HOPA NEWS

Pharmacists Optimizing Cancer Care

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Fertility Preservation in Patients with Cancer

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HOPA
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Pharmacists Optimizing Cancer Care®

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FEATURE

Fertility Preservation in Patients with Cancer

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It is estimated that more than 90,000 adolescents and young adults (AYAs) aged 19 to 39 years are diagnosed with cancer each year in the United States.[1] With advances in detection, treatment, and supportive care for various malignancies, long-term survival for this patient population is high—greater than 80% at 5 years.[1] This results in a growing number of cancer survivors of reproductive age. These patients may undergo a wide variety of therapies for cure, including radiation, chemotherapy, and surgery; however, the therapies may entail risks for subsequent treatment-related infertility, including azoospermia in men and premature ovarian failure in women. Alkylating agents, cranial radiation, and targeted radiation to the abdomen or pelvis pose the highest risk for infertility. The impact of cancer treatment on fertility is related to the age of the patient at the time of treatment and is dependent on the type, duration, and dose intensity of treatment. As efforts are focused on achieving the primary objective of cancer treatment—survival—reproductive health issues, including fertility preservation, may often be overlooked.

The importance of fertility to AYA survivors, however, has been well documented. In a study conducted at a large pediatric academic center, 80% of male AYAs reported a desire to have a biological child.[2] Another study revealed that almost 45% of male AYAs ranked fertility as one of the "top 3 life goal[s]."[2] Similar trends have been noted in female survivors. For example, a multi-institutional study of more than 600 AYA breast cancer patients showed that 50% of females expressed concerns about fertility at the time of diagnosis.[1] In addition, fertility concerns can negatively affect quality of life and cause significant psychological distress and depressive symptoms for survivors.[3] This was demonstrated in a prospective case-control study involving hematopoietic stem cell transplant recipients, in which 55% of survivors reported that infertility had a negative impact on their emotions, relationships, and self-worth.[4]

"Despite recognition in the literature that fertility preservation can be an essential part of the treatment plan, it remains one of the most underprescribed and least implemented services provided to adolescent and young adult patients with cancer."

With the aim of increasing awareness, knowledge, and opportunities related to cancer treatment and fertility, oncofertility has emerged as an interdisciplinary field intersecting oncology and reproductive medicine in order to expand fertility options for cancer survivors.[5] In addition, clinical practice guidelines vaguely highlight the importance of fertility discussions with patients of reproductive age at the time of diagnosis. For example, the National Comprehensive Cancer Network recommends referral for fertility preservation clinics within 24 hours for all patients who are interested in pursuing fertility preservation upon diagnosis.[6] In addition, the American Society of Clinical Oncology, the American Society for Reproductive Medicine, and the American Academy of Pediatrics have all issued recommendations (albeit brief ones) relating to education and referrals for patients interested in fertility preservation.[7,8]

Despite recognition in the literature that fertility preservation can be an essential part of the treatment plan, it remains one of the most underprescribed and least implemented services provided to AYA patients with cancer.[6,9] A survey of cancer

survivors revealed that 30%–40% of patients did not recall any sort of fertility discussion with their provider. In another survey, 45% of respondents reported self-initiation of the discussion.[10] Furthermore, a number of patients recalled discussions of fertility impairment occurring not at diagnosis, but after treatment initiation. Although it is possible that the discussion of reproductive health was lost among the overwhelming emotions and abundance of information that accompany a new cancer diagnosis, studies of healthcare professionals suggest that infertility discussions are not routinely performed.[7] A number of barriers have been cited and include oncologists' lack of knowledge about fertility preservation techniques, lack of awareness of appropriate resources and referral centers, concern about potential treatment delay posed by the various preservation methods, the complexity of parental involvement in decision making and child assent, and lack of time for discussion.[7,8,11]

Concerns about fertility seem to be similar for men and women; however, the options available for fertility preservation are quite different. Interestingly, sex-based differences in initiation of reproductive health discussions have been highlighted in the literature. One study showed that the majority of men had discussed fertility-related aspects of their treatment with their physician, while only half of women reported a similar discussion.[10] Proposed explanations for this phenomenon include the ease and reliability of methods available for men versus those for women. Sperm banking is an effective and well-established method in which treatment delay is generally minimal. In addition, only a small amount of sperm is needed to generate a pregnancy.[10] Female fertility preservation, on the other hand, is more complex, and in some cases may not be as easy or effective as sperm banking.

Fertility preservation options and important considerations for men and women are summarized in **Tables 1 and 2,** respectively.

A multidisciplinary team composed of oncologists, reproductive endocrinologists, urologists, nurses, social workers, financial assistance personnel, bioethicists, psychologists, and pharmacists may be advantageous in optimizing the future reproductive health of cancer survivors. Specifically, a pharmacist may contribute through

- identification of patients of reproductive age eligible for consideration of fertility preservation
- patient education summarizing the risks associated with chemotherapy
- medication counseling and side-effect management in situations whereby pharmacotherapeutic methods are initiated
- consideration of alternative regimens whereby exposure to alkylating agents is reduced or eliminated without compromising care.

Fertility preservation and the possibility of having children are important for AYA cancer survivors. The lack of clear direction in clinical practice guidelines may contribute to the trend of documented underuse of fertility preservation in this patient population. Patients should be proactively informed and educated on the risk that cancer treatment poses to their fertility and the preservation options available. Having children may not be at the forefront of an AYA's mind. Therefore, it may be helpful to initiate fertility discussions with a developmental perspective; for example, discussing what may be important in the present versus in the future.[2] In additional to the physical, emotional, and psychosocial support given during cancer treatment, addressing fertility and sexual health and function are essential to optimize cancer outcomes, particularly for AYAs. ●●

Table 1. Fertility Preservation Options for Men

Sperm banking	• Sperm obtained through masturbation and cryopreserved • Collection made prior to the initiation of treatment because sperm quality and integrity can be compromised after a single treatment[12] • Some cancers, including testicular cancer, lymphoma, and leukemia, associated with lower-quality sperm even prior to treatment initiation[1]
Electroejaculation	• Mild electric current delivered via a rectal probe to stimulate an ejaculation for collection • Generally performed under anesthesia by a urologist • May serve as an alternative for those unable to collect through masturbation for physical, emotional, religious, or cultural reasons[8]
Testicular sperm extraction (Onco-TESE)	• Testicular biopsy or percutaneous aspiration to obtain sperm • May serve as an alternative for those unable to collect through masturbation for physical, emotional, religious, or cultural reasons[8,11]
Testicular shielding	• Use of external lead shields to protect the testicles from the effects of radiation • Not always reliable because damage may result from radiation scatter[8] • Provides no protection against the effects of systemic chemotherapy
Testicular tissue banking	• Surgical removal and cryopreservation of testicular tissue for future re-implantation or grafting • Currently considered experimental[8,12] • Theoretical risk of re-introduction of cancer cells with implantation; contraindicated in patients with hematologic malignancies or testicular cancer[13] • Does not require sexual maturity
Hormonal therapy	• Manipulation of hypothalamic-pituitary-gonadal axis with gonadotropin-releasing hormone agonists and antagonists • Has not shown success in preserving male fertility and is therefore not currently recommended[12]
Spermatogonial stem cell cryopreservation	• Investigational procedure aimed to preserve fertility in prepubertal boys[11]

Table 2. Fertility Preservation Options for Women

Intensity-modulated radiation therapy	• Modulation of radiation field to minimize dose to ovaries • Provides no protection against the effects of systemic chemotherapy
Fertility-sparing surgery	• May be considered in early-stage cervical, uterine, or ovarian cancer • Example: radical trachelectomy (surgical removal of the cervix with preservation of the uterus)[1]
Ovarian shielding	• Use of external lead shields to protect the ovaries from the effects of radiation • Not always reliable because damage may result from radiation scatter[8] • Provides no protection against the effects of systemic chemotherapy
Ovarian transposition (Oophoropexy)	• Surgical repositioning of the ovaries out of and away from the radiation field (generally movement up into the abdominal cavity) • Separation of fallopian tubes/ovaries from uterus required in adults; therefore, in-vitro fertilization (IVF) required for future pregnancies • Not always reliable, as damage may result from radiation scatter • Provides no protection against the effects of systemic chemotherapy
Oocyte banking	• Requires 10–14 days of controlled ovarian stimulation (COS) with subsequent transvaginal oocyte harvest and cryopreservation • Potential attractive option for those who do not have a partner, do not wish to use donor sperm, or have religious or ethical objections to embryo cryopreservation[12] • Hormonal stimulation and subsequent pregnancies may increase recurrence risk of estrogen-dependent cancers; aromatase-inhibitor- or tamoxifen-based COS protocols may be used to decrease estradiol exposure, although long-term follow-up data are not available.[1,13] • Advances in COS allow initiation on any day of the menstrual cycle, which may help decrease treatment delay.[1] • Introduction of ethical or legal concerns in the event of patient expiration[13]
Embryo banking	• Requires 10–14 days of COS with subsequent transvaginal oocyte harvest • Oocytes IVF for cryopreservation as embryos • Partner or donor sperm required • Hormonal stimulation and subsequent pregnancies may increase recurrence risk of estrogen-dependent cancers; aromatase-inhibitor- or tamoxifen-based COS protocols may be used to decrease estradiol exposure, although long-term follow-up data are not available.[1,13] • Advances in COS allow initiation on any day of the menstrual cycle, which may help decrease treatment delay.[1] • Introduction of ethical or legal concerns in the event of patient expiration[13]
Ovarian tissue banking	• Surgical removal and cryopreservation of ovarian cortical tissue for future re-implantation, in-vitro follicle maturation or IVF • Hormonal stimulation not required • Sexual maturity not required[11,12] • Theoretical risk of re-introduction of cancer cells with implantation; contraindicated in patients with hematologic malignancies or ovarian cancer[13] • Introduction of ethical or legal concerns in the event of patient expiration[13] • Mean duration of ovarian function after transplantation is approximately 5 years.[13] • Currently considered experimental [8,12]
Ovarian suppression	• Manipulation of hypothalamic-pituitary-gonadal axis with gonadotropin-releasing hormone (GnRH) agonists and antagonists • Limited and inconsistent results as method of fertility preservation • GnRH therapy should not be considered a reliable fertility preservation method at this time. • May be offered in hopes of reducing the likelihood of chemotherapy-induced ovarian insufficiency if proven methods are not feasible[12] • Side effects: hot flashes, night sweats, mood changes, and vaginal dryness
Oogonial stem cell cryopreservation	• Investigational procedure aimed to preserve fertility in prepubertal girls or women who have experienced premature ovarian failure as a result of treatment[13]

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Learning to Drink from a Fire Hose

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I can still hear my preceptor's voice, with just a hint of derision, say, "That's a good guess." It was the first rotation of my post-graduate year 2 (PGY-2) oncology pharmacy residency. I thought I knew my stuff, so I was more than a little embarrassed when I hesitantly and uncertainly answered "thrombocytopenia" to the question about carboplatin dose-limiting toxicity.

Shortly thereafter, we had what Southerners call a come-to-Jesus meeting. My preceptor stressed the importance of knowing the fundamentals of chemotherapy, but staying current was equally important. If I didn't know the basics about carboplatin, how could I learn the basics about the next new anticancer agent? And oncology was changing at a fast pace, he observed: "The *New England Journal of Medicine* has an oncology paper every week. The *Journal of Clinical Oncology* is now being published several times a month. The amount to be learned is overwhelming—it's like drinking from a fire hose."

This was before PD-1/PD-L1 inhibitors. Before VEGF-targeting TKIs that didn't begin with the letter s. Before ibrutinib. This was when platinum doublet was the answer to every question about non-small-cell lung cancer. When chronic myeloid leukemia patients were still considered for hematopoietic stem cell transplantation. When daunorubicin 45 mg/m^2 versus 60 mg/m^2 was the big controversy in treating acute myeloid leukemia. The American Society of Clinical Oncology had a single journal then. Now it has five.

My preceptor-initiated awakening set off an almost epigenetic change in how I consumed new drug information. I subscribed to the e-mail table of contents for *New England Journal of Medicine, Journal of Clinical Oncology, Blood,* and other journals. I subscribed to e-mail listservs that pushed out daily updates. I attended HOPA's annual conference yearly (except the year I had a 3-month-old at home). I learned how to stay current. But it took a while to figure out the best way to do that. It required prioritization. I began each workday with 10–15 minutes of skimming e-mails for updates that merited greater attention. I set aside this time just to see what was new and noteworthy. Anything that required in-depth reading I printed for consumption later in the day. Even if I didn't have time to read the whole article, I would read the abstract. Then I was better prepared to critique the article when I did have time to read it in its entirety.

I also learned to focus on the disease states I encounter routinely in clinical practice. For some disease states (e.g., lung cancer), I read the whole paper and pay particular attention to details such as supportive care information that is available only in the appendix or the online-only protocol. For others (e.g., endometrial cancer), I read only the abstract. And I consider myself lucky if I get to read even the title of a paper on a pediatric malignancy.

Over time I became more efficient. I began to see trends. I could predict which primary endpoints would be used for a chronic lymphocytic leukemia study and how they would differ from those in a pancreatic cancer study. I started looking at the supplementary appendix to answer questions not dealt with in the paper. Of course, I often had to consult this publication or that package insert several times to truly master the necessary information. But I knew what literature was out there, where to find it, and how to evaluate it efficiently.

As a general oncology clinical pharmacist, I need to know a lot about the most common malignancies. However, I'm not able to devote the time to dive deep into every malignancy, especially rarer cancers. It's not that I don't have an interest in cutaneous T-cell lymphomas; it's that I don't see those patients often enough to justify the time to read about them in depth. What does one do in that case?

It was around this time that I starting listening to podcasts. I found them to be a great way to learn, laugh, or otherwise be entertained while running errands, exercising, or washing dishes. I failed to find any oncology pharmacy podcasts that fit my needs, so I started my own. OncoPharm, the podcast, launched in November 2017 and was listened to more than 8,500 times in 2018. The podcasts usually fall into one of three categories. The Foundations of Oncology Pharmacy series covers the "must-know" information for chemotherapy. These podcasts are ideal for learners, especially PGY-2 trainees in advance of that weekly topic discussion on anthracyclines. The Landmarks in Oncology Pharmacy series covers landmark publications (e.g., MOSAIC for colon cancer) that provide the basis for much of our current treatment practice. The last category covers current events and includes recent notable publications, new drug approvals, and changes to guidelines.

It is my hope that OncoPharm (available on most podcast apps) helps oncology pharmacists and other oncology clinicians consume a small, but pharmacy-focused, amount of information from the multitude of information released weekly. By keeping the podcasts to under 20 minutes, I hope listeners are able to retain the key points about a new drug approval or a notable publication.

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Embedding Quality Improvement Skills into an Organization Through a Green Belt Certification Program

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The focus on quality processes, care, and outcomes has never been more prevalent than it is today, particularly in the oncology world, given the rapidly rising cost of care. The opportunity to read, hear, and learn about efforts related to quality has been a focus for HOPA in recent years. In a recent issue of *HOPA News*, we learned about the efforts of HOPA's Quality Oversight Task Force to increase members' knowledge and equip them with tools and resources related to quality.[1] Those who attended HOPA's 2019 Practice Management program had multiple opportunities to learn and engage in quality-focused discussion—both at the American Society of Clinical Oncology (ASCO) Quality Training Program's 1-day preconference workshop and in the conference sessions related to value-based care. Several members who attended the ASCO workshop asked how others incorporate quality work into their day-to-day activities and gain buy-in from senior leadership.

Beginning in 2016, one senior leader at Children's Hospital Colorado identified the need to embed quality improvement skills into his team members. This leader partnered with the Process Improvement Department to brainstorm ways to root the Six Sigma methodology into his organization. The Process Improvement Department, which consists of team members who hold Green Belt, Black Belt, and Master Black Belt certifications, knew they could effectively complete up to three quality improvement projects per year on their own. This was not enough, given their goals related to quality work and the pace of value-based health care. A new idea was needed, and thus an internal organizational Green Belt Certification Program was born, allowing up to 12 quality improvement projects to be completed each year. In addition, those who complete the program are called upon to return to their departments and continue embedding the quality skills they have acquired through continued project work and mentorship of others.

Each director in the Professional Support Services Division identifies and nominates two leadership-level or frontline team members to participate in the Green Belt Certification Program each year. The director works with the Green Belt mentee to identify possible projects and sponsors the mentee and project throughout the certification. Each Green Belt mentee is matched with a Black Belt or Master Black Belt, who provides mentorship for quality improvement skills and the identified project. The program leads two cohorts of a total of 12 Green Belt mentees per year and is designed as follows:

Green Belt Classroom (Week 1)

- Process improvement history and overview of define, measure, analyze, improve, and control (DMAIC) tollgates
- Define: project charter, SIPOC (suppliers, inputs, process, outputs, and customer), voice of the customer, stakeholder analysis, communication plan, project timeline
- Measure: process mapping, data collection plan, measurement system analysis, working with data, change leadership
- Analyze: 5 whys, cause and effect, fishbone, failure modes effect analysis, lean simulation

Green Belt Mentee and Mentor Work (Weeks 2–4)

- Meet with Green Belt mentor weekly
- Complete define tollgate

Green Belt Classroom (Week 5)

- Improve: hypothesis testing, facilitation basics, generating solutions, implementing solutions, improve risk analysis, working with data
- Control: control plan, transition plan, lessons learned

Green Belt Mentee and Mentor Work (Weeks 6–36)

- Complete tollgates with multidisciplinary core team and Master Black Belt mentor
- DMAIC tollgate readouts to cohort and senior leadership
- Green Belt Certification graduation

The Pharmacy Department has participated in the program by sending an operational and clinical supervisor to complete department-level projects, and additional pharmacy team members have been nominated for the upcoming 2020 cohorts. The program also engages other departments in the organization, including nursing, nutrition, imaging, and finance, and has successfully graduated 12 Green Belts; an additional 12 are currently nearing project completion and graduation. Their projects have focused on creating safety for magnetic resonance imaging, decreasing anesthesiology same-day conversions for all imaging, optimizing total fluid management, improving scheduling and prior authorization processes, and improving documentation of opioid waste.

I had the privilege of participating in the Green Belt Certification Program, working on a project that focused on the workflow of our clinical and operational oncology pharmacists in our pharmacy satellite. Analysis revealed that the oncology pharmacy team was performing manual calculations to prepare chemotherapy; this did not allow the team to work at the fullest scope and resulted in double and triple work by both pharmacy technicians and pharmacists.

Although error in the process was near zero, the opportunity for error existed, and the risk was extremely high if error did occur. A multidisciplinary core team that included providers, clinical and operational pharmacists, pharmacy technicians, and workers in patient safety, information technology, and clinical applications was identified. The core team participated in completing each tollgate and is championing change in the oncology pharmacy satellite. The project is currently in progress, and work in several areas is nearing completion: eliminating manual chemotherapy calculations, building standard electronic medical record oncology drug files for commercial and investigational agents, improving real-time dispense preparation, eliminating 22 steps in the process of preparing a chemotherapy agent for administration, and returning as much as 30 minutes per day to clinical pharmacists so they can focus on direct patient care!

The impact of quality work completed has been recognized across the organization, and the program is continuing to grow. The process improvement team is now offering Lean Bootcamp Training, Lean Simulations, Change Management Training for Sponsors, and Black Belt Certification. The organization also holds a yearly Quality Improvement Poster Symposium that highlights quality improvement work from all departments. The 2019 symposium will have 65 poster presentations, including seven completed by pharmacists and one poster that was previously presented at the 2019 conference of the Association of Pediatric Hematology/Oncology Nurses; that poster discusses improving the admission process and decreasing the length of stay for high-dose methotrexate admissions. That quality improvement team will be saving the organization up to $600,000 annually because of its work on decreasing the length of stay for both osteosarcoma and leukemia patients secondary to bundled reimbursement.[2]

This Green Belt Certification Program is just one example of how to integrate quality improvement skills and principles into an organization from the front line to senior leadership. As evidenced by the lively participation at ASCO's Quality Training Program 1-day workshop, many of you are completing similar quality improvement programs and learning new skills related to quality improvement that help optimize care for patients. I challenge each of us as HOPA members to continue to find opportunities to build our quality improvement skills and put these skills to work on a daily basis in our organizations. Ask your senior leadership about expanding your own internal quality improvement program, or learn about external programs such as ASCO's. We have nothing to lose and so much to gain for our patients and our organizations! ●●

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Learning to Drink from a Fire Hose *(continued from p. 7)*

Then when the time comes, they'll know where to go to review the information before making decisions affecting patient care. Admittedly, a breast cancer expert listening to OncoPharm probably won't learn anything new about treating breast cancer. But that breast cancer expert may not be fully aware of the latest updates on treating chronic myeloid leukemia or prostate cancer.

To that end, I hope OncoPharm offers something for everyone, even if it does not do so every week. Some of the episodes I'm proudest of offer historical perspectives on how far we've come in treating EGFR-mutated non-small-cell lung cancer ("Tales of Brave Iressa") or how we ended up with a "standard" rituximab dose of 375 mg/m^2 ("Rituximab"). As OncoPharm grows, I'd like to host guests who could talk about their experience with newly approved drugs from investigational studies and offer clinical pearls based on their expertise. In the meantime, I will still focus on producing podcasts with basic information related to traditional and targeted antineoplastics. And I still have to record the carboplatin episode so I can convincingly answer the question regarding its dose-limiting toxicity. ●●

HOPA's Successful Inaugural Quality Improvement Workshop

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Attendees of HOPA's 2019 "Introduction to Quality Improvement" workshop

HOPA's Quality Oversight Committee (QOC) hosted the association's inaugural "Introduction to Quality Improvement" workshop, held on September 12, 2019, and led by the American Society of Clinical Oncology's (ASCO) Quality Training Program (QTP) faculty. HOPA brought this workshop to its members after the 2018 Quality Oversight Task Force's baseline survey of HOPA Committee leaders and external liaisons indicated that HOPA members desired more education, greater access to quality and value-based tools, and more partnerships with leaders in oncology quality.

ASCO created its QTP to help prepare interdisciplinary oncology teams to design, implement, and lead successful quality improvement activities in their practice settings.[1] The program spans 6 months and includes 5 days of in-person learning in three sessions. Although many teams focus on projects that involve medication management issues, most have not had pharmacists participate as core members of the team. When they have, the pharmacists involved have found the experience valuable. Notably, HOPA QOC member George Carro, RPh MS BCOP, participated in a 2016 session that addressed financial toxicity in ambulatory oncology practice. With the skills learned from the ASCO QTP, his project team was able to increase the percentage of patients receiving information about financial risk and financial support services from 0% to 54% and increased the proportion of patients starting treatment after prior authorization from 50% to 94%.[2] ASCO QTP's focus on oncology care, the prior successful involvement of HOPA members in the program, and ASCO's willingness to bring HOPA a tailored 1-day program was the impetus for HOPA to partner with ASCO in this workshop.

The HOPA-supported "Introduction to Quality Improvement" workshop, held in Charlotte, NC, before the 2019 Practice Management program, accommodated 30 attendees who had applied to participate. Participants were asked to complete a baseline assessment prior to the workshop; the response rate was 83% (25 of 30). The majority of workshop attendees have been in practice for more than 8 years, with 40% having 15 or more years of experience. The primary reasons given for participation were to lead multidisciplinary oncology initiatives within their organization and to increase their skills to complete quality improvement projects. Interestingly, more than half of the attendees indicated that their job responsibilities relating specifically to quality improvement were increasing. Participants' answers to questions related to knowledge and applications of program content will be assessed by HOPA's QOC and ASCO's QTP faculty.

Three ASCO members led the workshop: Michael Keng, MD, of the University of Virginia; Vedner Guerrier, MBA LSSBB, of Memorial Healthcare; and Amy Morris, PharmD, of the University of Virginia. All are alumni of ASCO's QTP, and Dr. Morris is the first pharmacist to be named a QTP coach. The extensive agenda covered these topics: quality improvement (QI) overview, problem and aim statements, tools for QI, project charters, understanding data, psychology and team effectiveness, theory and knowledge of the Plan-Do-Study-Act method, metrics for practice, and sustaining gains, along with an example of a pharmacy QI project and reflections on the day. Although the day was long and the schedule full, attendees engaged energetically in the multiple hands-on exercises offered during the workshop.

The workshop leaders discussed several ideas with the participants, with a focus on providing additional education and resources for HOPA members and incorporating quality training into postgraduate year 2 (PGY-2) oncology residency experiences. Both topics will be discussed by HOPA's QOC for follow-up.

Team event at HOPA's 2019 "Introduction to Quality Improvement" workshop

The University of Virginia (UVA) offered an example of a recent success related to PGY-2 oncology residency training. In 2018, residency program director and quality improvement workshop attendee Kathy DeGregory, PharmD BCOP, sent her resident, Meredith Mort, PharmD, along with a UVA oncology fellow and other team members, to ASCO's QTP. The team gained skills related to oncology QI, and their quality project, evaluating cardiomyopathy in patients with acute myeloid leukemia, was recently published in the *Journal of Oncology Pharmacy Practice*.[3]

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How to PIK? A Review of Current PI3K Inhibitors

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The integration of phosphatidylinositol 3-kinase (PI3K) inhibitors in clinical oncology practice was initiated with the 2014 approval of idelalisib, a PI3K-delta inhibitor, for the treatment of relapsed chronic lymphocytic leukemia (CLL), B-cell non-Hodgkin lymphoma, and small lymphocytic lymphoma (SLL). Since the time of idelalisib's approval, other PI3K inhibitors have been approved, including copanlisib, a PI3K-alpha and -beta inhibitor, for relapsed follicular lymphoma; duvelisib, a PI3K-delta and -gamma inhibitor, for refractory CLL and SLL; and most recently, alpelisib, a PI3K-alpha inhibitor, for metastatic hormone-receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2) nonamplified breast cancer. The use of PI3K inhibitors for other indications continues to be investigated in clinical trials.

The PI3K/AKT/mTOR signaling pathway is important for the regulation of growth, survival, metabolism, and angiogenesis. This pathway is dysregulated in many cancers, including breast, colorectal, and hematologic malignancies. Currently approved PI3K inhibitors are small-molecule inhibitors of specific isoforms (p110-alpha, p110-beta, p110-delta, and p110-gamma) of PI3K that inhibit downstream signaling, resulting in reduced tumor growth and apoptosis. While PI3K-alpha and PI3K-beta are commonly found, PI3K-delta and PI3K-gamma expression is primarily seen only in hematopoietic cells, which is significant when one is considering drug targets and on-target toxicities.[1,2]

Given the oral availability and the toxicities seen with PI3K inhibitors, pharmacists play a unique role in patient and provider education as well as in appropriate monitoring and toxicity management.

> **"Numerous ongoing trials are evaluating the use of PI3K inhibitors in solid tumors, which will likely lead to more approvals in the future."**

Current PI3K Inhibitors

Idelalisib

Idelalisib received approval by the U.S. Food and Drug Administration (FDA) in 2014 for CLL on the basis of data from the phase 3 RETRO-Idel trial. This trial evaluated 220 CLL patients with relapsed disease and disease progression within 24 months from the last treatment with either a CD20-antibody-based regimen or a minimum of two prior cytotoxic regimens. Patients were randomized to receive either idelalisib (150 mg by mouth [PO]) twice daily with rituximab (375 mg/m^2 intravenously [IV]) once, followed by 500 mg/m^2 every 2 weeks for four doses, then every 4 weeks for three doses or placebo PO twice daily with rituximab. Patients who received idelalisib had significant improvement in progression-free survival (PFS) at 24 weeks compared to those receiving placebo: 93% versus 46%, respectively (adjusted hazard ratio [HR] 0.15; 95% confidence interval [CI] 0.08–0.28; $p < .001$). A benefit in overall survival at 12 months of 92% with idelalisib compared to 80% with placebo was also observed (HR 0.28; 95% CI 0.09–0.86; $p = .02$).[3] Idelalisib has since gained approval for treatment of relapsed follicular B-cell lymphoma and relapsed lymphocytic lymphoma.

Copanlisib

The CHRONOS-1 trial led to the accelerated FDA approval of copanlisib in 2017. This phase 2 trial assessed efficacy and safety of copanlisib (60 mg by IV route on days 1, 8, and 15 of 28-day cycles) in 142 patients with relapsed or refractory indolent B-cell lymphomas, the majority of which were follicular lymphomas, after two or more lines of therapy consisting of rituximab and alkylating agents. The objective response rate (ORR), defined as a complete or partial response, surpassed the predefined study threshold of 40% and was found to be 59% (95% CI, 51%–67%; $p < .001$).[4] Though the trial included numerous indolent B-cell lymphomas, 73% of patients in the trial had a diagnosis of follicular lymphoma, which led to the FDA approval of copanlisib in this setting.

Duvelisib

In 2018, duvelisib received FDA approval for treatment of relapsed or refractory CLL and SLL. The DUO trial was a phase 3 trial comparing duvelisib (25 mg PO twice daily) with ofatumumab (300 mg IV on day 1; 1,000 mg on day 8 of cycle 1; and then 1,000 mg on day 1 of subsequent 28-day cycles) monotherapy. In total, 319 patients who had disease progression or a relapse after at least one prior line of therapy were evaluated in this trial. Significant improvements in PFS were observed in patients receiving duvelisib compared to ofatumumab: 13.3 months versus 9.9 months (HR 0.52; $p < .0001$), respectively. Differences were also observed in the overall response rate in favor of duvelisib: 73.8% compared to 45.3% with ofatumumab ($p < .0001$).[5] The improvement in PFS and overall response rate observed in this trial in patients on duvelisib led to FDA approval. Following the initial FDA approval, duvelisib has also been approved for use in treating relapsed or refractory follicular lymphoma.

Alpelisib

FDA approval was obtained in 2019 for alpelisib for PIK3CA-mutated, hormone receptor–positive, human epidermal growth factor receptor 2–negative advanced breast cancer in combination with fulvestrant on the basis of results of the SOLAR-1 trial. This trial randomized 572 patients to receive either alpelisib (300 mg PO once daily) with fulvestrant (500 mg by intramuscular route on days 1 and 15 of cycle 1, and day 1 of subsequent 28-day cycles) or placebo (PO once daily) with fulvestrant. Of note, this study included patients from both the PIK3CA-mutated and nonmutated subgroups, though the primary endpoint and key secondary endpoint specifically evaluated the PIK3CA-mutated subgroup. The primary endpoint of PFS in the PIK3CA-mutated cohort demonstrated significant improvement at 20 months with alpelisib and fulvestrant compared to placebo and fulvestrant: 11 months with the use of alpelisib compared to 5.7 months with placebo (HR 0.65; 95% CI 0.50–0.85; $p < .001$).[6] Alpelisib is the first PI3K inhibitor to receive FDA approval for a nonhematologic malignancy indication.

Safety

Three of the current PI3K inhibitors (idelalisib, duvelisib, and alpelisib) are orally administered either once daily or twice daily. Copanlisib is the only IV PI3K inhibitor on the market. This class of drugs has the potential to cause gastrointestinal (GI) toxicity, hyperglycemia, cutaneous reactions, infection, fatigue, and elevations in serum creatinine and transaminase levels.

All four PI3K inhibitors are major substrates of CYP3A4, and as a result, careful attention should be paid to patients' medication and supplement lists to minimize the potential for significant drug interactions. Copanlisib in particular has specific dose reduction recommendations when it is co-administered with a strong CYP3A inhibitor; these cannot be ignored. In comparison to other PI3K inhibitors, idelalisib is not only a substrate of CYP3A4 but also a strong CYP3A4 inhibitor, and it may have an impact on other medications that are major substrates of CYP3A4.

Gastrointestinal Toxicity[7-11]

Many patients receiving a PI3K inhibitor experience GI toxicities, of which diarrhea is the most common. Diarrhea can develop as early onset (typically within the first 8 weeks of therapy initiation), is self-limited, and responds well to antimotility agents. Late-onset diarrhea typically presents 6 months after initiation, responds poorly to antimotility agents, is thought to be immune-mediated, and may require the use of steroids, including budesonide or prednisolone, for management. Workup for severe diarrhea should include *Clostridium difficile* testing and stool culture, as well as colonoscopy for atypical cases. The incidence of diarrhea (any grade) varies between agents, with higher incidences among oral agents idelalisib, duvelisib, and alpelisib (47%, 50%, and 58%, respectively) compared to the IV PI3K inhibitor, copanlisib (36%). Of note, all three oral PI3K inhibitors have warnings in their package inserts regarding development of severe diarrhea (grade 3 or higher) as a potential adverse event to monitor for, and this should be included in patient education. The development of diarrhea should prompt initiation of antidiarrheal agents and maintenance of adequate fluid intake to help prevent dehydration.

Nausea and vomiting can also occur in patients receiving PI3K inhibitors. Among these agents, alpelisib has the highest reported incidence of nausea and vomiting (any grade) at 45% and 27%, respectively. Idelalisib, copanlisib, and duvelisib have an incidence of approximately 25%–30% for nausea and approximately 15% for vomiting. The use of antiemetics as needed can be used to help manage this adverse effect.

Hyperglycemia[8,10,11]

Hyperglycemia seen with PI3K inhibitors is an on-target effect secondary to inhibition of the PI3K-alpha subunit that is involved in insulin signaling and glucose homeostasis. With copanlisib, blood glucose generally peaks 5–8 hours postinfusion before returning to baseline, though blood glucose levels remain elevated for approximately 18% of patients 1 day postinfusion. Most patients in clinical trials were asymptomatic and were managed with adequate hydration of oral fluids. Although hyperglycemia with copanlisib is more transient, hyperglycemia secondary to alpelisib is continuous, with elevations in blood glucose seen by day 8 and 15, and thus requiring weekly fasting blood glucose (FBG) monitoring for the first 2 weeks of therapy. Patients should have their hemoglobin A1c and FBG drawn prior to initiation of alpelisib. In clinical trials, approximately 80% of patients experienced hyperglycemia, with 87% of those patients requiring management with antihyperglycemics, including treatment with metformin as a single agent or in combination with other antihyperglycemics. Metformin and other insulin-sensitizers are recommended for hyperglycemia management. Given that alpelisib is a CYP2C9 inducer, agents such as glipizide, glyburide, and glimepiride may not be as effective in controlling blood glucose. When treatment with antihyperglycemics is required, patients should monitor FBG weekly. Patients with type 2 diabetes mellitus should be treated only following adequate glucose control and should be closely monitored. In the SOLAR-1 study, patients were included only if they had an A1c of 6.4% or less. Of note, grade 3 or 4 hyperglycemia occurred in 41% of patients receiving copanlisib and in 37% of patients receiving alpelisib; two cases of diabetic ketoacidosis were reported with alpelisib. All patients should receive education regarding diet modifications prior to initiation of therapy, as well as adequate education and monitoring for antihyperglycemics. Alpelisib dose modifications and hyperglycemia management should be followed in accordance with the package insert.

Cutaneous Reactions[7-11]

Severe cutaneous reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported in as many as 3% of patients receiving PI3K inhibitors. Pruritis, dry skin, and rash are more common and typically occur within the first 2 months. Treatment includes topical corticosteroids, oral antihistamines, and low-dose oral corticosteroids. Topical and oral antibiotics may be considered if skin lesions remain uncontrolled. Of note, it is recommended that patients start an antihistamine prior to the initiation of alpelisib for rash prevention.

Infection[7,9]

Both idelalisib and duvelisib contain black-box warnings for risk of infection, including diarrhea or colitis, serious cutaneous reactions, and pneumonitis. Most common infections included pneumonia, sepsis, febrile neutropenia, and lower respiratory infections. Infection onset was typically seen within 3 months of therapy initiation with duvelisib. Fatal or serious infections occurred in 31% of patients treated with duvelisib and in 21% of patients who received idelalisib. Prophylaxis for *Pneumocystis jirovecii* pneumonia should be given during duvelisib and idelalisib treatment. Monitoring and prophylactic antivirals to prevent cytomegalovirus infection or reactivation should also be considered.

Fatigue[7-10]

Fatigue can occur in up to 42% of patients on PI3K inhibitors, which can affect patients' quality of life. Fatigue was listed as the reason for discontinuation of therapy in up to 2.5% of patients in the approval trials. Fatigue should prompt greater discussion with patients to determine any potential underlying causes that should be addressed.

Elevations in Serum Creatinine[7-10]

The use of duvelisib and alpelisib has been associated with elevations in serum creatinine. If serum creatinine elevation occurs during treatment, other potential contributing causes should be assessed, such as dehydration and the use of nephrotoxic medications. No dose modifications are listed for any PI3K inhibitors, though it should be noted that these drugs have not been studied in the setting of renal impairment.

Elevations of Transaminase Levels[7-11]

Elevations in transaminase levels should be monitored carefully because incidences of severe hepatotoxicity have occurred in 18% of patients receiving idelalisib and in 10% of patients receiving duvelisib. Severe autoimmune transaminitis has been seen with the use of idelalisib. Although elevations in transaminases have been observed in patients receiving alpelisib, grade 3 or 4 elevations were observed in only 3.5% of patients. Transaminases should be monitored to assess the need for dose reduction or discontinuation. Patients receiving idelalisib should be counseled to avoid concurrent use of hepatotoxic drugs.

Future Directions

Numerous ongoing trials are evaluating the use of PI3K inhibitors in solid tumors, which will likely lead to more approvals in the future. Ongoing trials include the SAFIR trial comparing alpelisib and fulvestrant to chemotherapy for maintenance therapy in PIK-3CA-mutated advanced breast cancer; a phase 1 trial evaluating the combination of a PI3K-beta inhibitor (AZD8186) and docetaxel to treat advanced breast and pancreatic cancers with phosphatase tensin homologue (PTEN) or PIK3CB mutations; and the BYLieve trial, a phase 2 study evaluating the role of alpelisib in treating patients with advanced HR-positive breast cancer following disease progression after treatment with a CDK4/6 inhibitor.[12] Pharmacists are well-positioned to play an integral role in educating patients and providers about the safe use and monitoring of PI3K inhibitors. ●●

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Keeping Ahead in Residency: Perspectives of a Program Director and a Resident

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We asked a postgraduate year 2 (PGY-2) oncology residency program director (RPD) and a current resident to give our trainee readers some suggestions on how to stay on top of a busy residency schedule. We hope you gain some helpful tips from Caitlin Siebenaller, PGY-2 oncology residency program director, and Catherine Gawronski, PGY-2 oncology pharmacy resident.

What are some tips and tricks you have used to plan for the days, weeks, and months ahead? What tools do you use to organize your calendar?

Caitlin: I try to keep all my organization electronic as much as possible. I keep my Outlook calendar up to date and add reminders for important deadlines. For my daily tasks, I use a checklist of things I would like to get done. Similarly, I like to check things off as they occur each week. For the long term, I use reminders and appointments through Outlook. I also use color codes to help me distinguish priorities or categories of all the activities on my calendar. For example, patient care–related items are one color, and RPD and residency activities are another color.

Catherine: I hang a 3-month calendar by my desk. I write down all my presentations, research deadlines, staffing days, and topic discussions on the calendar, using different colors for each category of assignment. Color-coding my calendar entries helps me keep track of deadlines and see the bigger picture over the coming weeks. I can add or take things off my to-do list based on what is coming up in the next week and month, and having the list makes it very easy for me to prioritize what needs to be done first. I also use an Outlook calendar to organize meetings or smaller tasks during the week. In addition, I make sure that my "bigger picture" paper calendar agrees with the Outlook calendar on my computer.

How do you communicate your schedule to those you work with?

Caitlin: Keeping my Outlook calendar up to date helps to communicate my availability and schedule to those I work with. I also use it to block times I know I will be unavailable so co-workers can see my availability when scheduling meetings. In communicating rotation activities with residents I am working with, I have found it helpful to draft a template of a calendar with activities and ask the resident to fill in all their responsibilities throughout the rotation so that I know when they are available and when they are not. In addition, I send rotation activities to our residents as Outlook appointments.

Catherine: To communicate my schedule to those I work with, I make sure my Outlook calendar is up to date. At the beginning of each new rotation, I go over with my preceptor any big schedule conflicts I have or expect to have during the rotation. I have found, and very much appreciate, that my preceptors have created calendars at the beginning of each rotation and have had me fill in meetings or other commitments. They have also added topic discussions or meetings that they would like for me to attend. This allows me to plan the month in advance and know when I will have time to schedule other meetings, if necessary.

What strategies do you use to help you accommodate new projects and requests?

Caitlin: I like to use a stepwise approach when considering new projects and requests. I find it helpful to first do the background research, reading, and so on to ensure that I am informed about the request or the project. I will then be sure to ask any follow-up questions so I am clear on the task at hand. Then I like to draw a timeline for myself to set my goal deadlines in order to make sure I stay on task.

Catherine: To accommodate new projects, I evaluate the turnaround time and what tasks are required. I see how a project fits in on my "bigger picture" calendar to determine whether any deadlines overlap. If I have any concerns about the deadlines of a new project, I communicate those issues to the preceptor and try to come up with solutions for getting the project done.

How do you approach projects or requests that you are not able to accommodate?

Caitlin: This is usually done as part of a discussion with my team. If there is something that I am not able to accommodate, I have a great team of co-workers that I am able to run things by—they are always willing to help team members out. We are in constant communication with each other about the projects we are working on to ensure that anyone who needs help gets it, or anyone who can offer to help has the chance to do so. The biggest key is communication with the people you work with.

Catherine: If I am not able to accommodate a new project, I let the preceptor know as soon as possible. I tell them my concerns about the project and how it fits into my schedule. I also ask if the deadlines are flexible, if there is a different aspect of the project I could work on to help get it done, or if they think something in my schedule could be moved around to allow me to accommodate the project.

What strategies do you use to prevent burnout?

Caitlin: I recommend having hobbies outside of work that you can maintain on a daily or weekly basis. Whether this be a workout routine, socializing with friends, or outdoor activities, it's important to keep those things as part of your routine to prevent burnout. Even setting up routine coffee dates with friends is something small but very helpful. I am also grateful to work with a group of people who enjoy talking about their hobbies, weekends, etc., so we are all good at keeping up with each other's life outside of work. This helps prevent burnout as well.

Catherine: Spending time with my family, friends, and dog helps me relax and decompress from work. I also really enjoy working out and have found that making time a few days a week to go to a class or the gym provides much needed downtime. ●●

HOPA's Successful Inaugural Quality Improvement Workshop

(continued from p. 10)

Oncology pharmacists are well equipped to have a positive impact on patients with cancer through leadership in QI activities, involvement in interdisciplinary oncology quality research, and education and mentorship provided to those interested in oncology. HOPA's support of this 1-day workshop brings oncology pharmacists one step closer to being leaders in the area of oncology quality improvement. ●●

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Novel Agents for the Treatment of Graft-Versus-Host Disease Following Allogeneic Hematopoietic Stem Cell Transplantation

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Allogeneic hematopoietic stem cell transplantation (HSCT) is a potentially curative therapy for a variety of malignant and non-malignant hematologic disorders, but its efficacy is often limited by transplant-related complications. Graft-versus-host disease (GVHD) is one such complication. For the past 60 years, GVHD has remained a major cause of morbidity and mortality following allogeneic HSCT, with acute GVHD affecting 20%–80% of patients and chronic GVHD affecting 25%–80% of patients.[1,2] Despite the prevalence of GVHD after HSCT, the overall severity of GVHD has been decreasing over time, primarily because of increased use of reduced-intensity conditioning regimens prior to HSCT and the development of novel regimens for prophylaxis and treatment of GVHD.[3,4]

Acute Graft-Versus-Host Disease

Acute GVHD develops through a series of complex immunological steps. Damage from HSCT conditioning chemotherapy causes activation of antigen-presenting cells, which release inflammatory cytokines to recruit immune effector cells to the area of injury. As a result of exposure to these cytokines, T cells from the HSCT donor become activated and erroneously recognize recipient tissue as foreign. This leads to a profound activation of the donor's immune system against recipient tissues. The skin, liver, and gastrointestinal (GI) tract are the most common organ systems affected, and the development of acute GVHD in any of these organ systems can result in severe dysfunction and damage.[5] Corticosteroids remain the first-line agents used in the treatment of acute GVHD, but response rates are suboptimal at 40%–50%.[6,7] In addition, no second-line agent has proven superior to another, highlighting the need for more effective therapeutic modalities.

"Given the role of cytokines in the activation and proliferation of T cells, inhibition of the JAK/STAT pathway has been heavily investigated as a potential treatment option for acute graft-versus-host disease."

Janus Kinase Inhibition

The Janus kinase (JAK) family of tyrosine kinases are signal transducers that activate intracellular transcription factors of the signal transducer and activator of transcription (STAT) protein family. Activation of the JAK/STAT pathway is essential for numerous cellular processes, including cytokine-mediated intracellular signaling of lymphocytes.[8] Given the role of cytokines in the activation and proliferation of T cells, inhibition of the JAK/STAT pathway has been heavily investigated as a potential treatment option for acute GVHD.

Ruxolitinib is an oral selective JAK1/JAK2 inhibitor recently approved by the U.S. Food and Drug Administration (FDA) for acute steroid-refractory GVHD. Preclinical studies demonstrated that ruxolitinib suppresses several aspects of the immune response, including reducing T-cell proliferation and inhibiting cytokine production.[9] The phase 2 REACH1 trial investigated the use of ruxolitinib in combination with corticosteroids for the treatment of steroid-refractory acute GVHD. Patients received ruxolitinib 5 mg twice daily orally plus methylprednisolone 2 mg/kg/day (or equivalent). The overall response rate (ORR) at day 28 was 54.9%, with a complete response (CR) rate of 26.8%. Ruxolitinib also allowed for rapid tapering of the corticosteroid dose, with 55.8% of patients having a ≥50% reduction in their corticosteroid dose at day 28. Two additional clinical trials, REACH2 and REACH3, are ongoing and will determine the utility of ruxolitinib alone versus best available therapy in acute and chronic GVHD, respectively.[8] In addition, two large ongoing phase 3 trials, GRAVITAS 301 and GRAVITAS 309, are investigating a selective JAK1 inhibitor, itacitinib, for the treatment of acute and chronic GVHD, respectively.

Integrin Inhibition

The integrins are a family of cell-surface proteins consisting of alpha and beta subunits that are widely expressed on leukocytes, including lymphocytes. These proteins are heavily involved in the trafficking of lymphocytes from the circulation into sites of inflammation.[10] For patients with inflammatory bowel disease, integrin antagonists have been used to block integrin adhesion molecules, preventing lymphocyte migration into the intestinal mucosa.[11] Given that acute GVHD of the GI tract results from profound inflammation in the intestinal mucosa, integrin inhibitors have also been investigated as a treatment modality for acute GI GVHD.

Natalizumab is a humanized monoclonal antibody directed against the alpha 4 subunit of integrin molecules and is currently FDA approved for treatment of multiple sclerosis and Crohn's disease. A small phase 2 study of 18 patients investigated natalizumab and corticosteroids for the treatment of newly diagnosed acute GI GVHD. The ORR at day 28 was 75% and at day 56 was 62.5%. Natalizumab has been associated with progressive multifocal leukoencephalopathy (PML), a potentially life-threatening demyelinating neurologic disease, but it is important to note that none of the patients in this study developed PML.[12]

Vedolizumab is a humanized monoclonal antibody directed against the alpha 4/beta 7 subunit of integrin molecules and is currently FDA approved for the treatment of Crohn's disease and ulcerative colitis. A small retrospective analysis investigated off-label use of vedolizumab for the treatment of 29 patients with steroid-refractory acute GI GVHD. The ORR at 2 months was 64%, with 28% of patients achieving a CR. However, 25 (86%) of the 29 patients developed infections, 12 of which were considered severe adverse effects.[13]

Future Targets

Sirtuin 1 (Sirt-1) is a member of a family of proteins that belong to the class 3 histone deacetylases. Sirt-1 regulates various biological processes, including inflammatory responses and immune cell activation. Preclinical data have demonstrated that Sirt-1-deficient mice experience diminished T-cell activation and reduced severity of acute GVHD.[14] Although pharmacologic inhibitors of Sirt-1 do exist, the only data available on their use are in mouse models. Nonetheless, inhibition of Sirt-1 may be a promising therapeutic target for controlling acute GVHD.

Conclusion

Despite improvements in the understanding of the pathophysiology of GVHD, treatment of this complication remains a challenge. Corticosteroids remain the standard of care today, and no clearly superior agent for managing corticosteroid-refractory GVHD has been identified. Nonetheless, numerous new and promising therapeutic targets exist for the treatment of GVHD that are not mentioned in this article. As these therapeutic modalities are further developed, we can be hopeful that the improvement in treatment outcomes for patients suffering from GVHD seen over the past 2 decades will continue. ●●

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FOR METASTATIC EGFRm NSCLC

FIRST-LINE TAGRISSO

GROUNDBREAKING PFS AND

OVERALL SURVIVAL

18.9 vs 10.2

months median PFS

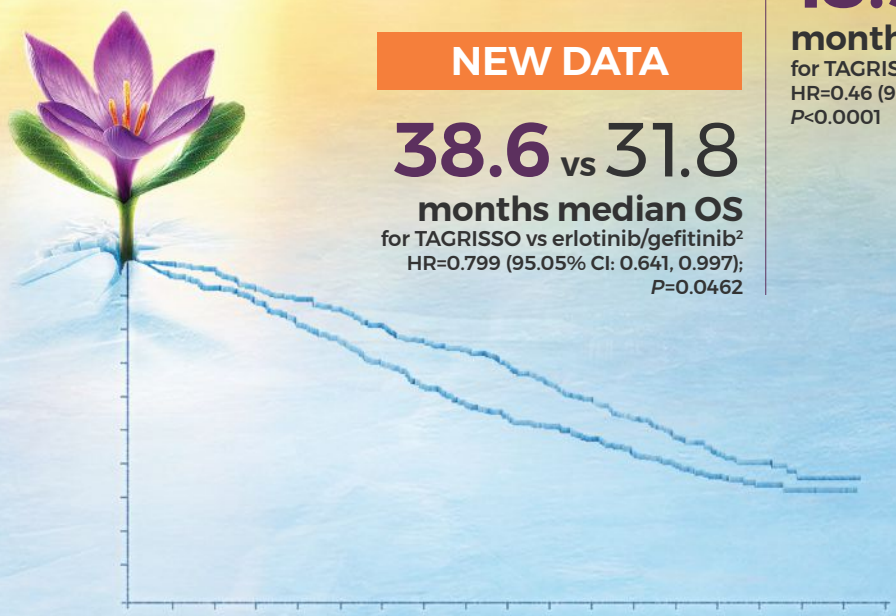
for TAGRISSO vs erlotinib/gefitinib[1]
HR=0.46 (95% CI: 0.37, 0.57);
P<0.0001

NEW DATA

38.6 vs 31.8

months median OS

for TAGRISSO vs erlotinib/gefitinib[2]
HR=0.799 (95.05% CI: 0.641, 0.997);
P=0.0462



INDICATION

TAGRISSO is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test.

SELECT SAFETY INFORMATION

- There are no contraindications for TAGRISSO
- Interstitial lung disease (ILD)/pneumonitis occurred in 3.9% of the 1142 TAGRISSO-treated patients; 0.4% of cases were fatal. Withhold TAGRISSO and promptly investigate for ILD in patients who present with worsening of respiratory symptoms which may be indicative of ILD (eg, dyspnea, cough and fever). Permanently discontinue TAGRISSO if ILD is confirmed
- Heart rate-corrected QT (QTc) interval prolongation occurred in TAGRISSO-treated patients. Of the 1142 TAGRISSO-treated patients in clinical trials, 0.9% were found to have a QTc > 500 msec, and 3.6% of patients had an increase from baseline QTc > 60 msec. No QTc-related arrhythmias were reported. Conduct periodic monitoring with ECGs and electrolytes in patients with congenital long QTc syndrome, congestive heart failure, electrolyte abnormalities, or those who are taking medications known to prolong the QTc interval. Permanently discontinue TAGRISSO in patients who develop QTc interval prolongation with signs/symptoms of life-threatening arrhythmia
- Cardiomyopathy occurred in 2.6% of the 1142 TAGRISSO-treated patients; 0.1% of cardiomyopathy cases were fatal. A decline in left ventricular ejection fraction (LVEF) ≥10% from baseline and to <50% LVEF occurred in 3.9% of 908 patients who had baseline and at least one follow-up LVEF assessment. Conduct cardiac monitoring, including assessment of LVEF at baseline and during treatment, in patients with cardiac risk factors. Assess LVEF in patients who develop relevant cardiac signs or symptoms during treatment. For symptomatic congestive heart failure, permanently discontinue TAGRISSO

AstraZeneca

CNS PFS

A 52% reduction in the risk of CNS progression in patients with CNS metastases at baseline (HR=0.48 [95% CI: 0.26, 0.86]; *P*=0.014)[3]

- Median CNS PFS not reached with first-line TAGRISSO vs 13.9 months for erlotinib/gefitinib

NCCN PREFERRED

Osimertinib (TAGRISSO) is the only National Comprehensive Cancer Network® (NCCN®) preferred first-line therapy option in metastatic EGFRm NSCLC[4*]

*The NCCN Guidelines® for NSCLC provide recommendations for individual biomarkers that should be tested and recommend testing techniques but do not endorse any specific commercially available biomarker assays.

FLAURA study design: Randomized, double-blind, active-controlled trial in 556 patients with metastatic EGFRm NSCLC who had not received prior systemic treatment for advanced disease. Patients were randomized 1:1 to either TAGRISSO (n=279; 80 mg orally, once daily) or EGFR-TKI comparator (n=277; gefitinib 250 mg or erlotinib 150 mg orally, once daily). All US patients in the comparator arm received erlotinib. Crossover was allowed for patients in the EGFR-TKI comparator arm at confirmed progression if positive for the EGFR T790M resistance mutation. Patients with CNS metastases not requiring steroids and with stable neurologic status were included in the study. The primary endpoint of the study was PFS based on investigator assessment (according to RECIST v1.1). Secondary endpoints included OS, ORR, CNS PFS, and DoR.[1,3,5,6]

SELECT SAFETY INFORMATION

- Keratitis was reported in 0.7% of 1142 patients treated with TAGRISSO in clinical trials. Promptly refer patients with signs and symptoms suggestive of keratitis (such as eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye) to an ophthalmologist
- Verify pregnancy status of females of reproductive potential prior to initiating TAGRISSO. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TAGRISSO and for 6 weeks after the final dose. Advise males with female partners of reproductive potential to use effective contraception for 4 months after the final dose
- Most common adverse reactions (≥20%) were diarrhea, rash, dry skin, nail toxicity, stomatitis, fatigue and decreased appetite

Abbreviations: CI, confidence interval; CNS, central nervous system; DoR, duration of response; HR, hazard ratio; ORR, overall response rate; OS, Overall Survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria In Solid Tumors; TKI, tyrosine kinase inhibitor.

References: 1. TAGRISSO [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2018. **2.** Ramalingam SS, Gray JE, Ohe Y, et al. Osimertinib vs comparator EGFR-TKI as first-line treatment for EGFRm advanced NSCLC (FLAURA): final overall survival analysis [oral presentation]. Presented at: European Society of Medical Oncology; September 27-October 1, 2019; Barcelona, Spain. Abstract LBA5. **3.** Reungwetwattana T, Nakagawa K, Cho BC, et al. CNS response to osimertinib versus standard epidermal growth factor receptor tyrosine kinase inhibitors in patients with untreated EGFR-mutated advanced non-small-cell lung cancer. *J Clin Oncol*. 2018. doi:10.1200/JCO.2018.78.3118. [Epub ahead of print.] **4.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for NSCLC V.7.2019. ©National Comprehensive Cancer Network, Inc. 2019. All rights reserved. Accessed August 30, 2019. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. **5.** Soria JC, Ohe Y, Vansteenkiste J, et al; FLAURA Investigators. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *N Engl J Med*. 2018;378(2):113-125 [protocol]. **6.** Soria JC, Ohe Y, Vansteenkiste J, et al; FLAURA Investigators. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *N Engl J Med*. 2018;378(2):113-125.

Learn more at **TagrissoHCP.com**.

Please see Brief Summary of Prescribing Information on adjacent pages.

TAGRISSO® osimertinib

TAGRISSO® (osimertinib) tablets, for oral use

Brief Summary of Prescribing Information.

For complete prescribing information consult official package insert.

INDICATIONS AND USAGE

First-line Treatment of EGFR Mutation-Positive Metastatic Non-Small Cell Lung Cancer (NSCLC)

TAGRISSO is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test *[see Dosage and Administration (2.1) in the full Prescribing Information]*.

DOSAGE AND ADMINISTRATION

Patient Selection

Select patients for the first-line treatment of metastatic EGFR-positive NSCLC with TAGRISSO based on the presence of EGFR exon 19 deletions or exon 21 L858R mutations in tumor or plasma specimens *[see Clinical Studies (14) in the full Prescribing Information]*. If these mutations are not detected in a plasma specimen, test tumor tissue if feasible.

Information on FDA-approved tests for the detection of EGFR mutations is available at http://www.fda.gov/companiondiagnostics.

Recommended Dosage Regimen

The recommended dosage of TAGRISSO is 80 mg tablet once a day until disease progression or unacceptable toxicity. TAGRISSO can be taken with or without food.

If a dose of TAGRISSO is missed, do not make up the missed dose and take the next dose as scheduled.

Administration to Patients Who Have Difficulty Swallowing Solids

Disperse tablet in 60 mL (2 ounces) of non-carbonated water only. Stir until tablet is dispersed into small pieces (the tablet will not completely dissolve) and swallow immediately. Do not crush, heat, or ultrasonicate during preparation. Rinse the container with 120 mL to 240 mL (4 to 8 ounces) of water and immediately drink.

If administration via nasogastric tube is required, disperse the tablet as above in 15 mL of non-carbonated water, and then use an additional 15 mL of water to transfer any residues to the syringe. The resulting 30 mL liquid should be administered as per the nasogastric tube instructions with appropriate water flushes (approximately 30 mL).

Dosage Modifications

Adverse Reactions

Table 1. Recommended Dosage Modifications for TAGRISSO

Target Organ	Adverse Reaction[a]	Dosage Modification
Pulmonary	Interstitial lung disease (ILD)/Pneumonitis	Permanently discontinue TAGRISSO.
Cardiac	QTc[†] interval greater than 500 msec on at least 2 separate ECGs[b]	Withhold TAGRISSO until QTc interval is less than 481 msec or recovery to baseline if baseline QTc is greater than or equal to 481 msec, then resume at 40 mg dose.
	QTc interval prolongation with signs/ symptoms of life-threatening arrhythmia	Permanently discontinue TAGRISSO.
	Symptomatic congestive heart failure	Permanently discontinue TAGRISSO.
Other	Adverse reaction of Grade 3 or greater severity	Withhold TAGRISSO for up to 3 weeks.
	If improvement to Grade 0-2 within 3 weeks	Resume at 80 mg or 40 mg daily.
	If no improvement within 3 weeks	Permanently discontinue TAGRISSO.

[a] Adverse reactions graded by the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (NCI CTCAE v4.0).
[b] ECGs = Electrocardiograms
[†] QTc = QT interval corrected for heart rate

Drug Interactions

Strong CYP3A4 Inducers

If concurrent use is unavoidable, increase TAGRISSO dosage to 160 mg daily when co-administering with a strong CYP3A inducer. Resume TAGRISSO at 80 mg 3 weeks after discontinuation of the strong CYP3A4 inducer *[see Drug Interactions (7) and Clinical Pharmacology (12.3) in the full Prescribing Information]*.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Interstitial Lung Disease/Pneumonitis

Interstitial lung disease (ILD)/pneumonitis occurred in 3.9% of the 1142 TAGRISSO-treated patients; 0.4% of cases were fatal.

Withhold TAGRISSO and promptly investigate for ILD in patients who present with worsening of respiratory symptoms which may be indicative of ILD (e.g., dyspnea, cough and fever). Permanently discontinue TAGRISSO if ILD is confirmed *[see Dosage and Administration (2.4) and Adverse Reactions (6) in the full Prescribing Information]*.

QTc Interval Prolongation

Heart rate-corrected QT (QTc) interval prolongation occurs in patients treated with TAGRISSO. Of the 1142 patients treated with TAGRISSO in clinical trials, 0.9% were found to have a QTc > 500 msec, and 3.6% of patients had an increase from baseline QTc > 60 msec *[see Clinical Pharmacology (12.2) in the full Prescribing Information]*. No QTc-related arrhythmias were reported.

Clinical trials of TAGRISSO did not enroll patients with baseline QTc of > 470 msec. Conduct periodic monitoring with ECGs and electrolytes in patients with congenital long QTc syndrome, congestive heart failure, electrolyte abnormalities, or those who are taking medications known to prolong the QTc interval. Permanently discontinue TAGRISSO in patients who develop QTc interval prolongation with signs/symptoms of life-threatening arrhythmia *[see Dosage and Administration (2.4) in the full Prescribing Information]*.

Cardiomyopathy

Across clinical trials, cardiomyopathy (defined as cardiac failure, chronic cardiac failure, congestive heart failure, pulmonary edema or decreased ejection fraction) occurred in 2.6% of the 1142 TAGRISSO-treated patients; 0.1% of cardiomyopathy cases were fatal.

A decline in left ventricular ejection fraction (LVEF) ≥ 10% from baseline and to less than 50% LVEF occurred in 3.9% of 908 patients who had baseline and at least one follow-up LVEF assessment.

Conduct cardiac monitoring, including assessment of LVEF at baseline and during treatment, in patients with cardiac risk factors. Assess LVEF in patients who develop relevant cardiac signs or symptoms during treatment. For symptomatic congestive heart failure, permanently discontinue TAGRISSO *[see Dosage and Administration (2.4) in the full Prescribing Information]*.

Keratitis

Keratitis was reported in 0.7% of 1142 patients treated with TAGRISSO in clinical trials. Promptly refer patients with signs and symptoms suggestive of keratitis (such as eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye) to an ophthalmologist.

Embryo-Fetal Toxicity

Based on data from animal studies and its mechanism of action, TAGRISSO can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, osimertinib caused post-implantation fetal loss when administered during early development at a dose exposure 1.5 times the exposure at the recommended clinical dose. When males were treated prior to mating with untreated females, there was an increase in preimplantation embryonic loss at plasma exposures of approximately 0.5 times those observed at the recommended dose of 80 mg once daily. Verify pregnancy status of females of reproductive potential prior to initiating TAGRISSO. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TAGRISSO and for 6 weeks after the final dose. Advise males with female partners of reproductive potential to use effective contraception for 4 months after the final dose *[see Use in Specific Populations (8.1, 8.3) in the full Prescribing Information]*.

ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

Interstitial Lung Disease/Pneumonitis *[see Warnings and Precautions (5.1) in the full Prescribing Information]*

QTc Interval Prolongation *[see Warnings and Precautions (5.2) in the full Prescribing Information]*

Cardiomyopathy *[see Warnings and Precautions (5.3) in the full Prescribing Information]*

Keratitis *[see Warnings and Precautions (5.4) in the full Prescribing Information]*

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.

The data in the Warnings and Precautions section reflect exposure to TAGRISSO in 1142 patients with EGFR mutation-positive NSCLC who received TAGRISSO at the recommended dose of 80 mg once daily in two randomized, active-controlled trials [FLAURA (n=279) and AURA3 (n=279)], two single arm trials [AURA Extension (n=201) and AURA2 (n=210)], and one dose-finding study, AURA1 (n=173) *[see Warnings and Precautions (5) in the full Prescribing Information]*.

The data described below reflect exposure to TAGRISSO (80 mg daily) in 558 patients with EGFR mutation-positive, metastatic NSCLC in two randomized, active-controlled trials [FLAURA (n=279) and AURA3 (n=279)]. Patients with a history of interstitial lung disease, drug induced interstitial disease or radiation pneumonitis that required steroid treatment, serious arrhythmia or baseline QTc interval greater than 470 msec on electrocardiogram were excluded from enrollment in these studies.

Previously Untreated EGFR Mutation-Positive Metastatic Non-Small Cell Lung Cancer

The safety of TAGRISSO was evaluated in FLAURA, a multicenter international double-blind randomized (1:1) active controlled trial conducted in 556 patients with EGFR exon 19 deletion or exon 21 L858R mutation-positive, unresectable or metastatic NSCLC who had not received previous systemic treatment for advanced disease. The median duration of exposure to TAGRISSO was 16.2 months.

The most common adverse reactions (≥20%) in patients treated with TAGRISSO were diarrhea (58%), rash (58%), dry skin (36%), nail toxicity (35%), stomatitis (29%), and decreased appetite (20%). Serious adverse reactions were reported in 4% of patients treated with TAGRISSO; the most common serious adverse reactions (≥1%) were pneumonia (2.9%), ILD/pneumonitis (2.1%), and pulmonary embolism (1.8%). Dose reductions occurred in 2.9% of patients treated with TAGRISSO. The most frequent adverse reactions leading to dose reductions or interruptions were prolongation of the QT interval as assessed by ECG (4.3%), diarrhea (2.5%), and lymphopenia (1.1%). Adverse reactions leading to permanent discontinuation occurred in 13% of patients treated with TAGRISSO. The most frequent adverse reaction leading to discontinuation of TAGRISSO was ILD/pneumonitis (3.9%).

Tables 2 and 3 summarize common adverse reactions and laboratory abnormalities which occurred in FLAURA. FLAURA was not designed to demonstrate a statistically significant reduction in adverse reaction rates for TAGRISSO, or for the control arm, for any adverse reaction listed in Tables 2 and 3.

Table 2. Adverse Reactions Occurring in ≥10% of Patients Receiving TAGRISSO in FLAURA*

Adverse Reaction	TAGRISSO (N=279)		EGFR TKI comparator (gefitinib or erlotinib) (N=277)	
	Any Grade (%)	Grade 3 or higher (%)	Any Grade (%)	Grade 3 or higher (%)
Gastrointestinal Disorders				
Diarrhea[a]	58	2.2	57	2.5
Stomatitis	29	0.7	20	0.4
Nausea	14	0	19	0
Constipation	15	0	13	0
Vomiting	11	0	11	1.4

Table 2. Adverse Reactions Occurring in ≥10% of Patients Receiving TAGRISSO in FLAURA* (cont'd)

Adverse Reaction	TAGRISSO (N=279)		EGFR TKI comparator (gefitinib or erlotinib) (N=277)	
	Any Grade (%)	Grade 3 or higher (%)	Any Grade (%)	Grade 3 or higher (%)
Skin Disorders				
Rash[b]	58	1.1	78	6.9
Dry skin[c]	36	0.4	36	1.1
Nail toxicity[d]	35	0.4	33	0.7
Pruritus[e]	17	0.4	17	0
Metabolism and Nutrition Disorders				
Decreased appetite	20	2.5	19	1.8
Respiratory, Thoracic and Mediastinal Disorders				
Cough	17	0	15	0.4
Dyspnea	13	0.4	7	1.4
Neurologic Disorders				
Headache	12	0.4	7	0
Cardiac Disorders				
Prolonged QT Interval[f]	10	2.2	4	0.7
General Disorders and Administration Site Conditions				
Fatigue[g]	21	1.4	15	1.4
Pyrexia	10	0	4	0.4
Infection and Infestation Disorders				
Upper Respiratory Tract Infection	10	0	7	0

* NCI CTCAE v4.0

[a] One grade 5 (fatal) event was reported (diarrhea) for EGFR TKI comparator

[b] Includes rash, rash generalized, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pustular, rash pruritic, rash vesicular, rash follicular, erythema, folliculitis, acne, dermatitis, dermatitis acneiform, drug eruption, skin erosion.

[c] Includes dry skin, skin fissures, xerosis, eczema, xeroderma.

[d] Includes nail bed disorder, nail bed inflammation, nail bed infection, nail discoloration, nail pigmentation, nail disorder, nail toxicity, nail dystrophy, nail infection, nail ridging, onychoclasis, onycholysis, onychomadesis, onychomalacia, paronychia.

[e] Includes pruritus, pruritus generalized, eyelid pruritus.

[f] The frequency of "Prolonged QT Interval" represents reported adverse events in the FLAURA study. Frequencies of QTc intervals of >500 ms or >60 ms are presented in Section 5.2.

[g] Includes fatigue, asthenia.

Table 3. Laboratory Abnormalities Worsening from Baseline in ≥ 20% of Patients in FLAURA

Laboratory Abnormality[a,b]	TAGRISSO (N=279)		EGFR TKI comparator (gefitinib or erlotinib) (N=277)	
	Change from Baseline All Grades (%)	Change from Baseline to Grade 3 or Grade 4 (%)	Change from Baseline All Grades (%)	Change from Baseline to Grade 3 or Grade 4 (%)
Hematology				
Lymphopenia	63	5.6	36	4.2
Anemia	59	0.7	47	0.4
Thrombocytopenia	51	0.7	12	0.4
Neutropenia	41	3.0	10	0
Chemistry				
Hyperglycemia[c]	37	0	31	0.5
Hypermagnesemia	30	0.7	11	0.4
Hyponatremia	26	1.1	27	1.5
Increased AST	22	1.1	43	4.1
Increased ALT	21	0.7	52	8
Hypokalemia	16	0.4	22	1.1
Hyperbilirubinemia	14	0	29	1.1

[a] NCI CTCAE v4.0

[b] Each test incidence, except for hyperglycemia, is based on the number of patients who had both baseline and at least one on-study laboratory measurement available (TAGRISSO range: 267 - 273 and EGFR TKI comparator range: 256 - 268)

[c] Hyperglycemia is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: TAGRISSO (179) and EGFR comparator (191)

DRUG INTERACTIONS

Effect of Other Drugs on Osimertinib

Strong CYP3A Inducers

Co-administering TAGRISSO with a strong CYP3A4 inducer decreased the exposure of osimertinib compared to administering TAGRISSO alone *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*. Decreased osimertinib exposure may lead to reduced efficacy.

Avoid co-administering TAGRISSO with strong CYP3A inducers. Increase the TAGRISSO dosage when co-administering with a strong CYP3A4 inducer if concurrent use is unavoidable *[see Dosage and Administration (2.4) in the full Prescribing Information]*. No dose adjustments are required when TAGRISSO is used with moderate and/or weak CYP3A inducers.

Effect of Osimertinib on Other Drugs

Co-administering TAGRISSO with a breast cancer resistant protein (BCRP) or P-glycoprotein (P-gp) substrate increased the exposure of the substrate compared to administering it alone *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*. Increased BCRP or P-gp substrate exposure may increase the risk of exposure-related toxicity.

Monitor for adverse reactions of the BCRP or P-gp substrate, unless otherwise instructed in its approved labeling, when co-administered with TAGRISSO.

Drugs That Prolong the QTc Interval

The effect of co-administering medicinal products known to prolong the QTc interval with TAGRISSO is unknown. When feasible, avoid concomitant administration of drugs known to prolong the QTc interval with known risk of Torsades de pointes. If not feasible to avoid concomitant administration of such drugs, conduct periodic ECG monitoring *[see Warnings and Precautions (5.2) and Clinical Pharmacology (12.3) in the full Prescribing Information]*.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on data from animal studies and its mechanism of action *[see Clinical Pharmacology (12.1) in the full Prescribing Information]*, TAGRISSO can cause fetal harm when administered to a pregnant woman. There are no available data on TAGRISSO use in pregnant women. Administration of osimertinib to pregnant rats was associated with embryolethality and reduced fetal growth at plasma exposures 1.5 times the exposure at the recommended clinical dose *(see Data)*. Advise pregnant women of the potential risk to a fetus.

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

When administered to pregnant rats prior to embryonic implantation through the end of organogenesis (gestation days 2-20) at a dose of 20 mg/kg/day, which produced plasma exposures of approximately 1.5 times the clinical exposure, osimertinib caused post-implantation loss and early embryonic death. When administered to pregnant rats from implantation through the closure of the hard palate (gestation days 6 to 16) at doses of 1 mg/kg/day and above (0.1 times the AUC observed at the recommended clinical dose of 80 mg once daily), an equivocal increase in the rate of fetal malformations and variations was observed in treated litters relative to those of concurrent controls. When administered to pregnant dams at doses of 30 mg/kg/day during organogenesis through lactation Day 6, osimertinib caused an increase in total litter loss and postnatal death. At a dose of 20 mg/kg/day, osimertinib administration during the same period resulted in increased postnatal death as well as a slight reduction in mean pup weight at birth that increased in magnitude between lactation days 4 and 6.

Lactation

Risk Summary

There are no data on the presence of osimertinib or its active metabolites in human milk, the effects of osimertinib on the breastfed infant or on milk production. Administration to rats during gestation and early lactation was associated with adverse effects, including reduced growth rates and neonatal death *[see Use in Specific Populations (8.1) in the full Prescribing Information]*. Because of the potential for serious adverse reactions in breastfed infants from osimertinib, advise women not to breastfeed during treatment with TAGRISSO and for 2 weeks after the final dose.

Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating TAGRISSO.

Contraception

TAGRISSO can cause fetal harm when administered to pregnant women *[see Use in Specific Populations (8.1) in the full Prescribing Information]*.

Females

Advise females of reproductive potential to use effective contraception during treatment with TAGRISSO and for 6 weeks after the final dose *[see Use in Specific Populations (8.1) in the full Prescribing Information]*.

Males

Advise male patients with female partners of reproductive potential to use effective contraception during and for 4 months following the final dose of TAGRISSO *[see Nonclinical Toxicology (13.1) in the full Prescribing Information]*.

Infertility

Based on animal studies, TAGRISSO may impair fertility in females and males of reproductive potential. The effects on female fertility showed a trend toward reversibility. It is not known whether the effects on male fertility are reversible *[see Nonclinical Toxicology (13.1) in the full Prescribing Information]*.

Pediatric Use

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

Geriatric Use

Forty-three percent (43%) of the 1142 patients in FLAURA (n=279), AURA3 (n=279), AURA Extension (n=201), AURA2 (n=210), and AURA1, (n=173) were 65 years of age and older. No overall differences in effectiveness were observed based on age. Exploratory analysis suggests a higher incidence of Grade 3 and 4 adverse reactions (13.4% versus 9.3%) and more frequent dose modifications for adverse reactions (13.4% versus 7.6%) in patients 65 years or older as compared to those younger than 65 years.

Renal Impairment

No dose adjustment is recommended in patients with creatinine clearance (CLcr) 15 - 89 mL/min, as estimated by Cockcroft-Gault. There is no recommended dose of TAGRISSO for patients with end-stage renal disease (CLcr < 15 mL/min) *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*.

Hepatic Impairment

No dose adjustment is recommended in patients with mild to moderate hepatic impairment (Child-Pugh A and B or total bilirubin ≤ ULN and AST > ULN or total bilirubin 1 to 3 times ULN and any AST). There is no recommended dose for TAGRISSO for patients with severe hepatic impairment (total bilirubin between 3 to 10 times ULN and any AST) *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*.

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Patient Advocacy Organizations and Cancer Care

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At HOPA's 2019 Annual Conference, a survey was conducted during the patient outreach breakout session to better understand pharmacists' utilization and awareness of patient advocacy organizations as they provide resources to their oncology patients. Attendees at that session heard from a panel of representatives about a number of advocacy resources available. Panel members included a patient and also representatives of the Leukemia and Lymphoma Society (LLS), the Pancreatic Cancer Action Network (PanCAN), and the Society for Immunotherapy of Cancer (SITC).

Patient advocacy organizations work to ensure that oncology patients have access to a variety of services: education, financial assistance, support groups, and clinical trial availability. They often provide the extra support for patients and their caregivers that may be difficult for hospitals and clinics to provide. Each organization offers unique services. As an example, LLS offers copay assistance programs and a patient aid program that provides support for patients by giving financial assistance for expenses that occur as a result of cancer treatment. Outside of various forms of financial support, LLS offers educational webcasts on specific types of blood cancer and potential treatments, support groups for patients and caregivers, and the opportunity to become a part of the LLS community. PanCAN offers education on molecular profiling and personalized cancer treatment, as well as information connecting patients to clinical trials. PanCAN also provides personalized one-to-one support for patients and caregivers through its Patient Central program. SITC offers sources for free and reliable immunotherapy education on multiple cancer types and access to a patient resource guide for those receiving immunotherapy. These are just a few examples of how connecting patients to advocacy organizations can provide access to supportive care for both the patient and the caregiver beyond the scope of the healthcare system.

Our survey results identified a need for increased awareness of the resources available through patient outreach organizations. The majority (74%) of the 156 survey respondents said they had referred patients and caregivers to these organizations in only 20% of cases or fewer in the previous 6 months. Advocacy organizations are best known for giving patients access to copay assistance and free-drug programs, and our results support the notion that many of us access organization websites only for these reasons. When these resources were used for reasons other than locating financial assistance in obtaining medications, the purpose was likely to be finding information on local support groups and clinical trial availability. Lack of knowledge was identified as the number-one barrier to the use of patient advocacy resources, followed closely by time constraints in the work environment. In addition, some respondents indicated that making such information available was outside the pharmacist's job responsibilities.

These results highlight an important opportunity to expand awareness of patient advocacy organizations to pharmacists and other members of the healthcare team in order to improve support for patients and caregivers and give them greater access to resources. As integral members of the healthcare team who often spend a significant amount of time on patient education, pharmacists may be the first members of the team to recognize a patient's need. Understanding the role of advocacy organizations gives us the opportunity to fulfill those needs for our patients and their loved ones. The survey results also underscore the importance of a team-based approach to cancer care. As pharmacists, we can step in to educate our healthcare colleagues on the value of connecting patients to cancer advocacy organizations and their numerous resources.

> **"As pharmacists, we can step in to educate our healthcare colleagues on the value of connecting patients to cancer advocacy organizations and their numerous resources."**

In addition to providing patient education on the value of these advocacy organizations, pharmacists can become more involved as volunteers for these organizations or even members of their paid workforce. As pharmacists, we can offer a unique perspective to these groups and should consider involvement in their leadership and steering committees. These opportunities allow us to expand into nontraditional roles in the field of oncology pharmacy and challenge us in new ways that will ultimately help us provide better patient care. They also allow us to expand our provision of patient care on a national or even international scale.

Our survey results indicated that 30% of respondents have experienced a time during their practice when they could not find a resource they wanted to use. Respondents identified resources such as transportation, interpreter services, local and online support groups for patients and caregivers, complementary and alternative medicine, and copay assistance, many of which could be provided through cancer advocacy organizations. Our survey results indicate that not knowing about the valuable resources available to patients through advocacy organizations is common in our profession. In

(continued on p. 29)

Oral Chemotherapy Education

Your best resource for oral chemotherapy education for patients has arrived.

Oral Chemotherapy Education (OCE) is a concise, patient-friendly resource for healthcare professionals and patients alike. OCE provides information about oral chemotherapy drugs and their side effects to cancer patients and their caregivers.

Oral Chemotherapy Education is a collaboration between four organizations:

ACCC
Association of Community Cancer Centers

HOPA
Hematology/Oncology Pharmacy Association

NCODA
National Community Oncology Dispensing Association, Inc.
PASSION FOR PATIENTS

ONS
Oncology Nursing Society

See the full library and more information at **OralChemoEdSheets.com.**

Rate of Infusion for Intravenous Magnesium Replacement in Hematopoietic Cell Transplant Patients

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Hypomagnesemia is a frequent occurrence after hematopoietic cell transplantation (HCT). Correction of electrolyte disturbances is required to prevent neuromuscular and cardiac manifestations. Magnesium replacement is often provided via the intravenous (IV) route after HCT because of gastrointestinal disturbances from nausea or vomiting, mucositis, or diarrhea. Significant doses are often required to maintain therapeutic levels during concomitant receipt of magnesium-wasting therapies such as calcineurin inhibitors. However, administration of IV magnesium can be challenging because renal handling in a high-peak serum concentration leads to increased excretion and decreased tubular reabsorption. It has therefore been postulated that slowing the infusion rate can improve magnesium retention. A paucity of data exists to support this theory and any impact on clinical outcomes. Potential detrimental effects of prolonged infusion rates include labor and temporal factors, as well as the possibility for increased issues related to IV access availability and incompatibility with other medications.

In the first study to assess magnesium infusion rate in HCT patients, Snyder and colleagues evaluated 103 allogeneic HCT patients in an ambulatory care setting.[1] In this study, prolonging the rate of infusion did not change the primary endpoint of grams of magnesium replaced per clinic visit. However, this study compared administering 4 grams over 1 hour (4 g/hr rate) versus administering 4 grams over 2 hours (2 g/hr rate). The authors acknowledged that the study did not address the potential utility of giving higher doses over a longer duration.

To further address the impact of prolonged magnesium infusion rates in HCT recipients, a postgraduate-year-1 pharmacy residency research project was performed by Ku and colleagues at the Augusta University Medical Center in Augusta, GA.[2] In this study, researchers retrospectively examined two groups of HCT recipients. One group received prolonged magnesium infusions (0.5 g/hr; n = 41), and the second group received shorter magnesium infusions (>0.5 g/hr [median rate 2.07 g/hr, range 0.8–6 g/hr; n = 41]). The primary endpoint was percent of days with serum magnesium within the goal range (2–2.7 g/dL). Other endpoints included percent of days with serum magnesium within the therapeutic range (1.3–2.7 g/dL), total amount of IV magnesium administered, total number of days of IV magnesium replacement, and incidence of hypomagnesemia and hypermagnesemia. Both autologous and allogeneic HCT patients were included to allow generalizability to a transplant program or medical ward protocol. Baseline characteristics including receipt of magnesium-wasting therapies (44% vs. 32%; p = .25), presence of magnesium in IV fluids (2.4% vs. 4.9%; p = .56), receipt of parenteral nutrition (19.5% vs. 17.1%; p = .78), type of transplant (allogeneic HCT 49% vs. autologous HCT 32%; p = .11), and incidence of graft-versus-host disease (25% vs. 46%; p = .14) were similar between prolonged versus short infusion groups.

Overall, the mean age was 57 years with 54% male patients. Sixty percent received an autologous HCT, and 41% received high-dose melphalan conditioning chemotherapy. The percent of days in goal range (32.2% vs. 28.1%; p = .3) was not different between cohorts. Notably, the vast majority (>97%) of patients in both groups were in technical therapeutic range for most days. No difference existed in total amount of IV magnesium administered (22.5 g vs. 21.4 g, p = .81) or days of IV magnesium replacement (7.2 days vs. 6.2 days, p = .41). Incidence of hypomagnesemia and hypermagnesemia was low overall and not significantly different between cohorts (p = .43 each).

Nine patients (two patients from the prolonged-infusion-rate group and seven patients from the short-infusion-rate group) experienced at least one episode of hypomagnesemia (median level 1.2 mg/dL, range 0.9–1.2 mg/dL); notably, eight of these nine patients received allogeneic HCT. Seven patients (five patients from the prolonged-infusion-rate group and two from the short-infusion-rate group) experienced one episode of hypermagnesemia (median level 2.9 mg/dL, range 2.8–2.9 mg/dL, for the prolonged-infusion-rate group vs. median level 3 mg/dL, range 2.8–3.2 mg/dL, for the short-infusion-rate group). Notably, six of these seven patients received allogeneic HCT. Because of the retrospective design, researchers were unable to assess other safety outcomes for different infusion rates. On the basis of these data, we advised our hospital to abandon the prolonged-infusion-rate policy, and this recommendation was accepted.

Although this study was limited by its small sample size and retrospective design, no difference in practical outcomes was demonstrated between infusion rates. Further prospective studies would provide definitive information about using the optimal infusion rate for safety and efficacy outcomes while balancing practical concerns about administration. Prospective studies should include assessment of renal function, all sources of magnesium (e.g., dietary), and clinical outcomes such as potassium replacement and symptoms that are often difficult to assess and quantify from retrospective reviews.

Providers should carefully weigh the potential benefit of prolonged infusion rates with the administration challenges. Using a short infusion rate of 2–4 g/hr in HCT populations is a reasonable approach, given the limited available data. ●●

(continued on p. 29)

Updates in the ASCO 2019 Venous Thromboembolism Guidelines

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The first American Society of Clinical Oncology (ASCO) guideline on the management of venous thromboembolism (VTE) in patients with cancer was published in 2007.[1] This guideline was updated in 2013 and reaffirmed in 2015. Since 2015, advances have been made in the understanding of the relevance and impact of VTE in patients with cancer. Most notably, results from prospective randomized clinical trials have illustrated the potential use of direct oral anticoagulants (DOACs) in patients with cancer. To account for the expanded literature, ASCO published its most recent iteration of the VTE guideline on August 5, 2019.[2] In this article we summarize specific updates and review selected studies.

Risk Prediction of VTE in Cancer Patients

VTE risk among patients with cancer varies significantly. The guidelines recommend that patients with cancer be assessed for VTE risk both initially and periodically, particularly when they are starting systemic chemotherapy or at the time of hospitalization. The Khorana score is yielded by a validated scoring tool that includes patient-specific factors such as site of cancer, body mass index, and complete blood count values and may be used to predict VTE risk in patients with cancer. The Khorana score ranges from 0 to 7 points, where 0, 1–2, and 3 points or more represent low, intermediate, and high risk, respectively.[3,4] It is critical to educate patients on the signs and symptoms of VTE, especially during surgery and hospitalization and while they are receiving chemotherapy.

VTE Prophylaxis During Hospitalization or Systemic Chemotherapy

On the basis of a meta-analysis of three trials that failed to demonstrate a significant reduction in VTE risk among hospitalized patients with cancer, ASCO recommends that pharmacologic thromboprophylaxis be offered to patients with risk factors (e.g., infection, advanced age).[5] Patients without additional risk factors may be offered prophylaxis in the absence of active bleeding or other contraindications. However, patients undergoing stem-cell transplantation, chemotherapy infusions, or minor procedures should not be offered routine pharmacologic thromboprophylaxis.

In the ambulatory setting, pharmacologic thromboprophylaxis is also discouraged. Thromboprophylaxis should be offered only to high-risk outpatients with a Khorana score of 2 or higher. ASCO's recommendation of apixaban, rivaroxaban, or low-molecular-weight heparin (LMWH) is based on five meta-analyses and two randomized phase 3 trials. The first of these randomized controlled trials (RCTs), AVERT, compared apixaban 2.5 mg twice daily (n = 288) and placebo (n = 275) in patients initiating chemotherapy.[6] The primary efficacy outcome was objectively documented VTE during a 180-day follow-up period. Approximately 50% of the patients had gynecologic cancer or lymphoma, and the 6-month all-cause mortality was 11%. AVERT demonstrated an absolute risk reduction (ARR) of 6% (number needed to treat [NNT] 17) with use of apixaban. Major bleeding, however, was higher in the apixaban arm (modified intent-to-treat hazard ratio [HR] 2; 95% confidence interval [CI] 1.01–3.95).

The second RCT, CASSINI, studied rivaroxaban 10 mg once daily (n = 420) and placebo (n = 421) in patients beginning systemic antineoplastic therapy. The primary efficacy outcome was a composite VTE endpoint during a 180-day follow-up period. Over 50% had pancreatic or gastric cancer, and the 6-month all-cause mortality was 22%, which demonstrates the differences in tumor groups between CASSINI and AVERT. CASSINI showed an ARR of 3.8% (NNT 27) with use of rivaroxaban. The difference in major bleeding in the two groups was not statistically significant.[7]

Perioperative VTE Prophylaxis in Cancer Patients

As recommended in previous VTE guideline iterations, patients undergoing major cancer surgery should continue pharmacologic thromboprophylaxis with LMWH for at least 7–10 days. The duration of prophylaxis should be extended, however, in patients undergoing abdominopelvic cancer surgery. The 2019 guideline update recommends LMWH prophylaxis for up to 4 weeks after either open or laparoscopic abdominal or pelvic surgery. Given the data provided by two meta-analyses and an RCT, extending postoperative administration of LMWH for 30 days reduces the risk of VTE without increasing bleeding complications.[8-10]

Optimal Management of VTE in Cancer Patients

The 2019 ASCO VTE guidelines include LMWH, unfractionated heparin (UFH), fondaparinux, and rivaroxaban as options for the initial management of VTE in cancer patients. In the CLOT trial, LMWH was found to reduce the risk of recurrent thromboembolism (HR 0.48; p = .002) compared to vitamin K antagonists (VKAs) without increasing the risk of bleeding.[11] LMWH is preferred over UFH for the initial 5–10 days of parenteral anticoagulation in patients with newly diagnosed VTE and cancer. For long-term anticoagulation, LMWH, edoxaban, and rivaroxaban for at least 6 months are preferred over vitamin K antagonists. In a noninferiority trial, edoxaban (initiated after 5 days of parenteral anticoagulation) was noninferior to dalteparin for a composite outcome of recurrent VTE and major bleeding. When these outcomes were analyzed separately, edoxaban was associated with an increased risk of major bleeding, particularly in patients with gastrointestinal (GI) malignancies (HR 1.77; p = .04).[12] In the SELECT-D trial, patients treated with rivaroxaban had a lower risk of VTE recurrence at 6 months compared to LMWH (HR 0.43; 95% CI 0.19–0.99) but higher rates of nonmajor bleeding (HR 3.76; 95%

CI 1.63–8.69).[13] In addition to GI malignancies, caution with DOAC use is also warranted in genitourinary (GU) malignancies and in patients with mucosal tumors because of a higher risk of bleeding. Other key considerations for DOAC use include cost, drug interactions, GI absorption, and renal or hepatic impairment.

ASCO recommends that anticoagulation with LMWH, DOACs, or VKAs be continued beyond 6 months in selected patients with active cancer, such as those with metastatic disease or those receiving chemotherapy; the recommendation is based on studies showing that extended anticoagulation is associated with continued risk reduction and no increased risk of bleeding. However, the benefits of extended anticoagulation must be balanced against the risks.

Although no clear strategy exists for the management of patients with recurrent VTE while they are receiving anticoagulation, ASCO recommends treating with an alternative anticoagulant or increasing the dose of LMWH.[14] Patients should also be assessed for compliance. The addition of a vena cava filter to LMWH may be considered as a last-line option. Currently no evidence supports the switching of DOACs in the setting of recurrent VTE.

Incidental pulmonary embolism (PE) and deep vein thrombosis have been shown to carry a similar risk of VTE recurrence, bleeding, and mortality in patients with cancer when compared to those with symptomatic VTE and should therefore be treated in the same manner as symptomatic VTE.[15] There is also no clear strategy for the management of incidental VTE that includes splanchnic or visceral vein thrombosis and isolated subsegmental PE in cancer patients. The guidelines recommend that treatment for these be offered on a case-by-case basis with careful assessment of risks and benefits.

On the basis of inconclusive benefit and the long-term risk of VTE development, ASCO guidelines recommend against insertion of a vena cava filter for primary VTE prophylaxis or in patients with established VTE (a VTE diagnosis made earlier than within the past 4 weeks), but this course may be considered for patients with absolute contraindications to anticoagulation in the management of acute VTE (a VTE diagnosis made within the past 4 weeks).[16]

Patients with primary or metastatic central nervous system malignancies are at an increased risk for both thrombotic complications and intracranial hemorrhage.[17] Although anticoagulation should be offered to those with established VTE, the preferred anticoagulant remains a question.

In the CLOT trial, 24% of patients had baseline renal impairment. Recurrent VTE occurred in 2.7% of patients treated with LMWH and in 17% of patients treated with VKA.[11] ASCO recommends anti-Xa measurement if LMWH is used in patients with moderate to severe renal impairment because of a higher risk of bleeding in this patient population. If anti-Xa measurement is unavailable, UFH and VKAs are considered safer options for initial and long-term treatment, respectively. The guidelines support the use of LMWH as the preferred option in obese patients. Caution should be used with DOACs in patients weighing more than 120 kg because of limited enrollment of these patients in clinical trials evaluating DOACs.[18]

Because of insufficient evidence, the guidelines recommend against anticoagulant use in order to improve survival in patients with cancer without VTE.[19]

Conclusions

The 2019 ASCO VTE guidelines provide updates in the comprehensive management of VTE in patients with cancer. For prevention, high-risk outpatients with cancer may be offered thromboprophylaxis with apixaban, rivaroxaban, or LMWH. For treatment, initial anticoagulation may include LMWH, UFH, fondaparinux, or rivaroxaban. Options for long-term anticoagulation include LMWH, edoxaban, or rivaroxaban. Notably, the risk of major bleeding is higher with long-term anticoagulation with DOACs, especially in GI and potentially GU malignancies. When deciding appropriate pharmacologic intervention, one must consider the indication as well as drug costs, drug-drug interactions, and patient-specific risk factors.[2]

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Patient Advocacy Organizations and Cancer Care *(continued from p. 24)*

fact, neither of us was aware of the abundant resources offered by these organizations until we became involved with HOPA's Patient Outreach Committee. The survey demonstrates that our organization and those in our profession have a tremendous opportunity to expand awareness of patient advocacy organizations and their resources. Until now, this need was not in our view, and we are excited for the opportunity to learn more about using and educating others on these valuable resources for patients.

Visit the websites of these advocacy organizations to become familiar with the resources they provide:

- Leukemia and Lymphoma Society—https://www.lls.org
- Pancreatic Cancer Action Network—https://www.pancan.org
- Society for Immunotherapy of Cancer—https://www.sitcancer.org

Rate of Infusion for Intravenous Magnesium Replacement in Hematopoietic Cell Transplant Patients *(continued from p. 26)*

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HOPA AND MEDSCAPE ONCOLOGY EDUCATION

present

Pharmacist Focus on Oncology

HOPA has recently partnered with Medscape Oncology Education to provide a series of educational activities designed both for pharmacists who specialize in hematology/oncology and for those who practice in a broader setting and care for patients with cancer less frequently.

Learn more at www.medscape.org.

Board Update

HOPA's Expanding Initiatives and Collaborations

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It is hard to believe that summer is past and the beautiful fall season will quickly turn into winter. HOPA continues to build on summer's momentum by providing premier education in oncology pharmacy, advocating for our cancer patients, expanding work on quality- and health-related outcomes, and advocating for pharmacy-initiated research. Your commitment to helping HOPA expand and create new resources is a source of pride. Thank you!

In September HOPA held its seventh annual Practice Management program. For the first time, the program was moved from Chicago to the beautiful city of Charlotte, NC. We had a great turnout for this conference, so Practice Management will continue to move around the country in order to provide as many HOPA members as possible with the opportunity to attend! The attendees who joined us, both in Charlotte and virtually, learned about challenges facing oncology pharmacy managers and administrators and how HOPA members rise to meet these challenges to ensure that every cancer patient has the best possible care. Our Practice Management Program Committee tried some new educational strategies this year, including site visits and, for the session on biosimilars, a "flipped classroom" format where participants did advance preparation. Three successful preconference sessions were held on September 13: on investigational drug services, on the growing role of specialty pharmacy as an extension of the cancer care team (with a site visit to Walgreens), and on establishing a comprehensive oncology pharmacy team (with a site visit to Atrium Health's Levine Cancer Institute). The program featured outstanding lectures on a range of topics—for example, using consultants to help with transitions, battling burnout, and bringing precision medicine into practice—as well as an overview of integrative oncology. Steven Eisenberg, DO, provided this year's thoughtful Niesha L. Griffith Keynote Address, "CPR for the Oncologist's Soul." In addition, HOPA's own Heidi Finnes gave an inspirational inaugural HOPA Voices lecture titled "You Can Move Mountains." As a bonus, on the preceding day, an "Introduction to Quality Improvement" workshop was led by the American Society of Clinical Oncology's Quality Training Program faculty (see the "Quality Initiatives" column in this issue). We owe our heartiest thanks to the Practice Management Program Committee and HOPA staff members—their hard work and dedication made this program a truly impressive event!

HOPA members, committees, and task forces continue to do amazing work. For example, the Governance Committee recently reviewed and updated HOPA's bylaws. When this revision was completed, HOPA members were able to review the revised bylaws and give feedback to the committee. If all goes as planned, members will be able to vote on the new bylaws in November!

HOPA's Leadership Development Subcommittee is currently wrapping up work on its Pilot Mentorship Program matching HOPA leaders with members who are early in their career. Leadership Development chair Becky Fahrenbruch, as well as mentors and mentees, updated Practice Management attendees on this program and discussed the ways that HOPA is actively developing our members into our future leaders.

In September the Leadership Development Subcommittee also announced the publication of "Women in Oncology Pharmacy Leadership: A White Paper," authored by HOPA members Alexandra Shillingburg, Laura Michaud, Rowena Schwartz, Jaime Anderson, and David Henry on behalf of HOPA's Women in Leadership Summit Task Force. The article was published online by the *Journal of Oncology Pharmacy Practice* in September 2019; a link to the paper can also be found on HOPA's website (hoparx.org/misc-membership/american-pharmacists-month).

Finally, many of you saw the media releases about HOPA's collaboration with the Oncology Nursing Society on the position statement "Ensuring Healthcare Worker Safety When Handling Hazardous Drugs." This collaboration was a huge success, and we look for more to come from this partnership! The position statement was published in *HOPA News* (Vol. 16, no. 3) and can also be found on our website at hoparx.org/advocacy-activities/position-statements. These are just a few examples of the all amazing things HOPA members are doing!

In the days ahead, let's take time to appreciate the seasonal changes and all we have to be thankful for. I am so grateful to the people I have worked with and for the opportunities I have had at my institution and in my work with HOPA. What we do every day makes a difference in the lives of cancer patients. Our efforts are important and touch more people than we realize. Let's keep up the great work! ●●

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