HOPA NEWS

Pharmacists Optimizing Cancer Care

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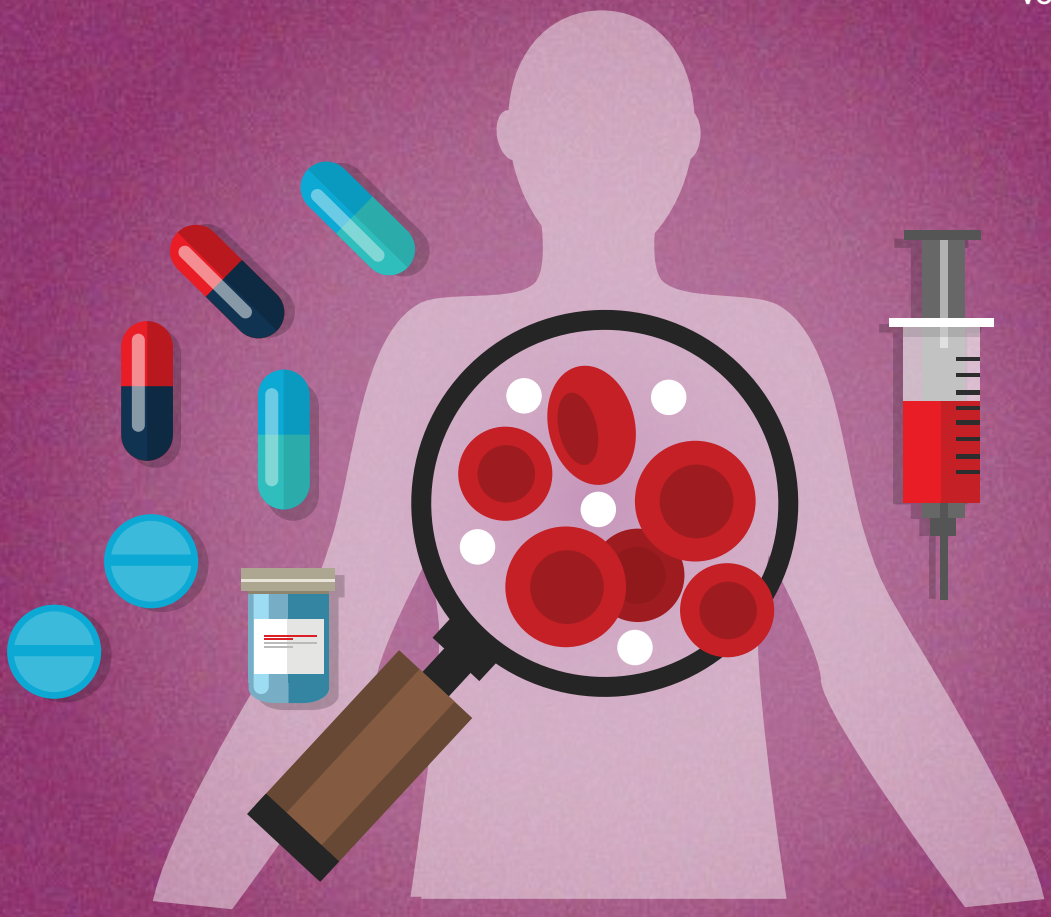

Updates on the Treatment of Acute Myeloid Leukemia

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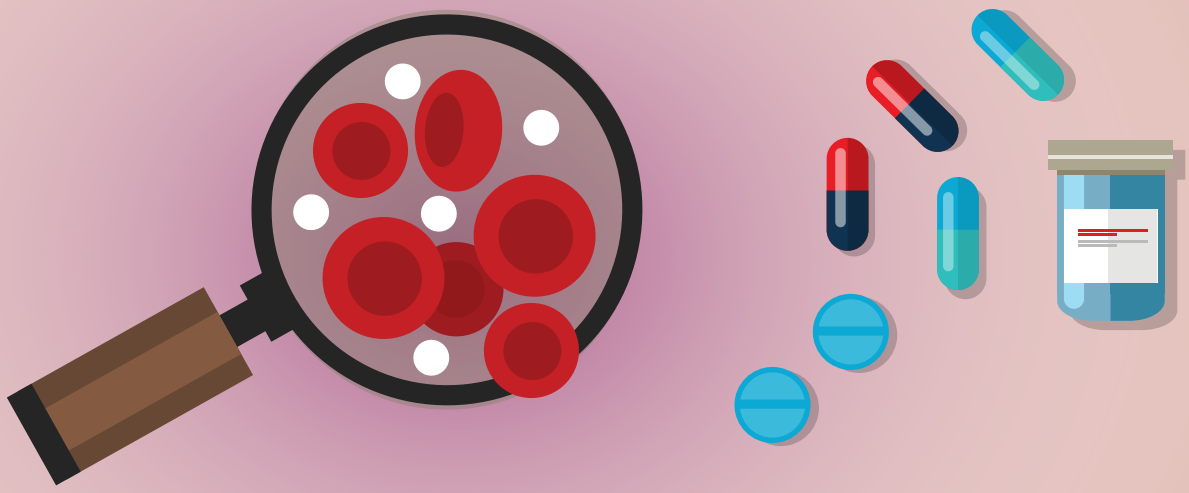

Updates on the Treatment of Acute Myeloid Leukemia

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Acute myeloid leukemia (AML) is a hematologic malignancy that impairs normal hematopoiesis and leads to anemia, neutropenia, and thrombocytopenia.[1] This disease is expected to make up only 1.1% of all new cancer cases in 2018, yet it will account for 1.8% of all cancer deaths. Five-year overall survival (OS) rates from 2008 to 2014 were low, at only 27.4%.[2]

Despite the poor outcomes associated with AML, an increased understanding of the disease, and significant advances in treating other hematologic malignancies, standard treatment of AML had remained relatively unchanged for decades.[3] Since 2017, however, the U.S. Food and Drug Administration (FDA) has approved five new drugs for the treatment of AML, potentially changing the treatment landscape for a disease that has proven difficult to treat.

Gemtuzumab Ozogamicin

Gemtuzumab ozogamicin (GO, Mylotarg) is a CD33-directed antibody drug conjugate linked to a cytotoxic antibiotic, calicheamicin. CD33 expression can be variable but is present on 40% or more leukemic blasts in three-fourths of patients.[4] GO was originally approved in May 2000 for relapsed CD33-positive AML in older patients but was subsequently removed from the market because of lack of efficacy and increased toxicity, including early death. Several studies investigating fractionated GO dosing established better safety and efficacy, resulting in its reapproval in September 2017. GO is now indicated for treating newly diagnosed CD33-positive AML either as a single agent or in combination with 7+3 and in the relapsed or refractory setting as a single agent.[5]

ALFA-0701 was a phase 3 study that compared 7+3 (daunorubicin 60 mg/m^2 on days 1–3 and cytarabine 200 mg/m^2 on days 1–7) to 7+3 with GO (3 mg/m^2 [maximum dose 5 mg] on days 1, 4, and 7) in patients 50–70 years of age with previously untreated AML. A second induction could be given with daunorubicin 60 mg/m^2 on days 1–2 and cytarabine 1,000 mg/m^2 every 12 hours on days 1–3. Consolidation courses consisted of daunorubicin 60 mg/m^2 for 1 day (first course) or 2 days (second course), with cytarabine 1,000 mg/m^2 every 12 hours on days 1–4 with or without GO 3 mg/m^2 (maximum dose 5 mg) on day 1. The primary end point of event-free survival (EFS) was significantly longer in the GO arm, with a median EFS of 15.6 versus 9.7 months and a 2-year EFS of 40.8% versus 17.1% (p = .0003). The secondary end point of OS was also significantly prolonged in the GO arm, with a median OS of 34 months versus 19.2 months and a 2-year OS of 53.2% versus 41.9% (p = .0368). In a subgroup analysis, patients with favorable or intermediate-risk cytogenetics seemed to gain the most benefit from the addition of GO. Patients in the GO arm experienced more prolonged cytopenias, required more platelet transfusions, and had more liver toxicity (13% vs. 6%, p = .10). Three patients developed veno-occlusive disease (VOD), resulting in two deaths.[6]

The AML-19 trial compared GO (6 mg/m^2 on day 1 followed by 3 mg/m^2 on day 8, then 2 mg/m^2 on day 1 every 4 weeks for up to 8 cycles) to best supportive care (BSC) as front-line treatment in patients older than 60 years with AML who were unable to undergo intensive induction chemotherapy. The primary end point of OS was significantly prolonged in the GO arm, with a median OS of 4.9 months versus 3.6 months (p = .005). The benefit was greater in patients with more than 80% CD33-positive blasts. Grade 3 or higher liver toxicity was slightly higher in the GO arm (7.2% vs. 6.1%), but no cases of VOD were reported.[7]

The Mylofrance-1 trial studied single-agent GO (3 mg/m^2 on days 1, 4, and 7 for 1 course) in 57 patients with AML in first relapse. Overall response rate (ORR) was 33.3%, with 26% achieving complete response (CR) and 7% achieving complete response with incomplete platelet recovery (CRp). Median OS was 8.4

months, with a 1-year relapse rate of 57.4% and median relapse-free survival of 11 months. No episodes of VOD were reported, even in the three patients receiving an allogeneic stem cell transplant after GO treatment.[8]

Major considerations for pharmacists include monitoring for liver toxicity, avoiding concomitant hepatotoxic medications, and recommending appropriate dosing schedule based on indication.[5]

Midostaurin

Midostaurin (Rydapt) is an oral tyrosine kinase inhibitor approved by the FDA in 2017 for the treatment of FLT3-positive AML. Although it is used for its effects on FLT3, it can also affect KIT receptor, platelet-derived growth factor receptor (PDGFR) alpha/beta, vascular endothelial growth factor receptor 2 (VEGFR2), and other PDGFRs.[9] In a study evaluating the mutational status of patients with cytogenetically normal AML, FLT3-ITD mutations were found in 31% and FLT-TKD in 11%. Although FLT3-ITD mutation is associated with poor outcomes, prognostic implications of a FLT3-TKD mutation are not as clear.[10]

The RATIFY trial (CALGB 10603) randomized 717 patients with FLT3 mutations to receive standard chemotherapy plus either midostaurin or placebo. Patients with both ITD (77.4%) and TKD (22.6%) mutations were included. Patients with FLT3-ITD mutations were also stratified based on high (29.8%) or low (47.6%) ratio of mutant to wild-type alleles. Midostaurin was given at a dose of 50 mg twice daily on days 8–21 of induction (7+3 with daunorubicin 60 mg/m^2 on days 1–3 and cytarabine 200 mg/m^2 on days 1–7) and consolidation (high-dose cytarabine 3,000 mg/m^2 every 12 hours on days 1, 3, and 5) chemotherapy. The primary outcome of median OS was significantly longer in the midostaurin group: 74.7 months compared to 25.6 months in the placebo group (p = .009). Adverse events were similar between groups, with more grade 3 or greater rash (14% vs. 8%) and anemia (93% vs. 88%) in the midostaurin group and more grade 3 or greater nausea (6% vs. 10%) in the placebo group.[11]

Major considerations for pharmacists include management of drug interactions (e.g., with CYP3A4 inhibitors and inducers), recommendations for monitoring (e.g., with electrocardiograms for QT prolongation and for signs and symptoms of rare but serious pulmonary toxicity (interstitial lung disease and pneumonitis), and patient counseling (e.g., regarding the drug's moderate emetogenic potential and the need to take it with food).[10]

Liposomal Daunorubicin/Cytarabine

Liposomal daunorubicin/cytarabine (Vyxeos) received FDA approval in 2017 for the treatment of therapy-related AML (t-AML) or AML with myelodysplasia-related changes (AML-MRC).[12] This agent, also known as CPX-351, is a liposomal combination of cytarabine and daunorubicin in a fixed 5:1 molar ratio, which was shown to be optimally synergistic in vitro.[13] This formulation was also compared to standard, or "free," chemotherapy in animal models, where it was shown to increase drug exposure in the bone marrow and preferentially affect leukemia cells over normal bone marrow cells.[14]

On the basis of this preclinical data and a subsequent randomized phase 2 trial that showed higher remission rates and improved OS and EFS with CPX-351 compared to 7+3 (daunorubicin 60 mg/m^2 on days 1–3 and cytarabine 100 mg/m^2 on days 1–7) in patients with secondary AML, a phase 3 trial was initiated.[15] This study compared CPX-351 to traditional 7+3 chemotherapy in 309 patients 60–75 years of age with high-risk or secondary AML. CPX-351 was given at the FDA-approved dose of daunorubicin 44 mg/m^2 (cytarabine 100 mg/m^2) on days 1, 3, and 5 for induction and at the same doses on days 1 and 3 only for a second induction if necessary. The dose used for consolidation was 29 mg/m^2 of daunorubicin (65 mg/m^2 cytarabine) on days 1 and 3. This was compared to standard 7+3 therapy. A second induction could be given if needed in the traditional treatment group with 5+2 (cytarabine 100 mg/m^2 over 5 days and daunorubicin 60 mg/m^2 on days 1 and 2). The primary outcome of median OS was significantly longer in the CPX-351 group at 9.56 months compared to 5.95 months with 7+3 therapy (p = .003). The benefit of CPX-351 was maintained across all age groups and subtypes of AML. Adverse events were similar between groups; however, median times to neutrophil (35 vs. 29 days) and platelet (36.5 vs. 29 days) recovery were longer with CPX-351 compared to 7+3. This finding did not correspond with an increase in infection-related events but may have been related to an increase in bleeding events (all grades: 74.5% with CPX-351 vs. 59.6% with 7+3; grades 3–5: 11.8% vs. 8.6%).[16]

Major considerations for pharmacists include look-alike and sound-alike precautions (black-box warning for confusion with other chemotherapy), oversight of complicated admixture, and recommendations for monitoring (e.g., bleeding, cumulative anthracycline toxicity).[12]

Enasidenib and Ivosidenib

Isocitrate dehydrogenase (IDH) enzymes, including IDH1 and IDH2, are responsible for the conversion of isocitrate to alpha-ketoglutarate as part of the citric acid cycle within the cells of the body, including myeloid cells. Mutant IDH reduces alpha-ketoglutarate to beta-hydroxyglutarate. This results in gene hypermethylation, which halts myeloid differentiation and allows immature myeloid blasts to proliferate. By blocking mutant IDH, enasidenib and ivosidenib restore myeloid differentiation.[17]

Enasidenib (Idhifa) was approved in 2017 for the treatment of relapsed and refractory AML with an IDH2 mutation, which is present in about 10%–15% of AML cases.[18] In a phase 1/2 study, enasidenib was investigated in adult patients with relapsed or refractory IDH2-mutated AML treated with enasidenib 100 mg by mouth (PO) daily (N = 109). The most common grade 3–4 treatment-related adverse events included hyperbilirubinemia (8%), IDH differentiation syndrome (IDH-DS) (7%), anemia (7%), and thrombocytopenia (5%). IDH-DS had a median time to onset of 48 days with a range of 10–340 days. Diagnosis of IDH-DS is often made by excluding other causes and should be suspected in patients with new or worsening respiratory symptoms, infiltrates or opacities on chest imaging, pleural or pericardial effusions, peripheral edema, rapid weight gain, or increased serum

creatinine.[19] Management includes systemic corticosteroids and dose interruption if symptoms persist beyond 48 hours after initiation of steroid treatment.[20] Ten patients in the study required dose interruption for IDH-DS without requiring permanent discontinuation of the drug. Hyperbilirubinemia was predominantly indirect, not associated with intrinsic liver toxicity, and was thought to be due to altered bilirubin metabolism by UGT1A1 inhibition. Adverse events generally decreased over time as treatment continued. ORR was 38.5% (median duration 5.6 months) with a CR or CR with incomplete count recovery (CRi) rate of 26.6% (median duration 8.8 months). Median time to first response was 1.9 months, with a median time to CR of 3.7 months. Ten percent of patients went on to receive allogeneic stem cell transplant. Median OS was 9.3 months, with an estimated 1-year survival rate of 39%. For patients with CR or partial response (PR), median survival was 19.7 months or 14.4 months, respectively. The phase 3 IDHENTIFY study comparing enasidenib to conventional care in late-stage IDH2-mutant AML is ongoing.[19]

Ivosidenib (Tibsovo) was approved in 2018 for the treatment of relapsed or refractory AML with a susceptible IDH1 mutation, an abnormality that occurs in 6%–10% of patients with AML. Approval was based on a phase 1 dose escalation and expansion study of ivosidenib 500 mg PO daily in 179 patients with relapsed or refractory AML. ORR was 41.6% (median duration 6.5 months) with a CR rate of 21.6% (median duration 9.3 months) and CR or CRi rate of 30.4% (median duration 8.2 months). The median time to response varied according to the type of response but ranged from 1.9 to 2.8 months. The most common grade 3–4 treatment-related adverse events in patients with relapsed or refractory AML treated with ivosidenib 500 mg daily were QT interval prolongation (7.8%), IDH-DS (3.9%), anemia (2.2%), thrombocytopenia (1.7%), and leukocytosis (1.7%). IDH-DS occurred in 10.6% overall in the relapsed or refractory AML population, with 5% of these cases being grade 3 or higher. Median time to onset of IDH-DS was 29 days (range 5–59 days). Treatment included glucocorticoids, diuretics, and hydroxyurea (in cases of concomitant leukocytosis), but no patients permanently discontinued ivosidenib because of IDH-DS.[21]

Major considerations for pharmacists include the need to educate patients on IDH-DS signs and symptoms (including possible late onset), QTc monitoring with ivosidenib, and the need for adequate duration of treatment prior to assessing disease status.[18-21]

Conclusion

The FDA approvals in treatment of AML since 2017 are changing the treatment paradigm for this disease in both the front-line and relapsed and refractory settings. Changes are likely to continue as new and more selective FLT3 inhibitors are being investigated, IDH inhibitors are being studied in the up-front setting in combination with standard chemotherapy, the role of venetoclax is being elucidated, and other new agents are being explored. As knowledge of molecular mutations continues to grow, these targets may be exploited to provide new therapies and improve outcomes in a disease state with historic 5-year OS rates less than 30%.●●

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Connecting the Dots: Conducting a National Pediatric Oncology Journal Club

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Currently, four American Society of Health-System Pharmacists–accredited postgraduate year-2 oncology pharmacy residencies in pediatric oncology are available. Six residency positions are offered annually among the programs at Norton Children's Hospital, St. Jude Children's Research Hospital, Memorial Sloan Kettering Cancer Center, and Seattle Children's Hospital. Despite being linked by our work in a subspecialized profession, we span the country geographically, and the distance between programs makes networking difficult. This challenge served as the impetus for developing a national pediatric oncology journal club series coordinated by the Norton Children's Hospital resident.

Our vision in developing the series was to provide a platform that encouraged networking while advancing participants' knowledge related to pediatric hematology, oncology, and stem cell transplantation. Over the course of the year, we held three sessions and covered six journal articles. Topics varied according to the presenting resident's interest and ranged from the use of sodium thiosulfate to prevent cisplatin-related ototoxicity to preparative regimens for stem cell transplant in those with neuroblastoma. After articles were reviewed by the presenting resident, an open forum followed, allowing participants to share practices and experiences from their own institution and foster learning by the preceptors, residents, and students in attendance.

Scheduling of the sessions required communication between all institutions. In order to promote face-to-face networking, we used a variety of platforms: Skype, WebEx screen sharing, and WebEx video conferencing. The communication platform proved the most challenging aspect of the sessions because we encountered some technical difficulties with each platform. Skype provided face-to-face contact, but its performance on certain computer systems was subpar, and document sharing was unavailable. WebEx screen sharing was the second platform tested, and while it allowed for all institutions to view the handouts online, it minimized face-to-face interactions. Last, we attempted to use WebEx video conferencing, and, like Skype, it was not successful for all institutions, and we experienced a great deal of auditory feedback.

"The sessions allowed for enhanced interaction among residents, preceptors, and program directors, which we hope will lead to lifelong professional and personal partnerships."

After completion of the journal club series, an eight-question survey was sent to the program directors to distribute to participants in order to identify strengths and opportunities for future years. Eight individuals completed the survey and stated that they were likely or highly likely to recommend the national journal club to a friend or colleague. All participants rated the national journal club as good, very good, or excellent and thought it had the right number of sessions per year. What individuals reported liking most about the journal club series was the opportunity for networking and idea sharing between institutions. The area identified as needing most improvement was technology optimization. Preferences for the platform varied, and suggestions of other options to explore included Zoom and conference calling.

Because of the positive feedback received, we hope to continue the sessions in future years. We hope to find solutions to the technological challenges by exploring other platforms. Overall, the sessions allowed for enhanced interaction among residents, preceptors, and program directors, which we hope will lead to lifelong professional and personal partnerships. ●●

Representing HOPA on HOPA Hill Day

On June 13, 2018, 29 HOPA members and our liaisons from District Policy Group, Jeremy Scott and Sarah Mills, were present on Capitol Hill to represent HOPA. Our objective was to meet with staffers for congressional members from the House and Senate to discuss who we are as an organization, explain what a hematology/oncology pharmacist is, and advocate on important legislative issues that will improve access to cancer care for our patients, specifically the Cancer Drug Parity Act of 2017 (HR 1409) and the Pharmacy and Medically Underserved Areas Enhancement Act (HR 592/S 109). In this article three HOPA members report on their experiences of HOPA Hill Day.

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When the call for applications for a travel grant to attend HOPA Hill Day came out, I wasn't sure I was going to apply. At the HOPA Annual Meeting, I frequently attend the Legislative Update session and am in awe of what our organization is doing, but I have always been a little hesitant to get involved on that level. But after reviewing the advocacy information on our website, particularly the section on ways to get involved (hoparx.org/advocacy/get-involved), I made the decision to apply.

A few weeks later I was notified that I was one of the fortunate members to receive a travel grant. Washington, DC, here I come!

When it was time to pack for HOPA Hill Day, I was both nervous and excited. We were e-mailed our schedule for our time in Washington and information to review in advance of our trip. We were provided with key talking points on HOPA, hematology/oncology pharmacists, patient anecdotes to bring up to enhance a discussion if needed, and HOPA's public policy agenda (hoparx.org/advocacy/health-policy-agenda).

The night before HOPA Hill Day, we had a preparatory meeting and dinner at the District Policy Group office with Jeremy and Sarah. They reviewed "Congress 101" and provided us with tips for our meetings. They even reviewed with us how a bill becomes a law, so it's OK if you don't remember *Schoolhouse Rock*. We also had plenty of time to network with other HOPA members and talk to those who had done this before. Their stories and affirmations of what a great experience they had calmed my anxiety, and I was confident I was prepared to meet with staffers the next morning. Before we departed, we were divided into teams of four or five members who would be working together to meet with staffers from their home states.

The following morning, Tim Tyler (Public Policy Committee Chair), Susanne Liewer (HOPA President-Elect), Taylor Monson (PGY-1 resident), and I piled into an Uber and headed to our first meeting on Capitol Hill. As we were on our way, the anxiety set in again. This meeting was with staff for a senator from my home state. We arrived at the Russell Senate Office Building and navigated our way to the meeting room. While we were waiting to meet with the staffer, Tim graciously offered to take the lead because he was the only one in our small group who had participated in HOPA Hill Day before. He provided a great example and engaged us all in the discussion. As we walked to the next meeting, I realized it wasn't so hard, and the rest of the day flew by with all of us participating in the discussions. In total we met with staff members in seven offices and were received with open ears. One staffer had even watched our YouTube video to prepare for our meeting.

I highly encourage all members to get involved when the next opportunity arises. As I reflect on the experience, my anxiety was not necessary, and the experience was actually energizing. I am looking forward to more opportunities to advocate on behalf of our organization and hematology/oncology pharmacists to improve access to care for our patients.

Taylor E. Monson, PharmD

As a student, I was actively involved in pharmacy advocacy and held several political leadership positions. I was able to interact with state and national legislators to discuss pharmacy issues and advocate for my future profession. I also earned a politics minor while in school, so this was the perfect way for me to combine two areas of interest. I wanted to continue advocating as a new pharmacist and resident, which is what drew me to applying for HOPA's Public Policy Committee. I was surprised but grateful to be selected for the committee as a young resident and excited at the prospect of sharing my experiences. When I was asked to attend HOPA Hill Day, I knew I had to say yes.

Although I had experience in talking to state officials and discussing pharmacy bills, this was my first national Hill Day visit. I was a little nervous about sharing my perspective as a new pharmacist. However, upon meeting all of the other pharmacists in attendance, my nerves were soon calmed. This was a group of



Twenty-nine HOPA members went out in small teams to visit legislators on HOPA Hill Day. Pictured in group 1 are Ashley Glode, Taylor Monson, Timothy Tyler, and Susanne Liewer; group 2, Jeremy Whalen, Brooke Bernhardt, and Susannah Koontz; group 3, Philip Schwieterman, Megan Hartranft, Kathryn Schiavo, and Sarah Hudson-DiSalle.

pharmacists with a wide array of experiences in advocacy, and they were all welcoming to a young resident in the group. I knew I was in good hands. Before sending us to the Hill, the District Policy Group staff shared some talking points on the policies we would discuss. This information was so helpful to me as a newer member of HOPA, and I took plenty of notes and reviewed the information carefully to familiarize myself with our top health issues.

I was assigned to a team with three other HOPA members, and we covered the California, Colorado, and Nebraska legislators. I felt lucky to be in a team with the Public Policy Committee chair, Tim Tyler—he was more than happy to lead our group through how to have a Hill meeting, what points to emphasize, and how to follow up with staffers. We let Tim take the lead on our first meeting, but by the time we entered our second meeting with a senator from my home state, Nebraska, I felt comfortable speaking up and talking about my role as a pharmacy resident. I was able to share how I care for my patients, the common issues and frustrations my oncology patients have relayed to me regarding their medications, and my perspective on how we could help our constituents receive better care.

The day was fast paced, and I quickly learned that some meetings take place in secluded corners of hallways. Staffers don't have a lot of time to discuss issues, so getting straight to the point is key with this group. I now feel confident in making "asks" of my legislators in order to support current bills or introduce new legislation to the legislative session. Most staffers have very limited knowledge about the role of pharmacists in health care, so it's our job as pharmacy advocates to establish ourselves as important members of the healthcare team and make our voices heard!

I am grateful for the experiences I had at the 2018 HOPA Hill Day, and I encourage all members, especially newer residents, to get involved! Although the prospect of speaking with legislators can be intimidating, the process was really simple. I look forward to my upcoming year on the Public Policy Committee, and I know that HOPA Hill Day gave me great tools for continuing to advocate in my home state.

Houry Leblebjian, PharmD BCOP

As a clinical pharmacist working with cancer patients on a daily basis, attending Hill Day seemed like an opportunity I couldn't miss. I didn't think twice about submitting my application for the travel grant HOPA was offering. It was very exciting getting the e-mail telling me that I had been chosen for this mission, but at the same time I was nervous about what the job entailed.

Weeks before the big date, I tried to read about Hill Day but didn't find much relevant information. I e-mailed Sarah Nicholson, HOPA's health policy and advocacy manager, who sent me some articles, but nothing I read could compare to the real experience I was about to have.

The night before the Hill Day, we sat in a conference room of the District Policy Group building meeting others and being trained about whom we would be meeting and what to expect. I wasn't the only one feeling nervous and excited at the same time. It was both a relief and an inspiration to see how many pharmacists go through the same challenges that I do and want to see a change. At the end of the night, I met the colleagues who would be in my group, and we were given the names of the staffers we would meet the next day.

The next morning was a beautiful day in Washington, DC, and what better way to spend it than advocating for a great cause! We arrived at our first meeting in the Russell building for a 9:30 am appointment with the legislative correspondent for a Massachusetts senator. Even though our group included two members who had been on Hill Day before, I volunteered to start the conversation because I was representing Massachusetts. She was a very pleasant person who listened and expressed her support for our cause and took notes, as did all the staffers I met that day. Some asked more questions than others, but all thought the legislative issues we discussed were important.

At the end of the day, I was tired—with 15,000 steps on my tracker—but feeling satisfied and hopeful that what we did could really make a difference.

I wouldn't have wanted to be anywhere else on June 13, 2018, than at Hill Day with a group of amazing people advocating for a great cause. I hope that HOPA, with the help of oncology pharmacists everywhere, continues these efforts to reach the hearts and minds of senators and representatives in order to make the life of our cancer patients and their caregivers better. ●●

Biosimilar Formulary Evaluation: A Pharmacist's Guide

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The growing market of biosimilars presents an increasing need for guidance and oversight regarding their role for insurers, hospital facilities, and patients. Biologic drugs or biological therapy, by definition, consists of large molecules such as enzymes or proteins derived from living organisms.[1] Because of higher manufacturing development costs and the complexities of working with these large molecules, biological drug spending continues to be a primary driver of increases in healthcare costs. Biosimilars were developed through an abbreviated approval pathway under the Biologics Price Competition and Innovation Act of 2009 as a way to help lower overall healthcare spending and improve patients' access to them. According to the U.S. Food and Drug Administration (FDA), a biosimilar must show no clinically meaningful differences in purity, safety, or efficacy from an original reference biological drug in clinical studies. To date, 12 biosimilars have been approved in the United States (**Table 1**),[2] but their adoption into the market raises questions regarding safety, interchangeability, and cost.[1] This article addresses some common concerns regarding biosimilars and provides practical guidance for implementing their use in a healthcare setting.

The first biosimilar product approved in the United States was Zarxio in 2015.[2] Prior to its approval, questions regarding the immunogenicity of biologic drugs were raised by European Union (EU) authorities because of an incidence of pure red cell aplasia (PRCA) related to use of a marketed biologic, erythropoietin.[3] This was found to be related to a changed formulation in the biological product and raised concerns about an increased risk of adverse immunogenic effects. Multiple published studies have subsequently evaluated switching between reference biologics and biosimilars and have found no reported increases in treatment-related safety events or efficacy differences. However, postmarketing pharmacovigilance of biosimilars is still recommended, along with good manufacturing practices, to ensure the quality of the products.

Table 1. FDA-Approved Biosimilars

Biosimilar	Approval Date
Nivestym (filgrastim-aafi)	July 2018
Fulphila (pegfilgrastim-jmdb)	June 2018
Retacrit (epoetin alfa-epbx)	May 2018
Ixifi (infliximab-qbtx)	December 2017
Ogivri (trastuzumab-dkst)	December 2017
Mvasi (bevacizumab-awwb)	September 2017
Cyltezo (adalimumab-adbm)	August 2017
Renflexis (infliximab-abda)	May 2017
Amjevita (adalimumab-atto)	September 2016
Erelzi (etanercept-szzs)	August 2016
Inflectra (infliximab-dyyb)	April 2016
Zarxio (filgrastim-sndz)	March 2015

Regulatory issues, such as biosimilar interchangeability or the ability of the pharmacist to substitute a reference product for an approved biosimilar without contacting the ordering prescriber, are often discussed. Unlike generic small chemical molecules, for which substitution may be allowed based on the FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* ("Orange Book"), only biosimilars with interchangeable status may be substituted without alerting the provider.[4] Currently, no biosimilars have that status. The FDA has deferred to various state laws regarding biosimilar substitution requirements. These laws may vary in their requirements regarding record keeping and processes for notifying or communicating with the physician or patient. Therefore, reviewing one's own state law regarding biosimilar substitution is advised.

The presumed lower cost for biosimilars has been a large selling point in their approval and acceptance among healthcare lawmakers and insurers.[1] However, cost saving for hospitals is often complicated by various payment models, reimbursement schemes, and regulatory uncertainties. Currently, the potential price reduction associated with biosimilars ranges from 10% to 30% and is based on projected cost-savings models from small chemical molecule markets. It is unclear whether the lower price for biosimilars will translate into actual cost savings for the patient because of specialty tiering, directed by pharmacy benefit managers, which could increase patients' coinsurance rates. Additionally, each biosimilar market is characterized by great heterogeneity because the availability of competing products can affect wholesale price. For example, in a larger market, such as granulocyte colony-stimulating factors, 14 products have been approved, including 3 biosimilar products, which will compete with one another as price and contracts are being determined. An insurer like Medicare has a great incentive to cover biosimilars because of lower prices, but actual savings for hospitals or patients may be less because of differences in inpatient versus outpatient reimbursement schemes.

Given the growing popularity of biosimilars and the unanswered questions about them, hospital facility staffs should consider taking several practical steps before making additions or substitutions to the formulary. First, a drug utilization review of the current formulary biological drugs used in the inpatient and outpatient settings should be compared with the available FDA-approved biosimilar agents to assess for potential cost savings. The main focus of the review will consist of an abridged cost minimization analysis (**Table 2**) that, assuming equal safety and efficacy, solely compares costs between the two products.[5,6] Drugs used primarily in the inpatient setting are typically reimbursed

Table 2: Abridged Cost Minimization Analysis: Example for an Inpatient

A = Wholesale acquisition cost: price per unit dose
B = Tier pricing per unit (based on utilization or market share), if applicable
C = Total units used within previous fiscal year
D = Total biosimilar estimated cost (A × C) or (B × C) if tier pricing is applicable
E = Total reference product estimated cost (A × C) or (B × C) if tier pricing is applicable
Total estimated cost difference % over reference product: [(D – E)/E] × 100

through diagnosis-related groups' bundled payments; and generally, the least costly option is preferred. In the outpatient setting, the analysis should include a breakdown of payer mixes (e.g., Medicare versus private insurers), along with special pricing considerations for 340b-eligible institutions. Note that for a 340b-eligible institution, hospital outpatient prospective payment system (OPPS) changes have been proposed by Medicare for 2019, which reduces part B reimbursement from average sales price (ASP) + 6% to ASP – 22.5%.[7] This change will exempt rural sole community hospitals, children's hospitals, prospective payment system-exempt cancer hospitals, and medications with designated pass-through status. Pass-through status is granted to innovative biologics, including biosimilars, for 2–3 years, which might incentivize early adoption of biosimilars on hospital outpatient formularies.

Additional considerations for the addition of biosimilars in outpatient settings include individual state regulations and potential reimbursement differences between payers.[2] States have different requirements for prescriber notification, patient notification, and pharmacy record retention. Workflow adjustments and early discussion with providers will be key to ensuring a smooth transition. Additionally, each hospital facility should evaluate the contract with its manufacturer or wholesaler group purchasing organization to determine eligibility for biosimilar interchanges without incurring any negative reimbursement consequences. Although Medicare has changed some of its reimbursement schemes for biosimilars in order to avoid financial incentives for higher cost medication, utilization, average sales prices, and percent reimbursed from private and government insurances should still be reviewed.

Following the addition of a biosimilar to the formulary, the efficacy and safety of biosimilar agents and their reference biologics, including signs of adverse immunogenic effects and any changes in manufacturers' product formulations, should continue to be monitored.[3,4] This safety review should include electronic alerts linking biological reference agents with their biosimilar product if patients have developed severe allergic reactions to either agent in the past.

The creation of a biosimilar policy, outlining the process for review, addition, and monitoring of biosimilar agents, will be useful in bringing healthcare providers more awareness of these agents and comfort with their use and will furthermore ensure smooth transition of their use in the outpatient setting. As more biosimilars arrive on the market, it could become cumbersome to review every product when its addition to the formulary is being considered. Therefore, it would be prudent to allow for an automatic substitution of biosimilar products with the reference product in the inpatient setting without needing the formal approval of the pharmacy and therapeutics committee. Additionally, outlining the steps based on individual state regulations for interchanging biosimilar products on the outpatient side should be well defined in the policy to maintain consistency and ensure compliance with legal requirements.

The biosimilar and biologic market is rapidly growing, and pharmacists serve as valuable resources in educating providers and patients about the safety, efficacy, and regulations pertaining to biosimilars. In addition, potential cost-saving opportunities in both inpatient and outpatient settings should be evaluated, taking into account the various regulatory requirements. Active pharmacovigilance with biosimilars should still be practiced, as with any biological product. ●●

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Daratumumab: A First-in-Class Agent with an Expanding Role in the Treatment of Multiple Myeloma

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Multiple myeloma is a plasma-cell dyscrasia that results in the overproduction of clonal malignant plasma cells.[1] These plasma cells can be detected in the bone marrow, blood, and urine, and their accumulation can lead to bone marrow and organ dysfunction in affected patients. Although the disease remains incurable, recent therapeutic advances have improved outcomes and allowed patients to live longer.

Daratumumab is a first-in-class immunoglobulin 1 kappa human monoclonal antibody that targets the CD38 antigen on the exterior of myeloma cells.[2] Daratumumab induces cancer cell death through several mechanisms, including complement-dependent cytotoxicity, antibody-dependent cell-mediated toxicity, apoptosis through Fc-mediated cross-linking, and modulation of CD38 enzyme activity.[2,3] The U.S. Food and Drug Administration (FDA) originally approved daratumumab as monotherapy for the treatment of patients with multiple myeloma (MM) who have received at least three prior therapies, including a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD) or who are double-refractory to PI and an IMiD. Daratumumab has also received additional FDA indications as combination therapy with lenalidomide or bortezomib and dexamethasone in MM patients who have received at least one prior line of therapy and with pomalidomide and dexamethasone in MM patients who have received at least two prior therapies, including lenalidomide and a PI. Most recently, it gained approval to be used in combination with bortezomib, melphalan, and prednisone in patients with newly diagnosed disease who are ineligible for transplant. The approved dosing schedule for daratumumab combination and monotherapy can be found in **Table 1**.

Table 1. Daratumumab Dosing Schedule[2]

Monotherapy and in combination with lenalidomide/dexamethasone	
Weekly	Weeks 1–8
Every other week	Weeks 9–24
Every 4 weeks	Week 25 onward until disease progression
Combination therapy with bortezomib/dexamethasone	
Weekly	Weeks 1–9
Every third week	Weeks 10–24
Every 4 weeks	Week 25 onward until disease progression

Note. Daratumumab is dosed at 16 mg/kg throughout all phases of the dosing schedule.

Clinical Trials

The initial approval of daratumumab was based on the results of the 2016 SIRIUS trial, an open-label phase 2 study that examined the use of the drug as a single agent in patients who had previously received at least three lines of therapy (including PIs and IMiDs).[4] Patients were randomly assigned to one of two dose levels (8 mg/kg or 16 mg/kg). Among the patients who received the 16 mg/kg dose (n = 108), the overall response rate (ORR) was 29.2%, with a median duration of response of 7.4 months. The median progression-free survival (PFS) was 3.7 months, and 64.8% of patients were alive at 1 year. Fatigue (40%) and anemia (33%) were the most commonly reported adverse effects.

Combination with PIs

Subsequent trials have examined the use of daratumumab in combination with other agents active in myeloma. In 2016, Palumbo and colleagues conducted a phase 3 trial (CASTOR) in which patients (N = 498) with relapsed or refractory disease were randomly assigned to receive bortezomib (1.3 mg/m^2) and dexamethasone (20 mg) either with or without daratumumab (16 mg/kg).[5] The primary end point of PFS was prolonged in the daratumumab arm compared to the control arm at the median follow-up period of 7.4 months (not reached vs. 7.2 months). The ORR was also improved in the daratumumab cohort versus the control group (82.9% vs. 63.2%, $p < .001$). The most prevalent grade 3–4 adverse effects in the daratumumab and control groups were hematologic (thrombocytopenia: 45.3% vs. 32.9%; anemia: 14.4% vs. 16%; neutropenia: 12.8% vs. 4.2%), and rates of grade 3–4 infection were similar between the two cohorts (21.4% vs. 19%).

In a more recent 2018 phase 3 study by Mateos and colleagues, transplant-ineligible treatment-naive patients (N = 706) received bortezomib, melphalan, and prednisone with or without daratumumab.[6] At the interim analysis cutoff (18 months), both the PFS rate and ORR were improved in the daratumumab group versus the control group (PFS at 18 months: 71.6% vs. 50.2%; ORR: 90.9% vs. 73.9%). Grade 3–4 adverse effects in the daratumumab arm were again mainly hematologic (neutropenia: 39.9%; thrombocytopenia: 34.3%; anemia: 15.9%) but also included diarrhea (2.6%) and peripheral sensory neuropathy (1.4%). The rate of grade 3–4 infections in the daratumumab and control groups were 23.1% and 14.1%, respectively.

Combination with IMiDs

In the 2016 phase 3 POLLUX trial, patients (N = 569) who had received at least one previous line of therapy were randomly assigned to receive lenalidomide and dexamethasone with or without daratumumab.[7] Patients in the daratumumab group experienced a significantly higher overall response rate compared to the control group (92.9% vs. 76.4%; $p < .001$) and improved PFS at 12 months (83.2% vs. 60.15%). Common grade 3–4 adverse effects in the daratumumab and control groups were again hematologic (neutropenia: 51.9% vs. 37%; thrombocytopenia: 12.7% vs. 13.5%;

anemia: 12.4% vs. 19.6%), with grade 3–4 infection marginally increased in the daratumumab group (28.3% vs. 22.8%).

Daratumumab has also been studied in combination with the IMiD pomalidomide. In a 2017 study conducted by Chari and colleagues, patients with relapsed or refractory MM who had received at least two previous lines of therapy were treated with daratumumab (16 mg/kg), pomalidomide (4 mg), and dexamethasone (40 mg).[8] At a median follow-up of 13.1 months, the estimated PFS was 8.8 months, with a 12-month survival rate of 66%. As seen in previous studies, common adverse effects were hematologic, although the incidence of grade 3–4 neutropenia was particularly pronounced (78% of patients). Upper respiratory tract infections and pneumonia occurred in 28% and 10% of patients, respectively. The incidence of grade 3–4 infection (32%) was comparable to previous studies that examined the use of pomalidomide and dexamethasone alone.

Safety

Although daratumumab is generally well tolerated, it is associated with a high incidence of infusion-related reactions (IRRs) (27.7%–56%; grade 3–4: 2%–9%).[2-8] The vast majority of IRRs (88%–98.2%) occur during the first infusion.[2,5,9] The manufacturer recommends both pre- and postmedications for daratumumab, including steroids, antipyretics, and antihistamines, with or without other supplementary agents (**Table 2**). Prescribing information also suggests using bronchodilators and inhaled corticosteroids for at least the first four infusions in patients with a history of chronic obstructive pulmonary disease to prevent an IRR.[1] In addition, the first dose is delivered in a larger dilution volume (1,000 ml) and at a slower rate of infusion to mitigate IRRs.

A limited number of studies have examined the utility of additional premedications beyond the prescribing information recommendations. In a 2016 multicenter open-label early-access study, a cohort of patients received recommended premedications plus montelukast (10 mg by mouth at least 30 minutes prior to daratumumab) at the investigator's discretion.[10] Infusion reactions with the first daratumumab infusion were reduced in patients who received montelukast compared to those who did not (38.0% vs. 58.5%). The infusion time for daratumumab was also 0.9 hours shorter in patients who received montelukast. Institutional practice may dictate the administration of supplemental premedications like montelukast for at least the first 1–2 daratumumab infusions.

Table 2. Prescribing Information Regarding the Pre- and Postinfusion Medication Regimen for the First and Second Daratumumab Infusions[2]

	Prescribing Information
Preinfusion (1 hour before start of infusion)	• diphenhydramine 25 mg–50 mg intravenous (IV) or by mouth (PO) • acetaminophen 650 mg–1,000 mg PO • methylprednisolone 100 mg (or equivalent) IV
Postinfusion	oral steroid (methylprednisolone 20 mg or equivalent) on days 2–3 (24 and 48 hours after the completion of daratumumab), per prescribing information

Daratumumab is associated with decreased hematologic parameters, including thrombocytopenia, anemia, and neutropenia as outlined in the studies above. Infection is also common, most notably upper respiratory tract infection (any grade: 21.6%–31%; grade 3–4: 0.7%–2.0%) and pneumonia (any grade: 10%–15.3%; grade 3–4: 9%–11.3%).[3,6-8] Other common nonhematologic adverse effects include fatigue, nausea, diarrhea, back pain, muscle spasms, pyrexia, dyspnea, peripheral edema, and peripheral sensory neuropathy.

Interference with Laboratory Testing

M-Protein Monitoring

An integral laboratory marker used in the diagnosis and monitoring of disease burden in MM is the monoclonal immunoglobulin protein (M protein).[11] This M protein is secreted by malignant plasma cells and can be detected in the blood and urine. It can be quantified using both serum protein electrophoresis (SPE) and immunofixation electrophoresis (IFE), processes that are able to separate and measure the specific protein.

Monoclonal antibodies, including daratumumab, are detectable on SPE and IFE and therefore can interfere with these monitoring assays.[11] The therapeutic antibody and monoclonal protein migrate closely on electrophoresis and are difficult to differentiate on analysis. Certain clonal protein subtypes (immunoglobulin G [IgG] kappa and kappa light chain MM) are harder to distinguish from daratumumab than others.[12] Measurement of daratumumab on the assays can be misinterpreted as an elevated M protein and can lead to an inaccurate response assessment. Strategies to mitigate M-protein monitoring interference are available; one is the use of a daratumumab-specific immunofixation electrophoresis reflex assay (DIRA).[11,12] DIRAs use antidaratumumab antibodies, which form a complex with daratumumab and alter its migration on IFE. By specifically shifting daratumumab on the assay, the M spike can be quantified with greater accuracy. Clinicians should be aware of this assay interference and take appropriate steps to ensure that treatment response is being measured appropriately.

Blood Typing and Transfusion Medicine

As stated previously, daratumumab is a human IgG monoclonal antibody that binds to CD38 receptors on malignant plasma cells; however, CD38 receptors are located on the surface of other cells, including red blood cells (RBCs) and platelets.[13] Daratumumab is therefore able to bind to RBCs and conceal the existence of antibodies in a patient's plasma. This binding can cause a false-positive result in blood compatibility testing (direct and indirect antiglobulin test), making it difficult to detect clinically relevant RBC antibodies in an assay. Because multiple myeloma patients frequently require RBC transfusions, this issue is particularly relevant.

Patients should complete baseline blood compatibility testing before initiating daratumumab therapy. If this testing is not an option, certain strategies can be used to overcome daratumumab antibody interference. Chemical denaturation of cell surface CD38 disulfide bonds using dithiothreitol (DTT) or trypsin is one such method.[14] These reducing agents cleave CD38 from the cell surface of RBCs, preventing the binding of daratumumab and

a subsequent false positive antiglobulin test. It should be noted that DTT can also degrade other blood antigens, most notably Kell antigens, and therefore patients should be given K-negative RBC units.[13] Daratumumab-positive blood samples can also be treated with soluble CD38, or anti-DARA idiotype antibodies, which bind and neutralize drug molecules. Although both denaturation and neutralization have been proven effective in preventing panreactivity, cost of the assay and availability of reagents may factor into a clinician's decision on which method to use.[13,14] It is also important to consider that daratumumab can interfere with RBC antibody screening for up to 6 months after the last daratumumab infusion.[13]

Conclusion

Daratumumab is a first-in-class anti-CD38 monoclonal antibody that can be used as monotherapy or in combination with PIs, IMiDs, alkylating agents, and corticosteroids for the treatment of MM. Although it is generally well tolerated, the medication has been associated with decreased blood counts, and patients should be monitored closely for infection (specifically upper respiratory tract infections and pneumonia). Infusion reactions may occur, especially during the first two infusions, and patients should follow an appropriate pre- and postmedication regimen according to the package insert and institutional standards. Daratumumab has the unique ability to interfere with laboratory testing, including M-protein monitoring and blood typing. It is important for clinicians to note this interaction, both during therapy and after its completion, and take appropriate steps to ensure that laboratory values are accurately interpreted. Daratumumab is one of the more recent therapeutic advances in the treatment of MM that is allowing patients to achieve improved outcomes. ●●

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FEATURE

A Review of Available Antidotes for Chemotherapy Overdoses

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In 1999, the Institute of Medicine published a report known as *To Err Is Human: Building a Safer Health System*.[1] The report emphasized the importance of a systematic approach to error prevention and the need for "well-designed processes of care [that] prevent, identify, and quickly recover from errors" in order to prevent patient harm. The delivery of oncology pharmacotherapy requires processes ensuring precise, meticulous, and detailed care.[2] The rate of documented inpatient errors is not well defined, and numerous studies have identified error rates in ambulatory settings. Weingart and colleagues, in a review published in 2018, estimated that chemotherapy error rates with potential for harm may range from 1 to 4 per 1,000 chemotherapy orders.[3] Although these error rates may be lower than rates seen in the general medicine population, the extent of harm they cause to patients is not known.

The narrow therapeutic range of oncology medications makes it vital to ensure that the correct dosage is given. Chemotherapy medications have a narrow therapeutic index and are often derived by complex dosing calculations to ensure that the patient is appropriately treated. Despite recommendations and guidelines to ensure safe oncology pharmacotherapy, errors still occur. One study noted that errors occurred throughout the entire medication process, with most centering on ordering and administration.[2] Risks for prescribing errors arise, for example, when orders have three or more chemotherapies, are placed by physicians who do not commonly use computerized prescription order entry, or are placed by physicians new to practice.[3] Special types of chemotherapy that should be carefully considered for error potential are intrathecal chemotherapy, oral chemotherapies, and chemotherapy treatments given over multiple days.

Our processes for ensuring safe medication use have improved over the years, but chemotherapy overdoses still occur. If a chemotherapy overdose does occur, one avenue to combat toxicities and prevent permanent sequelae is to administer antidotes. Unfortunately, direct antidotes do not exist for most chemotherapies, but it is important for pharmacists to understand the different agents that they could use if the need for one arose. With the exception of uridine triacetate, a U.S. Food and Drug Administration (FDA)–approved antidote for fluorouracil and capecitabine overdose and early-onset toxicity, data regarding antidotes for chemotherapy overdoses are limited to small studies and case reports.

Uridine Triacetate for Fluorouracil or Capecitabine Overdose or Early-Onset Toxicity

Uridine triacetate is currently indicated for treating fluorouracil (5-FU) or capecitabine overdose and for treating patients who develop early, life-threatening toxicities with these medications.[4] Overdoses from these medications may be accidental or intentional. The potential for error is related to 5-FU chemotherapy pump malfunctions or misprogramming and to accidental ingestion of capecitabine tablets. Severe toxicities that may be seen in the event of an acute overdose include cytopenias, acute cardiomyopathy, altered mental status, mucositis, severe nausea, and severe diarrhea. Additionally, genetic enzyme variants may enhance toxic effects in some patients at doses that are usually well tolerated.[5]

Uridine triacetate was studied in two open-label compassionate-use trials.[5] The goal of these studies was to evaluate the impact of uridine triacetate on patient outcomes in the setting of either an overt overdose, defined as administration of a larger dose of 5-FU (or a dose at a higher rate) than planned, or early-onset serious toxicity, defined as a patient's development of severe toxicities within 96 hours of a 5-FU infusion or within the standard 14-day course of capecitabine treatment. Because it was considered unethical to include a placebo arm in the trial, outcomes for uridine triacetate treatment for overdose were compared with those for a historical cohort treated with best supportive care. Adult dosing consisted of uridine triacetate 10 g orally every 6 hours; pediatric patients received 6.2 g/m^2 (max of 10 g) orally every 6 hours. A full treatment course consisted of 20 doses, ideally initiated within 96 hours of the last 5-FU or capecitabine dose. Patient survival or resumption of chemotherapy after 30 days was the primary end point, and adverse effects were documented to evaluate safety. The studies included 173 patients who were treated with uridine triacetate, 168 of whom were available for follow-up, and the historical comparator group included 25 patients. Efficacy results are displayed in **Table 1**. The most common adverse effects noted with uridine triacetate use were vomiting (8.1%), nausea (4.6%), and diarrhea (3.5%).

The study design had several limitations. Selecting patients to include in a historical cohort as the comparator group introduces risk for bias, given that severe cases may be more likely to be reported, although the authors did attempt to standardize toxicity severity and correlate it with expected outcomes. It is also difficult to directly compare the data between the historical cohort and the treatment cohorts. However, despite the limitations of this trial, the data demonstrated that uridine triacetate could play an important role in improving the survival of patients with early-onset toxicity or overdose from 5-FU or capecitabine, especially if it was initiated early after the chemotherapy was administered.

Uridine triacetate is distributed solely by Cardinal Health Specialty Pharmacy Distribution, and it is available for order 24 hours a day, 7 days a week.[4] The medication should be added to the

Table 1. Efficacy Outcomes Comparing Uridine Triacetate Treatment Cohorts and the Supportive Care Historical Cohort

	Uridine Triacetate (UT) Treatment Cohorts		Supportive Care Historical Cohort
Outcomes	**Early-Onset Toxicity (*n* = 26)**	**Overdose (*n* = 142)**	**Overdose (*n* = 25)**
Survival at day 30	21 (81%)	137 (96%)	4 (16%)
• UT received within 96 hours	18/18 (100%)	NA	NA
• UT received after 96 hours	3/8 (38%)	NA	NA
Chemotherapy resumption in <30 days	3	53/141 (38%)	NA
Early therapy discontinuation	5 (19.2%)	10 (6.8%)	NA

NA = not applicable.

formulary to ensure that providers can order it efficiently when it is needed. Given the high cost of this medication, pharmacy and therapeutics (P&T) committees will need to decide whether to keep a certain quantity in stock or order it as needed. Use should be restricted to overt overdoses and life-threatening toxicities within 96 hours of administration or ingestion. Because uridine triacetate may reduce the effectiveness of 5-FU and capecitabine, it should not be used for treating mild to moderate toxicities. Depending on the degree of toxicities patients are experiencing and how quickly they recover, they may be eligible for outpatient treatment. In this case, uridine triacetate must be dispensed through a specialty pharmacy, and care must be taken to ensure that the patient completes the full 5-day course without missing doses.

Uridine triacetate is supplied as oral granules in single-use 10-gram packets.[4] Granules should be mixed with soft food and taken within 30 minutes. It may also be given via nasogastric or gastric tubes in cases involving compromised mental status or severe mucositis. Uridine triacetate doses should be readministered if the patient vomits within 2 hours of administration.

Glucarpidase for Intravenous and Intrathecal Methotrexate Overdose

High-dose methotrexate (HDMTX), usually defined as intravenous (IV) doses at least 500 mg/m^2 given over 2–36 hours, is an important therapy for treating several malignancies.[6] Although leucovorin rescue, urine alkalinization, hydration, and avoidance of concomitant nephrotoxins reduce the risk of acute kidney injury associated with HDMTX, some patients may require the rescue agent glucarpidase to rapidly decrease methotrexate levels and prevent permanent sequelae of toxicities. Glucarpidase is FDA-approved for patients who experience toxic levels of systemic methotrexate secondary to severe HDMTX-induced renal impairment.[7] The medication is a recombinant bacterial enzyme that works by deactivating methotrexate into two inactive metabolites. It works quickly, achieving a reduction in serum methotrexate levels of over 97% within 15 minutes of administration.[7] Although the usual route of administration is IV, studies investigating administration via the intrathecal (IT) route in the setting of acute intrathecal methotrexate overdose have been conducted.

Overdoses of IT methotrexate are a rare but serious error and can occur when methotrexate doses meant for systemic administration are given intrathecally. Signs and symptoms suggestive of IT methotrexate overdose are likely dependent on the degree of overdose and may include severe headache, fatigue, and confusion; they may progress to seizures or death.[8] No antidote for IT methotrexate overdose has been approved by the FDA, nor do consensus guidelines on how to manage these situations exist, but several small studies have used IT glucarpidase, along with cerebrospinal fluid (CSF) exchange, in an attempt to reverse methotrexate effects. Other supportive care strategies noted in the literature include systemic IV leucovorin to decrease systemic methotrexate impacts and IV dexamethasone to reduce the risk of arachnoiditis.[8-12]

One small case series was conducted by Widemann and colleagues and published in 2004.[10] The investigators analyzed the effect of glucarpidase 2,000 units IT in seven pediatric and adult patients 3–9 hours after an IT methotrexate overdose occurred. Glucarpidase was given, along with standard supportive measures, which included leucovorin 100 mg IV every 6 hours and dexamethasone 4 mg IV every 6 hours, each for four doses. Four of the patients also received CSF exchange prior to receiving glucarpidase. In this study, all patients survived. Two patients had residual cognitive deficits, but five returned to their baseline cognitive function.

Another case report that used a similar treatment protocol was published in 2012.[11] This case report detailed the course of a 66-year-old female who accidentally received IT methotrexate at 10 times the intended dose. After the mistake was recognized, CSF fluid was removed through the reservoir through which the drug had been administered. The patient was subsequently hospitalized and treated with the same regimen followed in the previous discussed study, including glucarpidase 2,000 units IT. The patient reportedly returned to her baseline mental status.

Evidence regarding glucarpidase IT as an antidote to methotrexate IT overdose is limited to a small case series and case reports, but the patients in these studies appeared to have favorable outcomes with regard to avoiding permanent neurologic sequelae. Because the published studies used many treatment

modalities for toxicity management, it is difficult to estimate the degree that each medication or procedure played in overdose reversal. Small studies that used leucovorin IT in treating methotrexate IT overdose showed possible neurotoxic adverse effects, but glucarpidase did not demonstrate this effect in these very small studies.[11,12]

Glucarpidase is exclusively distributed by BTG Specialty Solutions Center.[7] It may be ordered 24 hours a day, 7 days a week to stock pharmacy inventory or for on-demand use. Health system P&T committees may choose to add it to the formulary to improve efficiency in physician ordering. Facilities that administer HDMTX may be more likely to keep glucarpidase in stock because of its more defined role in therapy in this setting and because it should be administered within 60 hours of HDMTX exposure. For administration of glucarpidase IV following HDMTX, use should be restricted to patients who have toxic levels of methotrexate with severe renal impairment. Institutions should implement protocols that specify how toxic levels of methotrexate will be defined and who is eligible to receive glucarpidase. Glucarpidase inactivates both leucovorin and methotrexate, so leucovorin should be administered at least 2 hours after glucarpidase infusions.[6] The protocol should also address how methotrexate levels will be monitored after glucarpidase administration. Because glucarpidase can falsely elevate methotrexate immunoassay measurements for about 48 hours after administration, a chromatographic method must be used during this time.

Facilities that do not administer HDMTX but do administer IT methotrexate injections will need to weigh the pros and cons of regularly stocking glucarpidase in anticipation of a rare but serious error. Pharmacists must be aware that the procedure for reconstituting glucarpidase for IT administration differs from that for IV administration (12 ml of preservative-free normal saline for 2,000 units of glucarpidase versus 1 ml of saline for each 1,000 units of glucarpidase, respectively).[10,11] It may be helpful for facilities to develop protocols for procuring, reconstituting, and administering glucarpidase to aid the healthcare team in the rare event of an IT methotrexate overdose.

Sodium Thiosulfate for Cisplatin Overdose

Cisplatin overdoses can have multi-organ system effects, including but not limited to, acute renal failure, myelosuppression, nausea and vomiting, and neurological effects such as ototoxicity and seizures.[13] No specific antidote for cisplatin overdose exists, and current treatment options are limited to aggressive supportive care.

Sodium thiosulfate, a medication originally used to treat acute cyanide poisoning, has been used to prevent cisplatin renal toxicity.[14] The agent is postulated to have renal-protective effects by binding free serum platinum and improving renal clearance of inactive metabolites. Evidence regarding the use of sodium thiosulfate for reversal of acute kidney injury secondary to cisplatin overdose is limited to case reports.

Erdlenbruch and colleagues reported their experience using sodium thiosulfate in an acute cisplatin overdose that occurred in a 14-year-old patient.[15] The patient received a cisplatin dose that was three times the intended amount. She subsequently developed hearing loss and acute renal failure and was treated with sodium thiosulfate 4 g/m^2 IV once and then 2.7 g/m^2/day IV in three divided doses for a total of 13 days. This treatment was initiated 70 hours after the cisplatin infusion, along with other supportive care measures such as aggressive hydration. The patient survived with residual hearing loss but did not develop chronic kidney damage. In two other published case reports, adult patients were treated with sodium thiosulfate, along with other modalities such as hemodialysis and plasmapheresis; in both reports the patient survived.[13]

The evidence for the use of sodium thiosulfate to treat cisplatin overdose is limited to case reports of single patients. This minimal evidence suggests that sodium thiosulfate could be used as a treatment modality, along with other supportive care measures.

Conclusion

The goal of oncology pharmacotherapy is to administer potentially lethal medications in a safe manner that will optimize therapeutic benefit and minimize harm. However, medication errors can still occur, and the goal in this scenario is to manage toxicity quickly in order to minimize harm to patients. After the FDA approval of uridine triacetate, the Institute of Safe Medication Practices (ISMP) published an article summarizing case reports of 5-FU overdoses and recommendations on how to manage these events.[16] The article applied to 5-FU overdoses, but the concepts could be generalized to managing chemotherapy overdoses that have specific antidotes. ISMP recommends training nurses and other healthcare professionals on recognizing chemotherapy toxicities and creating a treatment protocol that defines how to efficiently procure an antidote and manage the patient's toxicities. Pharmacists are uniquely positioned to serve as subject matter experts on chemotherapy agents and their respective antidotes and should be involved in developing chemotherapy antidote protocols. ●●

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Ibrutinib Therapy for Lymphoplasmacytic Lymphoma

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Ibrutinib, an oral Bruton's tyrosine kinase (BTK) inhibitor, is indicated for treatment of multiple hematologic malignancies, including previously treated mantle cell lymphoma, chronic lymphocytic leukemia or small lymphocytic lymphoma, previously treated marginal zone lymphoma, and Waldenstrom macroglobulinemia (WM). In August 2018 the U.S. Food and Drug Administration (FDA) approved ibrutinib, in combination with rituximab, for treatment of adult patients with WM. WM is a clinical subset of lymphoplasmacytic lymphoma (LPL), which causes an increase in serum immunoglobulin M (IgM) monoclonal proteins. LPL is a rare low-grade B-cell malignancy composed of small lymphocytes, plasmacytoid lymphocytes, and plasma cells that typically involve the bone marrow. It is characterized by an activating mutation of MYD88 (L265P). By inhibiting BTK, ibrutinib is thought to block downstream effects of MYD88 activation. Although some research in the literature supports the use of ibrutinib in WM, limited data are available on ibrutinib use in LPL in a real-life clinical practice setting.

Dr. Helber and colleagues conducted an observational study using ibrutinib in 23 patients with LPL.[1] Included were all sequential nonselected LPL patients who were treated by a dedicated specialty pharmacy service with ibrutinib, at a planned dose of 420 mg daily, for disease progression or disease complications. A pharmacy specialist was responsible for following all patients at least monthly in a lymphoma clinic and by telephone as well as prospectively collecting data. Data points included medication adherence, drug interactions, adverse events, and reasons for treatment interruptions and dose adjustments. MYD88 L265 genetic analysis was performed using a labeled-oligo melting curve assay. The authors evaluated ibrutinib response by monitoring immunoglobulin levels throughout the duration of treatment and hemoglobin levels for resolution of anemia (defined as hemoglobin of ≥10 g/dl or greater). Objective treatment responses were defined as very good partial response (90% or greater reduction or normalization of IgM), partial response (≥50% to <90% IgM reduction), and minor response (≥25% to <50% IgM reduction).

The median age was 71.9 years (range 41.1–91.7). Of the 23 patients, 70% were male, and 61% had been previously treated. The median time of initiating ibrutinib from LPL diagnosis was 3.3 years (range 0–21.2). At the time of data censoring, the median duration of ibrutinib therapy was 11 months (range 0.5–33.8).

"Because each patient was monitored by a dedicated pharmacy specialist, the researchers in this study exemplify the unique and significant role of pharmacy."

Twenty-two patients had detectable serum IgM monoclonal proteins, and one patient had immunoglobulin G (IgG) monoclonal proteins.

Of the 21 patients with sequential IgM levels, 19% had very good partial response, 57% had partial response, and 24% had minor response. The median maximum IgM decrease was 67% (range 31%–96%). Four patients had normalized IgM levels (<230 mg/dl). They had no clinical evidence of residual LPL. However, the authors could not document a complete remission because serum protein electrophoresis analysis or bone marrow restaging studies and images were not performed. The cumulative probability of reaching a 50% reduction in serum IgM level by 60 days and 90 days was 0.51 (95% confidence interval [CI]: 0.32–0.74) and 0.74 (95% CI: 0.53–0.91), respectively. Fifteen patients had a 50% or greater IgM reduction within 150 days of starting ibrutinib therapy (range 7–105). The one patient with IgG LPL had a 37% decrease in IgG levels. Resolution in anemia occurred in six of eight patients. No disease progression during ibrutinib treatment was documented.

In terms of safety, six patients required at least one ibrutinib dose reduction (one for drug interactions and five for adverse events or comorbidities). Three patients self-discontinued ibrutinib because of muscle weakness and pain. Nine patients interrupted therapy because of procedures, comorbidities, adverse events, and hospitalizations. Immunoglobulin levels were monitored during therapy interruptions. It was noted that a rapid increase in IgM levels was associated with ibrutinib interruption, and a subsequent decrease in IgM levels was seen after therapy was restarted. No treatment-related increase of serum monoclonal protein levels, or "flares," during ibrutinib therapy was reported.

Unique to this observational study is that Dr. Helber and colleagues included many LPL patients who would have been ineligible for the use of ibrutinib in LPL/WM clinical trials because of poor performance status, comorbidities, or organ failure. Two patients with end-stage renal failure were included. One LPL patient with severe renal failure and anemia, secondary to light chain nephropathy, was initiated on a lower dose (140 mg/day) and incrementally increased to 420 mg/day. This patient experienced intermittent grade-2 hematuria but tolerated the full dose. The other patient had nephrotic syndrome caused by lambda light chain renal amyloidosis. Her medication was initiated at the full dose and then decreased to 280 mg/day because of decreased renal function. Although the paraprotein levels were well controlled in ibrutinib therapy, the patient required chronic hemodialysis and died because of renal failure. Additionally, six patients

older than 80 years tolerated and responded to ibrutinib therapy appropriately.

The work of Dr. Helber and colleagues provides valuable insight into the use of ibrutinib in LPL. Their work—in which they observed a rapid decrease in IgM levels after the start of ibrutinib therapy and subsequent increases in IgM levels after therapy interruptions—confirms that ibrutinib inhibits IgM secretion by LPL cells. They observed no serious adverse events from ibrutinib therapy or disease progression during treatment. IgM flares have been reported after initiation of rituximab therapy in patients with WM; however, no flares were seen with ibrutinib therapy. This lack of flare with ibrutinib is especially important to note when treating patients with hyperviscosity syndromes. This study was also one of the first reports on using ibrutinib in end-stage renal failure. Last, because each patient was monitored by a dedicated pharmacy specialist, the researchers in this study exemplify the unique and significant role of pharmacy. ●●

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TAILORing the Decision to Have or Not Have Chemotherapy

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At the 2018 American Society of Clinical Oncology (ASCO) Annual Meeting, the landmark clinical trial TAILORx found no efficacy advantage in adding adjuvant chemotherapy to endocrine therapy for hormone receptor (HR)–positive, human epidermal growth factor receptor 2 (HER2)–negative, early breast cancer patients with a midrange Oncotype DX recurrence score of 11–25. The results indicate that nearly 70% of patients with the most common type of early breast cancer can forgo chemotherapy. However, an exploratory analysis did find benefit for chemotherapy in women 50 years of age or younger with a recurrence score of 16–25.[1]

Trial Design Centered on Recurrence Score

TAILORx was a prospective phase 3 multinational study that enrolled 10,273 women with HR-positive, HER2-negative, axillary lymph node–negative breast cancer based on their Oncotype DX Breast Recurrence Score.[1]

The 21-gene Oncotype DX breast cancer assay is a tool used in HR-positive, HER2-negative early breast cancer to help identify women who may benefit from the addition of adjuvant chemotherapy to endocrine therapy. This assay predicts the 10-year risk of distant recurrence, providing a recurrence score from 0 to 100 based on the patient's genetic profile.[2] The higher the score, the higher the risk of recurrence and the greater potential for chemotherapy benefit.[3,4]

Patients in TAILORx were assigned to one of four groups. Those with a recurrence score of 10 or less received endocrine therapy only, while those with a recurrence score of 26–100 received chemotherapy followed by endocrine (chemoendocrine) therapy. Women with a midrange recurrence score of 11–25 were randomized to receive either endocrine therapy alone or chemoendrocrine therapy. The purpose of this analysis, presented at ASCO 2018, was to use precision medicine to determine whether adjuvant chemotherapy is beneficial for those with a midrange recurrence score of 11–25.[1]

Pivotal End Points Support Endocrine Therapy Alone

The primary end point of TAILORx was invasive disease-free survival (IDFS)—freedom from invasive disease recurrence, second primary cancer, and death. At 9 years, adjuvant endocrine therapy was noninferior to chemoendocrine therapy in women with a recurrence score of 11–25 with an IDFS of 83.3% versus 84.3%, respectively (hazard ratio, 1.08; 95% confidence interval [CI], 0.94–1.24; $p = .26$).[1]

Similar rates were seen with secondary end points. At 9 years, those with a midrange recurrence score of 11–25 had similar freedom from disease recurrence at a distant site (94.5% endocrine therapy and 95% chemoendocrine therapy), freedom from disease recurrence at distant or local-regional site (92.2% and 92.9%), and overall survival (93.9% and 93.8%). No detriment in survival was evident when chemotherapy was avoided.[1]

Younger Patients with Scores 16–25 May Benefit from Chemotherapy

Of interest, an exploratory analysis of TAILORx highlighted the finding that patients age 50 years or younger with a recurrence score of 16–25 *did* benefit from adding chemotherapy to endocrine therapy, with a lower rate of distant recurrence over endocrine therapy alone (1.6% lower for recurrence score 16–20; 6.5% lower for recurrence score 21–25), although without a survival difference.[1] As a result, chemotherapy should be considered, but not mandated, in premenopausal patients age 50 or younger with a score of 16–25 (**Table 1**).[5] Yet the question remains whether chemotherapy is needed or whether similar reductions in disease recurrence can be achieved with the use of ovarian suppression and an aromatase inhibitor instead. Chemotherapy can induce menopause, creating a low estrogen environment that may be driving the benefit seen.

Ovarian suppression was not standardized in the design of TAILORx, which enrolled women between 2006 and 2010, although today it is considered standard for many in this population.[1] The SOFT/TEXT clinical trials paved the way for the addition of ovarian suppression (via luteinizing hormone-releasing hormone [LHRH] agonist, bilateral oophorectomy, or ovarian irradiation) to tamoxifen or an aromatase inhibitor in premenopausal women with operable breast cancer. The addition of ovarian suppression to tamoxifen increased 8-year disease-free and overall survival rates compared to tamoxifen alone, while the use of exemestane plus ovarian suppression resulted in even higher rates of freedom from recurrence.[6] Given that only 13% of premenopausal patients in TAILORx received ovarian suppression, it is unknown whether similar benefits can be achieved with the addition of ovarian suppression to endocrine therapy instead of chemotherapy.[1]

Results Not Applicable to Node-Positive Disease

It is important to remember that patients in TAILORx were axillary node negative. We are still awaiting prospective validation of this 21-gene assay in breast cancer patients with one to three lymph nodes from the RxPONDER trial.[7] ASCO's 2017 guideline on biomarker assays recommends against the use of this 21-gene assay to guide decisions on chemotherapy for node-positive patients who are HR-positive and HER2-negative, although clinical practice may differ.[8]

Final Word

The TAILORx results allow us to tell more breast cancer patients, "Your genetic makeup shows that you may not need chemotherapy." Rare but serious risks of adjuvant breast cancer chemotherapy such as cardiotoxicity and secondary malignancies can now be

Table 1. Recurrence Score Utility in HR-Positive, HER2-Negative, Node-Negative Early Breast Cancer[5]

Recurrence Score	Age	Chemotherapy Benefit	Estimated Percentage of Population
0–10	Any	May *avoid* chemotherapy	16%
11–15	50 years or older	May *avoid* chemotherapy	8%
16–25	50 years or older	May benefit from chemotherapy	14%
11–25	Less than 50 years	May *avoid* chemotherapy	45%
26–100	Any	Benefit from chemotherapy	17%

avoided because applying the data from TAILORx will spare many patients from unnecessary chemotherapy. It is clear that we must consider the recurrence score from this genomic assay, in combination with the clinicopathological features of the patient's individual disease, to help guide the patient through the difficult decision of whether or not to receive chemotherapy. ●●

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Board Update

From Summer to Winter

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As the dog days of summer have moved into the times of changing leaves of fall and the chill of winter, the amazing work that you all have been involved in through HOPA has continued without notice of the seasonal changes. Your dedication and tireless efforts are what continue to propel the work of this small but mighty pharmacy association across the country and around the globe.

The 2018 HOPA Pharmacy Practice Management program was held in Chicago in September and was a great success—as always. If you have never attended this program, launched in 2013 through the efforts of past-president Niesha Griffith, RPh MS, you should know that it is an amazing oncology pharmacy meeting! Focusing on the topics that keep oncology pharmacy managers and directors up at night, it continues to inspire the participants and push the boundaries of knowledge in our field. The brilliant team of the Practice Management Program Committee—Michelle Rockey (chair), John Valgus (vice chair), Renne Curtis-Freitag, Jim Koeller, Jeff Lombardo, Darcy Malard-Johnson, and Jeffrey Reichard—aided by the Practice Management Program Session Proposal Subcommittee of Dayna McCauley (chair), Carolyn Smith-Bondarenka (vice chair), Manpreet Chahal, Jeff Lombardo, Tim Miller, Audrea Szabatura, Sonia Thomas, Brian Verlizzo, and Deborah Ward as well as HOPA staff members Dawn Herman and Katy Meyer, generated a phenomenal 2-day event with fantastic presentations across the whole program. The speakers were riveting, teaching through experience, real-life examples, and explanations of the current issues at hand and keeping the crowd engaged throughout the sessions.

Education by HOPA members continues beyond HOPA's own offerings. Morgane Diven, Kate Jeffers, Patrick Kiel, and Rowena Schwartz led Board Certified Oncology Pharmacist (BCOP) education sessions at JADPRO Live in Hollywood, FL, in November. JADPRO Live is the annual conference of the Advanced Practitioner Society for Hematology and Oncology (APSHO). HOPA has developed a partnership with APSHO to certify BCOP opportunities at JADPRO Live. At the same time, Michelle Bustamante, Nicole Lubcke, and Kristin Wheatley were delivering BCOP education to our pediatric colleagues at the Pediatric Pharmacy Association's fall conference in Philadelphia, PA. HOPA members' outreach in education expands our ability to educate all oncology practitioners. It is this level of drive that propels us forward in the world of oncology and supports HOPA's Strategic Plan.

HOPA's Entry-Level Competencies Task Force has completed amazing work compiling resources and paving the way for graduates of Doctor of Pharmacy degree programs and postgraduate year-1 pharmacy residents to develop necessary skills and have a successful orientation into hematology/oncology pharmacy practice. These resources, designed specifically for didactic, experiential, and PGY-1 residency curricula, are available on HOPA's website in the Resources section, under "Professional Tools" (hoparx.org/resources/professional-tools). Let us take a moment to congratulate the team for their fine work: Ginah Nightingale (chair), Jill Comeau, Karen Fancher, Tim Miller, Cindy O'Bryant, Sarah Peters, Ila Saunders, and Jason Yeh.

Last, as we have been watching, playing, or coaching sports over the past few months, we have seen the power of teamwork displayed in many forms—whether at a child's Thursday night Little League game, in the Saturday afternoon college rivalries, or on "Monday Night Football." We have seen the players—engaged, motivated, and selfless—working together for the greater good. It is easy to see these qualities embodied in all of you: you are one massive team. You make plans and plays to push this association forward. Your one-handed catches and stolen bases are on our association's highlight reels. It is your effort and drive that continue to push the boundaries of what we do as an association. Without this team and your teamwork, our association would not be what it is today.

Continue this work that you love. Continue to participate in our educational offerings, and help us expand our reach. But do not forget to cheer for yourselves and accept the admiration and praise you deserve. We are Team HOPA, and working together, we make this association stronger.

Have a wonderful fall and a safe and happy holiday season, and then be ready for an exciting and amazing New Year. Go, team!

HOPA
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HOPA AHEAD 2019

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FORT WORTH CONVENTION CENTER
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Registration opens this month for our 15th Annual Conference.