HOPA NEWS

Pharmacists Optimizing Cancer Care

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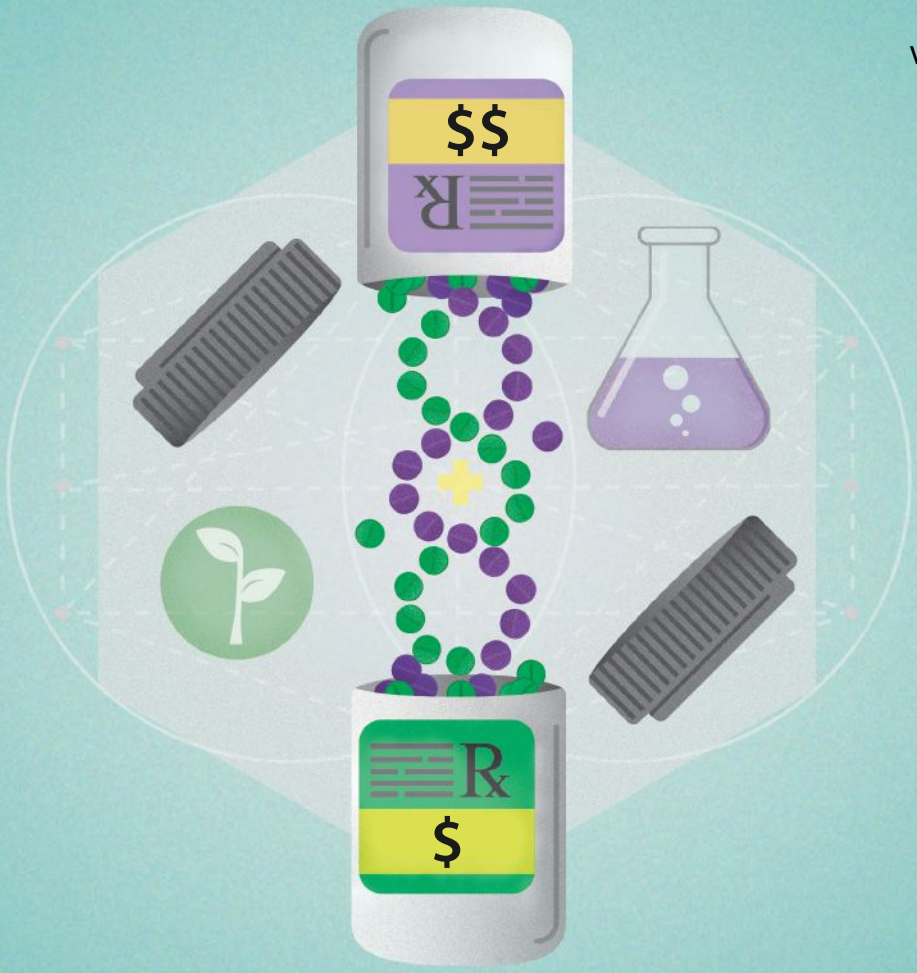

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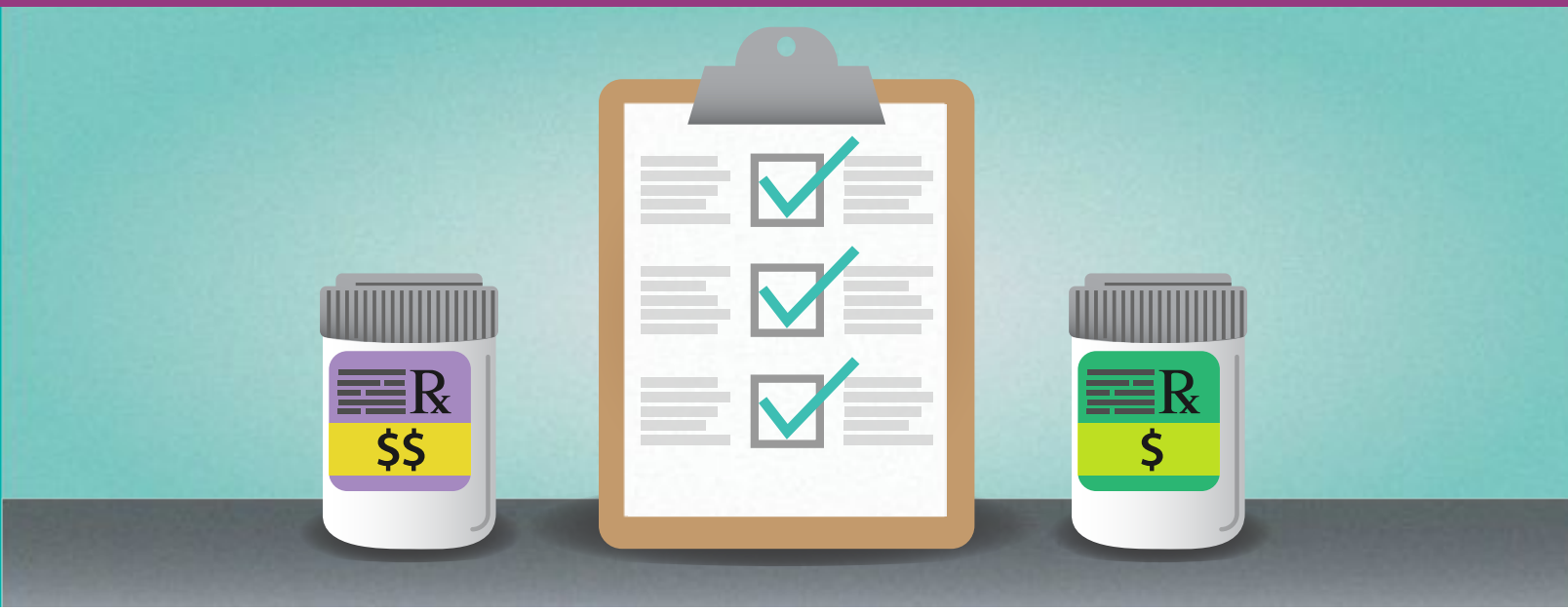

A Strategic Review of Biosimilars in Oncology Practice

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The introduction of biosimilars into the U.S. healthcare system has been met with mixed responses from key players, including healthcare providers, drug manufacturers, specialty and infusion pharmacies, health benefit providers (payers), and policy makers. Although these medications bring hope for minimizing cost and improving patient access to expensive medications, their presence has disrupted many channels in the specialty pharmacy market connected to drug pricing, formulary coverage, reimbursement, and clinical utilization. Many oncology pharmacists have become comfortable with the concept of biosimilars following the 2015 release of the first biosimilar agent in the United States, filgrastim-sndz (Zarxio), and a handful of other nononcology biosimilars. Two U.S. Food and Drug Administration (FDA) approvals in 2017, for bevacizumab-awwb (Mvasi) and trastuzumab-dkst (Ogivri), have brought increased attention to the use of biosimilars in the cancer setting because these agents are the first approved biosimilars for many biologics approved for the treatment of cancer.

According to the FDA, a biosimilar is a biological product that is highly similar to and has no clinically meaningful difference from an existing FDA-approved reference product.[1] The pathway for approval of biosimilar agents in the United States was established in 2009 by the Biologics Price Competition and Innovation Act (BPCIA), which updated section 351(k) of the Public Health Service Act of 1944. This update provided succinct details on how to bring biosimilars to market, including requirements for licensing, testing, manufacturing, safety, exclusivity, labeling, the definition of biosimilars versus interchangeable products, and required interactions with the manufacturer of the reference product. The BPCIA was eventually enacted as part of the 2010 Patient Protection and Affordable Care Act, and since that time, payers, manufacturers, and healthcare providers have been preparing for the release of biosimilar agents.

The FDA's Center for Drug Evaluation and Research maintains a list of all FDA-approved biologics. This online database, called the Purple Book, includes the medication names, respective dates of licensure, patent expiration dates, and other types of information for all biologics and biosimilars. To date, nine biosimilars have been approved by the FDA through the BPCIA pathway for six biologics, but only three are currently available for distribution and sale (see **Table 1**).[2,3]

The approval, manufacturing, and sale of many biosimilar products, including both bevacizumab-awwb and trastuzumab-dkst, have been held up in complicated lawsuits secondary to varying interpretations of patent law, as well as interpretations of the BPCIA as it relates to the type of communication that must occur between the manufacturer of the biosimilar product and the manufacturer of the reference product.

In November 2016, Amgen officially announced its intention to produce and market a biosimilar to bevacizumab (Avastin), which ultimately gained FDA approval 10 months later.[4] However, since November 2016, Genentech, the manufacturer of bevacizumab (Avastin), has filed multiple litigious complaints and patent infringement suits about varying interpretations of the BPCIA, which has slowed both the approval and market availability of the biosimilar.

Genentech and Roche, who manufacture and market trastuzumab (Herceptin), took a different approach when Mylan and Biocon communicated their interest in developing a trastuzumab biosimilar. In this case, the companies signed a collaborative global licensing agreement in March 2017 that was designed to "provide a clear pathway for Mylan to commercialize its trastuzumab product in various markets around the world."[5] Although details of the agreement remain confidential, it is obvious that Mylan and Biocon were committed to overcoming patent considerations

Table 1. Biosimilar Products Approved by the U.S. Food and Drug Administration[3]

Reference Product (Trade Name)	Manufacturer	Biosimilar	Manufacturer	Biosimilar's Availability on the U.S. Market
Adalimumab (Humira)	AbbVie	Adalimumab-adbm (Cyltezo)	Boehringer Ingelheim	Unavailable
		Adalimumab-atto (Amjevita)	Amgen	Unavailable (delayed until 2023)
Bevacizumab (Avastin)	Genentech	Bevacizumab-awwb (Mvasi)	Genentech	Unavailable
Etanercept (Enbrel)	Amgen	Etanercept-szzs (Erelzi)	Sandoz	Unavailable
Filgrastim (Neupogen)	Amgen	Filgrastim-sndz (Zarxio)	Sandoz	Available
Infliximab (Remicade)	Janssen	Infliximab-abda (Renflexis)	Merck	Available
		Infliximab-dyyb (Inflectra)	Pfizer	Available
		Infliximab-qbtx (Ixifi)	Pfizer	Unavailable
Trastuzumab (Herceptin)	Genentech/Roche	Trastuzumab-dkst (Ogivri)	Mylan/Biocon	Unavailable

early in the process, which paves the road for manufacturing and distributing their biosimilar, set for 2019.[6]

The litigation or "patent dance" observed with bevacizumab-awwb has been seen with the release of most other biosimilar products and may lead to months or years of delay for each product. Despite these delays, the ongoing approvals of these products will only increase, which means that oncology pharmacists should prepare for their utilization with the clinical, financial, and regulatory aspects in mind.

For pharmacist clinicians, a primary interest concerning the use of biosimilars is their clinical effectiveness and safety profiles compared with the reference product. Currently no interchangeable biologics are on the market that, according to the BPCIA, would allow the product to "be substituted for the reference product without the intervention of the health care provider who prescribed the reference product."[7] However, developers of the current noninterchangeable biosimilars must meet or present strict clinical, safety, purity, potency, analytical, and nonimmunogenicity data and manufacturing data to prove that the biosimilars are equivalent to the reference product. Critics of biosimilars are quick to point out that the clinical data required for approval through the BPCIA are limited to just "one or more appropriate conditions of use for which the reference product is licensed," meaning that the biosimilar may gain an FDA label for the full spectrum of indications for the reference product through the study of use in only one disease state.[7] Fortunately, the FDA's review process, coupled with biosimilar utilization in Europe and initial data in the United States, supports the view that these products have similar profiles to the reference product.

Another major implication of biosimilar use is the potential impact on drug cost and increased access for patients. A recent market study performed by the RAND Corporation estimated that the implementation of biosimilars would save the U.S. healthcare system $54 billion over the next decade, with a potential minimum and maximum savings of $25 billion and $150 billion, respectively.[8] Although this perspective proactively identifies the large potential swing of cost savings, even the conservative number is enough to cause excitement, especially because the roughly 3% of patients receiving specialty medications in the United States now account for more than 40% of total drug spending.[9] The cost savings associated with biosimilar implementation is secondary to the lower cost of the biosimilar products because less overhead is needed for research and development, and the costs of the reference products will remain lower as their manufacturers attempt to stay competitive in the market. In an ideal world, these lower costs would spur "top-down economics": pharmacies and clinics would purchase the medications for less, health insurance companies would see less spent per member, and patients would subsequently pay lower premiums and copays for their subspecialty care.

Although lowering overall healthcare costs is an important sociological endeavor, it is also important for dispensing pharmacies to understand the revenue cycle as it relates to the cost and reimbursement for both reference biologics and biosimilars to ensure their fiscal viability. Most of the biologics in the oncology setting that are nearing patent expiration and subsequently will become eligible for biosimilar competition are administered via the intravenous route by a healthcare professional. A recent poll of health insurers showed that 72% of payers cover intravenous oncology products solely under the medical benefit.[10] Because of complexities associated with revenue cycle billing through the medical benefit, infusion pharmacies will be at risk for dispensing a nonpreferred or uncovered product, which may lead to lack of payment for services rendered. Scenarios in which infusion pharmacies might not get paid through the medical benefit include these:[10]

- The reference product was dispensed when the payer's preferred formulary agent was a biosimilar.
- The biosimilar product was dispensed when the payer's preferred formulary agent was a reference product or another biosimilar.
- Biological parity exists (i.e., the use of biologics aligns with the payer's medical necessity policies), but an authorization was not obtained for any product.

- Authorization for one product was obtained, but another product was dispensed.
- The medication was approved through the prescription insurance but billed through the medical insurance.
- The patient recently lost or changed insurance coverage.

Accordingly, it remains crucial for oncology infusion pharmacies to maintain a strong and proactive financial support team to ensure that the biologic medications prescribed and dispensed align with the formulary for each specific health benefit payer.

Many payers, such as Medicare, will cover all forms of the biologics as long as biological parity exists. In this case, it is important to review both the purchasing costs of the reference and biosimilar products and their respective reimbursement amount. Though one product may be less expensive, the reimbursement amount may also be significantly less, meaning a smaller margin per each dispensing. Medicare has attempted to favorably adjust its reimbursement for biosimilars through Part B to incentivize their utilization.[11] However, Part B reimbursement methodologies have been scrutinized or changed without much consistency in recent years, so it is important to stay updated on current standards in this setting.

The management of biosimilars in an institution should also be driven by other factors. It is important to note that the reimbursement process for biosimilars within hospitals will likely vary greatly between the inpatient setting and the outpatient infusion setting. For that reason it is important to understand the revenue cycle in both areas across all payers when one is strategically assessing biologic and biosimilar utilization. Also, state laws may require that reference products or biosimilars be dispensed in certain instances. The Academy of Managed Care Pharmacy supports the Biosimilar Resource Center, "an unbiased, policy-neutral repository of educational resources and information on biosimilars" that provides links to each state's specific regulations.[12,13] Finally, the FDA makes available an abundance of information that will also aid in the assessment and implementation of biosimilars.[14]

Several biologics, including rituximab, cetuximab, eculizumab, and pegfilgrastim, will be nearing the end of their patent life in the coming years, making them eligible for biosimilar competition.[15] Although the rollout of these products into the market has been slow, their arrival is inevitable. It is therefore important for pharmacists to assess the value of these medications from a clinical and financial standpoint, considering both their own practice and the overall U.S. healthcare system. ●●

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Karen Sweiss, PharmD: Winner of HOPA's 2017 Oncology Pharmacy Practice Literature Award

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Karen Sweiss, PharmD, was awarded HOPA's 2017 Oncology Pharmacy Practice Literature Award at the 13th Annual HOPA Conference in Anaheim, CA. This award recognizes an author who has written an article, other than scientific research, that contributes significantly to the betterment of the hematology/oncology pharmacy profession and describes innovations in community, hospital, or healthcare system hematology/oncology pharmacy practice that are applicable beyond the practice site where they were developed or evaluated.

Dr. Sweiss is a clinical assistant professor at the University of Illinois at Chicago (UIC) College of Pharmacy and a clinical pharmacist specializing in hematology and bone marrow transplant (BMT) at UI Health. In addition to having rounding responsibilities with the medical team, she is actively involved with protocol writing, nursing and physician in-services, and the Foundation for the Accreditation of Cellular Therapy (FACT) accreditation process, and she has also helped to establish a collaborative MD-PharmD multiple myeloma clinic. She gives didactic lectures at the UIC College of Pharmacy and precepts students and residents. Throughout her career, Dr. Sweiss has done research in collaboration with BMT physicians and pharmacists, and she has published both retrospective and prospective studies. She was recognized for her lead authorship of a May 2016 article in *Bone Marrow Transplantation:* "Melphalan 200 mg/m^2 in Patients with Renal Impairment Is Associated with Increased Short-Term Toxicity but Improved Response and Longer Treatment-Free Survival."[1]

High-dose melphalan with autologous stem cell transplant (ASCT) is considered a standard-of-care approach for treating patients with multiple myeloma. Although renal impairment is a common complication of multiple myeloma, most studies evaluating pretransplant conditioning with melphalan 200 mg/m^2 (Mel200) have excluded patients with renal impairment. The rationale for this exclusion is related to concern for increased treatment-related morbidity and nonrelapse mortality, although pharmacokinetic studies of melphalan clearance are conflicting with regard to renal function. Despite conflicting data, major working groups, including the International Myeloma Working Group (IMWG) and the American Society for Blood and Marrow Transplantation (ASBMT), recommend a dose reduction to 140 mg/m^2 for patients with creatinine clearance (CrCl) less than 60 ml/min.

The objective of Dr. Sweiss's study was to evaluate the clinical outcomes and tolerability of melphalan 200 mg/m^2 in patients with normal and impaired renal function. This retrospective single-center study included patients with multiple myeloma who received ASCT with melphalan 200 mg/m^2; it excluded those who received melphalan 140 mg/m^2, were receiving hemodialysis, had had a previous allogeneic stem cell transplant, or had received a second autologous transplant within 6 months of the first transplant. Renal impairment was defined as CrCl less than 60 ml/min on admission, calculated using the Cockcroft-Gault equation. Median CrCl in the renal impairment group (n = 46) was 50 ml/min (range 20–59), compared to 83 ml/min (range 60–128) in patients with normal renal function (n = 103).

Patients with renal impairment had longer time to neutrophil engraftment (median 10 days vs. 9 days, p = .008) and platelet engraftment (median 12 days vs. 10 days, p < .001). Duration of hospitalization was also significantly longer in the renal impairment group (16 days vs. 14 days, p = .02). Grade 4 mucositis, grade 2–4 diarrhea, and documented infections occurred more frequently in the renal impairment group. Duration of use of total parenteral nutrition and duration of diarrhea were both significantly longer in patients with renal impairment (10 days vs. 6 days and 8 days vs. 5 days, respectively). However, renal function in patients with CrCl less than 60 ml/min was not negatively affected by Mel200. Although pre- and posttransplant disease response data were not available for all patients, a statistically significant increase of 20% in rate of complete response (CR) was observed in the renal impairment group. A nonsignificant increase of 14% in CR rate was observed in patients with normal renal function. No significant difference in overall survival was seen, but treatment-free survival was significantly longer in the renal impairment group (37 months vs. 17 months, p = .0025).

Sweiss and colleagues concluded that patients with CrCl less than 60 ml/min experienced increased toxicities following high-dose melphalan compared to patients with normal renal function. Despite the expected, reversible toxicities, patients with impaired renal function had improved outcomes. This research makes an important contribution to the understanding of approaches to drug dosing in transplant conditioning regimens and provides supporting literature to tailor treatment options for this patient population.

Dr. Sweiss explains, "The idea of 'one size fits all' does not apply in this setting. Our BMT team assesses each multiple myeloma patient individually (based on renal function, age, and performance status) and subsequently determines the appropriateness of dose reduction in those patients with renal impairment. We have given Mel200 to patients with moderate renal impairment despite IMWG recommendations recommending reduced dose in patients with a creatinine clearance less than 60 mL/min. Based on our data, we favor giving Mel200 to these patients despite these recommendations as long as we have also weighed the risks and benefits against each other."

(continued on p. 10)

International Pharmacy Experiences

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I had my first opportunity to practice pharmacy abroad during an advanced pharmacy practice experience (APPE) rotation in Cape Town, South Africa, offered through Child Family Health International. As a student pharmacist, I wanted to develop skills in working with culturally diverse patients and providers, learn to serve in a setting with limited resources, and gain insight into healthcare challenges both internationally and at home. Although I did not yet know that I would become an oncology pharmacist, I knew that during my career I would look for ways to serve as a pharmacist internationally. A few years later, I was able to participate in two medical mission trips to Kenya. In each place, I worked in an unfamiliar setting with a new patient population and gained a fresh perspective on healthcare disparities and my role as a pharmacist. My preceptors and colleagues modeled ways to provide excellent patient care when one had little to work with, and I remember many of the patients I encountered in these communities.

During my APPE month at Victoria Hospital in Cape Town, I participated in ward rounds and assisted with dispensing and projects in the pharmacy. Each pharmacist checked orders on a designated ward, including the medical, surgical, emergency, and pediatric wards. While the pharmacist reviewed charts to verify appropriate prescribing and to provide medications from the pharmacy, I would also look over the medication list and patient notes for drug interactions and proper use. On some mornings, I went on medical rounds with the physician assistant students who were also studying through Child Family Health International and the local medical students, residents, and an attending physician. While being attentive to the medication aspects of a patient's case, I was able to observe the importance of the physical exam in a hospital where costly diagnostic tests were not readily available.

Back in the pharmacy, while I was assisting with order verification, I became familiar with international drug names and the formulary restrictions of a public hospital. I also performed pill counts to check adherence for patients visiting the HIV clinic. As my project for the site, I conducted a survey of patients in the waiting room to assess wait times, adherence, medication storage and disposal, and preferences for counseling and labeling. These patients spoke nine primary languages, so noting their preferred language could help ensure that they were provided translation and counseling when needed. Though most patients also spoke English, 17% expressed a preference for receiving counseling in another language, and I did work with a translator for one interview. When I found that 54% of patients did not understand what happens in a pharmacy, a local intern was tasked with creating educational posters for patients to read during their lengthy waits.

Throughout my rotation, I observed a number of challenges in the South African healthcare system: access issues; health inequities; healthcare staff shortages; and the burden of HIV, tuberculosis, and noncommunicable diseases. The healthcare providers I met were committed to serving patients well, despite these barriers. For example, I watched my preceptor passionately advocate for a patient with diabetes who was admitted after struggling to travel safely to her local pharmacy for insulin and obtain it when she arrived. I appreciated the opportunity to communicate with patients on rounds and through my survey. I gained perspective both on their difficulties and on their gratitude for the health care they received.

More recently, I traveled to Kenya for medical mission trips in March 2016 and March 2017. Our team of pharmacists, physicians, nurses, and other volunteers filled suitcases with medications and set up a weeklong clinic for patients with limited access to health care. On the first trip, we set up our pharmacy in a tent near a growing community outside of Malindi. On the second trip, we traveled to a rural area a few hours from Mombasa that had a public health center but not the staff to hold daily clinics for sizable crowds.

Patients would first see the physicians or nurses and then proceed to the pharmacy with a card listing their complaints and prescriptions. In the pharmacy, we would often recommend a medication depending on our inventory and then provide an appropriate dose. Although nearly all patients received multivitamins and anthelmintics, to some patients we dispensed antibiotics, antihypertensives, acid suppressants, and other medications as indicated. We worked closely with our translators, many of whom were healthcare professionals, to provide medication counseling.

Our interventions often felt small and temporary in light of the striking resource disparities that our patients faced, but for some patients even a small supply of acetaminophen could be meaningful. Because the healthcare providers and churches we worked with not only showed wonderful hospitality to our team but also made connections with the hundreds of patients who came to our clinics, they provided continuity in addressing the physical and spiritual needs of our patients.

(continued on p. 10)

Budgeting for Oncology Drug Costs and Supplies

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In 2010, the National Cancer Institute projected that cancer treatment costs would escalate from $124 billion to $206 billion by 2020. This model included the expected increase in the number of cancer diagnoses and the costs incurred per patient throughout the phases of cancer care.[1] These increased expenditures are influenced by several factors. Over the past several years, many new drug approvals or expanded indications for existing drugs have occurred in the oncology arena. In addition, the implementation of U.S. Pharmacopeia (USP) Chapter 800 may increase the costs associated with the maintenance of hazardous drug facilities.

With constantly rising costs, one of the most challenging tasks that a pharmacy manager faces is developing an oncology pharmacy budget. With newly approved drugs, the choice of treatment is often contingent upon biomarkers and disease pathology. Consequently, traditional cost-reduction strategies used in general hospital pharmacy practice are not applicable.

In some cases, executive hospital leaders may mistakenly blame rising oncology drug costs on the inability of the pharmacy leadership to control costs, when several factors actually escalate oncology drug spending. This trend is more apparent in a health system that has multiple hospitals offering minimal oncology services and a separate cancer center facility.[2] Other factors that can influence a pharmacy budget include the patient diagnosis case mix, prescribing shifts occurring because of new publications or new indications, and the entrance of recently approved new drugs to the market.[3]

New biologics and antineoplastic agents are often expensive. They fall into one of three budgetary categories: low-, moderate-, or high-impact. Moderate- or high-impact drugs represent uncontrolled costs. Controlled drug costs are associated with medications used for symptom management, such as the bisphosphates and anti-emetics. These low-impact costs can be reduced through the use of traditional cost-containment strategies, such as therapeutic interchanges, preferred agent choices, and contract negotiations with drug wholesalers.[4] In contrast, uncontrolled drug costs cannot be contained by cost-minimization strategies or by manager influence because they are driven by tumor pathology.

Budgeting for Oncology Drugs

It is advisable to separate the oncology drug budget from the traditional inpatient pharmacy budget, including gross revenue, supply costs, and salary costs. This separation will help with the trending and identification of internal health-system factors that could negatively affect the financial performance of the pharmacy.

In addition, it is important for the pharmacy leader to ensure that the gross revenue for the oncology drugs is accurately reflected in the budget. Drug billing codes are most often set as increments of a package size, and this is a source of charging errors due to system interface and programming issues. The pharmacy leader should confirm that the charge for a new drug is proportional to the cost. This will help prevent the drug charge to the patient from accidentally being set below the actual cost of the drug. Other sources of revenue errors include improper configuration in the order set and drug build, interface issues between systems, human factors (e.g., manipulation of the claims by nonpharmacy personnel), and the billing of drug waste.

Effective budget planning can improve the financial performance of the department. It is preferable to subdivide the oncologic drugs from other, general drugs and into different categories, such as therapeutic class. This method allows for ease of analysis and identification of short-term and long-term trends. Because of the differences between an oncology pharmacy department and a traditional inpatient hospital pharmacy, budget projections prepared by the finance department may not take adequate account of the adoption of new drugs or prescribing shifts. Using this specific information, pharmacy leaders can validate the budget projections using their own models. The model below can be adapted by pharmacy leaders to create budget projections.

Example of a Budget Model

Keeping a monthly oncology drug inventory is advantageous for budgeting purposes. In this example of a budget model (see **Table 1**), a physical inventory is performed on the last day of the month. The monthly inventory can be used to adjust monthly drug spending to realize the actual drug expense in a calendar month. The total drug expense is obtained by totaling the drug invoices on the last business day of the month. When this is completed, the total can be compared with the previous month's inventory. If the inventory is less than the previous month's, the difference is added to the drug spending. If the inventory is more than the previous month's, the difference is subtracted from the drug spending. This inventory adjustment method provides a more accurate drug expense total for the month.

A financial ratio is created by dividing the total drug expense by the total drug revenue. Each month, this financial ratio is calculated and compared to the one from the previous month. The financial ratio will vary by location in the same health system, depending on the disease states, prescribing variances, and patient case mix.[5] A financial ratio can change over time because of charge master changes or cost variances. This financial ratio model will reflect charge master issues such as an improper revenue threshold or an explosion code loaded for a new drug.[6]

Table 1. Budget Projection Example for a Low-Volume Pharmacy with an Average of 15 Patients per Day

	March	April	May	Quarterly Total	Business Days per Quarter	Daily Average	Annualized Actual	Projection (Growth and Charge Master Increase of 3%)	Final Projections
Revenue	$3,200,000	$3,800,000	$4,200,000	$11,200,000	64	$175,000	$44,450,000*	$45,783,500*	$45,783,500
Expense	$320,000	$385,000	$440,000	$1,145,000	64	$17,891	$4,544,314	$4,680,644**	$4,727,450†
Ratio							0.1022††		0.1032††

*Annualized actual = average daily expense multiplied by the total number of business days (254 days).
**Projection = actual annualized expense multiplied by 1.03 (3% = projected volume growth provided by the finance department).
†A 1% buffer of $46,806 ($4,680,644 x 0.01) is added to the projected drug expense (which includes 3% growth) without an adjustment to drug revenue. This buffer will allow for the cost of new drugs coming to market and will increase the financial ratio.
††Cost ÷ revenue = financial ratio. The actual ratio is 0.102, and the projected financial ratio is 0.103 (which includes a buffer for the cost of new oncology drugs).

To model the drug gross revenue and the drug cost for a cost center, take the following steps:

1. Sum the revenue and expenses of the previous 3 months if this is an established oncology infusion area. This will be the quarterly total.
2. Next, determine the average daily gross revenue and average daily drug expense by dividing the quarterly totals by the number of business days for the quarter.
3. The average daily revenue and average daily expense can then be annualized using the total number of business days for the next year.
4. Consulting the finance department to correctly model the anticipated percent change in the growth of the cancer program is recommended. It is important to evaluate revenue integrity to determine whether the current fiscal year's charge master will be modified in the next fiscal year, because this information will also change projected revenues.
5. Then adjust the projected annualized numbers, incorporating the anticipated revenue changes and the volume adjustment. Consider adding between 1% and 2% to the annualized drug cost projections to allow for the costs of new drugs or expanded indications.
6. Spread the gross revenue and drug cost over the months, according to the number of business days each month.
7. Use the calculated ratio to predict drug spending and expected revenue throughout the year.

Accounting for Future Expenses

With the approaching deadline of USP <800>, it is important to budget for additional expenses required for guideline compliance. With the new requirements, costs for the monitoring of buffer areas and anterooms may increase. The average cost of buffer area and anteroom USP <797> certification is $2,500, and an additional $2,000 is needed for the viable testing. This testing is required every 6 months.[7] If the sterile compounding spaces are more than 5 years old, the maintenance cost of the rooms increases. It would be beneficial to add $2,000 to the budget projection to allow for repairs.

Expenses for personal protective equipment (PPE) and closed-system transfer devices (CSTDs) can also have an impact on the budget if the pharmacy staff is not currently using these products in accordance with USP <800>.[8] The cost of PPE and CSTDs can be analyzed, and a financial ratio established for the cost centers. This ratio can be used to monitor the financial impact of practice changes.[6] These costs can be further subdivided for additional analysis. The Orlando Health model estimates the CSTD, PPE, cleaning, and supply costs at 13% of drug costs (**Table 2**).

Table 2. Orlando Health Model Estimates for Supply Costs

Supplies	Percentage of Total Supply Costs
Closed-system transfer devices	73
Base solutions, syringes, etc.	15
Tubing	7
Personal protective equipment	3
Cleaning agents	2

Conclusion

The rapid pace of change in the oncology arena complicates the management of an oncology pharmacy budget. The increasing number of new oncology drugs entering the market, combined with the expanding indications for existing oncology drugs, requires the development of budget strategies. Additionally, the implementation of USP <800> may increase the costs associated with the maintenance of hazardous drug facilities. Close monitoring and the adoption of a financial analysis ratio system will position pharmacy leaders for budgetary success. ●●

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Karen Sweiss, PharmD: Winner of HOPA's 2017 Oncology Pharmacy Practice Literature Award *(continued from p. 6)*

Her future research objectives include identifying ways to further improve and individualize dosing of high-dose melphalan. When asked to comment on the significance of the HOPA Oncology Pharmacy Practice Literature Award for her personally, Dr. Sweiss responded, "It was a great honor to be recognized for my research by my colleagues and by HOPA. Although we are not trained as basic scientists or full-time researchers, as clinical pharmacists, we have clinical experience that is so valuable and that nobody else has, and I think this experience allows us to contribute uniquely to research in hematology/oncology. This award has motivated me to continue to conduct research and contribute ideas that will impact the care of oncology patients, especially in BMT, in order to optimize efficacy and minimize toxicity from drug therapy." ●●

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International Pharmacy Experiences *(continued from p. 7)*

It was a joy to serve on these trips, both when the pharmacy tent was flooded with fun-loving children and when our other pharmacy was literally flooded during an unexpected rain.

Working as a pharmacist in another country and culture will challenge you to be flexible and embrace the unfamiliar, but I would recommend the experience. These trips have made me more keenly aware of both the privileges of practicing health care in the United States and the inequities that are present here as well. In hematology and oncology pharmacy, our patients also have their own unique struggles. The importance of valuing and advocating for our patients is universal, and the responsibility of providing optimal medication management with finite resources always applies. Though I may travel back to Kenya or elsewhere in the future, for now I can serve my patients here compassionately and seek to support my colleagues around the world.

If you are interested in learning more about international rotations through Child Family Health International, information about these programs is available at https://www.cfhi.org/all-programs. I would also recommend looking for volunteer and mission opportunities through organizations in your own community. ●●

The Job Search: Timelines and Expectations

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"Choose a job you love, and you will never have to work a day in your life." These words never have more meaning than when you are selecting your first clinical specialist position following completion of pharmacy residency training. As I reflect on the transitions within my own career and serve as a mentor to a new class of residents searching for their dream job, I wish I had been better informed about the unique challenges involved in searching for and selecting a career.

When I speak to my residents about their ideal first job, I try to help them align their passions in pharmacy with the available positions. The number of specialty residents entering the workforce in oncology pharmacy has continued to increase, up to 152 in 2017,[1] and an increase in available positions has given postgraduate year 2 (PGY-2) residents a high rate of placement into their trained specialty.[2] However, despite an increase in available positions, the increased emphasis placed by national organizations on ambulatory, population health, and nontraditional opportunities for pharmacists,[3] as well as shifts in payer models in healthcare institutions, contrasts directly with the experiences focused largely on acute care that many residents receive in their residency training. As these residents begin searching for positions as oncology clinical specialists, they may face difficulties that could have a negative impact on their job satisfaction. I discuss a few of these difficulties below.

Having Rigid Career Goals and Interests

The American Society of Health-System Pharmacists (ASHP) purpose statement for PGY-2 residents specifies that "residents who successfully complete an accredited PGY2 pharmacy residency are prepared for advanced patient care, academic, or other specialized positions, along with board certification, if available."[4] This is a very broad statement, and it is often difficult for oncology residency programs to offer a wide enough array of experiences to provide specialist-level knowledge in all critical areas listed in the standard. Given the exposure to oncology services that many students and PGY-1 residents receive, a majority of incoming PGY-2 residents often have a strong interest in acute care.

As a residency director, I have often found it challenging to introduce the multitude of other rapidly expanding areas of clinical practice within oncology (ambulatory care, administration, research, academic work, information technology, specialty pharmacy) in a meaningful way within the confines of a 1-year specialty residency. Residents searching for a first position among the available career opportunities may easily be overwhelmed; so they may gravitate toward the practice areas in which they have had the most extensive protected exposure. Early communication with the residency director and an attempt to gain exposure to all practice areas early in the residency year can give a resident valuable insight during the search for positions and can make the search more manageable.

One of the largest challenges facing residents entering the workforce is caused by their setting geographic limits for positions they will accept. A 2017 ASHP survey showed that approximately one third of residency graduates compromise on geographic location when selecting an available position; however, an additional third compromise by taking a position outside their specialty area.[2] It is critical for residents to determine early in the residency year if geographic location will be an important factor in their career search; if so, discussing it with resource people in the program will help them establish networking opportunities and improve the likelihood that they can obtain a position in the desired location.

Feeling Stress Caused by Unfamiliar Timelines

The selection process for PGY-1 and PGY-2 residencies is highly standardized, which can be challenging and unnerving for potential specialist candidates after their residency training. Given budgetary timelines and restrictions, the availability of positions during the time frame of a residency search may be limited and cause angst. Also, because many institutions that are seeking specialists have overlapping residency programs, they often conduct interviews after completion of the match to allow for a dedicated assessment of residency candidates. Residents should be prepared to extend their career search well into the second half of the residency year and use alternative search strategies when evaluating the available positions around the country.

Making Inadequate Use of Job-Source Information

In addition to the extended timelines that are often part of the search for a first clinical position, new graduates may find cumbersome the number of avenues for identifying job prospects. Although using traditional avenues like the ASHP's personnel placement services may be a viable option, the aforementioned budgetary timelines mean that many institutions may not yet have secured funding for positions at this juncture and may not be present to recruit. Health systems may instead outsource the promotion of their available positions through career websites and recruiters. Residents should be diligent in exploring these options and vetting opportunities through mentors in their institution or directly through the prospective institution.

Within oncology, specialty meetings are an ideal forum used by employers to promote potential career opportunities to a targeted population of job seekers. HOPA offers a variety of ways for residents to connect directly with institutions and discuss career opportunities throughout the residency year. HOPA posts pharmacy jobs on its website (https://careers.hoparx.org) and holds a recruitment fair at the annual conference. At the recruitment fair residents can meet several prospective employers and build meaningful relationships while discussing available career options in a variety of practice areas. Finally, residents should use the

networking opportunities afforded by their own residency program to gain access to positions not yet posted to well-known career portals.

Rushing into Career Options That May Not Be the Best Fit

Because much of postgraduate training is based on concrete, short-term goals, residents may find it difficult to take the first step in a long-range career. Because they are unfamiliar with the intricacies of job selection and may be experiencing stress over timelines, they may inappropriately accept their first job offer out of fear that they will not obtain a clinical position. Residents should pursue career options in a variety of practice settings, if possible, and compare and contrast positions before making a selection. A strong desire to practice in a certain area may mean that other factors important in job satisfaction are given too little weight. Residents entering a job search should objectively assess these factors as well: organization size and practice philosophy, size of the specialist group, research and educational prospects, the ability to enact change within the department, specialist mentorship, and personality fit.

Before choosing their first clinical position, residents should consider their own understanding of the position and institution and other information provided by advisers from their pharmacy training. Your first postgraduate position does not dictate your future path as a pharmacist, but it should build the foundation for helping you reach your ultimate career goals.

Failing to Understand the Role of Negotiation

In many instances, residents think they do not have the ability to negotiate when they are selecting their first specialist position. Although many institutions may be firm on items like salary, in other areas residents can negotiate to improve their ultimate job satisfaction. Residents should ensure that they thoroughly understand the benefits of the position, in relation to both human resources and educational opportunities. Previously established factors in career satisfaction should, at a minimum, be discussed, if not reconciled, prior to acceptance of the terms of a position.

The transition from PGY-2 resident to a clinical or academic position is an exciting, yet challenging time in a pharmacist's career. It is crucial that a resident be able to identify the key components of a first career option that will allow for a successful transition into long-term career opportunities. The hectic nature of residency training, especially in the PGY-2 year, can make it difficult for residents to reflect upon what they are seeking in a career, especially if they wish to pursue an area within their specialty practice that they have not been heavily exposed to. Candidates should take initiative early on to establish the trajectory of oncology pharmacy practice and consider how this trajectory may affect the number and type of available positions when the time for selecting a post arrives. Although unfamiliarity with recruiting processes and timelines may make the resident uncomfortable in this transitional period, using national organizations and institutional mentors can make possible a successful first step into the professional postgraduate arena. ●●

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Here We GO Again: The Reapproval of Gemtuzumab Ozogamicin

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Induction therapy with 7+3 has been the hallmark of chemotherapy for newly diagnosed acute myeloid leukemia (ND-AML) for several decades. The year 2017 resulted in several U.S. Food and Drug Administration (FDA) approvals for AML, increasing the therapeutic armamentarium. The fourth AML therapy approved in 2017, gemtuzumab ozogamicin (GO), was previously approved for CD33-positive AML but was withdrawn from the market in 2010. Given the return of GO to our treatment options, it is important that we understand differences between the past and present approvals and the data that emerged in the interim and allowed the reapproval.

CD33 is expressed on myeloid precursors, maturing myeloid cells, and monocytes. CD33 is present on at least some leukemia blasts in almost all patients with AML, with about 50% of patients expressing CD33 on more than 75% of blasts.[1] Despite CD33's status as a common marker in AML, early studies of CD33 antibodies had shown limited clinical benefit.[2] However, because antibody binding to CD33 results in rapid internalization of the antigen and antibody, conjugation of other molecules to enhance efficacy of therapy was considered. Calicheamicins are potent antitumor antibiotics that bind into the minor groove of DNA, resulting in single- and double-strand breaks. Because of the potency and toxicity of calicheamicins, it is not clinically feasible to give them in their conventional form. Binding of a calicheamicin derivative to the CD33 antibody with an acid-labile linker allows for cytotoxicity against CD33-positive leukemia cells, while decreasing off-target toxicity.[3]

Clinical Trials

The initial FDA approval of GO in 2000 was as a single agent, for the treatment of CD33-positive AML in patients age 60 or older in first relapse who were deemed not to be candidates for other cytotoxic chemotherapy. This approval was based on two uncontrolled phase-2 studies, where GO-treated patients in first relapse achieved a complete response (CR) in 16.2% of cases and CR with incomplete platelet recovery (CRp) in 13.4%.[4,5] This approval made GO the first FDA-approved antibody-drug conjugate.[6] On the basis of these early studies showing complete or nearly complete CD33-binding saturation with a dose of 9 mg/m^2, this became the recommended dose, with administration separated by 2 weeks.[3]

As part of postapproval investigation, Southwest Oncology Group study S0106 was conducted to confirm the therapeutic benefit of GO. S0106 was a prospective trial of patients up to age 60 with *de novo* AML randomized to receive standard induction with or without GO 6 mg/m^2 given on day 4. Patients receiving GO were given a reduced dose of daunorubicin (45 mg/m^2) compared to the control group (60 mg/m^2). The results of this study showed that GO-treated patients had increased treatment-related mortality (TRM) (5.5% vs. 1.4%, p = .0062), including fatal hemorrhage, without any improvement in CR or overall survival (OS) compared to patients receiving standard induction alone.[7] Because of the results of S0106, as well as a higher rate of sinusoidal obstruction syndrome (SOS) following approval, GO was withdrawn from the commercial market in 2010, pending additional clinical trial review.

Subsequent trials such as NCRI AML-17 showed that GO given at a dose of 6 mg/m^2 showed no improvement in CR, relapse, or OS compared to 3 mg/m^2 but did confer higher TRM and SOS risk.[8] Further analysis showed that the risk of SOS correlated with higher C_{max} with the first dose of GO.[9] Levels of CD33 molecules are downregulated following GO exposure but return to baseline after 72 hours.[10] This data led to the hypothesis that lower, fractionated doses of 3 mg/m^2 on days 1, 4, and 7 may be safer and equally efficacious compared to higher doses of 6 or 9 mg/m^2 separated by 2 weeks.

A meta-analysis of five randomized controlled trials adding GO to induction therapy showed a reduced risk of relapse and improved 5-year OS, along with fewer early deaths in patients receiving 3 mg/m^2 compared to 6 mg/m^2. In these studies, survival benefit was seen in patients with favorable cytogenetics (odds ratio [OR] .47, .31–.73; p = .0006) and intermediate cytogenetics (OR .84, .75–.95; p = .005), but not in patients with adverse cytogenetics (OR .99, .83–1.18; p = .9). In comparison with studies using higher single doses, the use of lower fractionated doses of GO did not increase TRM.[11] On the basis of the data supporting the efficacy and safety of lower fractionated doses, this dosing schedule was accepted for the pivotal trial ALFA-0701.[12]

ALFA-0701 was a multicenter open-label randomized phase-3 trial of conventional induction chemotherapy with or without GO for induction and consolidation in 271 patients 50–70 years old with ND-AML. In the induction regimen of both treatment arms, patients received 60 mg/m^2 of daunorubicin as part of the 7+3 regimen. The primary end point of event-free survival (EFS) was extended with the addition of GO to 7+3 versus 7+3 alone (17.3 vs. 9.5 months, p < .001). OS was also increased in GO-treated patients (19.2 vs. 34 months, p = .0368). Persistent grade 3 and 4 thrombocytopenia was reported in 4 (3%) patients in the control group and in 22 (16%) in the GO group (p < .001).[12]

GO was also studied as first-line monotherapy for older patients unable to receive intensive chemotherapy. Patients were randomized to receive either GO 6 mg/m^2 on day 1 and 3 mg/m^2 on day 8 or best supportive care (BSC). Patients receiving GO had a median OS of 4.9 months versus 3.6 months for BSC.[13] Thirty-day all-cause mortality was similar for the groups, suggesting that the fractionated schedule limited the additional TRM observed in previous high-dose studies.[14]

GO has shown benefit in AML patients with relapsed disease. In the Mylofrance-1 trial, 57 patients in first relapse following a remission of 3–18 months received fractionated GO 3 mg/m^2 on

days 1, 4, and 7. By day 43, 15 patients achieved CR, and 4 patients achieved CRp. In this study, no significant difference in remission based on age, cytogenetic risk, or duration of first remission was seen.[15]

Safety

Although fractionated dosing of GO has decreased TRM risk, hepatotoxicity, including SOS, remains a concern. In the ALFA-0701 study, 6 patients (4.6%) developed SOS, either during GO treatment or after hematopoietic stem cell transplant (HSCT). The median time of onset of SOS after GO was 9 days (range: 2–298 days), with most events occurring within 4 weeks of GO administration.[12,16] Rates of SOS increase in patients with baseline hepatic impairment, and GO should be delayed until hepatic function normalizes in this population. Because of the risk of SOS in GO patients receiving HSCT, the ALFA-0701 study recommended at least 2 months between the last GO dose and HSCT.[12,16] Because of the risk of high mortality of SOS, close monitoring for signs of SOS and prompt management are warranted. Further analysis of prophylactic strategies to prevent SOS following GO may be useful, though previous reports assessing ursodiol did not show a benefit when GO was given at higher doses.[17]

Infusion reactions, including dyspnea, hypotension, and anaphylaxis, have been seen with GO. Because patients with higher pretreatment peripheral blast counts may be at higher risk of severe infusion reactions, cytoreduction is currently recommended in patients with white blood cell counts above 30,000/mm^3. Premedication with acetaminophen, diphenhydramine, and corticosteroids is currently recommended prior to the administration of GO.[16]

GO-treated patients can develop myelosuppression, including thrombocytopenia. Persistent thrombocytopenia occurred in 16% of the patients treated with GO in the AML-0701 trial, leading to an increased need for platelet transfusions compared to patients treated with standard induction chemotherapy. Fatal bleeding events occurred in 3% of patients receiving GO.[12,16] The study protocol was also amended to omit GO in the consolidation regimen in patients who did not achieve platelet recovery after induction.[12] Therefore, patients treated with GO should be monitored closely during and after therapy for need for transfusions as well as for signs of bleeding.

Other calicheamicin-containing therapies have been observed to cause QT interval prolongation. Current labeling recommends monitoring for QTc prolongation during GO therapy, in particular when GO is administered with known QTc-prolonging medications and in patients with a history of QTc prolongation.[16]

Preparation and Administration

Prior to reconstitution, the drug product vials should be allowed to reach ambient temperature for approximately 5 minutes. The reconstituted solution should be used immediately or within an hour if refrigerated. The reconstituted solution should be added to normal saline (NS) to make a total volume of 50 ml or 100 ml, depending on the dose.[16] According to the manufacturer (Pfizer, e-mail communication, October 2017), the stability data for GO infusions was based on a concentration range of .075–.234 mg/ml. Following dilution into NS, the solution can be stored at room temperature for up to 6 hours or refrigerated for up to 12 hours. GO should be infused over 2 hours using an in-line .2-micron polyethersulfone (PES) filter. During infusion, the intravenous bag should be protected from light with the use of a light-blocking cover. The infusion line does not need to be protected from light.[16]

Future Directions

Calicheamicin is a substrate of ATP-binding cassette (ABC) transporters, including P-glycoprotein (Pgp). One characteristic of some AMLs with adverse cytogenetics is high expression of Pgp, which may explain why this patient subgroup does not show significant improvement with GO therapy.[3] Coadministration of inhibitors of ABC transporters with GO may help to increase the intracellular concentration of free calicheamicin and improve calicheamicin-induced cytotoxicity. Further experience with fractionated dosing with GO may also lead to improved tolerability and enhanced response.[10]

Because of the high density of CD33 expression in patients with acute promyelocytic leukemia (APML), the addition of GO to all-trans retinoic acid (ATRA) has been shown to be effective for both newly diagnosed and relapsed disease. In one study where GO could be given in addition to ATRA and arsenic trioxide in high-risk APML, 4-year OS was 89% (95% confidence interval [CI] 70%–96%) in those patients receiving GO.[18] Further comparisons to idarubicin-containing regimens may be warranted.

The induction and consolidation regimens used concurrently with GO could warrant further review. In S0106, daunorubicin doses in the GO group were decreased to 45 mg/m^2 to prevent toxicity. In ALFA-0701, induction daunorubicin doses were 60 mg/m^2, and the study included a population of patients 50–60 years of age. With the current data showing that treatment-related toxicity is significantly improved with lower fractionated doses of GO, research into higher daunorubicin doses of 90 mg/m^2 in younger patients with good cytogenetics to further enhance response and survival may be useful.

The recent reapproval of GO comes at a time when several other new treatments have arisen for patients with AML. Evaluating patients for GO-containing therapy compared to other new regimens is important prior to initiation of treatment. In comparison to the time when 7+3 was the standard of care for all patients, initiation of therapy may now be delayed in order to confirm cytogenetics and molecular status so that the most appropriate induction regimen is chosen. Studies evaluating the combination of GO with other recently approved therapies may also be useful in developing more effective AML treatment regimens in the future. ●●

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Cyclin-Dependent Kinase 4/6 Inhibitors in the Management of Breast Cancer

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Cyclin-dependent kinases (CDKs) are a family of proteins involved in the regulation of the cell cycle. Cyclins regulate the cell cycle by activating CDKs to phosphorylate other molecules. This activation then signals the cell that it is ready to pass into the mitotic phase of the cell cycle where cell division occurs. In many cancers, either CDKs are overactive or CDK-inhibiting proteins are not functional, causing overproliferation of cancer cells.[1,2] CDKs act on different parts of the cell cycle. Specifically, CDK 4/6 is a key component of cell growth and proliferation for both normal and cancerous cells. A major target of CDK 4/6 during cell cycle progression is the retinoblastoma protein (Rb). Rb is a tumor-suppressor protein that prevents excessive cell growth by inhibiting the cell-cycle progression between the G_1 checkpoint and the S phase until a cell is ready to divide. Hyperphosphorylation of Rb by CDK 4/6 inactivates its growth-suppressive properties, leading to overproduction of cancer cells.[2,3] Therefore, it is rational to target CDKs, particularly CDK 4/6, to prevent unregulated proliferation of cancer cells. Recently, advances have been made in using highly selective CDK 4/6 inhibitors in the treatment of breast cancer. The CDK 4/6 inhibitors that are currently available commercially include palbociclib, ribociclib, and abemaciclib (**Table 1**).

Currently Approved CDK 4/6 Inhibitors

Palbociclib

Palbociclib (Ibrance), in combination with letrozole in the PALOMA-2 trial, was granted accelerated approval by the U.S. Food and Drug Administration (FDA) in February 2015 for the treatment of hormone receptor (HR)–positive/human epidermal growth factor receptor 2 (HER2)–negative advanced breast cancer.[3] In this double-blind phase 3 study, patients were randomly

Table 1. Summary of Approved CDK 4/6 Agents

	Palbociclib (Ibrance)	Ribociclib (Kisqali)	Abemaciclib (Verzenio)
Indication(s)	Advanced or metastatic HR-positive/HER2-negative breast cancer • in combination with aromatase inhibitor for postmenopausal women as first-line therapy • in combination with fulvestrant following disease progression on endocrine therapy	Advanced or metastatic HR-positive/HER2-negative breast cancer • in combination with aromatase inhibitor for postmenopausal women as first-line therapy	Advanced or metastatic HR-positive/HER2-negative breast cancer • in combination with fulvestrant following disease progression on endocrine therapy • monotherapy following disease progression on endocrine therapy and prior chemotherapy
Dosing and dose modifications	125 mg by mouth daily (21 days on and 7 days off) Same dosage given when used in combination with fulvestrant +/- LHRH agonist in pre- and perimenopausal women Modify or hold doses based on toxicity: hematologic, hepatic, and any grade 3 or 4 toxicity	600 mg by mouth daily (21 days on and 7 days off) in combination with aromatase inhibitor Modify or hold doses based on toxicity: hematologic, hepatic, cardiovascular, and any grade 3 or 4 toxicity	150 mg by mouth twice daily in combination with fulvestrant +/- LHRH agonist in pre- and perimenopausal women 200 mg by mouth twice daily (monotherapy) Modify or hold doses based on toxicity: hematologic, hepatic, diarrhea, any other persisting grade 2 toxicity, and any grade 3 or 4 toxicity
Adverse effects	Neutropenia, gastrointestinal toxicity, infections	Neutropenia, hepatobiliary toxicity, QT prolongation	Diarrhea, neutropenia, elevated LFT results, thromboembolism
Metabolism	CYP3A4*, weak inhibition of CYP3A4	CYP3A4*, moderate inhibition of CYP3A4	*BCRP*/ABCG2, CYP3A4*, P-glycoprotein/ABCB1

*Major substrate.
Note. BCRP/$ABCG_2$ = breast cancer resistance protein/ATP-binding cassette subfamily G member 2; CYP3A4 = cytochrome P450 3A4; LFT = liver function test; LHRH = luteinizing hormone-releasing hormone.

assigned, in a 2:1 ratio, to receive 125 mg of palbociclib by mouth (PO) daily for 21 consecutive days followed by 7 days off or the placebo; all patients received 2.5 mg of letrozole PO daily. A total of 666 postmenopausal women with HR-positive/HER2-negative breast cancer who had not received prior treatment for advanced disease were enrolled in this study. Median progression-free survival (PFS) was 24.8 months (95% confidence interval [CI], 22.1 to "not estimable") in the palbociclib-letrozole group compared with 14.5 months (95% CI, 12.9–17.1) in the placebo-letrozole group (hazard ratio [HR] for disease progression or death, .58; 95% CI, .46–.72; two-sided $p < .001$). Most common adverse events of grade 3 or 4 in the palbociclib-letrozole group were neutropenia (66.4%) and leukopenia (24.8%).[4]

Palbociclib was studied further in the PALOMA-3 trial to assess the safety and efficacy of the combination of palbociclib and fulvestrant in premenopausal or postmenopausal women with HR-positive advanced breast cancer that progressed during prior endocrine therapy. This double-blind phase 3 study included 521 women with advanced HR-positive/HER2-negative breast cancer that had relapsed or progressed during prior endocrine therapy. Patients were randomly assigned, in a 2:1 ratio, to receive palbociclib 125 mg per day (for 3 weeks followed by 1 week off) and fulvestrant 500 mg intramuscularly (day 1, day 15, day 29, and then every 4 weeks) or matching placebo and fulvestrant. Median PFS was 9.5 months (95% CI, 9.2–11) for the palbociclib-fulvestrant group and 4.6 months (95% CI, 3.5–5.6) for the placebo-fulvestrant group (HR .46; 95% CI .36–.59; $p <$ .0001). The most common grade 3 or greater adverse event was neutropenia (65%).[4] The PALOMA-2 and PALOMA-3 trials yielded FDA approvals in the first-line and endocrine refractory settings, respectively.[5]

Ribociclib

Ribociclib (Kisqali) was approved by the FDA on March 13, 2017, in combination with letrozole for treatment of postmenopausal women with HR-positive/HER2-negative advanced or metastatic breast cancer.[6] Approval was based on a randomized double-blind placebo-controlled international clinical trial, MONALEESA-2. A total of 668 postmenopausal women with HR-positive/HER2-negative advanced or metastatic breast cancer were randomized to receive either oral ribociclib 600 mg or placebo once a day for 21 consecutive days, followed by 7 days off, with letrozole 2.5 mg for a total of 28 days. Treatment continued until the disease progressed or unacceptable levels of toxicity were reached. After 18 months, the PFS rate was 63% (95% CI, 54.6–70.3) in the ribociclib-letrozole group versus 42.2% (95% CI, 34.8–49.5) in the placebo-letrozole group (HR .56; 95% CI, .43–.72; $p = 3.29 \times 10^{-6}$ for superiority). The objective response rate in patients with measurable disease was 52.7% in the ribociclib-letrozole group versus 37.1% in the placebo-letrozole group. Overall survival (OS) data are immature. The most common grade 3 or 4 adverse events observed in patients taking ribociclib were neutropenia (59.3%), leukopenia (21.0%), hypertension (9.9%), abnormal liver function tests (increased alanine aminotransferase 9.3%, increased aspartate aminotransferase 5.7%), and lymphopenia (6.9%).[7]

The MONALEESA-7 trial is a phase 3 randomized double-blind placebo-controlled trial investigating the efficacy and safety of ribociclib in combination with oral hormonal therapies and goserelin versus endocrine therapy (ET) alone in premenopausal or perimenopausal women with HR-positive/HER2-negative advanced breast cancer who had not previously received ET for advanced disease. The primary end point for the study was PFS, with secondary end points of OS, overall response rate, and clinical benefit rate. In the study, in the ribociclib plus tamoxifen/nonsteroidal aromatase inhibitor arm the median PFS was 23.8 months (95% CI, 19.2 to "not reached") compared to 13 months in the placebo arm (95% CI, 11–16.4). The primary end point was met in reference to PFS (HR = .553; 95% CI, .441–.694; $p = 9.83 \times 10^{-8}$). The adverse events reported were consistent with those in other randomized clinical trials involving ribociclib and ET: all grades—neutropenia {76%), hot flashes (34%), nausea (32%), leukopenia (31%), and arthralgia (30%).[8]

Abemaciclib

Abemaciclib (Verzenio) was granted FDA approval for stand-alone use on September 28, 2017, for the treatment of HR-positive/HER2-negative advanced or metastatic breast cancer with disease progression following ET based on the MONARCH 1 trial.[9] It was designed to evaluate the single-agent activity and adverse-event profile of abemaciclib. In this phase 2 single-arm open-label study, 132 women with HR-positive/HER2-negative metastatic breast cancer whose disease had progressed on or after prior ET and had received one or two chemotherapy regimens in the metastatic setting were enrolled. Patients were given abemaciclib 200 mg PO every 12 hours until the disease progressed or an unacceptable level of toxicity was reached. The primary objective of the MONARCH 1 trial was investigator-assessed objective response rate. The objective response rate in MONARCH 1 was 19.7% (95% CI, 13.3–27.5; 15% not excluded). Secondary end points of clinical benefit rate (CBR), PFS, and OS were also analyzed. The CBR was 42.4%, the median PFS was 6 months, and the median OS was 17.7 months. The most common treatment-emergent adverse events of any grade were increased creatinine (98.5%), diarrhea (90.2%; managed with loperamide and fluids), decreased neutrophil count (87.7%), anemia (68.5%), fatigue (65.2%), and nausea (64.4%). Discontinuations due to adverse events were infrequent (7.6%).[10]

The approval for the drug in combination with fulvestrant was based on results of the MONARCH 2 trial.[11] The MONARCH 2 trial compared the efficacy and safety of abemaciclib-fulvestrant versus fulvestrant alone in patients with advanced breast cancer. This double-blind phase 3 study included 670 women with HR-positive/HER2-negative advanced breast cancer whose disease had progressed while they were receiving neoadjuvant or adjuvant ET, less than 12 months from the end of adjuvant ET, or while they were receiving first-line ET for metastatic disease. Patients were randomly assigned in a 2:1 ratio to receive abemaciclib 150 mg twice a day on a continuous schedule and fulvestrant 500 mg per label

or matching placebo and fulvestrant. Women in the abemaciclib-fulvestrant group had a median PFS of 16.4 months compared with 9.3 months in the placebo-fulvestrant group (HR .553; 95% CI, .449–.681; $p < .001$). The most common adverse events seen in the abemaciclib-fulvestrant group were diarrhea (86.4%), neutropenia (46.0%), nausea (45.1%), and fatigue (39.9%).[11]

Future Direction of CDK 4/6 Inhibitors

Palbociclib, ribociclib, and abemaciclib have shown activity in a variety of treatment settings in breast cancer patients. Palbociclib has been incorporated into the adjuvant endocrine treatment setting in HR-positive/HER2-negative early-stage breast cancer in the PALLAS trial. The PALLAS trial is a prospective two-arm international multicenter randomized open-label phase 3 trial evaluating the benefit of 2 years of palbociclib 125 mg (3 weeks on and 1 week off) with the standard 5 years of ET compared to 5 years of ET alone. The primary outcome measure of the PALLAS trial will be invasive disease–free survival.[12]

Ribociclib is also being evaluated in the adjuvant setting of HR-positive/HER2-negative patients in the EarLEE-1 and EarLEE-2 trials. Both studies are multicenter randomized double-blind phase 3 clinical trials that will evaluate the safety and efficacy of ribociclib with ET as adjuvant therapy in pre- and postmenopausal women. EarLEE-1 will assess ribociclib plus adjuvant ET compared to adjuvant ET alone in women with HR-positive/HER2-negative high-risk early breast cancer, and EarLEE-2 will enroll women with HR-positive/HER2-negative intermediate-risk early breast cancer. In both trials the primary outcome measure is invasive disease–free survival.[13]

Abemaciclib is also being investigated outside the metastatic setting of breast cancer. The NeoMONARCH study is analyzing the benefits of abemaciclib for 14 weeks in combination with letrozole (14 weeks of abemaciclib 150 mg PO twice daily only vs. 14 weeks of abemaciclib 150 mg PO twice daily plus anastrazole 1 mg PO daily vs. anastrazole 1 mg PO daily alone). End points in the trial include change in Ki-67, pathological complete responses, complete responses, and radiological responses.[14] CDK 4/6 inhibitors are being investigated in the adjuvant, neoadjuvant, and metastatic setting in combination with the mammalian target of rapamycin inhibitors and other novel targeted agents as well.

Conclusion

Palbociclib, ribociclib, and abemaciclib are CDK 4/6 inhibitors currently approved by the FDA for the treatment of HR-positive/HER2-negative advanced breast cancer. The CDK 4/6 inhibitors are an important addition to the treatment options available for the management of breast cancers and are also being evaluated for treatment of other malignancies. CDK 4/6 inhibitors are being studied clinically in other tumor types, specifically non-small-cell lung cancer, especially the KRAS-mutant subset. Additionally, the drugs are being looked at preclinically and clinically in a variety of other tumor types, including melanoma, glioblastoma, pancreatic cancer, and colorectal cancer. ●●

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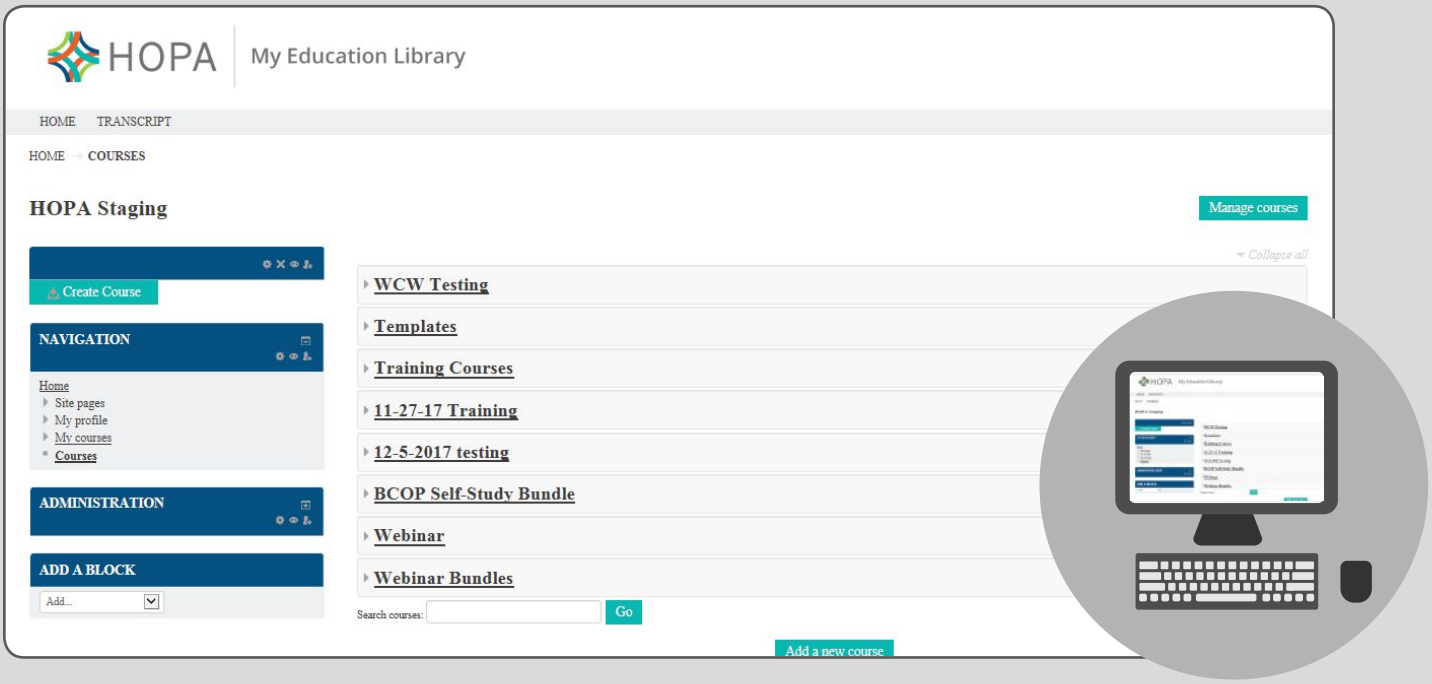

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HOPA Hosts Women Leadership Summit

This report was prepared by HOPA's Nominations and Leadership Development Committee (NLDC). The 2015–2017 committee included Laura Michaud (2016–2017 chair), Jane Pruemer (2015–2016 chair), Jaime Anderson, George Carro, David Henry, Lauren McBride (2016–2017 vice chair), Rowena Schwartz, and Laura Wiggins. The NLDC has now been divided into two subcommittees: the Nominations Subcommittee and the Leadership Development Subcommittee.

Participants in HOPA's Women Leadership Summit (*from left to right*): Debbie Stockwell, Jane Pruemer, Scott Soefje, Rebecca Finley, David Henry, Rowena Schwartz, Sandra Swain, Michele Galioto, Nicky Dozier, Laura Michaud, Jill Kolesar, Marie Chisholm-Burns, Susan Goodin, Jaime Anderson, and George Carro

HOPA took an important step in the fall of 2017: the organization hosted a summit to explore leadership issues for women that have the potential to affect our membership and our profession. A 1-day meeting was held on September 14, 2017, before the HOPA Practice Management Program meeting in Chicago, IL, and included participants from across the fields of oncology and pharmacy. The meeting is a part of the strategic leadership initiative developed through the work of the HOPA Nominations and Leadership Development Committee (NLDC) in 2016. The Women Leadership Summit provided an opportunity to collaborate with colleagues in cancer care and pharmacy to develop a leadership strategy for HOPA.

What was the goal of the HOPA Women Leadership Summit?

The goal of the Summit was to help HOPA *set priorities for leadership development for our membership.* Members of the NLDC have worked together on a strategic plan to facilitate the development and growth of leaders in the HOPA membership. We realized that leadership means different things to different people, and we wanted to be sure that we considered the needs of our broad membership. In addition, we were excited to learn from the experiences of others who have worked at setting a leadership strategy for their organizations—we wanted to learn from these experts.

Who participated in the HOPA Women Leadership Summit?

HOPA is not the first pharmacy or oncology organization to tackle this issue. To capitalize on the work done by other organizations (e.g., the American Society of Health-System Pharmacists and the American Society of Clinical Oncology), we felt it was imperative to bring together individuals from these organizations to learn from their work. We asked participants to come to the Summit and share their successes and growth experiences. In addition, we invited HOPA members from a variety of practice and professional environments to ensure that the Summit represented our broad membership. Although limited by the number of attendees that we could reasonably invite, we invited individuals who could provide insights and differing views. We knew that from this diverse group of professionals we would hear wide-ranging views. Learning from others is important to help HOPA continue to move forward in developing leadership resources for all members, regardless of gender. It is important to note that *issues for women in leadership were a focus, but HOPA took this opportunity to learn more broadly about leadership opportunities for the whole organization.*

What was the agenda for the Summit?

The Summit planning committee used information provided by HOPA members to develop an agenda for this working meeting. In the summer of 2017, we asked HOPA members to tell us what they saw as issues related to women in leadership. Although we heard clearly that leadership is an issue that extends beyond women, we also learned that 60% of respondents had personally experienced or witnessed barriers to women in leadership development. Additionally, HOPA members were asked to rank topics that the NLDC felt were important to address at the Summit. We were happy to receive a number of additional topics from the membership to include in the Summit discussion.

What was learned from the Summit? What steps are planned as a result of the Summit?

- **What the literature tells us:** Marie Chisholm-Burns, PharmD MPH MBA FCCP FASHP FAST, opened the Summit with a keynote address reviewing the published data surrounding women in leadership in pharmacy. This thought-provoking presentation emphasized some key challenges faced by women in leadership positions and served as a foundation for group discussion. To learn more, see Dr. Chisholm-Burns's article published in 2017 in the *American Journal of Health-System Pharmacy.*[1]
- **Participants' discussion:** The NLDC's written report to the HOPA Board of Directors stated that "the highlight of the Summit was the dynamic discussion of the participants." The discussion that began following Dr. Chisholm-Burns's address continued throughout the day. Roundtable discussions helped

to capture ideas and develop priorities. The format of the day was guided open discussion, with the goal of identifying issues that are important to our membership. The group (pictured in the photo on p. 21) was interested in hearing about what our members shared in the membership survey, and these ideas and experiences helped the group to better define priorities.

- **Priority setting**: The objective of the meeting was to set HOPA's priorities both for leadership development and for leadership development for women. These priorities (see **Table 1**) have been shared with the HOPA board and the Leadership Development Subcommittee (2017–2018) for further action. The Leadership Development Subcommittee is now working to implement many of the priorities identified and is working closely with other HOPA committees to determine how best to move forward on those ideas. In addition to the priorities listed, it is imperative that we establish additional strategies to optimize the global availability of this effort to all HOPA members.
- **A HOPA-sponsored publication**: The lessons learned from this Summit are being compiled so that they can be shared in more detail with the HOPA membership.

Table 1: Key Leadership Priorities for HOPA

Set an educational strategy to introduce and support leadership for HOPA members.
Establish a leadership mentoring program and strategy for HOPA members.
Identify existing resources for HOPA members regarding leadership.
Establish a networking opportunity to discuss leadership opportunities for HOPA members.

Thanks to all who provided their thoughts and ideas through the HOPA membership survey and discussions over the course of the last year. It is clear that HOPA has the opportunity to continue to help members in leadership development, and HOPA remains committed to that effort.

We also thank the HOPA board for its support of the Summit. The NLDC appreciates the support of the committee's board liaison, Scott Soefje, for helping make the idea of a Summit become a reality. ●●

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Board Update

Work of Many Hands

Susannah E. Koontz, PharmD BCOP FHOPA, HOPA President (2017–2018)
Principal, Koontz Oncology Consulting, LLC
Houston, TX

"Many hands make light work" is the proverbial wisdom of John Heywood, a 16th-century English writer. Its meaning is quite straightforward: complex tasks and large projects can be done more easily when people work together. This adage stands the test of time and accurately describes how we in HOPA are able to carry out such a wide array of activities with results that have great impact.

We closed out 2017 with several colleagues traveling both near and far on behalf of HOPA to represent your professional interests and build relationships with stakeholders. In early October, I attended the British Oncology Pharmacy Association (BOPA) 20th Anniversary Symposium in Glasgow, Scotland. There I copresented with Klaus Meier, president of the European Society of Oncology Pharmacy, on opportunities for international hematology/oncology pharmacy groups to collaborate on education, research, and advocacy. We continued the conversation later that evening with our BOPA hosts during their anniversary gala *cèilidh*. I returned home to Houston (just in time for the American League Championship Series) with a few ideas on how HOPA can expand its collaborative reach around the globe.

Washington, DC, was the epicenter of HOPA activity during the month of November. First, Angela Urmanski and Sandra Cuellar participated in the Center for Drug Evaluation and Research Small Business and Industry Assistance Regulatory Education for Industry (CDER SBIA REdI) Prescription Drug Labeling Conference held by the U.S. Food and Drug Administration (FDA). The overarching goal of the conference was to provide helpful information to overcome challenges in developing prescribing information, patient labeling, and structured product labeling. Specific to hematology/oncology pharmacy, our colleagues identified weaknesses in current practices of investigational drug product labeling. HOPA will continue to explore ways to identify best practices in labeling investigational agents to ensure that these lifesaving drugs are delivered to our patients in the safest manner.

Next, to address research gaps in treating older adults with cancer, the FDA and the American Society of Clinical Oncology jointly hosted a Geriatric Oncology Workshop on November 6. This group of diverse stakeholders, including HOPA's Ginah Nightingale, discussed improving the evidence base for treatment of older cancer patients, increasing enrollment of older patients in cancer trials, and identifying infrastructure elements necessary for executing clinical trials in geriatric oncology. Activity in the field of geriatric oncology will undoubtedly increase, and we expect to see growing opportunities for our members for education, research, and advocacy related to this subject.

On November 8, the Patient Equal Access Coalition (PEAC) hosted a briefing on Capitol Hill to educate lawmakers on the importance of parity legislation. Sarah Hudson-Disalle, a member of HOPA's Public Policy Committee, was a featured speaker during the event. PEAC, of which HOPA is a member, is a group dedicated to ensuring that patients have equality in access to cancer medications and insurance coverage for the medications, regardless of the delivery method. Sarah spoke about how the Cancer Drug Parity Act of 2017 (H.R. 1409) would improve cancer care by helping to curb "financial toxicity," a leading reason that many of our patients cannot adequately adhere to their prescribed therapies.

Finally, HOPA returned to Capitol Hill at the end of November, this time represented by members of the HOPA Board of Directors

"The adage 'Many hands make light work' stands the test of time and accurately describes how we in HOPA are able to carry out such a wide array of activities with results that have great impact."

and the Public Policy Committee. Fifteen of us visited congressional offices to continue to advocate for cancer parity legislation and the designation of pharmacists as healthcare providers under the Social Security Act (Pharmacy and Medically Underserved Areas Enhancement Act [H.R. 592/S. 109]). Progress continues on achieving pharmacist provider status in 2018: the second session of the 115th Congress opened with more than 240 cosponsors for H.R. 592 and support from just over 50% of the Senate for S. 109.

At the Advanced Practitioner Society for Hematology and Oncology (APSHO) JADPRO Live 2017 meeting in Houston, November 2–5, we had our first opportunity to offer Board Certified Oncology Pharmacist (BCOP) recertification programming outside of our internal curriculum. Ashley Glode, Donald Harvey, Patrick Kiel, and Edward Li delivered high-quality presentations to receptive audiences. Building on the success of this education platform, we are exploring additional opportunities to partner with peer organizations to increase our live BCOP recertification offerings across the country.

HOPA and our members were prominent in the activities of the American Society of Health-System Pharmacists (ASHP) Midyear Meeting in Orlando, FL, in December. Early in the meeting we cohosted with *Pharmacy Times* Continuing Education, working in collaboration with Walgreens Corporation, a seminar titled "Pharmacists Reaching Out®: Improving Treatment and Care in Patients with Lung Cancer." Our colleague Maryann Cooper served as HOPA faculty in this session combining a didactic lecture and a skills workshop aimed at educating pharmacists in the multidisciplinary care of lung cancer patients. Ryan Bookout, incoming HOPA president, reported overwhelmingly positive feedback, a testimony to how oncology pharmacists are integral to optimizing the care of cancer patients.

Our booth in the exhibit hall, staffed by HOPA members Justina Frimpong, Kate Jeffers, Edward Li, Jacky Olin, Brandon Shank, and me, along with HOPA staff members Julie Ichiba and Sarah Tiwana, received a lot of traffic during the Midyear Meeting. We were busy touting the value of HOPA membership as part of our effort to increase the number of "available hands" within our organization to advance our mission.

One of the highlights of the Midyear Meeting for me was seeing our programs and members recognized for their exceptional contributions to the field of hematology/oncology pharmacy. HOPA's position statement *Dose Rounding of Biologic and Cytotoxic Anticancer Agents* (hoparx.org/resources/professional-tools) received high praise during a standing-room-only session focused on strategies for reducing pharmaceutical waste. And ASHP awards were bestowed on several HOPA members. Brandi Anders, LeAnne Kennedy, and Brian Marlow, along with their colleagues, were honored with a 2017 Best Practices Award for their project "Evaluation of a Pharmacist Led Outpatient Autologous Hematopoietic Stem Cell Transplantation Program" at Wake Forest Baptist Health, Winston-Salem, NC. Joshua Elder of Norton Children's Hospital in Louisville, KY, was recognized for his teaching and mentoring skills with the 2017 New Preceptor Award. Please join me in congratulating our colleagues on their achievements.

With only a handful of days left in my presidency, I look forward to continuing to work on your behalf as past president after handing over the leadership reins to Ryan Bookout and to celebrating HOPA's many accomplishments with you at HOPA's 14th Annual Conference in Denver. ●●

HOPA
Hematology/Oncology
Pharmacy Association

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