HOPA NEWS

Pharmacists Optimizing Cancer Care

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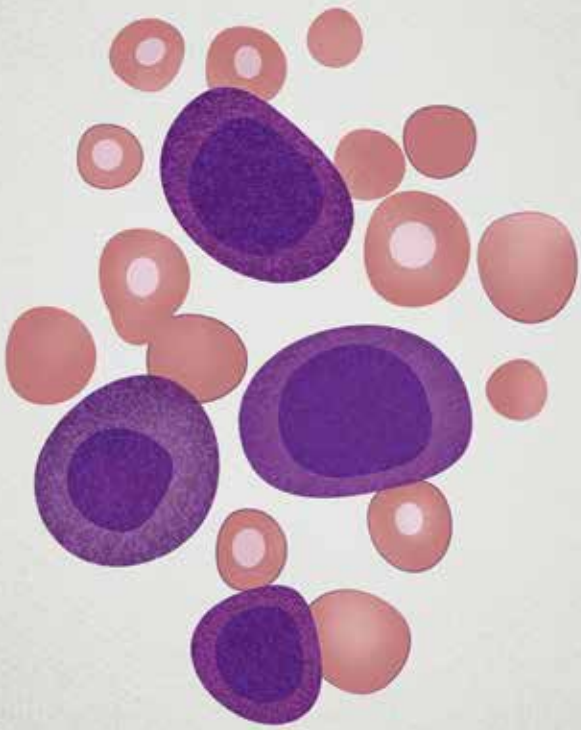

Updates on the Management of Chronic Lymphocytic Leukemia

page 3

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Pharmacists Optimizing Cancer Care

COLUMNS

FEATURE

Updates on the Management of Chronic Lymphocytic Leukemia

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Chronic lymphocytic leukemia (CLL), a disease state that has seen impressive treatment changes over the past 5 years, continues to drive oncologic therapeutic innovation. Advances in the biologic and genetic understanding of CLL, the increasing ability to accurately risk-stratify patients, and the development of targeted therapies have increased the median progression-free survival (PFS) and, as a result, the median overall survival (OS) for these patients. With the introduction of targeted therapies, 5-year relative survival has most recently been reported at 82.6% (2006–2012), up from 67.5% in 1975.[1] Before the introduction of newer agents to the market, relapsed or refractory (R/R) CLL was typically treated with chemoimmunotherapy consisting of rituximab or ofatumumab plus various cytotoxic agents such as bendamustine, fludarabine, or chlorambucil. Some of the most exciting developments in the realm of targeted CLL therapy include (1) expanded applications for ibrutinib, (2) significant responses to the substitution of venetoclax for patients intolerant to kinase inhibitors, (3) lenalidomide maintenance therapy, and (4) introduction of the novel phosphoinositide 3-kinase-delta (PI3K-δ) inhibitor idelalisib.

Updates on Ibrutinib

Ibrutinib, the first-in-class oral Bruton's tyrosine kinase (BTK) inhibitor, gained approval from the U.S. Food and Drug Administration (FDA) in November 2013 for mantle cell lymphoma. An FDA indication for CLL for patients who had received at least one previous therapy followed shortly in February 2014. The overall response rate (ORR) of patients treated with single-agent ibrutinib was 71%.[2] Since that time, its CLL indications have expanded significantly, and in March 2016, it was approved for first-line treatment. A number of positive clinical trials have contributed to these expanded applications.

The phase 3 HELIOS study assessed response to bendamustine and rituximab (BR) plus either ibrutinib or placebo in R/R CLL or small lymphocytic lymphoma (SLL) patients who had received one or more prior systemic cytotoxic regimens. Patients with del(17p) were excluded secondary to known poor prognosis with the BR regimen. In the study, 578 patients were evenly randomized to receive BR given in cycles of 4 weeks (bendamustine: 70 mg/m^2 on days 2–3 of cycle 1 and on days 1–2 of cycles 2–6; rituximab: 375 mg/m^2 on day 1 of cycle 1 and 500 mg/m^2 on day 1 of cycles 2–6) with either ibrutinib (420 mg daily) or placebo until the disease progressed or an unacceptable level of toxicity was reached. The addition of ibrutinib resulted in a statistically significant increase in median PFS (PFS not reached [NR] vs. 13.3 months; $p < .0001$). Median OS was not reached in either group and is difficult to assess because of the indolent disease course and the allowance of crossover in the study. The most common grade 3–4 adverse events (AEs) were neutropenia (54% vs. 51%) and thrombocytopenia (15% in each group). Overall, similar side effect profiles were seen in the experimental and control groups.[3]

The phase 3 RESONATE trial compared ibrutinib to ofatumumab in R/R CLL or SLL patients who had received one or more previous therapies and who were considered to be inappropriate candidates for purine analogue treatment (i.e., who experienced a short PFS following chemoimmunotherapy, had a coexisting illness, were age 70 years or older, or had chromosome 17p13.1 deletion). These patients were randomized to receive ibrutinib 420 mg/day until the disease progressed or an unacceptable level of toxicity was reached ($n = 195$) or ofatumumab 300 mg intravenous followed by 2,000 mg for 11 doses over 24 weeks according to package labeling ($n = 196$). The primary goal of this study was to provide updated efficacy and AE data relative to genetic features and prior treatment exposure over a median duration of 16 months. PFS was NR in the ibrutinib group and 8.1 months in the ofatumumab group ($p < .0001$). Most AEs were grade 1 and included diarrhea, fatigue, nausea, pyrexia, cough, neutropenia, anemia, upper respiratory infection, peripheral edema, sinusitis, arthralgia, muscle spasms, constipation, headache, pneumonia, thrombocytopenia, and vomiting. Seven percent of patients in the ibrutinib arm experienced atrial fibrillation, and 8% experienced bleeding.[4] Approximately 32% of patients included in the RESONATE trial had CLL with del(17p). Recent data on a subset analyses of the RESONATE trial reported worse outcomes in the presence of del(11q) in ofatumumab patients but the ibrutinib cohort did not seem to be affected.[5]

CLL is primarily a disease of the elderly, with a median age of diagnosis of 72 years. The phase 3 RESONATE-2 trial compared ibrutinib to chlorambucil in untreated CLL or SLL patients age 65 years or older. Of note, patients with chromosome 17p13.1 deletion were ineligible for inclusion in this trial because ibrutinib was already a primary first-line therapy according to consensus guidelines at the time the trial was initiated. A statistically significant increase in PFS and OS was seen in the ibrutinib group versus the chlorambucil patients (PFS NR vs. 18.9 months; $p < .001$ and estimated 2-year OS of 98% vs. 85%; $p = .001$). AEs were largely the same in the two groups, and ibrutinib was determined to be tolerable in this patient population. Ibrutinib exhibited superior efficacy compared with chlorambucil in high-risk subgroups, including genetic abnormalities and immunoglobulin heavy chain variable region (IGHV)–unmutated patients; however, data demonstrating improved outcomes with the addition of CD-20 antibody therapy to chlorambucil were not available at the time of trial initiation.[6] Comparisons of up-front use of ibrutinib with more common first-line CLL regimens (BR, fludarabine-cyclophosphamide-rituximab [FCR], and obinutuzumab-chlorambucil) are in progress.[7]

In a large single-center study, Maddocks and colleagues reported the indications for discontinuing ibrutinib seen in their practice. Disease progression, more common later in therapy, or intolerable toxicities, more common early in therapy, or both were the most common reported indications for discontinuation. B-cell lymphoma 6 (BCL6) abnormality and complex karyotype resulted in statistically significant increases in discontinuation because of progression, with hazard ratios (HRs) of 2.70 (p = .01) and 4.47 (p = .007), respectively. Characteristics associated with an increased rate of ibrutinib discontinuation because of toxicity included 10-year increase in age and number of prior treatments (HR 1.87; 95% confidence interval [CI] 1.33–2.64; p < .001; and HR 1.09; 95% CI 1.00–1.19; p = .054, respectively). It is important to note that the data indicate that patients who discontinue ibrutinib because of disease progression have poor outcomes, and additional therapies and targets are needed following ibrutinib failure.[8]

Acalabrutinib and BGB-3111 are second-generation BTK inhibitors with mechanisms of action similar to those of ibrutinib. These agents are more selective for BTK in vitro than ibrutinib, which may decrease interference with other kinases and result in fewer AEs. Because both acalabrutinib and BGB-3111 bind to the same site as ibrutinib, they are unlikely to overcome mutations conferring primary resistance to ibrutinib.[9,10]

Increasing knowledge of CLL biology and drug-resistance mechanisms will aid our understanding of how best to use our growing arsenal of treatment options.

Idelalisib

Idelalisib is an oral PI3K-δ inhibitor that works by inducing apoptosis and inhibiting proliferation of malignant B-cells via inhibition of chemotaxis, reduction in cell adhesion, and decreased cell viability.[11] In a phase 3 trial, rituximab was studied with and without idelalisib in relapsed CLL patients who were not candidates for cytotoxic therapy and had histories of one or more prior anti-CD20 therapies or two or more prior cytotoxic therapies. Patients were then randomized to receive either idelalisib 150 mg twice daily plus rituximab (n = 110) or placebo twice daily plus rituximab (n = 110). Patients in the idelalisib group who experienced progression had their dose increased to 300 mg twice daily, and patients in the placebo group were started on idelalisib 150 mg twice daily. Idelalisib plus rituximab resulted in a statistically significant increase in PFS and OS compared with the placebo plus rituximab group (PFS NR vs. 5.5; p < .0001 and OS 92% vs. 80% at 12 months; p = .02). The most significant AEs in the treatment group were neutropenia, thrombocytopenia, diarrhea, transaminase elevations, and pneumonitis.[12] In a phase 3 study comparing idelalisib plus BR with BR alone in the R/R setting, it was shown that the three-drug combination resulted in a statistically significant increase in PFS over BR alone (PFS 23.1 vs. 11.1; p < .0001).[13] Although there is interest in using idelalisib in the first-line setting, the increased risk of death, primarily due to infectious complications, in phase 3 trials assessing the use of idelalisib in the up-front setting resulted in suspension of the trial. An FDA alert to healthcare professionals has also been issued.[11]

Venetoclax

CLL is a disease characterized by high B-cell lymphoma 2 (BCL2) protein expression. Venetoclax is an oral, highly selective inhibitor of BCL2, a protein that promotes survival of B-lymphocytes in CLL, and results in caspase-mediated apoptosis through release of cytochrome C.[14] It recently received accelerated approval by the FDA for patients with relapsed CLL harboring del(17p) on the basis of a phase 1 dose-escalation trial conducted by Roberts and colleagues.[15] In a phase 2 single-arm study, patients with del(17p) R/R CLL were given venetoclax in a dose-escalating manner up to a final dose of 400 mg daily until disease progression or discontinuation for another reason. At a median follow-up of 12.1 months, overall response was assessed in the 107 patients enrolled in the study and found to be 79.4%. Median PFS and OS were not reached at time of median follow-up. Grade 3–4 AEs reported were neutropenia (40%), infection (20%), anemia (18%), and thrombocytopenia (15%). Patients who were switched from a failing regimen to venetoclax experienced high response rates and attainment of minimum residual disease (MRD). Because of its activity in reducing CLL cells, venetoclax initiation was associated with an increased risk of tumor lysis syndrome (TLS) and required risk mitigation strategies such as assignment of TLS risk category (low, medium, high), admission to hospital for TLS prophylaxis prior to first doses, and appropriate TLS lab monitoring. Overall, this therapy appears to be active for patients with high-risk R/R CLL with a favorable tolerability profile.[16] An ongoing phase 3 trial is evaluating venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab in previously untreated CLL (NCT02242942).

Lenalidomide Maintenance

According to the interim results of the phase 3 CLLM1 trial by the German CLL Study Group, lenalidomide maintenance after front-line therapy substantially prolonged PFS in patients with high-risk CLL. In this study, patients were stratified into the high-risk category if they had MRD levels of 10^{-2} or greater or MRD levels of greater than 10^{-4} to less than 10^{-2} with unmutated IGHV, del(17)p, or TP53 mutation and were randomized to receive either lenalidomide or placebo until disease progression. At a median follow-up of 17.7 months, the median PFS in the placebo group was 14.6 and NR in the lenalidomide group (p < .0006). Lenalidomide was associated with more significant rates of neutropenia (30.4% vs. 3.4%), gastrointestinal disorders (55.4% vs. 27.6%), central nervous system disorders (30.4% vs. 13.8%), respiratory disorders (35.7% vs. 13.8%), and skin disorders (60.7% vs. 27.6%). Infections and thrombotic disorders showed no difference in event rates between the two arms. These data show that lenalidomide maintenance in high-risk CLL patients after chemoimmunotherapy is a reasonable option that improves PFS over placebo and increases the induction rate of MRD negativity.[17]

CLL Treatments on the Horizon

An intergroup phase 3 trial of ibrutinib plus rituximab versus FCR has finished enrolling young, fit CLL patients in an attempt to determine the role of targeted therapies in this patient population (NCT02048813). Results of this phase 3 trial, if positive, will result in a paradigm shift in the standard of care. Similarly, the phase 3 Alliance A041202 study (NCT01886872) compared ibrutinib alone versus ibrutinib in combination with rituximab versus BR in patients 65 years of age and older. Results of these trials are eagerly awaited because it is hoped that they will help determine the ideal regimen in the up-front setting of younger and older CLL in the era of novel agents.[18]

The more selective BTK inhibitor, acalabrutinib, is being studied in a phase 3 study for previously untreated patients with CLL and a high Cumulative Illness Rating Scale (CIRS) score as single-agent acalabrutinib versus acalabrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab (NCT02475681).Venetoclax in combination with various agents (including venetoclax plus rituximab, venetoclax plus obinutuzumab, and venetoclax plus BR) for use in R/R CLL is being studied in multiple phase 1 trials. A phase 1b study of dose-escalation of venetoclax plus obinutuzumab/ibrutinib for up to 14 cycles in the absence of unacceptable toxicity or progression of disease is under way and will be followed by a phase 2 study. The German CLL Study Group is conducting a phase 2 open-label study of ibrutinib plus venetoclax/obinutuzumab. In the United Kingdom CLARITY trial, investigators are conducting a phase 2 study of ibrutinib plus venetoclax. Duvelisib, a PI3K γ/δ inhibitor, is being studied for relapsed CLL in phase 3 trials (NCT02004522). Some limited data support the use of chimeric antigen receptor (CAR) T-cells targeting CD19, and further data are necessary to determine their role in CLL management.[19]

Conclusions

With the addition of new targeted agents such as ibrutinib, idelalisib, and venetoclax to the CLL treatment landscape, traditional chemoimmunotherapy is increasingly becoming displaced as the standard of care for treatment-naive patients. Targeted agents hold the promise of reduced toxicity and decreased risk of secondary malignancies, especially in elderly patients who do not tolerate standard treatments as well. In addition to their reduced toxicity, these agents have proven efficacy in patients with high-risk disease such as del(17p) and TP53 mutations. Increasing knowledge of CLL biology and drug-resistance mechanisms will aid our understanding of how best to use our growing arsenal of treatment options. Ongoing trials will also seek to answer questions related to the optimal combinations and sequence of therapies for the management of CLL and SLL. ●●

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Dose Rounding of Cytotoxic Drugs and Monoclonal Antibodies

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Given the high cost of antineoplastic agents and monoclonal antibodies, many institutions have adopted dose-rounding policies in order to minimize waste—both financial and physical—while still providing optimal patient care.

Several studies have addressed the cost-effectiveness and feasibility of dose rounding for specific agents. For example, a 2013 retrospective study by Patel and Le examined the feasibility of rounding rituximab to the nearest vial size. Authors determined that 99% of the 2,028 reviewed orders fell within 10% dose deviation, and 66.1% fell within 5% if rounded to the nearest 100 mg vial.[1]

Winger and colleagues also looked at potential cost savings that could be achieved by rounding seven biologic agents during a 3-month period.[2] In total, 126 orders for these agents were processed during the study period. Even when the cost of nonadherence to rounding practices was included, the actual cost savings was $15,922 out of a potential reported savings of $24,434.[2]

A third example of dose rounding came from Francis and colleagues in 2015.[3] The authors selected three agents—bevacizumab, trastuzumab, and cetuximab—to target and compared the cost of prescribed doses to the cost of theoretically rounded doses (5% or 10%) if a decrease in the number of vials was expected.[3] The authors reported that of 425 doses, 51 would have qualified for rounding at a 5% dose reduction, which translated to a potential cost savings of $60,648. At the 10% threshold, 24 doses qualified for dose rounding, which translated to a potential cost savings of $112,585.[3]

With the widespread interest in this topic and its potential impact on practice in mind, the Hematology/Oncology Pharmacy Association (HOPA) recently released a draft position statement on dose rounding. Six recommendations were established:

1. Based on the limited published data, HOPA recommends that monoclonal antibodies and other biologic agents currently available be dose rounded to the nearest vial size within 10% of the prescribed dose.
2. For monoclonal antibodies with a cytotoxic constituent, HOPA favors using the dose-rounding recommendation applied to cytotoxic agents.
3. HOPA recommends that traditional cytotoxic agents be considered independently for dose rounding within 10% of the prescribed dose.
4. On the basis of the inference that dose rounding will influence clinical safety or effectiveness, HOPA supports the use of the same threshold for dose rounding of anticancer drugs as for palliative and curative therapy.
5. When oral chemotherapy is supplied in more than one strength of capsule or tablet, it is recommended that one strength be used and that the final dose be rounded to avoid confusion for the patient and to eliminate the possibility of multiple copayments.
6. Institutions should develop policies through interdisciplinary efforts, which can be endorsed by a policy-managing body such as a pharmacy and therapeutics committee or an oncology subcommittee. The policy should describe which cytotoxic and monoclonal antibody classes are subject to dose rounding, rounding limits for each class, the process for rounding ordered doses, documentation of such changes, and any applicable exceptions such as drugs supplied in multidose vials or circumstances where prescribers should be consulted before any rounding is done by the pharmacist.

The draft position statement is an excellent resource (and publication of the final position statement is planned for April 2017), but HOPA recommends that each institution develop its own dose-rounding policy addressing both monoclonal antibodies and cytotoxic drugs. ●●

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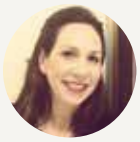
Reflection on Personal Impact *and* Growth

Representing HOPA on HOPA Hill Day



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On April 27, 2016, a sunny spring day in Washington, DC, I sat in the cramped waiting area outside the office of Senator Rand Paul. The then-immediate past president of HOPA, Mike Vozniak, HOPA lobbyist Jeremy Scott, and I were patiently waiting our turn. It was #HOPAHillDay! My role was to represent HOPA members as HOPA Member-at-Large. Our day was packed with meetings with elected officials from Kentucky and Pennsylvania in both the House of Representatives and the Senate. The purpose of HOPA Hill Day is to share with our elected representatives our perspectives on the contemporary issues affecting care for patients with cancer and to illustrate the valuable role that hematology/oncology pharmacists play in healthcare delivery (as outlined in our HOPA Health Policy Agenda at www.hoparx.org/advocacy/health-policy-agenda).

We were supporting three major bills during our meetings:

- The Pharmacy and Medically Underserved Areas Enhancement Act, also known as the provider status bill. This bill was reintroduced in January 2017 in the Senate as S. 109 (Chuck Grassley [R-IA], Sherrod Brown [D-OH], and Bob Casey [D-PA]) and in the House of Representatives as H.R. 592 (Brett Guthrie [KY-02], G. K. Butterfield [NC-01], Ron Kind [WI-03], and Tom Reed [NY-23]).
- The Cancer Drug Coverage Parity Act of 2015 (H.R. 2739), also known as the oral chemotherapy parity bill. This bill was reintroduced in March 2017 in the House as H.R. 1409 (Leonard Lance {R-NJ] and Brian Higgins [D-NY]).
- The Patients' Access to Treatments Act of 2015 (H. R. 1600), also referred to as the specialty-tier drugs act.

The day on the Hill was a golden opportunity to have the attention of the individuals entrusted with making decisions that affect our profession and the care of our patients, and it was truly exciting! We made the most of our 20 minutes, and (dare I say?) we even had fun. I am optimistic that our concerns did not fall on deaf ears and that we inspired some to represent the oncology pharmacy community and our patients' needs by joining us in promoting efforts to enhance access to cancer care. Nonetheless, this wasn't a one-and-done program. As individual pharmacists and as an organization, we in HOPA must persevere in our efforts and be persistent in advocating for our profession.

In reflecting on this particular advocacy activity and my overall experience on the HOPA board, I find myself inspired. My experiences have challenged me to seek a broader understanding of our profession. For most of my professional life, the focus of my learning has been an unadulterated, naive pursuit of clinical knowledge. The number of competing agendas outside and inside our own profession, as well as those of other industry markets that influence our profession, other healthcare providers, buying groups, the pharmaceutical industry, managed care, our patients, and ultimately our ability to provide any pharmacy service, is massive. My own lack of a focused study of these outside influences—which have both afforded me the luxury of clinical practice and also threatened it—is a cause of great regret. I now have a better appreciation of the healthcare system and a healthier view of it. I am very grateful for the exposure HOPA has provided me as a volunteer and as a board member, opening my eyes to areas of needed growth. Being part of HOPA has had a tremendous impact on my personal and professional growth. Along the way, I have been encouraged by the many amazingly talented individuals that make HOPA exceptional. It is a privilege to be able to represent our membership. ●●

Jill Rhodes and Mike Vozniak represent HOPA on Capitol Hill.

Professional Organizations: If You Want to Go Fast, Go Alone. If You Want to Go Far, Go Together.

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Getting involved and being active at the state or national levels of a professional pharmacy organization may sound daunting, perhaps not even worthwhile, but it looks good on your CV and applications, so you just do it, right? Wrong! A young pharmacy professional who gets actively involved in organizations gets so many benefits! If you go beyond just joining and become an active part of that community, you will reap the many benefits offered and be able to contribute to the organization's cause in a very meaningful way—whether you are a new practitioner, a resident, or a student.

I, too, was skeptical at first. As a student, I had been only superficially involved in a few organizations—until I found the one that aligned with my goals as a pharmacist. Through our Student Society of Health-System Pharmacists chapter, I found that the priorities and objectives of the American Society of Health-System Pharmacists were exactly what I wanted to focus on as a professional, but it was within our state-affiliate organization, the West Virginia Society of Health-System Pharmacists, that I was motivated to become involved. I felt loyalty toward the patients and colleagues in my state and pride in what I could provide as a pharmacist, and this state organization gave me an avenue to implement meaningful change and enhance the unity of practitioners attempting to do the same thing across the state. After implementing a workshop on student leadership development the first year after my residency, chairing the New Practitioners Committee, and being elected as the north regional vice president in my second year, I was voted president-elect and became a member of the board of directors at age 27. Please keep in mind: I'm not some superstar pharmacist, I did not have a 4.0 GPA, I don't have a dozen research publications to my credit, and I didn't do an administration residency. I just had a passion for improving the efforts of the organization and promoting what it does for patients and pharmacy professionals in my home state. I wanted to make things better, and I contributed the effort and dedication that the organization needed. And though this all sounds great, the professional growth I have experienced and the satisfaction of seeing the positive outcomes of those efforts have been far more valuable than anything that could be represented on my CV.

Over the course of my involvement in this organization, I've gained enough perspective and experience to be able to debunk a few myths that residents or new practitioners may believe about becoming involved in a professional organization, so I'd like to share that knowledge here.

Myth 1: I'm not good enough or experienced enough to be on a committee.

Motivation and problem-solving skills are often all that are needed from a committee member. If you are willing to help achieve the goals of that committee, you will be an asset. Committees typically need more help than they have volunteers, and so a handful of people carry most of the weight. New and ambitious young practitioners are normally welcomed and can provide a fresh perspective to a group. Years of clinical experience are not needed to organize member elections, promote upcoming meetings, or develop continuing education program agendas and secure speakers. By joining these committees, you will gain a sense of ownership in the organization's goals and a feeling of belonging. You'll also have a great opportunity to network with influential members of your organization all across the country.

Myth 2: I can just sign up, get the e-mails, and not really do anything but still get the benefit of involvement in the organization.

I hope you haven't read this far and still believe this myth. Filling out the online application and paying your dues does not add anything to your growth as a pharmacy professional. Taking advantage of the opportunities to enhance your clinical knowledge with continuing education and meeting attendance, building your professional network by interacting with colleagues at numerous institutions, and developing your organizational and leadership skills through being involved in a committee, helping to plan or organize meetings, or serving in an elected office will provide you essential experience that may not be available to you in your job. Working with organizations also gives you the opportunity to lead change—rather than just respond to it—through advocacy efforts. You can also affect patient care on a wide scale and reach many more patients than just those who walk through your hospital or clinic doors.

Myth 3: It looks better to be in a national organization, so I won't bother joining state organizations.

State organizations are a great place to make a difference and gain experience running committees, organizing meetings, speaking publicly, and serving in leadership roles. State organizations are smaller networks than national ones, so you very likely already have connections at your institution with active members or committee chairs who would love to have your help. Involvement in a state organization is a great way to showcase your abilities across your state, build connections, and gain valuable experience. Most important, the effect of the changes you implement will be highly visible right in your own community.

Myth 4: It doesn't matter which organization you choose because they're all basically the same.

If you believe myth number 2, then sure, but if you really want to realize the full benefit of being in an organization, then this statement couldn't be further from the truth. Dozens and dozens of professional pharmacy organizations exist, each one with a particular vision and mission. Some organizations center on the practice setting—for example, the American Association of Colleges in Pharmacy (AACP), the Academy of Managed Care Pharmacy (AMCP), and the National Association of Chain Drug Stores (NACDS). Some organizations focus on a particular specialty—for example, the Hematology/Oncology Pharmacy Association (HOPA), the Pediatric Pharmacy Advocacy Group (PPAG), and the College of Psychiatric and Neurologic Pharmacists (CPNP). Others are multidisciplinary or even physician focused but have a pharmacy section or interest group, such as the American Society for Blood and Marrow Transplantation (ASBMT), which has a Pharmacy Special Interest Group.

Myth 5: It's too expensive to join professional organizations.

Most of the time, membership is fairly affordable, particularly for students, residents, or new practitioners. Many organizations offer reduced rates (or sometimes even free membership). The resident rate for HOPA membership is only $60 (60% off the fee for full members), and the student rate is $40 (73% off). Which organizations you join is also important. It is much more beneficial to you (and looks better on your résumé) if you maintain membership in only a few organizations that you are able to actively contribute to and benefit from, rather than simply renewing your membership in a dozen organizations.

Myth 6: I don't want to join an organization because I may change my mind later on or decide to practice in a different specialty.

Change is a part of life, and very few people stay in exactly the same role throughout their entire career. Even pharmacists who stay in oncology may decide along the way to focus more on other areas, such as quality, information technology, administration, or managed care. After such changes, they may find that the organizations they had chosen to join are no longer relevant or beneficial, and involvement in different organizations may become more worthwhile. That is all perfectly OK—you can join or leave organizations at any time, and the experience you gained with one may translate wonderfully to the next. Continue to be involved in the groups that matter to you and what you do.

Myth 7: I'll be putting in a lot of work without getting any personal benefit.

The benefits to you are numerous. In addition to the benefits discussed above—leadership experience, networking opportunities, the ability to make a community impact, practice in advocacy, involvement in patient care initiatives, and personal growth—each organization offers other benefits. You can often gain access to job postings specific to your field, attend educational sessions to prepare you for your specialty board certifications, have the opportunity to apply for scholarship awards and gain recognition of professional achievements, and learn about other specific resources available to you.

Involvement in an organization helps keep you informed about current happenings outside your hospital or clinic walls. It gives you the opportunity to be involved on the front line to make changes to improve yourself, your community, your profession, and ultimately the care that is provided to your patients and their families. ●●

Clinical Benefit of Oncology Agents in the Accelerated Approval Era: Broken Promises or Field of Dreams?

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In the past 3 years, the U.S. Food and Drug Administration (FDA) has given 73 oncology-related approvals, 30% of which were under accelerated approval.[1] The FDA instituted its Accelerated Approval Program (AAP) in 1992 to hasten the approval process and enhance access to lifesaving therapies to treat serious conditions and fill an unmet medical need based on a surrogate end point. A *surrogate end point* is defined by the FDA as "a marker such as a laboratory measurement, radiographic image, physical sign, or other measures thought to predict a clinical benefit, but … not itself a measure of clinical benefit."[2] The realm of cancer care is most definitely encompassed in the AAP, with more than a million new cases of cancer in 2016 and more than half a million deaths related to cancer in 2016.[3]

In oncology, overall survival (OS) is the gold-standard end point for clinical efficacy. However, determining the true OS benefit of a drug can take years and can require a large sample size, delaying access to that drug by a patient population in need. A surrogate end point can overcome the barriers of measuring OS.[4] With the use of surrogate end points, the work of the AAP has hastened cancer patients' access to medications and is thought to have aided in improving the 5-year OS rates of all cancer types from 50% in 1980 to approximately 70% in 2008.[3]

The pillars of drug safety and efficacy date to 1962, with the Kefauver-Harris Amendment of the 1938 Food, Drug and Cosmetic Act. With the awareness that patient needs may accelerate more quickly than the drug approval process, the FDA allowed early-access programs in the 1960s to offer limited patient access to investigational drugs, also known as compassionate-use programs. In the 1980s, the FDA created a fast-track component to its rules to allow for expedited development of agents being studied for serious and life-threatening conditions by, for example, eliminating phase 3 trials from the initial approval phase. This allowed faster medication access to patients in need while the postapproval phase 3 and phase 4 studies were being completed for official FDA approval. This change reduced the average clinical development time from 8.9 to 6.2 years. The enactment of the AAP in 1992 allowed approval based on various surrogate end points, like progression-free survival (PFS) and objective response rates, that were likely to predict OS benefit and shortened the average clinical development time to 4.2 years, with a correlated shortening of new drug application review times from more than 30 months in the 1980s to as little as 9.9 months in 2011.[5]

Despite these advances, the AAP has also caused a fair share of turmoil. One such example of the controversial use of surrogate end points was the use of bevacizumab for metastatic breast cancer. Bevacizumab in combination with paclitaxel was approved for HER2-negative, treatment-naive metastatic breast cancer in 2008. The accelerated approval was based on a statistically significant 5.9-month increase in the median PFS and increased objective response rates (36.9% vs. 21.2%) for the combination of paclitaxel and bevacizumab over paclitaxel alone in the E2100 study.[6] However, the confirmatory phase 4 trials (AVADO and RIBBON-1) and maturation of the E2100 data painted a different picture from what was originally predicted and threatened the regular FDA approval of bevacizumab for metastatic breast cancer.[7,8] Ultimately, the results of all three trials did not show an OS benefit. The AVADO trial even demonstrated a smaller benefit in median PFS with bevacizumab 7.5 mg/kg (9 months vs. 8.1 months, $p = .045$) and 15 mg/kg (10 months vs. 8.1 months, $p < .001$) than originally proposed. In addition, all three studies showed increased toxicity in the bevacizumab-containing treatment arms, with the most common side effects being hypertension, proteinuria, cerebrovascular ischemia, all-grade bleeding, and neutropenia.[6-8] In response to these findings, the FDA approval was withdrawn for bevacizumab in metastatic breast cancer.[9]

Much debate still surrounds the accurate and appropriate use of surrogate end points, and discussion continues regarding a lack of translation to OS benefit when confirmatory data matures. Despite this concern, the number of trials using surrogate end points has increased. According to the *Journal of Clinical Oncology*, the proportion of randomized controlled trials of systemic therapy published from 1975 to 2009 using PFS as an end point increased from 0% to 26% in breast, colorectal, and non–small cell lung cancer.[7] However, correlation does not necessarily imply causation, or in the case of oncology, surrogacy as described in the example of bevacizumab. It has been postulated that reasons for this discrepancy are multifold, including these: the changes in tumor size needed for progression are too small to affect OS; studies are underpowered to detect an improvement in OS by the same absolute amount as PFS; date of progression is more difficult to measure and capture accurately than date of death; and available studies often allow for crossover, and thus the sequence of administration—not the impact of the new treatment—is being evaluated.[10]

Although the initial approval under the AAP is based on a surrogate end point, this program places the burden of proof for clinical benefit on the drug companies. Unfortunately, the manufacturers' diligence in pursuing these phase 4 confirmatory trials is lackluster at best. In a 2009 government accountability report, the agency was criticized for failing to enforce postmarketing study commitments for surrogate approvals.[11] As of 2011, postmarketing study commitments for more than 40% of drugs approved through the AAP had not yet been started. Furthermore, according to the Office of Oncology Drug Products, the completion time of these studies has ranged widely from 0.8 years to 12.6 years.[5] However,

despite these shortcomings, the FDA has not removed the drugs involved from the market.[11]

Notwithstanding the concerns related to the impact of early access to therapy, shortened development time, and faster review times of agents, the FDA has yet to tighten the reins on the AAP program. In fact, in 2012, a new pathway was sanctioned, referred to as "breakthrough therapy (BT)."[12] To be eligible for this designation, drugs must have "an effect on a pharmacodynamic biomarker that does not meet criteria for an acceptable surrogate endpoint, but strongly suggests the potential for a clinically meaningful effect on the underlying disease."[12] Drugs approved through BT status must also be eventually approved or rejected under the normal FDA approval standards; however, as observed in confirmatory trials following AAP approval, this confirmation may not be required for several years.[5] Drugs that have recently received BT approval include pembrolizumab, nivolumab, daratumumab, elotuzumab, and atezolizumab.[13]

Through use of the BT and AAP pathways, the FDA runs the risk of allowing products that are clinically ineffective or unsafe, or possibly both, into the market for a period of time before confirmatory data mature. The impact of these pathways was most recently evaluated in the 2016 analysis by Salas-Vega and colleagues, published in *JAMA Oncology*, which reviewed the OS, quality of life (QoL), and safety of 53 new FDA and European Medical Agency (EMA) molecular entities with primary oncology indications approved between 2003 and 2013 as evaluated by English, French, and Australian health technology assessments. It was found that 43% of the drugs increased OS by 3 months or longer, 11% by less than 3 months, and 15% by an unknown magnitude. The remaining 30% of cancer drugs did not demonstrate an increase in OS compared with alternative treatments, either because no difference was found or a determination could not be made on the basis of the available evidence at the time. Where OS could be quantified, it was determined that a total mean improvement in OS of 3.43 months was attained related to the treatments that were available in 2003. However, the greatest benefits in OS were seen in breast, renal, and skin cancers, with little or no benefit in OS observed in thyroid, lung, and hematological cancers. In addition, benefits were concentrated among specific classes of agents, most notably immunologic therapies, which were better at extending OS compared with nonimmunologic drugs (5 months vs. 2.3 months).[14]

With regard to QoL, it was determined that 42% of the drugs evaluated improved this parameter, 4% reduced it, and 2% were associated with mixed evidence. Notably, 53% did not demonstrate a difference in QoL relative to the best alternative treatments available at the time. However, not all of these opinions were based on empiric evidence with validated QoL instruments. For five drugs (pertuzumab, trametinib, ziv-aflibercept, sipuleucel-T, and vemurafenib), testimony from patient representatives and clinical experts was used to quantify QoL benefits.[14]

Regarding the safety assessments associated with these new therapies, it was found that 24 of the 53 drugs (45%) reduced patient safety, as evaluated by the following parameters: incidence of adverse events (AEs), incidence of severe or serious AEs, time to first AE greater than grade 3, treatment discontinuation or dose reduction, overall tolerance and safety profile (not otherwise specified), treatment-related deaths, and input from patient representatives or clinical experts. Of the remaining 29 drugs evaluated, 15% were found to improve safety, 19% had mixed evidence with regard to safety outcomes, and 21% did not demonstrate any difference in safety compared with alternative treatments available at the time of approval.[14]

The clinical benefit of these agents can be quantified in this way: of the 23 drugs that increased OS by at least 3 months, 65% were found to improve QoL, but 48% reduced patient safety. Salas-Vega and colleagues concluded that gains in OS and QoL often come at the cost of safety.[14]

The enactment of the AAP has undoubtedly contributed to many advances in cancer care during the last 25 years. However, the magnitude of benefit varies widely and must be considered when one is making treatment decisions, given that one in three newly approved cancer medications has not been associated with an OS benefit.[14] Furthermore, in light of the recent BT designation, clinicians must remain steadfastly focused on evidence-based practices, seek clinical benefit data when they are available, and ensure that safety and quality of care are not being sacrificed during expedited approval. Finally, an area not addressed by the FDA or available literature is the importance of education and empowerment of patients with regard to the different ways that agents are approved and brought to market. In order to make well-informed shared decisions with their treatment team, patients should be made aware of whether a given therapy improved overall survival and QoL or reduced safety. ●●

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FDA Recommendations for the Naming and Interchangeability of Biosimilars and the Potential Impact on the American Society of Clinical Oncology Guideline Update of 2015: Use of White Blood Cell Growth Factors

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FDA Guidance

In January 2017, the U.S. Food and Drug Administration (FDA) issued a guidance document on the nonproprietary naming of biological products.[1] In it the FDA also discusses the impact of biological product naming on pharmacovigilance and the differences between a biosimilar product and an interchangeable product. For a product to be deemed interchangeable, the manufacturer must provide information in the application requesting this type of approval. A product that is interchangeable with the reference product may be substituted without intervention of the prescriber.

The FDA recommends that biological products licensed under the Public Health Service Act contain a nonproprietary name including an FDA-designated 4-letter suffix that is without meaning.[1] Using this guidance, each originator biological product, related biological product, and biosimilar product would have the same core name but with its own unique suffix. This recommendation applies to both previously licensed and newly licensed products, but the process for implementing these recommendations still needs to be determined. This guidance document focuses on naming convention only.

A potential benefit of streamlining the naming process for biologics is the allowance for pharmacovigilence with these products.[1] If the products have distinctive names, patients and healthcare providers will be able to more easily and accurately identify specific products. The unique suffix given to each product should decrease the risk of inadvertent substitution of any product that has not yet been determined to be interchangeable. Implementation of this recommendation for naming of biological products should support the standard use of the designated suffix in all areas of practice and minimize incorrect opinions on the safety and effectiveness of biological products.

The concern about inadvertent substitution of these products relates to safety concerns associated with the immunogenicity of biological products.[1] Related biological products and biosimilar products may have approvals differing from that of the reference product and may be packaged in different delivery systems. Because of these potential variations from the reference product, it is important to confirm that the correct product is prescribed, dispensed, and administered. The *Purple Book* is a reference that may be consulted to determine whether the FDA considers a biological product to be biosimilar to or interchangeable with a reference product.

Biologic drugs have a major role in the management of cancer, and with the development of a biosimilar approval pathway, the number of biologic drug approvals has increased. In 2015, the first biosimilar drug approved by the FDA was a white blood cell (WBC) growth factor, filgrastim-sndz (Zarxio), which is a biosimilar to filgrastim (Neupogen), its reference product.[2] The naming recommendations for biologics will be implemented in clinical practice following the convention used for filgrastim-sndz.[1]

Update by the American Society of Clinical Oncology (ASCO)

The evolution of biosimilar drug approvals has required that major organizations update their clinical practice guidelines to incorporate these new products. In October 2015, ASCO published an update to its 2006 clinical practice guidelines for the use of hematopoietic colony-stimulating factors (CSFs) including these new agents.[3] Data from October 2005 to September 2014 were reviewed to update the 2006 guidelines. Although the majority of the manuscript includes an update of the literature that further supports the 2006 recommendations, a few major changes in the 2015 update include recommendations for the use of biosimilar CSFs, modifications to the recommendation of CSF use to allow chemotherapy dose-density, and removal of recommendations for CSFs in acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS).[4]

Dosing of CSFs

New to the 2015 guidelines are recommendations for initiation, duration, dosing, and administration of CSFs, including the recently approved biosimilar products. The FDA-approved biosimilar product filgrastim-sndz carries the FDA-labeled indications, warnings, and dosing recommendations that filgrastim has.[5] Tbo-filgrastim is a labeled biological product and not a biosimilar; the biosimilar approval pathway had not yet been put into place when the drug was approved in 2013.[6] Tbo-filgrastim is approved only to prevent severe neutropenia in patients receiving myelotoxic chemotherapy at a dose of 5 mcg/kg/day subcutaneously beginning

1–3 days after the end of treatment.[7] No changes have been made regarding the dose of filgrastim, pegfilgrastim, and sargramostim.

Although administration of pegfilgrastim 1 to 3 days after chemotherapy is still recommended, some recent studies evaluate alternatives if this timeframe is not feasible. Alternatives include use of the newly approved pegfilgrastim automated-inject device and administration of pegfilgrastim immediately following (or 4 days after) chemotherapy. In a series of phase 2 randomized controlled trials, administration of same-day pegfilgrastim was compared with administration of pegfilgrastim 24 hours after chemotherapy. In this analysis, same-day pegfilgrastim increased the duration of severe neutropenia compared with next-day pegfilgrastim.[8] Two trials also compared pegfilgrastim on day 2 versus day 4. Though one trial showed a reduced incidence of grade 3 or 4 leukopenia with day 4 administration compared to day 2 administration (70% vs. 43.3%, $p < .001$), the larger of the two studies found no significant difference between day 2 and day 4 administration in rates of leukopenia, febrile neutropenia, or infection.[9,10] Although these alternatives may not be more effective than pegfilgrastim administered during days 1 through 3, they should be considered because they provide more benefit than withholding pegfilgrastim entirely.

Differences in Efficacy

As mentioned in the 2006 guidelines, no data suggest that any CSF is overwhelmingly superior to another. One meta-analysis of five randomized controlled trials comparing pegfilgrastim to filgrastim after chemotherapy suggested a decreased incidence of febrile neutropenia with pegfilgrastim (relative risk [RR] 0.66, 95% CI, 0.44 to 0.98), but further studies have failed to confirm this benefit.[11-15] In the effort to obtain FDA approval of filgrastim-sndz as a biosimilar product, filgrastim-sndz was compared to filgrastim following administration of myelotoxic chemotherapy in two phase 3 non-inferiority trials. Both studies concluded that filgrastim-sndz demonstrated efficacy and safety similar to that to filgrastim, showing no statistically significant difference in the duration of severe neutropenia, time to count recovery, or incidence in febrile neutropenia between groups.[16,17] Based on these data, the choice of CSF should be determined on the basis of patient convenience, cost, and the clinical scenario.

Increasing the Dose Density of Chemotherapy

In 2006, it was suggested that the use of CSFs to increase dose density showed benefit in node-positive breast cancer and possibly in non-Hodgkin lymphoma, although further confirmation was required before results could be generalized. The 2015 update presented new evidence showing differing results based on cancer type. Outside of a clinical trial, data exist to support CSF use with dose-dense chemotherapy in the adjuvant breast cancer setting as well as with high-dose-intensity methotrexate, vinblastine, doxorubicin, and cisplatin in urothelial cancer. The use of CSFs to increase chemotherapy dose density in non-Hodgkin lymphoma is not recommended. Two phase 3 randomized controlled trials compared R-CHOP (**r**ituximab, **c**yclophosphamide, doxorubicin [**h**ydroxydaunomycin], vincristine [**O**ncovin], **p**rednisolone) given at 14- or 21-day intervals, both of which showed no difference in overall survival or event-free survival with the dose-dense regimen.[18,19]

Use in Acute Myeloid Leukemia or Myelodysplastic Syndrome

The 2006 guidelines commented on the role of CSF during AML induction, consolidation, and priming, as well as in the treatment of MDS and acute lymphocytic leukemia. The 2015 panel omitted this discussion altogether; thus, no recent literature was presented, nor were recommendations made regarding this matter.[3,4]

Overall, the 2015 guideline update provided more guidance regarding the role of biosimilar products and ideal candidates for use of CSFs to increase chemotherapy dose density. More data were presented supporting previous recommendations for CSF use during prophylaxis or treatment of neutropenia. No new data, however, have emerged regarding the use of CSFs during concomitant chemotherapy and radiation or following the treatment of radiation injury. The inclusion of the newly approved biosimilar products was an important step in integrating these medications into evidence-based clinical practice. The FDA guidance statement regarding the naming of biological products will allow practitioners to safely prescribe the correct product and will allow for appropriate interchange of products to minimize medication errors. Additional filgrastim-biosimilar products and pegfilgrastim-biosimilar products are being evaluated.[20] Additional updates will need to be made to clinical practice guidelines as these agents are added to the market. ●●

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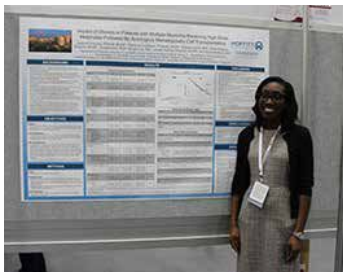
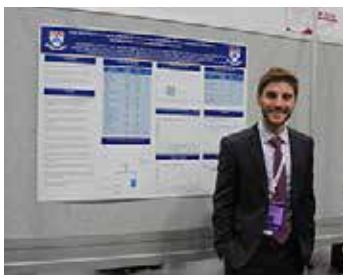
Pharmacists Present Their Research at the 2016 American Society of Hematology Meeting

The 58th Annual American Society of Hematology (ASH) Meeting and Exposition was held December 3–6, 2016, in San Diego, CA. HOPA members Justina Frimpong, Alex Ganetsky, Lauren Levine, Jigar Trivedi, and Tracy Wiczer presented their research. Summaries of their abstracts are provided here.



Justina Frimpong, PharmD BCOP

Dr. Frimpong presented "Impact of Obesity in Patients with Multiple Myeloma Receiving High-Dose Melphalan Followed by Autologous Hematopoietic Cell Transplantation." In this retrospective cohort study, outcomes and toxicities of high-dose melphalan followed by autologous hematopoietic cell transplantation (HCT) were evaluated in a total of 462 nonobese (body mass index [BMI] <30 kg/m^2), obese (BMI 30–34.9 kg/m^2), and severely obese (BMI ≥35 kg/m^2) multiple myeloma patients. All three cohorts had similar baseline characteristics except for age ≤65 years and the use of adjusted body weight for melphalan dosing (nonobese, 4.5%; obese, 25.7%; severely obese, 41.2%; p < .001). Across all three cohorts, no significant differences were seen in the primary end points of nonrelapse mortality (NRM) and overall survival (OS). Durie-Salmon Stage (DSS) 3 was the only independent predictor of inferior OS, and in a multivariate analysis, actual-weight dosing was associated with a decreased risk of NRM (p = .003). In patients receiving actual-weight dosing of melphalan, febrile neutropenia was more common in nonobese patients compared with obese and severely obese patients (71.4% vs. 56.4% and 62.5%, respectively; p = .03). The authors concluded that administration of high-dose melphalan and autologous HCT can be performed safely in obese myeloma patients, but further research is needed to evaluate the effect of dose adjustments on outcomes. To read the full abstract for Dr. Frimpong's research, visit https://ash.confex.com/ash/2016/webprogram/Paper90208.html.



Alex Ganetsky, PharmD BCOP

Dr. Ganetsky presented two posters at the meeting. In the poster titled "Tocilizumab Is Highly Active for Severe Steroid-Refractory Acute Graft-Versus-Host Disease of the Gastrointestinal Tract," Dr. Ganetsky provided retrospective data evaluating the efficacy of tocilizumab, an interleukin-6 receptor antagonist, for the treatment of severe steroid-refractory gastrointestinal graft-versus-host disease (GI-GVHD). Five patients with grade 4 steroid refractory, biopsy-proven GVHD received intravenous tocilizumab 8 mg/kg every 2 weeks until achievement of a complete response (CR). After a median time of 9 days, all five patients (100%) achieved a CR. Two patients achieved a CR after 1 tocilizumab dose, and three patients required 2–4 doses. Serum levels of pro-inflammatory cytokines were measured, but no association was seen between cytokine levels and response to tocilizumab. To read the full abstract for Dr. Ganetsky's research, visit https://ash.confex.com/ash/2016/webprogram/Paper90150.html.

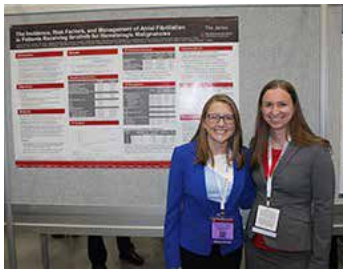
The second poster presented by Dr. Ganetsky was "Oral Vancomycin Is Highly Effective in Preventing Clostridium Difficile Infection in Allogeneic Hematopoietic Stem Cell Transplant Recipients." Clostridium difficile infection (CDI) is a common infectious complication in allogeneic hematopoietic stem cell transplantation (alloHCT). Dr. Ganetsky conducted a retrospective study evaluating the effectiveness of oral vancomycin 125 mg twice daily versus no prophylaxis in 105 adult patients undergoing alloHCT. During the inpatient admission for alloHCT, no cases of CDI were reported in the oral vancomycin prophylaxis group (0/50; 0%) compared with 11/55 (20%) of patients in the no-prophylaxis group. No cases of vancomycin-resistant enterococcus bloodstream infections were reported in patients who received vancomycin prophylaxis. The authors concluded that prophylactic vancomycin is highly effective in preventing CDI in alloHCT recipients but acknowledged that longer follow-up is needed. To read the full abstract for Dr. Ganetsky's research, visit https://ash.confex.com/ash/2016/webprogram/Paper93290.html.

Jigar Trivedi, PharmD MSc

Dr. Trivedi presented two posters at the meeting. One poster, "Optimizing Progenitor Cell Mobilization in Patients with Myeloma: Effect of a Pre-Emptive Day 4 Plerixafor-Based Mobilization Algorithm," provides an algorithm for using pre-emptive day 4 plerixafor to maximize collection-day peripheral blood (PB) CD34+ cell numbers in patients undergoing peripheral blood progenitor cell (PBPC) mobilization. Data from 105 patients with multiple myeloma undergoing autologous hematopoietic stem cell transplantation (AHSCT) were analyzed retrospectively. On day 4, patients with PBCD34+ <50 cells/μL (90% of patients studied) received either one subcutaneous dose of plerixafor 0.24 mg/kg or a 12-mg fixed dose. The fixed dose was administered to patients

who could be paired with another patient who was simultaneously undergoing PBPC mobilization. No significant difference was seen in the collection yield (median 10.95 million CD34+ cells/kg) of the two dosing groups. Optimal mobilization occurred in 96.2% of patients and was achieved with only 1 day of collection in 94.2% of patients. The authors concluded that pre-emptive use of day 4 plerixafor is effective and results in a high percentage of optimal day 1 collections, which demonstrated the utility of the plerixafor-based mobilization algorithm. To read the full abstract for Dr. Trivedi's research, visit https://ash.confex.com/ash/2016/webprogram/Paper97191.html.

The second poster presented by Dr. Trivedi was "CYP2C19 Genotype-Guided Dosing and Voriconazole Concentrations in Hematopoietic Stem Cell Transplant (HSCT) Patients Receiving Antifungal Prophylaxis." Voriconazole is an azole antifungal agent metabolized via CYP2C19. Drs. Patel, Trivedi, and colleagues performed the first prospective clinical study investigating the impact of CYP2C19 genotype-guided voriconazole dosing on trough concentrations and clinical outcomes in adult allogenic HSCT patients. Patients harboring the *1/*1 (rapid metabolizers [RMs]) or *17/*17 (ultra-rapid metabolizers [UMs]) genotypes received oral voriconazole 300 mg twice daily post-transplant, whereas the standard 200 mg twice-daily dose was administered to all other patients. Data for 26 patients was available at the time of interim analysis, and of these patients, 8% were UMs, 23% RMs, 46% normal, 19% intermediate, and 4% poor metabolizers. This voriconazole dosing strategy reduced the percentage of patients with subtherapeutic levels at days 5–7 from historically 50% to 30.8% ($p = .038$). No RMs or UMs were at subtherapeutic levels, compared with 80% in historical controls ($p < .001$). In addition, no supratherapeutic trough concentrations or grade 3/4 drug-related adverse events were observed. To read the full abstract for Dr. Trivedi's research, visit https://ash.confex.com/ash/2016/webprogram/Paper94963.html.



Tracy Wiczer, PharmD BCOP, and Lauren Levine, PharmD BCOP

Drs. Wiczer and Levine presented "Management and Outcomes of Atrial Fibrillation in Patients Receiving Ibrutinib for Hematologic Malignancies at a Single Center." Ibrutinib, an oral Bruton's tyrosine kinase inhibitor, has been associated with a 2%–16% reported incidence of atrial fibrillation (a-fib). An increased bleeding risk has also been associated with ibrutinib, which may be exacerbated by anticoagulation and antiplatelet therapy. To provide data for this clinical quandary, Wiczer and Levine performed a retrospective analysis in which they identified 72 patients with incident or recurrent a-fib while taking ibrutinib. The majority of the a-fib events were grade 1 or 2 (93%); 7% were grade 3. First-line therapy included rate-control (75%), interventional procedural strategies (11.1%), rhythm control (4.2%), or no intervention (9.7%). A major bleeding event occurred in six patients (8.3%), and two of these patients had a second major bleed. Of these eight major bleeding events, three occurred while the patient was on antiplatelet agents, and none occurred while the patient was on anticoagulation. In addition, 25% of patients experienced a nonmajor bleeding event. The authors concluded that patients experiencing an a-fib event while on ibrutinib could be easily managed, but the optimal strategy for stroke prophylaxis in this patient population is unclear. To read the full abstract for Wiczer and Levine's research, visit https://ash.confex.com/ash/2016/webprogram/Paper92564.html. ●●

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FOR PREVENTION OF CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING*

HELP YOUR PATIENTS WEATHER CHEMOTHERAPY BETTER[1†]

*ALOXI® was studied in MEC, including AC-based chemotherapy.

Powerful

A single IV dose is clinically proven to prevent CINV for up to 5 days following MEC[1,2]

Proven

Efficacy and safety studied across a variety of patients, chemotherapy regimens, and concomitant agents in multiple clinical trials[1-3]

Preferred

Palonosetron (ALOXI) is the preferred 5-HT_3 receptor antagonist prior to MEC listed in both the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) and ASCO guidelines[4,5]

Anthracycline-cyclophosphamide (AC).

†Double-blind, randomized, phase III noninferiority trial comparing single doses of ALOXI (n=189) with ondansetron (n=185) with a primary endpoint of complete response during the acute phase (Day 1) following MEC. ALOXI demonstrated significantly greater complete response in the acute phase (81.0% vs 68.6%, p=0.0085) and in the delayed phase (74.1% vs 55.1%, p<0.001). Clinical superiority over other 5-HT_3 receptor antagonists has not been adequately demonstrated in the acute phase.[1,2]

Learn more about the preferred choice at **ALOXI.com/hcp**

Indication

ALOXI® injection is indicated in adults for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic chemotherapy, and the prevention of acute nausea and vomiting associated with initial and repeat courses of highly emetogenic chemotherapy.

Important Safety Information

CONTRAINDICATIONS

- ALOXI is contraindicated in patients known to have hypersensitivity to the drug or any of its components

WARNINGS AND PRECAUTIONS

- Hypersensitivity reactions, including anaphylaxis, have been reported with or without known hypersensitivity to other 5-HT_3 receptor antagonists
- Serotonin syndrome has been reported with 5-HT_3 receptor antagonists alone, but particularly with the use of serotonergic drugs. Serotonin syndrome can be life threatening. Symptoms may include the following combination of signs and symptoms: mental status changes, autonomic instability, neuromuscular symptoms, seizures, and gastrointestinal symptoms. Patients should be monitored for the emergence of serotonin syndrome, and if symptoms occur, discontinue ALOXI and initiate supportive treatment. Patients should be informed of the increased risk of serotonin syndrome, especially if ALOXI is used concomitantly with other serotonergic drugs

ADVERSE REACTIONS

- In adults, the most commonly reported adverse drug reactions include headache (9%) and constipation (5%)

Please see brief summary of Full Prescribing Information on the following page.

Moderately emetogenic chemotherapy (MEC). National Comprehensive Cancer Network® (NCCN®). American Society of Clinical Oncology (ASCO).

References: 1. ALOXI® (palonosetron HCl) injection. Full Prescribing Information. **2.** Gralla R, Lichinitser M, Van der Vegt S, et al. Palonosetron improves prevention of chemotherapy-induced nausea and vomiting following moderately emetogenic chemotherapy: results of a double-blind randomized phase III trial comparing single doses of palonosetron with ondansetron. *Ann Oncol*. 2003;14: 1570-1577. **3.** Aapro MS, Grunberg SM, Manikhas GM, et al. A phase III, double-blind, randomized trial of palonosetron compared with ondansetron in preventing chemotherapy-induced nausea and vomiting following highly emetogenic chemotherapy. *Ann Oncol*. 2006;17:1441-1449. **4.** Hesketh PJ, Bohlke K, Lyman GH, et al. Antiemetics: American Society of Clinical Oncology Focused Guideline Update. *J Clin Oncol*. 2016;34:381-386. **5.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Antiemesis V2.2016. © National Comprehensive Cancer Network, Inc. 2016. All rights reserved. Accessed June 20, 2016. To view the most recent and complete version of the guideline, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.

Aloxi®
palonosetron HCl injection
0.25 mg/5 mL
LASTING PREVENTION 5 DAYS STRONG†

Eisai HELSINN

ALOXI® (palonosetron HCl) injection
BRIEF SUMMARY – See package insert for full Prescribing Information.

DOSAGE AND ADMINISTRATION

Recommended Dosing

Chemotherapy-Induced Nausea and Vomiting

Age	Dose*	Infusion Time
Adults	**0.25 mg x 1**	Infuse over **30 seconds** beginning approx. 30 min before the start of chemo
Pediatrics (1 month to less than 17 years)	**20 micrograms per kilogram** (max 1.5 mg) x 1	Infuse over **15 minutes** beginning approx. 30 min before the start of chemo

*Note different dosing units in pediatrics

Postoperative Nausea and Vomiting

Dosage for Adults - a single 0.075 mg intravenous dose administered over 10 seconds immediately before the induction of anesthesia.

Instructions for Intravenous Administration

ALOXI is supplied ready for intravenous administration at a concentration of 0.05 mg/mL (50 mcg/ mL). ALOXI should not be mixed with other drugs. The infusion line should be flushed with normal saline before and after administration of ALOXI. Parenteral drug products should be inspected visually for particulate matter and discoloration before administration, whenever solution and container permit.

CONTRAINDICATIONS

ALOXI is contraindicated in patients known to have hypersensitivity to the drug or any of its components.

WARNINGS AND PRECAUTIONS

Hypersensitivity: Hypersensitivity reactions, including anaphylaxis, have been reported with or without known hypersensitivity to other 5-HT_3 receptor antagonists.

Serotonin Syndrome: The development of serotonin syndrome has been reported with 5-HT_3 receptor antagonists. Most reports have been associated with concomitant use of serotonergic drugs (e.g., selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors, mirtazapine, fentanyl, lithium, tramadol, and intravenous methylene blue). Some of the reported cases were fatal. Serotonin syndrome occurring with overdose of another 5-HT_3 receptor antagonist alone has also been reported. The majority of reports of serotonin syndrome related to 5-HT_3 receptor antagonist use occurred in a post-anesthesia care unit or an infusion center.

Symptoms associated with serotonin syndrome may include the following combination of signs and symptoms: mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, with or without gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Patients should be monitored for the emergence of serotonin syndrome, especially with concomitant use of ALOXI and other serotonergic drugs. If symptoms of serotonin syndrome occur, discontinue ALOXI and initiate supportive treatment. Patients should be informed of the increased risk of serotonin syndrome, especially if ALOXI is used concomitantly with other serotonergic drugs.

ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Chemotherapy-Induced Nausea and Vomiting

Adults: In clinical trials for the prevention of nausea and vomiting induced by moderately or highly emetogenic chemotherapy, 1374 adult patients received palonosetron. Adverse reactions were similar in frequency and severity with ALOXI and ondansetron or dolasetron. Following is a listing of all adverse reactions reported by ≥ 2% of patients in these trials (Table 1).

Table 1: Adverse Reactions from Chemotherapy-Induced Nausea and Vomiting Studies ≥ 2% in any Treatment Group

Event	ALOXI 0.25 mg (N=633)	Ondansetron 32 mg I.V. (N=410)	Dolasetron 100 mg I.V. (N=194)
Headache	60 (9%)	34 (8%)	32 (16%)
Constipation	29 (5%)	8 (2%)	12 (6%)
Diarrhea	8 (1%)	7 (2%)	4 (2%)
Dizziness	8 (1%)	9 (2%)	4 (2%)
Fatigue	3 (< 1%)	4 (1%)	4 (2%)
Abdominal Pain	1 (< 1%)	2 (< 1%)	3 (2%)
Insomnia	1 (< 1%)	3 (1%)	3 (2%)

In other studies, 2 subjects experienced severe constipation following a single palonosetron dose of approximately 0.75 mg, three times the recommended dose. One patient received a 10 mcg/kg oral dose in a postoperative nausea and vomiting study and one healthy subject received a 0.75 mg I.V. dose in a pharmacokinetic study.

In clinical trials, the following infrequently reported adverse reactions, assessed by investigators as treatment-related or causality unknown, occurred following administration of ALOXI to adult patients receiving concomitant cancer chemotherapy: Cardiovascular: 1%: non-sustained tachycardia, bradycardia, hypotension, < 1%: hypertension, myocardial ischemia, extrasystoles, sinus tachycardia, sinus arrhythmia, supraventricular extrasystoles and QT prolongation. In many cases, the relationship to ALOXI was unclear. Dermatological: < 1%: allergic dermatitis, rash. Hearing and Vision: < 1%: motion sickness, tinnitus, eye irritation and amblyopia. Gastrointestinal System: 1%: diarrhea, < 1%: dyspepsia, abdominal pain, dry mouth, hiccups and flatulence. General: 1%: weakness, < 1%: fatigue, fever, hot flash, flu-like syndrome. Liver: < 1%: transient, asymptomatic increases in AST and/or ALT and bilirubin. These changes occurred predominantly in patients receiving highly emetogenic chemotherapy. Metabolic: 1%: hyperkalemia, < 1%: electrolyte fluctuations, hyperglycemia, metabolic acidosis, glycosuria, appetite decrease, anorexia. Musculoskeletal: < 1%: arthralgia. Nervous System: 1%: dizziness, < 1%: somnolence, insomnia, hypersomnia, paresthesia. Psychiatric: 1%: anxiety, < 1%: euphoric mood. Urinary System: < 1%: urinary retention. Vascular: < 1%: vein discoloration, vein distention.

Pediatrics: In a pediatric clinical trial for the prevention of chemotherapy-induced nausea and vomiting 163 cancer patients received a single 20 mcg/kg (maximum 1.5 mg) intravenous infusion of palonosetron 30 minutes before beginning the first cycle of emetogenic chemotherapy. Patients had a mean age of 8.4 years (range 2 months to 16.9 years) and were 46% male; and 93% white.

The following adverse reactions were reported for palonosetron: Nervous System: <1%: headache, dizziness, dyskinesia. General: <1%: infusion site pain. Dermatological: <1%: allergic dermatitis, skin disorder. In the trial, adverse reactions were evaluated in pediatric patients receiving palonosetron for up to 4 chemotherapy cycles.

Postmarketing Experience: The following adverse reactions have been identified during postapproval use of ALOXI. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Very rare cases (<1/10,000) of hypersensitivity reactions including anaphylaxis and anaphylactic shock and injection site reactions (burning, induration, discomfort and pain) were reported from postmarketing experience of ALOXI 0.25 mg in the prevention of chemotherapy-induced nausea and vomiting.

DRUG INTERACTIONS

Palonosetron is eliminated from the body through both renal excretion and metabolic pathways with the latter mediated via multiple CYP enzymes. Further *in vitro* studies indicated that palonosetron is not an inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2D6, CYP2E1 and CYP3A4/5 (CYP2C19 was not investigated) nor does it induce the activity of CYP1A2, CYP2D6, or CYP3A4/5. Therefore, the potential for clinically significant drug interactions with palonosetron appears to be low.

Serotonin syndrome (including altered mental status, autonomic instability, and neuromuscular symptoms) has been described following the concomitant use of 5-HT_3 receptor antagonists and other serotonergic drugs, including selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs).

Coadministration of 0.25 mg I.V. palonosetron and 20 mg I.V. dexamethasone in healthy subjects revealed no pharmacokinetic drug-interactions between palonosetron and dexamethasone.

In an interaction study in healthy subjects where palonosetron 0.25 mg (I.V. bolus) was administered on day 1 and oral aprepitant for 3 days (125 mg/80 mg/80 mg), the pharmacokinetics of palonosetron were not significantly altered (AUC: no change, C_{max}: 15% increase).

A study in healthy volunteers involving single-dose I.V. palonosetron (0.75 mg) and steady state oral metoclopramide (10 mg four times daily) demonstrated no significant pharmacokinetic interaction.

In controlled clinical trials, ALOXI injection has been safely administered with corticosteroids, analgesics, antiemetics/ antinauseants, antispasmodics and anticholinergic agents.

Palonosetron did not inhibit the antitumor activity of the five chemotherapeutic agents tested (cisplatin, cyclophosphamide, cytarabine, doxorubicin and mitomycin C) in murine tumor models.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category B

Risk Summary: Adequate and well controlled studies with ALOXI have not been conducted in pregnant women. In animal reproduction studies, no effects on embryo-fetal development were observed with the administration of oral palonosetron during the period of organogenesis at doses up to 1894 and 3789 times the recommended human intravenous dose in rats and rabbits, respectively. Because animal reproduction studies are not always predictive of human response, ALOXI should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether ALOXI is present in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants and the potential for tumorigenicity shown for palonosetron in the rat carcinogenicity study, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Chemotherapy-Induced Nausea and Vomiting: Safety and effectiveness of ALOXI have been established in pediatric patients aged 1 month to less than 17 years for the prevention of acute nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including highly emetogenic cancer chemotherapy. Use is supported by a clinical trial where 165 pediatric patients aged 2 months to <17 years were randomized to receive a single dose of palonosetron 20 mcg/kg (maximum 1.5 mg) administered as an intravenous infusion 30 minutes prior to the start of emetogenic chemotherapy. While this study demonstrated that pediatric patients require a higher palonosetron dose than adults to prevent chemotherapy-induced nausea and vomiting, the safety profile is consistent with the established profile in adults.

Safety and effectiveness of ALOXI in neonates (less than 1 month of age) have not been established.

Postoperative Nausea and Vomiting Studies: Safety and efficacy have not been established in pediatric patients for prevention of postoperative nausea and vomiting. Two pediatric trials were performed.

Pediatric Study 1, a dose finding study, was conducted to compare two doses of palonosetron, 1 mcg/kg (max 0.075 mg) versus 3 mcg/kg (max 0.25 mg). A total of 150 pediatric surgical patients participated, age range 1 month to <17 years. No dose response was observed.

Pediatric Study 2, a multicenter, double-blind, double-dummy, randomized, parallel group, active control, single-dose non-inferiority study, compared I.V. palonosetron (1 mcg/kg, max 0.075 mg) versus I.V. ondansetron. A total of 670 pediatric surgical patients participated, age 30 days to <17 years. The primary efficacy endpoint, Complete Response (CR: no vomiting, no retching, and no antiemetic rescue medication) during the first 24 hours postoperatively was achieved in 78.2% of patients in the palonosetron group and 82.7% in the ondansetron group. Given the pre-specified non-inferiority margin of -10%, the stratum adjusted Mantel-Haenszel statistical non-inferiority confidence interval for the difference in the primary endpoint, complete response (CR), was [-10.5, 1.7%], therefore non-inferiority was not demonstrated. Adverse reactions to palonosetron were similar to those reported in adults.

Geriatric Use: Population pharmacokinetics analysis did not reveal any differences in palonosetron pharmacokinetics between cancer patients ≥ 65 years of age and younger patients (18 to 64 years). Of the 1374 adult cancer patients in clinical studies of palonosetron, 316 (23%) were ≥ 65 years old, while 71 (5%) were ≥ 75 years old. No overall differences in safety or effectiveness were observed between these subjects and the younger subjects, but greater sensitivity in some older individuals cannot be ruled out. No dose adjustment or special monitoring are required for geriatric patients. Of the 1520 adult patients in ALOXI PONV clinical studies, 73 (5%) were ≥65 years old. No overall differences in safety were observed between older and younger subjects in these studies, though the possibility of heightened sensitivity in some older individuals cannot be excluded. No differences in efficacy were observed in geriatric patients for the CINV indication and none are expected for geriatric PONV patients. However, ALOXI efficacy in geriatric patients has not been adequately evaluated.

Renal Impairment: Mild to moderate renal impairment does not significantly affect palonosetron pharmacokinetic parameters. Total systemic exposure increased by approximately 28% in severe renal impairment relative to healthy subjects. Dosage adjustment is not necessary in patients with any degree of renal impairment.

Hepatic Impairment: Hepatic impairment does not significantly affect total body clearance of palonosetron compared to the healthy subjects. Dosage adjustment is not necessary in patients with any degree of hepatic impairment.

Race: Intravenous palonosetron pharmacokinetics was characterized in twenty-four healthy Japanese subjects over the dose range of 3 – 90 mcg/kg. Total body clearance was 25% higher in Japanese subjects compared to Whites, however, no dose adjustment is required. The pharmacokinetics of palonosetron in Blacks has not been adequately characterized.

OVERDOSAGE

There is no known antidote to ALOXI. Overdose should be managed with supportive care.

Fifty adult cancer patients were administered palonosetron at a dose of 90 mcg/kg (equivalent to 6 mg fixed dose) as part of a dose ranging study. This is approximately 25 times the recommended dose of 0.25 mg. This dose group had a similar incidence of adverse events compared to the other dose groups and no dose response effects were observed.

Dialysis studies have not been performed, however, due to the large volume of distribution, dialysis is unlikely to be an effective treatment for palonosetron overdose. A single intravenous dose of palonosetron at 30 mg/kg (947 and 474 times the human dose for rats and mice, respectively, based on body surface area) was lethal to rats and mice. The major signs of toxicity were convulsions, gasping, pallor, cyanosis and collapse.

PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information).

Instructions for Patients

Patients should be advised to report to their physician all of their medical conditions, including any pain, redness, or swelling in and around the infusion site.

Advise patients of the possibility of serotonin syndrome, especially with concomitant use of ALOXI and another serotonergic agent such as medications to treat depression and migraines.

Advise patients to seek immediate medical attention if the following symptoms occur: changes in mental status, autonomic instability, neuromuscular symptoms with or without gastrointestinal symptoms.

Patients should be instructed to read the Patient Information.

Rx Only

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NEW

Now Approved

Introducing a new PARP inhibitor

Rubraca is indicated as monotherapy for the treatment of patients with deleterious *BRCA* mutation (germline and/or somatic) associated advanced ovarian cancer who have been treated with two or more chemotherapies. Select patients for therapy based on an FDA-approved companion diagnostic for Rubraca.

This indication is approved under accelerated approval based on objective response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Rubraca™
(rucaparib) tablets

Select Important Safety Information

There are no contraindications with Rubraca.

Myelodysplastic Syndrome (MDS)/Acute Myeloid Leukemia (AML) was reported in 2 of 377 (0.5%) patients with ovarian cancer treated with Rubraca. The duration of Rubraca treatment prior to the diagnosis of MDS/AML was 57 days and 539 days. Both patients received prior treatment with platinum and other DNA damaging agents.

AML was reported in 2 (<1%) patients with ovarian cancer enrolled in a blinded, randomized trial evaluating Rubraca versus placebo. One case of AML was fatal. The duration of treatment prior to the diagnosis of AML was 107 days and 427 days. Both patients had received prior treatment with platinum and other DNA damaging agents.

Do not start Rubraca until patients have recovered from hematological toxicity caused by previous chemotherapy (≤ Grade 1).

Monitor complete blood count testing at baseline and monthly thereafter. For prolonged hematological toxicities, interrupt Rubraca and monitor blood counts weekly until recovery. If the levels have not recovered to Grade 1 or less after 4 weeks, refer the patient to a hematologist for further investigations, including bone marrow analysis and blood sample for cytogenetics. If MDS/AML is confirmed, discontinue Rubraca.

Rubraca can cause fetal harm when administered to pregnant women based on its mechanism of action and findings from animal studies. Apprise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment and for 6 months following the last dose of Rubraca.

Most common adverse reactions (≥ 20%; Grade 1-4) were nausea (77%), asthenia/fatigue (77%), vomiting (46%), anemia (44%), constipation (40%), dysgeusia (39%), decreased appetite (39%), diarrhea (34%), abdominal pain (32%), dyspnea (21%), and thrombocytopenia (21%).

Most common laboratory abnormalities (≥ 35%; Grade 1-4) were increase in creatinine (92%), increase in alanine aminotransferase (ALT) (74%), increase in aspartate aminotransferase (AST) (73%), decrease in hemoglobin (67%), decrease in lymphocytes (45%), increase in cholesterol (40%), decrease in platelets (39%), and decrease in absolute neutrophil count (35%).

Because of the potential for serious adverse reactions in breast-fed infants from Rubraca, advise lactating women not to breastfeed during treatment with Rubraca and for 2 weeks after the final dose.

You may report side effects to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Clovis Oncology, Inc. at 1-844-258-7662.

Please see Brief Summary of full Prescribing Information on adjacent pages for additional Important Safety Information.

Reference: Rubraca [prescribing information]. Boulder, CO: Clovis Oncology; 2016.

CLOVIS ONCOLOGY

For more information, visit **www.Rubraca.com**

PP-RUCA-US-0230

12/2016

RUBRACA™ (rucaparib) tablets, for oral use

BRIEF SUMMARY: Please see package insert for full prescribing information.

INDICATIONS AND USAGE

Rubraca™ is indicated as monotherapy for the treatment of patients with deleterious *BRCA* mutation (germline and/or somatic) associated advanced ovarian cancer who have been treated with two or more chemotherapies. Select patients for therapy based on an FDA-approved companion diagnostic for Rubraca *[see Dosage and Administration (2.1) in the full prescribing information]*.

This indication is approved under accelerated approval based on objective response rate and duration of response *[see Clinical Studies (14) in the full prescribing information]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Myelodysplastic Syndrome/Acute Myeloid Leukemia

Myelodysplastic syndrome (MDS)/Acute Myeloid Leukemia (AML) was reported in 2 of 377 (0.5%) patients with ovarian cancer treated with Rubraca. The duration of Rubraca treatment prior to the diagnosis of MDS/AML was 57 days and 539 days. Both patients received prior treatment with platinum and other DNA damaging agents.

In addition, AML was reported in 2 (< 1%) patients with ovarian cancer enrolled in a blinded, randomized trial evaluating Rubraca versus placebo. One case of AML was fatal. The duration of treatment prior to the diagnosis of AML was 107 days and 427 days. Both patients had received prior treatment with platinum and other DNA damaging agents.

Monitor complete blood count testing at baseline and monthly thereafter. Do not start Rubraca until patients have recovered from hematological toxicity caused by previous chemotherapy (≤ Grade 1). For prolonged hematological toxicities, interrupt Rubraca and monitor blood counts weekly until recovery. If the levels have not recovered to Grade 1 or less after 4 weeks, refer the patient to a hematologist for further investigations, including bone marrow analysis and blood sample for cytogenetics. If MDS/AML is confirmed, discontinue Rubraca.

Embryo-Fetal Toxicity

Rubraca can cause fetal harm when administered to a pregnant woman based on its mechanism of action and findings from animal studies. In an animal reproduction study, administration of rucaparib to pregnant rats during organogenesis resulted in embryo-fetal death at maternal exposure that were 0.04 times the AUC in patients receiving the recommended dose of 600 mg twice daily. Apprise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment and for 6 months following the last dose of Rubraca *[see Use in Specific Populations (8.1, 8.3) and Clinical Pharmacology (12.1) in the full prescribing information]*.

ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Myelodysplastic Syndrome/Acute Myeloid Leukemia *[see Warnings and Precautions]*.

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Rubraca 600 mg twice daily as monotherapy, has been studied in 377 patients with ovarian cancer treated in two open-label, single arm trials. In these patients, the median age was 62 years (range 31 to 86), 100% had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, 38% had *BRCA*-mutated ovarian cancer, 45% had received 3 or more prior lines of chemotherapy, and the median time since ovarian cancer diagnosis was 43 months (range 6 to 197).

Adverse reactions led to dose reduction or interruption in 62% of patients, most frequently from anemia (27%), and fatigue/asthenia (22%). Adverse reactions led to dose discontinuation in 10% of patients, most frequently from fatigue/asthenia (2%). The median duration of treatment was 5.5 months (range 0.1 to 28.0).

Table 2 and Table 3 summarize the common adverse reactions and abnormal laboratory findings, respectively, observed in patients treated with Rubraca.

Table 2. Adverse Reactions Reported in ≥ 20% of Patients with Ovarian Cancer Treated with Rubraca 600 mg Twice Daily

	All Ovarian Cancer Patients (N = 377) %	
Adverse Reaction	**Grades[a] 1-4**	**Grades 3-4**
Gastrointestinal Disorders		
Nausea	77	5
Vomiting	46	4
Constipation	40	2
Diarrhea	34	2
Abdominal Pain	32	3
General Disorders		
Asthenia/Fatigue	77	11
Blood and Lymphatic System Disorders		
Anemia	44	25
Thrombocytopenia	21	5
Nervous System Disorders		
Dysgeusia	39	0.3
Metabolism and Nutrition Disorders		
Decreased appetite	39	3
Respiratory, Thoracic, and Mediastinal Disorders		
Dyspnea	21	0.5

[a] National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE version 4.03)

The following adverse reactions have been identified in < 20% of the 377 patients treated with Rubraca 600 mg twice daily: dizziness (17%), neutropenia (15%), rash (includes rash, rash erythematous, rash maculopapular and dermatitis) (13%), pyrexia (11%), photosensitivity reaction (10%), pruritus (includes pruritus and pruritus generalized) (9%), Palmar-plantar erythrodysaesthesia syndrome (2%), and febrile neutropenia (1%).

Table 3. Laboratory Abnormalities Reported in ≥ 35% of Patients with Ovarian Cancer Treated with Rubraca 600 mg Twice Daily

	All Patients with Ovarian Cancer (N = 377) %	
Laboratory Parameter	**Grade 1-4 [a]**	**Grade 3-4**
Clinical Chemistry		
Increase in creatinine	92	1
Increase in ALT[b]	74	13
Increase in AST[b]	73	5
Increase in cholesterol	40	2
Hematologic		
Decrease in hemoglobin	67	23
Decrease in lymphocytes	45	7
Decrease in platelets	39	6
Decrease in absolute neutrophil count	35	10

[a] At least one worsening shift in CTCAE grade and by maximum shift from baseline.

[b] Increase in ALT/AST led to treatment discontinuation in 0.3% of patients (1/377).

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on findings from animal studies and its mechanism of action, Rubraca can cause fetal harm when administered to pregnant women. There are no available data in pregnant women to inform the drug-associated risk. In an animal reproduction study, administration of rucaparib to pregnant rats during organogenesis resulted in embryo-fetal death at maternal exposure that were 0.04 times the $AUC_{0\text{-}24h}$ in patients receiving the recommended dose of 600 mg twice daily *[see Data]*. Apprise pregnant women of the potential risk to a fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In a dose range-finding embryo-fetal development study, pregnant rats received oral doses of 50, 150, 500, or 1000 mg/kg/day of rucaparib during the period of organogenesis. Post-implantation loss (100% early resorptions) was observed in all animals at doses greater than or equal to 50 mg/kg/day (with maternal systemic exposures approximately 0.04 times the human exposure at the recommended dose based on $AUC_{0\text{-}24h}$).

Lactation

Risk Summary

There is no information regarding the presence of rucaparib in human milk, or on its effects on milk production or the breast-fed infant. Because of the potential for serious adverse reactions in breast-fed infants from Rubraca, advise lactating women not to breastfeed during treatment with Rubraca and for 2 weeks after the final dose.

Females and Males of Reproductive Potential

Pregnancy Testing

Pregnancy testing is recommended for females of reproductive potential prior to initiating Rubraca.

Contraception

Females

Rubraca can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations]*. Advise females of reproductive potential to use effective contraception during treatment and for 6 months following the final dose of Rubraca.

Pediatric Use

The safety and effectiveness of Rubraca in pediatric patients have not been established.

Geriatric Use

One hundred and sixty (42%) of the 377 ovarian cancer patients in clinical trials of Rubraca were 65 years of age or older. No overall differences in safety were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out. The effectiveness of Rubraca in patients with *BRCA*-mutant ovarian cancer who were 65 years of age or older could not be assessed due to the small number of patients (N=38).

Hepatic Impairment

No starting dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin less than or equal to upper limit of normal [ULN] and AST greater than ULN, or total bilirubin between 1.0 to 1.5 times ULN and any AST). No recommendation of starting dose adjustment is available for patients with moderate to severe hepatic impairment (total bilirubin greater than 1.5 times ULN) due to a lack of data *[See Clinical Pharmacology (12.3) in the full prescribing information]*.

Renal Impairment

No starting dose adjustment is recommended for patients with mild to moderate renal impairment (creatinine clearance [CLcr] between 30 and 89 mL/min, as estimated by the Cockcroft-Gault method). There is no recommended starting dose for patients with CLcr less than 30 mL/min or patients on dialysis due to a lack of data *[See Clinical Pharmacology (12.3) in the full prescribing information]*.

OVERDOSAGE

There is no specific treatment in the event of Rubraca overdose, and symptoms of overdose are not established. In the event of suspected overdose, physicians should follow general supportive measures and should treat symptomatically.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

MDS/AML: Advise patients to contact their healthcare provider if they experience weakness, feeling tired, fever, weight loss, frequent infections, bruising, bleeding easily, breathlessness, blood in urine or stool, and/or laboratory findings of low blood cell counts, or a need for blood transfusions. These may be signs of hematological toxicity or a more serious uncommon bone marrow problem called 'myelodysplastic syndrome' (MDS) or 'acute myeloid leukemia' (AML) which have been reported in patients treated with Rubraca *[see Warnings and Precautions]*.

Embryo-Fetal Toxicity: Advise females to inform their healthcare provider if they are pregnant or become pregnant. Inform female patients of the risk to a fetus and potential loss of the pregnancy *[see Use in Specific Populations]*. Advise females of reproductive potential to use effective contraception during treatment and for 6 months after receiving the last dose of Rubraca *[see Warnings and Precautions and Use in Specific Populations]*.

Photosensitivity: Advise patients to use appropriate sun protection due to the increased susceptibility to sunburn while taking Rubraca *[see Adverse Drug Reactions]*.

Lactation: Advise females not to breastfeed during treatment and for 2 weeks after the last dose of Rubraca *[see Use in Specific Populations]*.

Dosing Instructions: Instruct patients to take Rubraca orally twice daily with or without food. Doses should be taken approximately 12 hours apart. Advise patients that if a dose of Rubraca is missed or if the patient vomits after taking a dose of Rubraca, patients should not take an extra dose, but take the next dose at the regular time *[see Dosage and Administration (2.1) in the full prescribing information]*.

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Board Update

Big ideas

Sarah Scarpace Peters, PharmD MPH BCOP, HOPA President (2016–17)
Associate Professor of Pharmacy Practice
Albany College of Pharmacy and Health Sciences
Albany, NY

HOPA's founders (see HOPA's history at www.hoparx.org/about/history-of-hopa) had a "big idea" when they recognized that the emerging specialty of hematology/oncology pharmacy needed its own forum for education and sharing of research in the field. As with the genesis of other big ideas in history, legend has it that two of the original founders sketched the idea for what would become HOPA on the back of a napkin in the Atlanta airport. HOPA has come a long way since then—expanding its education programs, establishing a health policy agenda, and being invited to sit at more and more tables. All these have been opportunities to continue to establish the value proposition for hematology/oncology pharmacy services. The ultimate "big idea" for HOPA today is for patients, providers, payers, professional associations, and policymakers alike to ask for hematology/oncology pharmacists by profession and by name.

In the 2 months since I wrote the last Board Update for *HOPA News*, a hematology/oncology pharmacist has again been requested by name to give input on important initiatives. HOPA member John Valgus, PharmD BCOP, current chair of the Practice Management Program work group, served as HOPA's representative on a task force of the Joint Commission of Pharmacy Practitioners (JCPP) that was asked to provide comment on the new Systematized Nomenclature of Medicine: Clinical Terms (SNOMED CT) codes (see the press release at www.prnewswire.com/news-releases/pharmacy-stakeholders-release-standardized-documentation-of-medication-therapy-management-mtm-services-using-snomed-ct-codes-300354025.html). This is an important historical milestone for HOPA: we have been an observer organization of the influential JCPP for 2 years, and it was symbolically meaningful that we were invited to participate on the task force without being a JCPP member (a first for HOPA).

Dr. Valgus's consistent participation on a series of calls and e-mail exchanges undoubtedly added to JCPP's favorable opinion of HOPA, and on December 6, 2016, we were formally invited to become a full member of JCPP. The HOPA board approved our membership at our meeting on December 15, 2016.

In November 2016, I attended two meetings on HOPA's behalf: at one, to contribute perspectives (some offered by HOPA's Research Committee) as a stakeholder organization in the American Association of Colleges of Pharmacy's Academic Research Fellows Program, and at another, to engage with payers and others on "driving value and outcomes in oncology" at an Oncology Partnership Forum of the Academy of Managed Care Pharmacy.

The HOPA board is also pleased to announce that we approved HOPA's participation in three additional external relationships: (1) the National Quality Forum, (2) the University of Maryland Hazardous Drug Safety Center, and (3) Walgreens/*Pharmacy Times* continuing education opportunity for training the non-BCOP pharmacist on lung cancer. For each of these relationships, we are seeking HOPA members to serve as our representative.

Some committee and task force chairs were invited to join me in January 2017 for an hour-long *Voice of America* radio show and podcast hosted by the Cancer Support Community to reach cancer patients and explain to them how to best utilize their hematology/oncology pharmacist.

A final note on this front is that President-Elect Susannah Koontz Webb, PharmD BCOP FHOPA, Executive Director Suzanne Simons, MS, and I had a very productive and engaging meeting with Cliff Hudis, MD, the new CEO of the American Society of Clinical Oncology (ASCO), during which several opportunities for collaboration were identified. Dr. Koontz Webb had an additional meeting with Dr. Ken Miller to further explore HOPA's participation in ASCO's CancerLinQ, an ambitious endeavor by ASCO to collect and use real-world patient data (learn more at http://cancerlinq.org). Thanks to this work by Dr. Koontz Webb and former HOPA president Donald Harvey and others, we were invited to join the ASCO CancerLinQ Leadership Council; the

"The growth of an organization necessitates reflection and learning from challenges, and though the process can be difficult and uncomfortable, the lessons learned will make HOPA even stronger in the future."

HOPA board approved our participation at its December 15, 2016, meeting.

While HOPA has been very busy pursuing big opportunities external to the organization, we have also been working on some big initiatives internally. We congratulate Mike Vozniak for submitting the Big Idea proposal that was selected by the membership for implementation: to establish a hematology/oncology pharmacy competency and certificate program. The training of non-BCOP- or non-PGY-2-trained oncology pharmacists is a frequent topic of HOPA Central discussions; who better to implement such a program than HOPA? In a complementary effort, two additional task forces are hard at work, one led by Ginah Nightingale, PharmD BCOP, and Ila Saunders, PharmD BCOP, to define entry-level competencies for the new PharmD graduate, and a second led by Lisa Holle, PharmD BCOP (HOPA president, 2012–2013), to update HOPA's 2010 "Scope of the Hematology/Oncology Pharmacist" document.

The board also made a very difficult decision about another HOPA document at its November 2016 meeting. The Oral Chemotherapy Medication Therapy Management Standard Task Force, which had been at work for nearly 5 years, has been sunsetted. We struggled greatly with this decision over the course of the year, and ultimately, following the return of feedback from HOPA's members as part of the review process, the board finally came to terms with three very important issues: (1) so much has changed in the environment of oral chemotherapy that HOPA's members desired a major shift in focus—or, more accurately, multiple new foci—to support the work that they do every day in oral chemotherapy; (2) the board is ultimately responsible for the outcome of the standard, we learned that the original charge to the task force was not clear, and we had not modified the charge to keep pace with the environmental changes that occurred over the course of the standard's development; and (3) we were so distressed at the prospect of losing the work, energy, and trust of those HOPA members who had spent so much time working on this project that we had been reluctant to intervene sooner. I had an honest and productive call with the primary authors (Moe Schwartz, PharmD BCOP, HOPA president, 2010–2011; Steve Stricker, PharmD MS BCOP; and Danielle Roman, PharmD BCOP) after the November board meeting, and we have a plan in place to use the work that has already been done. The board will be sending out a call for a new task force before June 2017 and will give its members very specific charges. We also hosted a meeting with the Standards Committee and two other HOPA members who have experience writing standards, guidelines, and position papers for other organizations on December 15, 2016, at HOPA's headquarters to establish procedures for how each type of HOPA document will be created. That meeting was very productive, and we've made excellent progress in drafting procedures for creating these documents. The growth of an organization necessitates reflection and learning from challenges, and though the process can be difficult and uncomfortable, the lessons learned will make HOPA even stronger in the future.

Last, but certainly not least, we held an open-comment period for some proposed HOPA bylaw changes to support our new committee structure. This committee restructuring is another very big idea that has been necessitated by the rapid growth of our programs, outreach, and reputation. I hope that you took the opportunity to review the proposed changes and submit your feedback—your comments are very valuable! The changes to the bylaws were approved by a vote of HOPA members in early March.

Big plans, big lessons, and big ideas. We hope that you are as energized by our continued progress and development as we on the HOPA Board of Directors are!

HOPA
Hematology/Oncology
Pharmacy Association

8735 W. Higgins Road, Suite 300
Chicago, IL 60631
hoparx.org

We are pleased to present the class of 2017 Fellows of the Hematology/Oncology Pharmacy Association.

Fellowship in HOPA is a recognition of excellence in oncology pharmacy and sustained contributions to HOPA.

Sally Yowell Barbour, PharmD BCOP CPP
Duke University Medical Center

Kerry Parsons, PharmD BCOP
AstraZeneca Pharmaceuticals, LP

John G. Kuhn, PharmD FCCP
University of Texas College of Pharmacy

Timothy Tyler, PharmD FCSHP
Desert Regional Medical Center

Susanne E. Liewer, PharmD BCOP
Nebraska Medical Center

Michael Vozniak, PharmD BCOP
Hospital of the University of Pennsylvania

Congratulations to our 2017 HOPA Fellows!