills, and keeping up with which pharmacies have access to limited distribution oncology medications,” Hasenei said.

PA requirements are not the only cause of delay at the practice level. A recent study analyzed chemotherapy treatment delays in ambulatory oncology practices. Delays occurred across stages of the care process and originated within organizational structure, communication/coordination, and communication technologies.

A significant challenge impeding medication access for oncology patients is financial toxicity. The cost of oncology medication often significantly exceeds household income for most patients. Patients with higher out-of-pocket costs are more likely to be non-adherent or to discontinue treatment.

Additionally, issues such as financial toxicity are compounded by health disparities. Cancer health disparities are widely documented and include obstacles in obtaining timely access to care. The experience of these disparities by patients can lead to additional burdens and different treatment outcomes and can be found to correlate to race, disability, gender identity, geographic location, income, education, age, sexual orientation, and national origin.

**Role of Specialty Pharmacy**

Specialty pharmacies play an important role in facilitating timely access to prescribed therapy. Coordinating support across health care stakeholders, specialty pharmacies can reduce barriers to care throughout the treatment process.

“Specialty pharmacies following a center of excellence model focus their competencies and clinical acumen to address critical issues such as therapy initiation times,” said Joshua Stoneking, PharmD, vice president, oncology, BioMatrix Specialty Pharmacy. “Coordinated efforts by a multidisciplinary, »
Specialty pharmacies can help oncologists stretch resources and provide support that can lead to improved outcomes.

As new therapies are approved, specialty pharmacies capture important real-world data (RWD), demonstrating the impact of prescribed therapy. Working with patients, drug manufacturers, prescribers, and clinical research organizations, specialty pharmacies can help provide this data to advance evidence-based treatment protocols. This RWD provides valuable insight as the health care system pivots to a more sustainable, value-based model of care.

Patient navigation services improve timely access to cancer care. Specialty pharmacies employing patient-centric support reduce barriers at the individual patient level—including for populations at a greater risk of experiencing cancer disparities.

“Specialty pharmacies providing culturally competent care recognize and appropriately address issues that may impede patients from accessing and maintaining prescribed therapy,” said Royce Burruss, MBA, RPh, FASCP, corporate director, clinical services, BioMatrix Specialty Pharmacy. “Understanding constraints that can prohibit patients from accessing care allows us to deploy appropriate resources that bridge coverage gaps, provide financial assistance, and coordinate referrals to appropriate local service programs.”

Conclusions
Timely access to prescribed therapy is an essential component of quality cancer treatment. Increasing TTI can threaten quality of life and survivability for patients with newly diagnosed cancer.

Access to quality care is influenced by SDOH, which can ultimately impact TTI. Specialty pharmacies providing service-oriented, patient-centric support can reduce barriers to care, increase clinical support, and provide data that can facilitate the transition to a value-based model of care.
Melanoma is a highly malignant tumor that is responsible for 80% of skin cancer deaths. For patients who develop metastases or distant disease, the 5-year survival rate is about 30%.\(^1\) Melanoma is also one of the most highly mutated malignancies primarily due to ultraviolet radiation-induced DNA damage.\(^2\)

Activating v-Raf murine sarcoma viral oncogenes homolog B1 (\(BRAF\)) mutations are present in about 50% of melanomas;\(^2\) about 90% of these mutations lead to substitution of valine to glutamate at codon 600 (V600E). In a normal cell, the \(BRAF\) gene encodes for \(BRAF\) kinase, a component of the mitogen activated protein kinase (MAPK), signaling cascade that regulates cell growth. In melanoma, mutated \(BRAF\) kinase is constitutively active resulting in unchecked cell growth and ultimately tumor development.\(^3\)

Prior to targeted therapies, patients with \(BRAF\)-mutated metastatic melanomas had poorer prognosis and overall survival.\(^3\) Early trials demonstrated rapid antitumor response with \(BRAF\) kinase inhibitors. However, duration of responses with \(BRAF\) inhibitor monotherapy is usually limited because of the development of resistance against \(BRAF\) inhibition.\(^4\)

COMBI-v and COMBI-d were the first phase 3 studies to evaluate the dual inhibition of \(BRAF\) and MEK, an intracellular signaling kinase downstream of \(BRAF\). In comparison to \(BRAF\) inhibition alone with dabrafenib, combination therapy with dabrafenib and trametinib led to significant improvement in progression-free survival and overall survival in patients with \(BRAF\)-mutated metastatic melanoma.\(^5,6\)

Following these discoveries, a new era of orally administered agents for patients with melanoma emerged. Before 2004, no systemic therapies for melanoma had been shown to provide a survival benefit.\(^4\) However, within the last decade, several checkpoint inhibitors and \(BRAF\)/MEK-targeted therapies have been approved for use in advanced stage and metastatic melanoma (Figure).\(^7\)

CASE

DT is a 49-year-old woman who initially received a diagnosis of \(BRAF\) V600E–mutated stage IIIA cutaneous melanoma of the left thigh. Eight months ago, she was treated with wide local excision without subsequent recurrence. Unfortunately, she recently found out during a surveillance visit that her disease had metastasized to the right inguinal and axillary lymph nodes. She was then initiated on combined \(BRAF\)/MEK-targeted therapy with vemurafenib (Zelboraf) and cobimetinib (Cotellic).
To date, 3 different combinations of BRAF/MEK inhibitors have been approved for BRAF V600–mutated melanoma: dabrafenib plus trametinib (D+T), vemurafenib plus cobimetinib (V+C), and encorafenib plus binimetinib (E+B). As the landscape of melanoma therapy continues to change, pharmacists play an important role to help melanoma patients stay informed and navigate the unique adverse effect (AE) profiles of these novel therapies.

Brown Bag Consult®

Today, DT brought in her new medications to the pharmacy counter to speak with a pharmacist about her new therapy.

You recognize DT from a recent counseling visit for blood glucose monitoring following her being started on metformin for newly diagnosed type 2 diabetes. Glad to see a familiar face, DT expresses her concerns for starting not 1, but 2 new medications. She is worried about not being able to recognize serious AEs and hopes you can help.

After acknowledging DT’s concerns, you offer to provide a quick brown bag consult to address specific questions about combined BRAF/MEK inhibitor therapy and raise suggestions for management of common therapy-related AEs. DT graciously accepts the offer and shows you her latest medication list which includes:

- Lisinopril 10 mg daily
- Metformin ER 500 mg twice daily
- Ondansetron 8 mg as needed every 8 hours
- Vemurafenib 960 mg twice daily
- Cobimetinib 60 mg daily
- Acetaminophen 650 mg every 6 hours as needed for fever

Unlike DT’s other oral medications, V+C has unique toxicity profiles that can be paradoxical and intimidating to manage at home. According to the trials that evaluated combination treatment with BRAF and MEK inhibitors, 96% to 99% of patients reported therapy-related AEs. Common AEs to expect include fever, chills, fatigue, rash, headache, photosensitivity, nausea, diarrhea, and arthralgia. Other notable but less frequently observed AEs are cutaneous squamous cell carcinoma (cSCC), uveitis, and reduced left ventricular ejection fraction.

Interestingly, coadministration of BRAF and MEK inhibitors reduces the incidence of some of BRAF inhibitor–associated AEs, such as cSCC. The table illustrates the frequency of key AEs for each approved combination of BRAF/MEK inhibitors, as reported by their respective pivotal clinical trials.

You first explain to DT that fever is very common and usually occurs within the first 4 weeks of taking V+C. These periodic fever episodes are usually not representative of infections if no other localizing symptoms are present. If a patient’s temperature is less than 101.3 °F (38.5 °C), she may use acetaminophen 650 mg by mouth every 6 hours to alleviate symptoms, but not to exceed 4000 mg acetaminophen per day. However, the maximum total daily dose of acetaminophen should be reduced for hepatic impairment.
Temperatures higher than 101.3 °F (38.5 °C) may not respond to an antipyretic alone and would require the patient to contact her oncologist’s office to see if interruption of therapy is necessary. Therefore, DT should obtain an oral or axillary thermometer to watch for these higher temperatures.

DT asks if the fever will improve with time. You inform the patient that in 50% of cases, fever resolves in less than 1 month. In fact, most of the common AEs were shown to have a median time to resolution of less than 2 months. Therefore, it would be prudent for DT to get evaluated for any new abnormal skin growth.

Dermatological toxicities associated with BRAF/MEK inhibitors can be unpleasant surprises for melanoma patients. While the incidence of secondary cutaneous malignancies is lower with V+C vs vemurafenib alone (4% vs 12.6%), it is still important that DT receives dermatological evaluation every 2 months during the treatment period to look for suspicious skin lesions.

For example, BRAF inhibitor–induced cSCC causes self-limiting lesions that may develop within the first 2 to 6 months of therapy. These lesions usually have wartlike characteristics and they are not always distinguishable from new melanoma. Therefore, it would be prudent for DT to get evaluated for any new abnormal skin growth.

Another relatively less common AE that DT should be counseled on is uveitis. The probability of developing uveitis during a 1-year treatment with BRAF/MEK inhibitors is less than 10%.

### TABLE. COMMON AES OF BRAF- AND MEK-TARGETED THERAPIES

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Vemurafenib and cobimetinib</th>
<th>Dabrafenib and trametinib</th>
<th>Encorafenib and binimetinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pivotal trials</td>
<td>coBRIM®</td>
<td>COMBI-V®</td>
<td>COLUMBUS®</td>
</tr>
<tr>
<td><strong>AEs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Fatigue</td>
<td>+++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Rash</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Fever</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Vomiting</td>
<td>+++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Reduced left ventricular ejection fraction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increase in transaminases</td>
<td>+++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Headache</td>
<td>++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Hypertension</td>
<td>++</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Alopecia</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Acneiform dermatitis</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Constipation</td>
<td>+</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Cutaneous squamous cell carcinoma</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>---</td>
<td>++</td>
<td>++</td>
</tr>
</tbody>
</table>

AE, adverse effect. Listed are AE frequencies of all grades. No death related to any AE was reported in the relevant trials. Frequency for each AE is represented by “+”.

---, data not reported; ++, <10%; +++, 10%-20%; ++++, >20%-30%; +++++, >30%-40%; ++++++, >40%.

Disclaimer: Direct comparison of AE incidence cannot be made between combination therapies because of inherent differences between trials. Trends should be observed instead.
MEK inhibitors is about 5%. From reported cases in the literature, it appears uveitis can occur at any time during the treatment period. Uveitis is inflammation of the uvea, the middle layer of the eye between the retina and the sclera. The constellation of symptoms may include worsening visual acuity, eye redness, eye dryness, and sharp eye pain with or without floaters. If recognized and treated in a timely fashion, uveitis-related ocular symptoms are reversible. However, if untreated, uveitis can damage vital eye tissue, leading to permanent vision loss.

While uveitis is mainly associated with BRAF inhibition, retinal damage is possible with MEK inhibition. Therefore, DT should contact her oncology clinic to report any visual changes so her symptoms can be assessed and triaged appropriately. Once diagnosed, uveitis can be treated with ophthalmic steroids, cycloplegics, and temporary holding of treatment if necessary, while the duration of treatment can depend on results of the follow-up eye examination.

You noticed that DT is also taking medications to manage her hypertension and diabetes. V+C can increase DT’s blood pressure (BP) and blood glucose (BG), making it harder to maintain her BP and BG goals. You encouraged DT to check her BP and fasting BG at least once daily at the start of therapy and reach out to her primary care provider if these numbers consistently fall out of range.

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4. Safety and Efficacy of COVID-19 Vaccines: Understanding the Clinical Trials (Immunizations Credit)
5. Bloodborne Pathogens and Essentials of COVID-19 Vaccine Storage and Administration (Immunizations Credit)
6. Advancements in COVID-19 Treatment Options
7. Coping With COVID-19: Examining the Psychology of Vaccine Hesitancy and Barriers to Achieving Herd Immunity
8. COVID-19 and Vaccine Literacy: Practical Communication to Empower the Patient
9. COVID-19 Vaccine Update: Implementation and Best Practices
10. COVID-19 Post-Vaccination Considerations and Requirements (Immunizations Credit)

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Driving Out Disparities in Cancer Care

One of the most popular sessions at the 2021 Directions in Oncology Pharmacy® conference was titled Overcoming Cancer Care Disparities: Opportunities for Health Care Providers, presented by Maurice Alexander, PharmD, BCOP, CPP.

Dr. Alexander began the session with a review of factors contributing to disparities in cancer care, including race/ethnicity, disability, age, gender, socioeconomic status, sexual orientation, and geography. Looking at social determinants specifically, there are known disparities in outcomes of patients with cancer by race and social determinants, which impact clinical outcomes. Dr. Alexander highlighted data showing differences in mortality across ethnic groups, and also showed the impact of geography on patient outcomes. As an example, Dr. Alexander showed differences in cancer incidence and mortality between Blacks and Whites: the incidence of many malignancies is higher in those of African American descent. Additionally, patients in a lower socioeconomic status are likely to be in rural communities, which may limit access to quality health care, and also impacts ability for timely care due to travel times. Those patients with lower health literacy may also be less willing to participate in cancer research, and may have difficulties with adherence to cancer screening and prevention strategies.

In the second half of the presentation, Dr. Alexander shifted the focus to identifying perspectives of pharmacists, physicians, and nurses in cancer care disparities. He reminded the audience of the role of health care providers, and highlighted specific statements from the Oncology Nursing Society on overcoming disparities, as well as strategies to unite pharmacists professionally to address disparities in health care. He encouraged an understanding of health equity, which can be accomplished through a multilevel process beginning with national health policies.

In the final portion, Dr. Alexander reviewed existing structural barriers within the health care workforce, specifically discussing the impact of implicit biases, cultural incompetence, systemic disparities, and creativity on diversity within the workforce. He illustrated multiple solutions to improve this, including:

- Mentoring opportunities for trainees
- Integrating health equity and diversity into institutional priorities
- Supporting career development
- Researching policy solutions

He then highlighted the importance of increasing awareness, as well as how we as health care providers can respond to interpersonal racism and how to educate ourselves and others.

Dr. Alexander engaged the audience in dialogue about disparities and racism in cancer care with case studies throughout the presentation, fantastic examples, and a question-and-answer period at the end of the program.
Bringing Out the Best in BTK Inhibitors

ANTHONY J. PERISSINOTTI, PHARMD, BCOP,
translated clinical trials into clinical practice
in a virtual 2021 Directions in Oncology
Pharmacy® conference session titled Updates for
Pharmacists on BTK Inhibitors in Treating B-Cell
Malignancies. Standard of care for mantle cell
lymphoma (MCL), Waldenström macroglobulinemia
(WM), and chronic lymphocytic leukemia (CLL)
now includes BTK inhibitors in the first-line and/or
relapsed/refractory settings; however, patients need
pharmacist support to remain on therapy.

Dr Perissinotti began the session by illus-
trating the mechanism of BTK inhibitors in
the pathophysiology of B-cell malignancies.
In CLL, BTK and BCL2 inhibitors have
replaced cytotoxic chemotherapy in both
frontline and relapsed/refractory disease.
Dr Perissinotti described similar efficacy
among acalabrutinib and ibrutinib; however,
tolerability is improved with acalabrutinib.
He noted zanubrutinib can be considered for
patients with CLL with intolerance or contraindication
to other BTK inhibitors. In MCL, BTK inhibitors are
recommended for second-line therapy. Dr Perissinotti
demonstrated that all 3 BTK inhibitors have activity
and there are no comparative data to guide preference.
In the management of WM, Dr Perissinotti illustrated
the role of zanubrutinib, or ibrutinib with or without
rituximab, as initial therapy in patients with signifi-
cantly symptomatic disease. He explained that patients
with WM whose response duration to previous therapy
was less than 3 years typically receive a BTK inhibitor
for relapsed/refractory WM. Dr Perissinotti wrapped
up the first half of the program by highlighting the
activity of an investigational agent, pirtobrutinib, in
patients with CLL, MCL, and WM, many of whom had
previous BTK inhibitor exposure. This contrasts with
acalabrutinib, ibrutinib, and zanubrutinib, which are
typically cross-resistant.

Anthony J. Perissinotti, PharmD, BCOP, illustrated that
“clinical pharmacists can impact clinical outcomes for
patients receiving a BTK inhibitor.”

BTK inhibitors are associated with rash, arthralgias,
 pneumonitis, infection, diarrhea, atrial fibrillation,
 bleeding, hypertension, and an increased risk of major
cardiovascular events. In a cross-study comparison of
adverse effects, Dr Perissinotti illustrated the incidence
of hypertension and atrial fibrillation are highest with
ibrutinib; however, the rates of major bleeding
are similar across all 3 BTK inhibitors. He
recommended individualized assessment of the
risk for atrial fibrillation using the Shanafelt
risk score and provided strategies for manage-
ment. He noted concomitant use of BTK inhibi-
tors and anticoagulants does increase the risk
of bleeding. Dr Perissinotti emphasized that
anticoagulants/antiplatelets are not contrain-
dicated; however, warfarin should be avoided.

He explained that no specific agent is recom-
mended to manage hypertension and highlighted drug–
drug interactions should be assessed as potential drivers
of hypertension. He emphasized that most patients who
change from ibrutinib to acalabrutinib or zanubrutinib
because of intolerance often have improved tolerance to
subsequent therapy.

Dr Perissinotti highlighted the role of pharmacists in
management of patients receiving BTK inhibitors given
10% to 20% of patients discontinue BTK inhibitor
therapy due to adverse effects. He explained that lever-
aging use of digital technology can:

- Identify and manage adverse effects early
- Reduce emergency department and inpatient
  admissions
- Keep patients on therapy longer
- Improve progression-free and overall survival
Checking in on Immune Checkpoint Inhibitors In Non–Small Cell Lung Cancer

With 4 FDA approvals for immune checkpoint inhibitors (ICIs) in metastatic non–small cell lung cancer (NSCLC) in the past year, the session titled Frontline Therapies for Non–Small Cell Lung Cancer: Optimizing Outcomes With Immune Checkpoint Inhibitors was a crowd favorite at the 2021 Directions in Oncology Pharmacy® conference.

Jocelyn Mohs, PharmD, BCOP, illustrated the current FDA-approved regimens in NSCLC (TABLE) before doing a deep dive into the clinical trial data. Dr Mohs highlighted that if an ICI is combined with chemotherapy, the regimen can be used regardless of programmed death ligand 1 (PD-L1) expression, but must be in respect to histology, either squamous or nonsquamous. She explained that PD-L1 is not a reliable biomarker of response to ICI therapy in NSCLC, but it does guide selection of ICI treatment in the first-line setting: monotherapy versus combination with chemotherapy. Dr Mohs clarified that for patients with PD-L1 expression greater than or equal to 50%, ICI monotherapy is preferred because of an improvement in survival and reduction in adverse effects compared with chemotherapy. For patients with no or unknown PD-L1 expression, patients receive an ICI combined with chemotherapy due to a survival benefit over chemotherapy alone. She explained that patients with PD-L1 expression of 1% to 49% represent a gray area where an ICI combined with chemotherapy is typically preferred. She wrapped up the first half of the presentation with a preview of emerging therapies including tislelizumab and combination therapy with durvalumab and tremelimumab.

In the second half of the presentation, Dr Mohs shifted the focus to endocrinopathies associated with ICI therapy. Immune-related endocrinopathies may include diabetes, hypothyroidism, hyperthyroidism, adrenal insufficiency, and hypophysitis. Patients with hypothyroidism typically continue ICI therapy and are managed with levothyroxine. Patients with hyperthyroidism continue ICI if they are asymptomatic and symptomatic patients are managed with propranolol. Dr Mohs explained that patients with symptomatic hypophysitis receive prednisone initially and will require lifelong hydrocortisone and levothyroxine. She noted that while diabetes is rare, steroids may exacerbate hyperglycemia; therefore, patients are typically managed with diet, lifestyle modification, and insulin if needed. She wrapped up the session by reinforcing the role of pharmacists in monitoring and managing immune-related endocrinopathies and educating patients on signs and symptoms.

<table>
<thead>
<tr>
<th>FDA-approved regimen</th>
<th>Biomarker</th>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monotherapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>PD-L1 ≥50% or PD-L1 tumor-infiltrating immune cells ≥10% of tumor area</td>
<td>Any</td>
</tr>
<tr>
<td>Cemiplimab-rwlc</td>
<td>PD-L1 ≥50%</td>
<td></td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>PD-L1 ≥1%</td>
<td></td>
</tr>
<tr>
<td><strong>ICI + ICI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nivolumab + ipilimumab</td>
<td>PD-L1 ≥1%</td>
<td>Nonsquamous</td>
</tr>
<tr>
<td><strong>ICI + chemotherapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atezolizumab + carboplatin + nab-paclitaxel</td>
<td>None</td>
<td>Squamous</td>
</tr>
<tr>
<td>Atezolizumab + bevacizumab + carboplatin + paclitaxel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pembrolizumab + pemetrexed + carboplatin/cisplatin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pembrolizumab + paclitaxel/nab-paclitaxel + carboplatin</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ICI + ICI + chemotherapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nivolumab + ipilimumab + pemetrexed + carboplatin/cisplatin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nivolumab + ipilimumab + paclitaxel + carboplatin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ICI, immune checkpoint inhibitor; PD-L1, programmed death ligand 1.
Iron Deficiency Anemia in Patients With Cancer and the Pharmacist’s Role

**EDUCATIONAL OBJECTIVES**

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

• Examine the epidemiology, pathophysiology, and diagnosis of iron deficiency anemia (IDA) in patients with cancer
• Identify and recommend patient-specific treatment options for IDA
• Determine the role of the pharmacist in managing IDA in patients with cancer

**TARGET AUDIENCE:** Health-system and oncology pharmacists. Pharmacists practicing across sub-specialties who have responsibilities that include interactions with patients with cancer will also be invited to participate.

**ACTIVITY TYPE:** Application

**RELEASE DATE:** November 16, 2021

**EXPIRATION DATE:** November 16, 2022

**ESTIMATED TIME TO COMPLETE ACTIVITY:** 2.0 hours

**FEE:** This lesson is offered for free at www.pharmacytimes.org.

**Introduction**

Anemia is a common and potentially devastating complication worldwide, compromising function and quality of life in various patient populations. According to the World Health Organization (WHO), anemia impacts approximately 25% of the global population, which is more than 1.6 billion individuals, and of those anemia cases, roughly 50% are due to iron deficiency.\(^1\) In patients with cancer, anemia prevalence varies, ranging from 30% to 90%, depending on multiple factors, including cancer type, stage of disease, patient age, and definition of anemia.\(^2\) It is understood that cancer-related anemia (CRA) occurs in greater than 30% of patients, even at diagnosis before initiation of antineoplastic therapy.\(^3\) CRA is defined as anemia that results from malignancy or through treatment of cancer (chemotherapy, radiotherapy, surgery).\(^4\) Antineoplastic therapy, specifically cytotoxic chemotherapy, leads to an increased prevalence of CRA, impacting greater than 67% of patients with cancer who have initiated treatment.\(^5\) Iron deficiency is commonly found in patients with cancer and often progresses to anemia.\(^6\) The initial step in iron deficiency is caused by reduced iron intake compared with the body’s iron requirements. This leads to iron stores being depleted in the bone marrow and a resulting increase in dietary iron absorption. Iron is an integral part of red blood cell synthesis and when iron stores are depleted, sufficient iron production fails and red blood cell synthesis will eventually be reduced, resulting in anemia.\(^7\) Ludwigs and colleagues conducted a study in more than 1500 patients with cancer across multiple tumor types, including solid and hematologic malignancies, to evaluate prevalence of iron deficiency anemia (IDA) and its impact on disease status.\(^8\) Iron deficiency was frequently observed in patients with cancer (>42%) and was associated with more advanced disease, poor performance status in patients with solid tumors, and proximity to cancer therapy. Iron deficiency rates were highest in patients with pancreatic cancer (>63%), followed...
Anemia was detected in greater than 50% of patients with iron deficiency who had solid tumors and in more than 43% of patients who had hematologic malignancies. Iron deficiency and anemia appear to be more common in patients with solid tumors compared with hematologic malignancies, but incidence varies greatly among solid tumor types. Among hematologic malignancies, anemia is highest in multiple myeloma, likely due to underlying disease in plasma cells/bone marrow and impact on renal insufficiency leading to multiple mechanisms for cause.

Anemia is often associated with fatigue, reduced physical function and capacity, and reduced quality of life. The impact anemia and iron deficiency have on patients with cancer is potentially even more devastating, with consequences possibly including reduced response to cancer treatments and even decreased survival. Based on the systematic review by Caro and colleagues evaluating 60 clinical trials, anemia in patients with cancer was associated with an overall increase of 65% in risk of mortality compared with patients with cancer without anemia. Among specific types of tumors, head and neck cancer displayed the highest risk of increased mortality, with an increase of 75% in mortality risk in patients with cancer with anemia versus those without anemia. Other tumor types resulting in increased mortality risk in patients with anemia compared with those without were lung cancer (19% increase), prostate cancer (47% increase), and lymphoma (67% increase). There is also a relationship between CRA and reduced efficacy of chemotherapy and radiotherapy. This correlation is likely multifactorial and possible causes include increased inflammation, increased tumor aggressiveness, and ultimately poor local tumor control in patients with cancer with anemia compared with patients with cancer without anemia.

CRA’s significant impact on patient’s quality of life and overall functional status can ultimately lead to poor adherence to anticancer regimens. While targeted therapy and immunotherapy availability and use in the oncology world are increasing, cytotoxic chemotherapy remains a common backbone of cancer treatment, thus anemia and IDA remain a common complication in patients with cancer. This article will review pathophysiology and etiology of iron deficiency in cancer, treatment options, and the role pharmacists play in managing the complexities surrounding iron deficiency in patients with cancer.

**STAR**

What is the main hallmark feature in terms of etiology of CRA?

*STOP, T = Think; A = Assess; R = Review* 

**Pathophysiology/Etiology**

The pathogenesis of CRA is complex and multifactorial. Different mechanisms can even prevail at different times in the same patient.
CRA occurs primarily due to chronic inflammation associated with synthesis of proinflammatory cytokines by both the immune system and cancer cells with advanced stage cancer. Iron homeostasis is maintained by a small peptide hormone produced by the liver called hepcidin. Hepcidin works in a negative feedback system to regulate systemic iron homeostasis but cancer-associated proinflammatory cytokines and chronic inflammation result in upregulation of hepcidin synthesis in the liver. Hepcidin is not the only factor impacted and this chronic inflammation hallmark of CRA is attributed to multiple mechanisms that lead to anemia:

- Reduced survival of erythrocyte cells in combination with increased erythrocyte destruction
- Suppressed erythropoiesis in the bone marrow
- Reduced erythropoietin production due to inflammatory effects on the kidney
- Increase in hepcidin leading to reduced absorption of iron from the gastrointestinal (GI) tract

Iron deficiency in patients with cancer also develops from multiple mechanisms (TABLE 18), again led by the hallmark immune-inflammation leading to increased hepcidin and ultimately blockage of iron absorption from the GI tract. Erythropoietin-stimulating agents (ESAs), such as epoetin alfa and darbepoetin alfa, can paradoxically increase in hepcidin leading to reduced absorption of iron from the gastrointestinal tract.

### Diagnostics and Laboratory Data

Anemia is considered a decreased erythrocyte mass associated with a decrease in hemoglobin (Hgb) and hematocrit (Hct) counts, resulting in the reduction of oxygen in circulating blood. Organizations differ on their laboratory definition of anemia. WHO defines anemia as Hgb lower than 11.9 g/dL in women and lower than 12.9 g/dL in men. National Comprehensive Cancer Network (NCCN) defines anemia as Hgb lower than 11 or Hgb decrease higher than 2 g/dL below baseline Hgb level, with no distinction between male and female in the definition.

### TABLE 1. ETIOLOGY OF ANEMIA IN PATIENTS WITH CANCER

<table>
<thead>
<tr>
<th>Cancer related</th>
<th>Treatment related</th>
<th>Patient related</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Chronic inflammation</td>
<td>• Blood loss (surgery)</td>
<td>• Poor appetite</td>
</tr>
<tr>
<td>• Blood loss</td>
<td>• Chemotherapy-induced bone marrow suppression</td>
<td>• Nutritional deficiency</td>
</tr>
<tr>
<td>• Hemolysis</td>
<td>• Radiotherapy-induced bone marrow suppression</td>
<td></td>
</tr>
<tr>
<td>• Tumor infiltration</td>
<td>• Myelosuppression/nephrotoxicity of chemotherapeutic agents</td>
<td></td>
</tr>
<tr>
<td>• Destruction of bone marrow</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Hormone dysfunction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Anemia of chronic disease</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The most frequently used tests to assess iron status and evaluate patients for iron deficiency are serum ferritin and transferrin saturation (TSAT, %) [serum iron/TIBC]x100. Ferritin is utilized as a biomarker to indicate total body iron stores. When reduced, ferritin levels are a good indicator of absolute IDA. The issue with evaluating ferritin is that it is an acute-phase reactant, meaning in conditions that cause inflammation (such as cancer), the ferritin result may be falsely elevated and may not be reliable at quantifying iron stores. TABLE 2 reviews common labs used to evaluate iron status. TSAT is a percentage indicating the iron availability throughout the body for erythropoiesis. The two main types of IDA syndromes are: (1) absolute IDA and (2) functional IDA. FIGURE 3 differentiates these 2 types of IDA syndromes. Absolute IDA is defined as low iron stores (serum ferritin <30 ng/mL or <100 ng/mL in patients with cancer due to the presence of
chronic inflammation) and low iron availability (TSAT <20%). Functional IDA involves low iron availability (TSAT <20%), but the iron stores are normal or elevated (serum ferritin 30-500 ng/mL or greater than 100 ng/mL in patients with cancer) indicating adequate iron stores but insufficient iron supply for erythropoiesis. Functional IDA is much more common in patients with cancer compared with absolute IDA. Absolute IDA more often occurs due to blood loss, malabsorption, or poor oral intake of iron in the diet. Chronic inflammation and release of cancer-associated proinflammatory cytokines (eg, IL-6, IL-1, TNF-α, interferon-γ) leading to increased hepcidin in the liver to shut down iron absorption through the GI tract is one of the key pathophysiologic features of functional IDA.

The common theme in both absolute IDA and functional IDA is that both involve a decrease in iron availability for erythropoiesis, leading to anemia. In absolute IDA, the loss of iron stores (low ferritin levels) is the main driver triggering anemia. In functional IDA, despite sufficient iron stores, the existence of the chronic inflammatory process leads to iron being trapped in macrophages and enterocytes, reducing its ability for bone marrow, consequently leading to anemia. Due to the inflammatory effects in patients with cancer, diagnosis of iron deficiency in this setting is difficult, leading to the higher cutoff in patients with cancer for serum ferritin levels (eg, <100 ng/mL). Measuring hepcidin is a promising tool for evaluating iron status but further validation is needed, and it is unclear when hepcidin assays will be widely available and used in clinical practice.

The key short-term goal of treatment in IDA in patients with cancer involves the correction of underlying etiology through correction of quantitative deficits of hemoglobin and erythrocytes. This will allow for proper oxygenation requirements of all tissues to be met and patient iron stores to be replenished. If successful in accomplishing this, the ultimate long-term goal should be reached, which is to increase quality of life through improvement in cognition, fatigue, and exercise tolerance.

This section will focus on treatment and correction of iron deficiency including use of oral and intravenous (IV) iron products, as well as ESAs and supportive care measures such as red blood cell (RBC) transfusions.

**Treatments**

**Oral Iron**

The first line of treatment for uncomplicated iron deficiency is often oral iron supplementation, due to wide availability, ease of administration, and low cost. Oral iron supplements are usually
provided as ferrous or ferric salts, with ferrous sulfate, gluconate, and fumarate being the most widely available formulations.\textsuperscript{34,36} The recommended daily dose for adults taking iron supplementation for iron deficiency is 100 to 200 mg of elemental iron.\textsuperscript{35} Ideal administration is to divide the dose and administer without food. Oral iron already has poor bioavailability, which ranges from 10% to 15% for ferrous preparations (and is even lower in ferric compounds).\textsuperscript{33} Iron absorption is impacted even more if administered with food.\textsuperscript{33} This is complicated by the toxicities of oral iron, which includes significant GI adverse effects (AEs) such as constipation, nausea, vomiting, and metallic taste.\textsuperscript{33} Up to 50% of patients on oral iron report GI AEs.\textsuperscript{33,37} This is a major concern, as poor tolerability and reduced tolerance may lead to poor adherence and poor outcomes in patients with iron deficiency. Administering oral iron with food does reduce the GI AEs but will result in reduced efficacy, leading to ineffective treatment and ultimately IV iron supplementation. The coadministration of other agents with oral iron, such as antacids or proton pump inhibitors, negatively impacts the absorption of iron and should be avoided.\textsuperscript{33} Concurrent use of oral iron with tetracycline antibiotics, ciprofloxacin, and levodopa/carbidopa may see marked decrease in bioavailability in these agents due to formation of iron-drug complexes.\textsuperscript{38}

Another step to attempt to improve tolerance to oral iron is dose reduction, as GI AEs seem to be dose related; however, lowering the daily dose may lower the chance of oral iron being effective at treating iron deficiency.\textsuperscript{39} A recent crossover iron absorption study in women with IDA by Stoffel and colleagues showed that iron absorption is increased in those patients who received oral iron supplementation on alternating days.\textsuperscript{40} In the study, patients received 100 mg or 200 mg either on alternate-day administration or consecutive-day administration. Fractional iron absorption was significantly higher

### TABLE 2. LABORATORY TESTS USED TO EVALUATE IRON STATUS\textsuperscript{2,6,9,27}

<table>
<thead>
<tr>
<th>Test</th>
<th>Reference interval</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum ferritin</td>
<td>Male 30-500 ng/mL, Female 12-240 ng/mL</td>
<td>• Lab value for iron stores</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Absolute iron deficiency indicated with value lower than reference range</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Acute phase reactant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• A normal or elevated value does not exclude iron deficiency in patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td>with inflammatory diseases such as cancer or liver disease</td>
</tr>
<tr>
<td>Serum iron</td>
<td>Male 50-170 mcg/dL, Female 30-160 mcg/dL</td>
<td>• Used to calculate transferrin saturation</td>
</tr>
<tr>
<td>TIBC</td>
<td>240-450 mcg/dL</td>
<td>• Often elevated in iron deficiency, signaling lack of iron availability</td>
</tr>
<tr>
<td>TSAT % (serum iron/TIBC) 100\textsuperscript{a}</td>
<td>20%-50%</td>
<td>• Indicates iron availability in the body for erythopoiesis</td>
</tr>
<tr>
<td>Hepcidin</td>
<td>Optimal threshold for response not yet defined</td>
<td>• Test not routinely available</td>
</tr>
<tr>
<td></td>
<td>Likely &lt;64.3 ng/mL (baseline) based on available data\textsuperscript{a}</td>
<td>• Strong correlation between baseline hepcidin level and response to IV iron in functional IDA</td>
</tr>
<tr>
<td>Mean corpuscular volume (MCV)</td>
<td>Male 83-98 fl, Female 85-98 fl</td>
<td>• Average size of RBC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Low sensitivity and specificity for iron deficiency since value is affected by drugs, liver disease, etc</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Low MCV may indicate iron deficiency (microcytic)</td>
</tr>
</tbody>
</table>

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**FIGURE 3. DIFFERENTIATING ABSOLUTE AND FUNCTIONAL IRON DEFICIENCY IN PATIENTS WITH CANCER\textsuperscript{28}**

Republished from Naoum FA. Rev Bras Hematol Hemoter. 2016;38(4):325-330, under the terms and conditions of the Creative Commons Attribution CC BY-NC-ND license.
in those who received 200 mg on alternate days compared with those who received 100 mg on consecutive days. The alternate-day scheduling did not show any significant difference in incidence of GI AEs compared with consecutive-day dosing. This may be a sign in treatment paradigm shift for use of oral iron dosing scheduling as alternate-day dosing of oral iron supplements may be preferable.

**TABLE 3. IV IRON PRODUCTS**

<table>
<thead>
<tr>
<th>IV Iron Product</th>
<th>Elemental iron</th>
<th>Test dose required</th>
<th>BBW</th>
<th>Dose</th>
<th>Pearls</th>
</tr>
</thead>
<tbody>
<tr>
<td>LWM iron dextran - 1992</td>
<td>50 mg/mL</td>
<td>Yes</td>
<td>Yes</td>
<td>• 100 mg x 10 doses</td>
<td>• Premedication required per NCCN</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• TDI: ≥1000 mg over 1-6 hours</td>
<td>• Avoid diphenhydramine as premedication</td>
</tr>
<tr>
<td>Ferric gluconate - 1999</td>
<td>12.5 mg/mL</td>
<td>No</td>
<td>No</td>
<td>• 125 mg IV weekly x 8 doses</td>
<td>• Smaller doses over several days or weeks</td>
</tr>
<tr>
<td>Iron sucrose - 2000</td>
<td>20 mg/mL</td>
<td>No</td>
<td>No</td>
<td>• 200 mg IV x 5 doses over 15 min</td>
<td>• Repeat doses at least 72 hours apart</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• 300 mg IV over 90 min</td>
<td>• Smaller doses over several days or weeks</td>
</tr>
<tr>
<td>Ferumoxytol - 2009</td>
<td>30 mg/mL</td>
<td>No</td>
<td>Yes</td>
<td>• 510 mg IV over 15 min x 2 doses</td>
<td>• Repeat doses after 3-8 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• 1020 mg IV over 30 min x 1</td>
<td>• MRI interaction up to 3 months after dose</td>
</tr>
<tr>
<td>Ferric carboxymaltose - 2013</td>
<td>50 mg/mL</td>
<td>No</td>
<td>No</td>
<td>• 750 mg IV over 15 min x 2 doses</td>
<td>• Repeat dose after 7 days</td>
</tr>
<tr>
<td>Ferric derisomaltose - 2020</td>
<td>100 mg/mL</td>
<td>No</td>
<td>No</td>
<td>• 1000 mg IV over ≥20 min x 1 dose (wt ≥ 50 kg)</td>
<td>• Transient hypophosphatemia (27%)</td>
</tr>
</tbody>
</table>

BBW, black box warning; IV, intravenous; LMW, low molecular weight; MRI, magnetic resonance imaging; NCCN, National Comprehensive Cancer Network; TDI, total dose infusion.

**STAR**

Which IV iron therapies are available as a single-dose treatment course for IDA?

**IV Iron**

To date, no IV iron formulation available has received FDA approval specifically for the treatment of patients with cancer. IV iron is still a mainstay treatment option for patients with cancer who develop iron deficiency. Compared with oral iron supplementation, IV iron offers high bioavailability and is fast acting, leading to increases in Hgb more quickly with minimal GI AEs. Cost of IV iron supplementation is relatively more expensive compared with oral iron products. IV iron supplementation is an option for patients with malabsorption of oral iron, intolerance or suboptimal response to oral iron, and those with significant blood loss or absolute IDA. Previously, IV iron use was limited due to high molecular weight iron resulting in significant hypersensitivity reactions, including anaphylaxis. Now, safer iron formulations are available and have modified the treatment of IDA in recent decades (TABLE 3).

**Iron dextran (INFeD)**

Low molecular weight (LMW) iron dextran was first approved for treatment of IDA in the United States in 1992. Compared with high molecular weight formulations, this formulation had much less risk of severe reactions but LMW iron dextran still carries a black box warning (BBW) for anaphylactic-type reactions, including fatalities. LMW iron dextran contains the equivalent of 50 mg of elemental iron in each milliliter and the FDA-approved dose is 100 mg for multiple doses over several days/weeks calculated via a dosing equation: Dose (mL) = 0.0442 (desired Hgb – observed Hgb) x lean body weight (LBW in kg) + (0.26 x LBW). However, the dose of LMW iron dextran often used in clinical practice is total dose infusion 1000 mg over 1-6 hours (doses >1000 mg often given over several hours) as a 1-time dose. LMW iron dextran has been given intramuscularly (IM) and the prescribing information for LMW iron dextran still includes this option for route of administration, but the IM route has fallen out of favor and NCCN guidelines state that IM administration is not recommended. Other caveats associated with LMW iron dextran include requirements of a test dose and premedication and NCCN guidelines do not recommend using premedications 30 minutes before the LMW iron dextran test dose.

IV Iron Product | Elemental iron | Test dose required | BBW | Dose                              | Pearls                                                                 |
<table>
<thead>
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<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Ferric derisomaltose - 2020</td>
<td>100 mg/mL</td>
<td>No</td>
<td>No</td>
<td>• 1000 mg IV over ≥20 min x 1 dose (wt ≥ 50 kg)</td>
<td>• Hypophosphatemia (3.5%)</td>
</tr>
</tbody>
</table>
The use of antihistamines, such as diphenhydramine, as premedication with IV iron is also controversial due to risk of exacerbation or ability of diphenhydramine to mimic signs and symptoms of hypersensitivity reaction.43 Because of this, antihistamines are not recommended for premedication with IV iron products and instead corticosteroids should be used.

**Ferric gluconate (Ferrlecit)**

Ferric gluconate was first approved by the FDA in 1999 as a follow-up to LMW iron dextran for adult patients with IDA and in pediatric patients 6 years or older undergoing chronic hemodialysis who are receiving supplemental epoetin therapy.41 The standard dose of ferric gluconate is 125 mg IV administered once weekly over 1 hour for 8 doses. Individual doses above 125 mg are not recommended based on clinical trial data.44,45 Ferric gluconate contains 12.5 mg of elemental iron per milliliter.44 This demonstrates an adjusted strategy with ferric gluconate compared with LMW iron dextran as ferric gluconate utilizes smaller doses given over several weeks but the total treatment course results in a similar total amount of elemental iron given (=1000 mg). Ferric gluconate also does not require a test dose or premedication unless desired by the prescribing physician based on risk for reaction. There is no BBW for anaphylactic reactions located in the prescribing information for ferric gluconate. It is important to note that ferric gluconate contains benzyl alcohol (9 mg/mL) as an inactive ingredient and therefore should not be used in neonates.

**Iron sucrose (Venofer)**

Iron sucrose was first approved in 2000 by the FDA for treatment of IDA in patients with CKD.45 Along with all other IV iron products, iron sucrose is used off-label to treat IDA in patients with cancer. There are some data with iron sucrose in patients with cancer compared with oral ferrous fumarate for the primary prevention of anemia.46 A total of 64 patients with gynecologic cancers were randomized to a single dose of 200 mg iron sucrose following each course of chemotherapy for 6 cycles versus daily ferrous fumarate.47 The number of patients requiring blood transfusion doubled in the oral iron group compared with the iron sucrose group (56.3% vs 28.1%; P = .02) and patients who received iron sucrose and did not require a lower median number of packed RBC units.46 The dose of iron sucrose can vary but the goal is like that of ferric gluconate: smaller doses of iron given over several days to weeks with a total treatment course reaching 1000 mg.45 There is a total of 20 mg of elemental iron per each mL. Iron sucrose doses of 200 mg or less may be given undiluted as an IV push administered over 2 to 5 minutes or as an IV infusion given over 15 minutes (total of 5 doses to equal 1000 mg given at least 72 hours apart). Doses of 300 mg or higher should be diluted and administered as an IV infusion over at least 90 minutes. Data are available for doses of iron sucrose ranging from 400 mg to 500 mg, but doses greater than 300 mg are not recommended due to increased risk of infusion reactions.48,49 Iron sucrose does not require premedication or a test dose prior to administration and there is no BBW for anaphylactic reactions with iron sucrose. Providers may utilize test dose and/or premedication based on their clinical discretion and patient risk of infusion reaction.

**Ferumoxytol (Feraheme)**

Ferumoxytol was first FDA approved in 2009 for the treatment of IDA in adult patients who have intolerance or unsatisfactory response to oral iron or who have CKD.46 The recommended dose of ferumoxytol is 510 mg IV administered over at least 15 minutes for a total of 2 doses (1020 mg) given 3 to 8 days apart. There are data for a single-dose option of 1020 mg administered once over 30 minutes.46 Ferumoxytol contains 30 mg of elemental iron per milliliter and this product marked the first time since LWM iron dextran that larger doses of iron are given over a minimal number of doses, attempting to improve patient convenience.46 No test dose or premedication is required with ferumoxytol but can be used at physician discretion based on patient risk for infusion reaction. There is an FDA BBW with ferumoxytol for anaphylactic-type reactions including fatal and serious hypersensitivity reactions that occurred in 0.4% of patients in a clinical study.46,49 A post hoc analysis evaluating pooled data from 2 randomized controlled phase 3 studies compared ferumoxytol or iron sucrose versus placebo in patients with cancer and IDA.46 The analysis showed that IV iron monotherapy increases Hgb from baseline and was safe in the cancer subgroup population compared with the overall population. The analysis concluded that IV iron is likely a safe and effective option for patients with cancer and IDA. Administration of ferumoxytol may also transiently affect the diagnostic ability of magnetic resonance imaging (MRI) scans.46 If MRI scans are necessary in patients receiving ferumoxytol, MRI should be conducted before initiating ferumoxytol as alteration of MRI studies may persist for up to 3 months following the last dose of ferumoxytol. Do not use T2-weighted sequence MRI prior to 4 weeks following ferumoxytol administration. Ferumoxytol will not interfere with x-ray, computed tomography, positron emission tomography, single photon emission computed tomography, ultrasound, or nuclear medicine imaging.46 The most common AEs of ferumoxytol are abdominal pain, diarrhea, and nausea.46,49

**Ferric carboxymaltose (Injectafer)**

Ferric carboxymaltose was first FDA approved in 2013 for IDA in adult patients who have an intolerance or unsatisfactory response to oral iron or in patients who have non-dialysis dependent CKD.47

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**Notes:**
1. www.pharmacytimes.org
2. DECEMBER 2021
3. www.pharmacytimes.org
The standard dose is 750 mg IV, in patients who weigh over 50 kg, administered over 7.5 minutes and repeated as a second dose 7 days later for a total treatment course of 1500 mg. Each milliliter of ferric carboxymaltose contains 50 mg (equal to that of LWM iron dextran). Recently in 2021, the FDA also approved a single treatment dose of 1000 mg of ferric carboxymaltose along with a new dosage form available as 1000-mg vials, creating a more convenient option for patients. Ferric carboxymaltose can be administered at high doses as a single infusion without risk of excessive iron exposure due to its stable iron complex, which allows for a slow and prolonged release of iron. A recent study in 84 patients with cancer demonstrated the safety and efficacy of ferric carboxymaltose in this patient population. An observational study involving 367 patients with solid or hematologic malignancies and IDA evaluated ferric carboxymaltose as monotherapy or in combination with an ESA and demonstrated improved median Hgb levels over a 3-month period. Test doses and premedication are not required with ferric carboxymaltose but can be given at the prescribing physician’s discretion based on risk for reaction. The risk of hypersensitivity reactions from ferric carboxymaltose is low (0.1%) and it is better tolerated than oral iron supplementation due to fewer GI AEs. Ferric carboxymaltose has been associated with severe phosphate deficiency that is often asymptomatic, which may lead to delayed time to diagnosis and can result in significant morbidity. Patients receiving ferric carboxymaltose should be closely monitored for hypophosphatemia. Hypophosphatemia has been observed in 27% (440/1638) of patients in clinical trials, and while often described as “asymptomatic,” the frequency and severity of hypophosphatemia may be underestimated in patients receiving IV iron, specifically ferric carboxymaltose.

**Ferric derisomaltose (Monoferric)**

Ferric derisomaltose is the most recent IV iron product available, receiving FDA approval in 2020 for adult patients with IDA who have intolerance or unsatisfactory response to oral iron or who have non-hemodialysis dependent CKD. This IV iron option also provides convenience to patients as it is offered as a single dose administered as 1000-mg (for patients weighing 50 kg or more) IV infusion over at least 20 minutes. Each milliliter of ferric derisomaltose contains 100 mg of elemental iron (the highest amount of elemental iron/mL to date). Ferric derisomaltose has not been evaluated prospectively in patients with cancer but it has been shown to be noninferior to iron sucrose in its ability to increase Hgb levels in multiple randomized phase 3 trials in patients with IDA. In the PHOSPHARE trials, the safety of ferric derisomaltose was compared with ferric carboxymaltose and it was determined that ferric derisomaltose demonstrated a significantly lower incidence of hypophosphatemia compared with ferric carboxymaltose (trial A: 7.9% vs 75%; trial B: 8.1% vs 73.7%). A test dose or premedication is not required for ferric derisomaltose unless desired by the prescribing physician based on patient risk for reaction. The most common AEs associated with ferric derisomaltose are hypophosphatemia (3.5%), nausea (1.2%), and rash (1%).

With multiple IV iron products available, it can be challenging to determine the most appropriate option for patients. IV iron products are equally effective in treating iron deficiency and all currently available IV iron formulations have a similar iron core but vary in terms of physicochemical and pharmacokinetic properties. A recent meta-analysis also evaluated the safety and risk of hypersensitivity reactions in more than 5000 patients, comparing iron dextran-containing products (LMW iron dextran, ferumoxytol, and ferric derisomaltose) versus non-iron dextran products (ferric carboxymaltose and iron sucrose). The meta-analysis results revealed no meaningful clinical differences in risk of reactions, hypersensitivity or anaphylactic, among the various iron products. Another meta-analysis published in 2015 showed that anaphylactic-type reactions with IV iron products is extremely rare (<0.1%), but the estimated cumulative risk when receiving a total iron dose of 1000 mg administered within a 12-week period is highest with LMW iron dextran (82 per 100,000 patients) and is the lowest for iron sucrose (21 per 100,000 patients). The newer IV iron formulations, ferumoxytol, ferric carboxymaltose, and ferric derisomaltose, do not readily dissociate under physiological conditions and are more stable allowing for higher, less frequent doses to be given. Iron sucrose and sodium ferric gluconate are less stable complexes and must be administered at lower doses or more slowly to avoid overwhelming the binding capacity of transferrin. Factors that should be taken into consideration for product selection include:

- Infusion time
- Length of course and number of doses
- Premedication requirement
- Risk of AEs such as hypersensitivity reaction or allergic reaction (anaphylaxis)
- Cost of product/contracts and formulary preferences

**IV Iron versus Oral Iron**

Unfortunately, in patients with cancer, oral iron use is unlikely to be of any benefit due to chronic inflammation and release of hepcidin resulting in poor absorption. Despite this, oral iron is often a first choice for iron supplementation in patients with cancer with iron deficiency due to insurance mandates, except in patients with profound absolute IDA. Patients with cancer who receive oral iron may be exposed to needless AEs and loss of time due to inef-
ective treatment and will often need to be transitioned to IV iron supplementation. Due to the chronic inflammation in patients with cancer, oral supplementation with iron should be considered inappropriate as it is less effective.24 IV iron can overcome the absorptive inflammatory blockade of iron common in patients with cancer and is the preferred treatment of choice for IDA in patients with cancer.28 Several studies have evaluated IV iron versus oral iron administration for chemotherapy-induced anemia in combination with ESAs.71,72 These trials demonstrate that IV iron supplementation increases Hgb response to ESAs as well as decreases the number of transfusions compared with oral iron supplementation. The meta-analysis by Mhaskar and colleagues confirmed superior efficacy of IV iron combined with ESAs compared with oral iron supplementation when evaluating hematopoietic response, need for RBC transfusion, and overall improvement in Hgb.73 IV iron supplementation should be recommended and considered in patients who do not have a response or cannot tolerate oral iron supplementation. NCCN guidelines state that IV iron has superior efficacy and should be considered for supplementation, especially when used in combination with ESAs.74 According to recent updates to European Society of Medical Oncology (ESMO) guidelines published in 2018, IV iron is recommended for patients receiving ongoing chemotherapy who present with anemia (Hgb ≤11 g/dL or Hgb decrease ≥2 g/dL from baseline level ≤12 g/dL) and absolute iron deficiency is present (ferritin <100 ng/dL).75 Patients with cancer who have functional IDA (TSAT <20% and serum ferritin >100 ng/dL) may qualify for monotherapy IV iron therapy.76 ESMO guidelines also state that IV iron treatment should be limited to patients with cancer who are on active chemotherapy treatment. In patients receiving cardiotoxic chemotherapy, IV iron should either be given before or after (not on the same day) administration of chemotherapy or wait until the end of a treatment cycle.77 There have been conflicting data in the literature regarding concern for IV iron potentially promoting inflammation and bacterial growth, leading to infection or worsening infection.24 A recent safety meta-analysis of IV iron products (including ferric carboxymaltose, ferric gluconate, ferumoxytol, iron dextran, iron sucrose, and iron isomaltoside) evaluated 103 trials and more than 10,000 patients determined that IV iron products are not associated with an increased risk of infection or serious AEs.73 NCCN guidelines still recommend against IV iron supplementation for patients with an active infection.24

**STAR**

*In what setting are ESAs appropriate to be used in patients with cancer who develop anemia?*

**ESAs**

ESAs, such as epoetin alfa (and biosimilars) and darbepoetin, have been used in patients with anemia for CKD since 1989.24 First approval in patients with cancer was achieved in 1993.75 The goal of therapy with ESA usage in patients with anemia is to improve symptoms through increase in Hgb and to avoid or reduce blood transfusions.24,41 It is important to note that these agents are indicated in patients with cancer only for those with chemotherapy-induced anemia and who are still on active treatment.41,74,76 ESAs are not appropriate for use in CRA that is not caused by treatment. There is considerable debate surrounding ESA use in patients with cancer due to the potential for decreased survival. Multiple meta-analyses and Cochrane reviews have been conducted with differing results.77,78

In 2010, a meta-analysis evaluating 60 clinical trials and more than 15,000 patients with cancer was published showing that ESA use in patients with cancer is not likely to be linked to increased mortality with an overall odds ratio (OR) of 1.06 (95% CI, 0.97-1.15).77 The clinical trials evaluated in this meta-analysis compared epoetin or darbepoetin versus placebo or standard of care. The patient population included patients with both CRA and treatment (chemotherapy)-related anemia as well as both solid and hematologic malignancies and Hgb levels less than and greater than 12 g/dL. The second major analysis was published in 2012 as a Cochrane review that evaluated 91 clinical trials and more than 15,000 patients.78 This review included similar patient populations with both solid and hematologic malignancies, CRA and treatment-related anemia, and patients with Hgb less than or greater than 12 g/dL included. Treatment arms were either epoetin or darbepoetin versus placebo or standard of care. Results demonstrated a significant increase in mortality in patients who received ESAs with an overall hazard ratio of 1.17 (95% CI, 1.06-1.29; P = .0022). The mortality risk was specifically seen in the ESA population when Hgb was greater than 12 g/dL with a hazard ratio of 1.37 (95% CI, 1.12-1.68; P = .0026) increase in risk of death. ESA agents have a general BBW in their product labeling for increased risk of myocardial infarction, stroke, venous thromboembolism (VTE), and vascular access thrombosis.74,76

This increased risk of thromboembolism with ESAs is seen regardless of Hgb level and when compared with placebo or standard of care, the relative risk (RR) is increased by 57% in patients receiving ESAs (RR, 1.57; 95% CI, 1.34-1.74).41,79 A meta-analysis confirmed this increased risk of VTE showing among 44 studies involving ESAs a significant increase in risk of VTEs in patients receiving ESAs (OR, 1.48; 95% CI, 1.28-1.72).77 Due to the potential risk of increased mortality in patients with cancer receiving ESAs, guidelines provide strict recom-
Mentions on their use. Guidelines from American Society of Clinical Oncology (ASCO) and American Society of Hematology (ASH) state to initiate ESAs when Hgb is less than 10 g/dL and there is no target Hgb recommended. The goal of treatment is focused on reducing blood transfusion requirements and patient condition and quality of life. NCCN, ESMO, and ASCO/ASH guidelines all state that it is appropriate to consider ESA agents in patients (1) with CKD, (2) patients receiving palliative treatments with myelosuppressive therapy, or (3) patients who refuse transfusions. Guidelines state that ESA agents should be avoided in patients who are (1) not receiving active therapy, (2) patients receiving non-myelosuppressive therapies, or (3) patients receiving treatment for curative intent (eg, early-stage breast cancer, Hodgkin/non-Hodgkin lymphoma, early-stage lung cancer). Recent labeling updates for ESAs state they are “not indicated for patients with cancer receiving myelosuppressive chemotherapy in whom the anemia can be managed by transfusion.” Considering the limitations of ESAs in patients with cancer, IV iron therapy likely can be offered as treatment to a larger population of patients due to ESA restrictions on their use.

There is clinical consideration to support the use of IV iron therapy with concurrent ESA use in patients with cancer and IDA (specifically absolute IDA). According to a study published in 2004, the addition of IV iron in conjunction with ESAs showed significant improvement in hematopoietic responses (Hgb increases) compared with oral iron or no iron supplementation (68% vs 36% vs 25%, respectively; P <0.01). LMW iron dextran was the IV iron product used in the study and patients who received IV iron therapy along with ESAs reported increased energy, activity, and overall improvement in quality of life from baseline. A Cochrane systematic review was published in 2016 that evaluated 8 studies and more than 2000 patients comparing ESA plus iron supplementation versus ESA use alone. The review findings show that the addition of IV iron to ESAs improves hematopoietic response (RR, 1.17; 95% CI, 1.09-1.26), reduces need for RBC transfusions (RR, 0.74; 95% CI, 0.60-0.92), increases Hgb levels (mean difference, 0.48; 95% CI, 0.10-0.86), and is well tolerated. The subgroup analysis evaluating patients with chemotherapy-induced anemia in patients with cancer suggest that IV iron supplementation is superior to oral iron supplementation.

Supportive care options for patients with severe anemia include RBC transfusions. RBC transfusions offer patients rapid improvement in symptoms through immediate increase of Hgb and Hct levels. Disadvantages of RBC transfusions include transfusion-related reactions, iron overload, potential for pathogen transmission (although this has significantly decreased with widespread implementation of screening), and alloimmunization. Alloimmunization is a specific immune response to foreign antigens that can occur in patients who require multiple or chronic transfusions. RBC transfusions in patients with cancer have also been linked to increased risk of thrombosis, cancer recurrence, and decreased survival. These negative outcomes in patients with cancer appear to be most important in GI, head and neck, and urological cancers and is less pronounced in breast, gynecological, and prostate cancers. ESMO guidelines recommend RBC in patients with cancer whose Hgb is lower than 7 to 8 g/dL and/or severe anemia-related symptoms and the need for immediate Hgb and symptom improvement.

NCCN guidelines differ in their recommendations as the guidelines focus on risk assessment as opposed to Hgb threshold levels. Patients who are symptomatic can be transfused per American Association of Blood Bank (AABB) standards. Transfusion can also be considered in patients who are asymptomatic but who are at high risk due to comorbidities (eg, patients with progressive decline in Hgb and undergoing intensive treatment, cardiac disease, chronic pulmonary disease, or cerebral vascular disease) per NCCN guidelines. AABB 2016 recommendations for transfusion include: (1) using an Hgb level of 7 g/dL as threshold for hospitalized adult patients who are hemodynamically stable, (2) using an Hgb level of 8 g/dL as a threshold for patients undergoing orthopedic or cardiac surgery, or those with preexisting cardiovascular disease, and (3) using RBC units selected at any point within their licensed dating period rather than limiting patients to transfusion of only fresh RBC units. However, there was a lack of evidence to provide specific recommendations for patients with cancer.

**STAR**

List the multiple ways pharmacists improve patient outcomes in the setting of IDA and cancer.

Pharmacists’ Impact and Role in IDA Management in Patients With Cancer

Pharmacists, including those with specialized training, such as postgraduate residencies, board certification, and specialty-focused work experience provide an array of services and skills to care teams and patients with cancer. Pharmacists across the health system have significant roles in educating patients, evaluating treatment plans and regimens for appropriateness, monitoring patient response and toleration, and providing communication and recommendations to providers to help optimize treatment strategies. Oncology pharmacy is a highly specialized area where pharmacists trained in oncology have the knowledge and skills to assist with managing patients with cancer and act as medication experts.
Multiple issues arise when managing anemia, specifically in the oncology population, including clinical, operational, and economic considerations. In their role, pharmacists are already a strong, integral part of the care for patients with cancer, giving pharmacists the opportunity to establish pharmacist-managed anemia clinics or use stakeholder power to increase involvement in the management of CRA, specifically IDA and the use of iron products and ESAs.

Close involvement of pharmacists in the management of patients with CRA can help identify those patients who may benefit from different treatment strategies, including iron supplementation, ESA use, and transfusions through evaluation based on clinical characteristics and laboratory values. With the strong knowledge of pharmacology, appropriate and optimal dosing strategies, and treatment regimens, pharmacists offer the best opportunity to optimize patient care in terms of iron deficiency in patients with cancer and anemia in patients with cancer overall. After implementation and treatment decisions, monitoring and follow-up are key to patient success.

Pharmacists offer unique approaches to monitoring and follow-up due to their ability to evaluate risk factors, recommend adjustments and preventive approaches, and closely monitor and follow up with patients regularly. A pharmacist-managed ESA anemia clinic in patients with anemia demonstrated strong justification for pharmacist-managed clinics by showing improvements in adherence to ESAs and ESA criteria, improvement in patient Hgb levels after 1 month \((P = .015)\), and significant cost savings. Another publication in 2008 focused on the oncology population and demonstrated benefits of establishing pharmacist-managed anemia clinics for patients with cancer. In addition to the clinical and financial justifications for the clinic, allowing pharmacists to manage aspects of supportive care such as anemia for these patients, physicians and providers can focus more time on diagnosis and optimal treatments for cancer. The key steps to establishing pharmacist-managed anemia clinics include:

- Creation of collaborative practice agreement
- Development of treatment algorithm
- Building of protocol templates
- Patient Counseling Video Vignettes

While the profession of pharmacy has evolved significantly over the past decade, especially in the oncology world, including anemia, the principles and education remain the same and ultimately only support the need for pharmacist-managed clinics even more so due to the increase in complexing of oncology care. Pharmacists continue to be easily accessible to patients and can adapt to needs of patients and the health care system. Office visits and telephone encounters were likely the most common interactions clinical pharmacists had with patients. Now, in the setting of the COVID-19 pandemic, the implementation and promotion of tele-health visits has dramatically increased, allowing for even better access to pharmacists and unique opportunities for clinic workflow. Through proper education, counseling, and follow-up, pharmacists can develop strong working relationships with patients, provide active coaching, discuss risks and benefits of different treatment options, review additional diet and lifestyle changes, and involve patients in their treatment decisions, allowing for improved success, better adherence, and excellent patient satisfaction. Evaluating the impact of IDA on patients with cancer and their quality of life, disease progression, and ultimately their survival, optimization of care and treatment regimens is critical. Pharmacists are in the best role to improve tolerability, adherence, efficacy, and positive impact on prognosis through providing services to patients and clinics and providing physicians and health care team members with recommendations on best evidence-based treatment strategies.

**Conclusion**

CRA and IDA are extremely complex and dynamic supportive care issues facing patients with cancer. Iron deficiency in patients with cancer is most often mediated by chronic inflammation and increased hepcidin release, but causes are multifactorial. Based on guidelines available (ESMO and NCCN), IV iron is recommended over oral iron supplementation for patients with cancer who develop IDA. IV iron supplementation can be used as monotherapy or in conjunction with ESAs, especially in patient absolute IDA. A large percentage of patients with cancer are impacted negatively by IDA. Pharmacists are crucial to the overall improvement of patient’s treatment course, including improved adherence, satisfaction, and outcomes. Development of pharmacist-led clinics will continue to improve patient care and streamline health care services for patients and health care systems.
REFERENCES


INSTRUCTIONS FOR EARNING CREDIT

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1. Which monitoring parameter listed below is important to evaluate and follow during treatment of iron deficiency anemia (IDA) in patients with cancer who are receiving ferric carboxymaltose?
   A. Renal function
   B. Hepatic function
   C. Calcium levels
   D. Phosphorus levels

2. Which type of cancer is associated with the highest level of iron deficiency rates?
   A. Lung cancer
   B. Multiple myeloma
   C. Pancreatic cancer
   D. Acute myeloblastic leukemia

3. Which of the following is a contributing factor to the development of IDA in patients with cancer?
   A. Inflammation and cytokine release
   B. Increased erythropoietin release
   C. Increased folic acid dietary intake
   D. Reduced hepcidin production by the liver

4. Which of the following intravenous (IV) iron products can be administered in a single treatment dose and does not require a test dose, making it a more convenient option for patients who may have accessibility concerns?
   A. Ferric gluconate
   B. Iron sucrose
   C. Ferric carboxymaltose
   D. Low molecular weight iron dextran

5. A 67-year-old man with stage IV non–small cell lung cancer receiving chemotherapy is here today for follow-up and labs as the patient has been feeling extra tired the past few weeks. The following labs are reported in clinic today related to complete blood count and iron panel:
   Hemoglobin (Hgb): 10.5 g/dL  
   Hematocrit (Hct): 31.3%  
   Iron: 40 mcg/dL  
   TIBC: 270 mcg/dL  
   TSAT: 15%  
   Serum ferritin: 150 ng/mL

   Based on the lab values for this patient, how would you classify his anemia?
   A. Absolute IDA
   B. Functional IDA
   C. No iron deficiency present; patient has chemotherapy-related anemia
   D. Moderate IDA

6. A 62-year-old woman with stage 3 colon cancer is initiated on FOLFOX chemotherapy with the goal of cure. After 2 cycles of therapy the following labs are as follows:
   Hgb: 9.2 g/dL  
   Hct: 27%  
   Platelets: 350,000/μL  
   Mean corpuscular volume (MCV): 72 fL  
   Serum ferritin: 15 ng/mL  
   TSAT: 10%

   Based on her baseline anemia and iron stores present on labs today, which of the following is the best option for this patient for treatment?
   A. Oral ferrous fumarate 325 mg by mouth twice daily
   B. Darbepoetin alfa 300 μg subcutaneously once every 3 weeks
   C. Withhold chemotherapy based on patient’s labs today
   D. Ferric derisomaltose 1000 mg IV x 1 dose
POSTTEST QUESTIONS (continued)

7. A 74-year-old woman with stage 4 metastatic head and neck cancer is receiving platinum-based chemotherapy. The patient reports increased fatigue and inability to focus while at home. The following labs are reported while the patient is in clinic today for follow-up:
   Hgb: 9.7 g/dL   Hct: 26%   Platelets: 280,000/μL
   MCV: 93 fL
   Serum ferritin: 200 ng/mL
   TSAT: 35%

   Based on her baseline anemia and iron stores present on labs today, which of the following is the best option for this patient?
   A. Ferric carboxymaltose 750 mg IV x 2 doses
   B. Oral ferrous succinate 325 mg by mouth once daily
   C. Darbepoetin 300 μg subcutaneously once every 3 weeks
   D. Iron sucrose 500 mg IV x 2 doses

8. Which of the following IV iron products requires a test dose based on National Comprehensive Cancer Network guideline recommendations?
   A. Iron sucrose
   B. Low molecular weight iron dextran
   C. Ferumoxytol
   D. Ferric carboxymaltose

9. Based on the pharmacist-managed anemia clinic discussed in the article by Clapp et al, which of the following best describes the impact pharmacists have on patient care as it relates to anemia?
   A. Significant cost savings
   B. Reduction in patient Hgb levels
   C. Improved overall survival
   D. Reduction in adverse effects

10. Which of the following is a key initial step needed in establishing a pharmacist-managed clinic for patients with cancer-related anemia?
    A. Recruitment of donors for financial support
    B. Build a new pharmacy clinic facility for better patient services
    C. Creation of collaborative practice agreement
    D. Hiring clinical coordinator and pharmacists to manage clinic
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