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Cardio-Oncology: A Focus on Chemotherapy-Induced Cardiomyopathy

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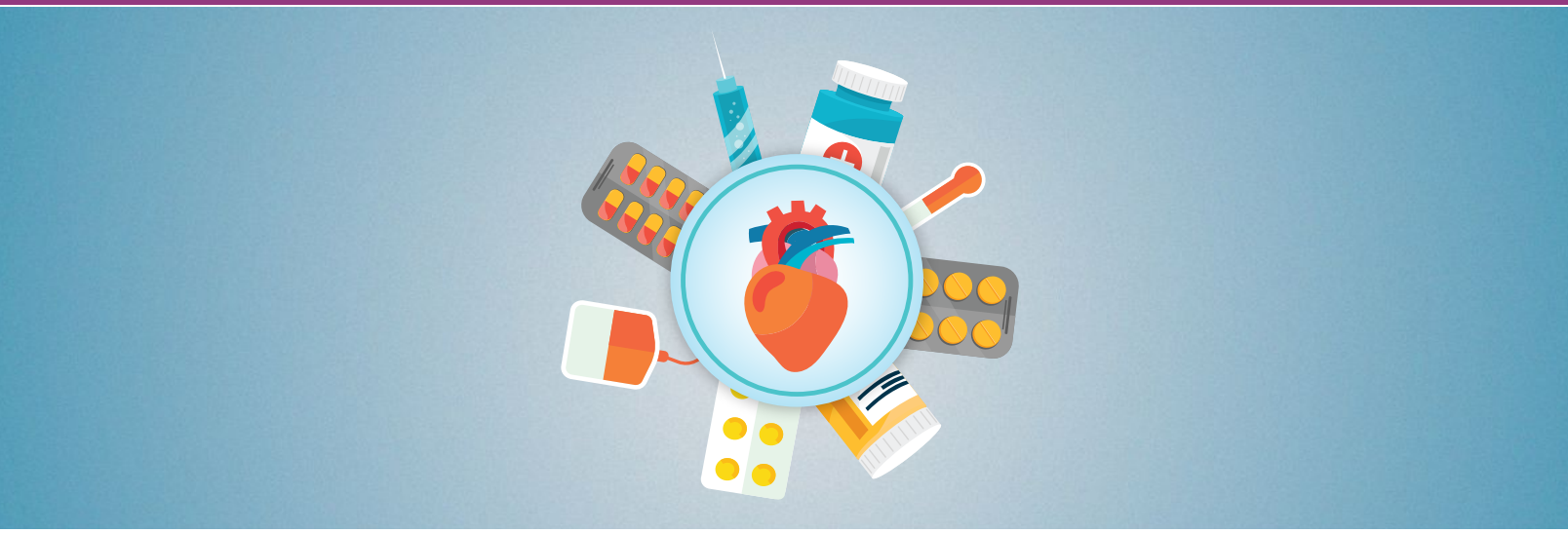

Cardio-Oncology: A Focus on Chemotherapy-Induced Cardiomyopathy

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Advances in oncology treatment and supportive care have led to the conversion of numerous cancers from a terminal illness into a chronic disease state. Nevertheless, cancer remains the second leading cause of death in the United States behind cardiovascular disease.[1] Certain cancer therapies, including chemotherapy, targeted therapy, and radiation therapy, may result in treatment-related cardiovascular complications; therefore, efforts to identify patient-specific risk factors prior to beginning cancer treatment and to recognize cardiac dysfunction during therapy have been given priority in order to lessen cardiovascular risks and their effects on cancer outcomes. The field of cardio-oncology has emerged as a new area of clinical practice, intertwining cardiology and oncology principles with the purpose of providing optimal oncology care to cancer patients without compromising cardiovascular health. Long-term cardiovascular complications related to cancer treatment may have an impact on survivorship; thus it is vital to incorporate cardio-oncology into clinical oncology patient care in order to optimize efficacy and survival outcomes and improve quality of life for patients.

Clinical presentations of cardiovascular complications from chemotherapy, targeted therapy, and radiation therapy include heart failure (HF), myocardial ischemia, myocarditis, hypertension, pericardial diseases, thromboembolic disorders, QTc prolongation and arrhythmias, and pulmonary hypertension.[2] Cancer therapy–induced cardiomyopathy is a historically recognized adverse event, and relevant cardio-oncology data are discussed below.

Heart Failure

The lifetime risk of developing HF is 20% for all adults 40 years of age or older in the United States, and patients with HF secondary to doxorubicin therapy have had significantly worse survival rates compared to patients with idiopathic cardiomyopathy.[3,4] As defined by the American College of Cardiology Foundation and the American Heart Association (ACCF/AHA), HF is a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood.[3] It is recognized as a progressive disorder, and onset during cancer therapy is of particular importance because it may result in the interruption or discontinuation of therapy, which may have a negative impact on oncology-related outcomes. Although no definition for HF in the cardio-oncology setting has been established, package labeling of known cardiotoxic cancer therapies, including anthracyclines and antihuman epidermal growth factor receptor (HER2)–targeted therapies, has characterized it as an absolute decrease in left ventricular ejection fraction (LVEF) of at least 16%–20% from baseline, a decline in LVEF by 10% or more from baseline to below the lower limit of normal, or an absolute LVEF of no more than 40%–45%.[5-9] The definition established by the Common Terminology Criteria for Adverse Events version 5.0 includes symptoms and their responsiveness to intervention as a standardized qualitative method for reporting HF and left ventricular (LV) systolic dysfunction in clinical trials.[10]

Diagnostic Workup

Although cardiac dysfunction may present as systolic or diastolic dysfunction or both, LVEF via echocardiogram (ECHO) remains the primary technique to assess cardiac structure and function during and after completion of anthracycline and anti-HER2 targeted therapy. Multigated acquisition scan (MUGA) or cardiac magnetic resonance imaging (MRI) are alternative monitoring approaches but may be limited by their high cost. When an ECHO cannot be performed, cardiac MRI is preferred over MUGA because it provides cardiac structural and functional information without exposing the patient to radiation.[2,11] All patients receiving cardiotoxic cancer therapy should undergo baseline LVEF measurement

and periodic monitoring during and after completion of therapy based on package labeling recommendations and as clinically indicated, using the same method at each time point throughout treatment.[11]

Other surveillance tools for monitoring LVEF include myocardial strain and serum biomarkers, but evidence to provide guidance on monitoring strategies for these tools is lacking.[11] Global longitudinal strain has detected preclinical changes in LV systolic function prior to quantifiable declines in LVEF and was shown to predict subsequent toxicity prior to the onset of HF symptoms.[12,13] Monitoring cardiac biomarkers such as troponin and brain natriuretic peptide may offer opportunities to identify early signs of myocardial damage: positive troponin I has been correlated with a higher incidence of HF and asymptomatic LV dysfunction.[14] Although still being investigated, these strategies may in the future offer benefit in detecting subclinical HF prior to detection on ECHO and allowing for earlier intervention to avoid long-term complications of cardiotoxicity.

Risk Factors

Risk factors for cardiac dysfunction in the form of LVEF decline in patients treated with an anthracycline or trastuzumab or both are well established. Modifiable risk factors include hypertension, diabetes, dyslipidemia, and smoking, all of which have had a significant association with cardiac dysfunction in this patient population, with hypertension being the most common risk factor. Patients with two or more modifiable risk factors have an added risk of HF. Patients 60 years of age and older have demonstrated 1.6- to 6.8-fold increased risks of cardiac dysfunction, and those with preexisting compromised cardiac function, including LVEF of 50%–55% at baseline or history of myocardial infarction or coronary artery disease, have demonstrated 3.6- to 11.8-fold increased risks of cardiac dysfunction.[11] Obesity and metabolic syndrome are other modifiable risk factors recognized by the ACCF/AHA as important risk factors for HF and should also be considered in patients treated with an anthracycline or anti-HER2 targeted agent.[3] Cancer therapy–related risk factors include exposure to anthracycline and anti-HER2 targeted agents and prior exposure to radiation therapy in which the heart was in the treatment field.[11] Specifically, the coadministration of doxorubicin and trastuzumab is not recommended because rates of cardiac dysfunction have been reported to be as high as 27% when doxorubicin and trastuzumab are given with cyclophosphamide.[15] It is recommended that patients with underlying cardiovascular risk factors be carefully evaluated prior to oncology treatment to ensure that the benefit outweighs the harm of therapy. Cancer patient populations at greatest risk include females with breast cancer because anthracyclines are commonly used for most breast cancer patients, and they are used in conjunction with trastuzumab if a patient has HER2-positive disease.

Anthracyclines

The association between anthracycline exposure and risk of LVEF decline is well established and is hypothesized to occur as a result of their interaction with topoisomerase 2β in cardiomyocytes, leading to three hallmarks of anthracycline-induced cardiotoxicity: apoptosis of myocytes, generation of reactive oxygen species, and mitochondriopathy.[2] Anthracycline-induced HF is related to cumulative drug exposure; may be irreversible; and may occur during therapy or months to years after discontinuation of therapy.[5] The American Society of Clinical Oncology recognizes high-dose anthracycline therapy—defined as doxorubicin in doses of 250 mg/m^2 or greater or epirubicin in doses of 600 mg/m^2 or greater—as placing recipients at increased risk for cardiac dysfunction, with the risk for delayed cardiotoxicity estimated to range from 1% to 2% at cumulative lifetime doses of doxorubicin 300 mg/m^2, 3%–5% at 400 mg/m^2, 5%–8% at 450 mg/m^2, and 6%–20% at 500 mg/m^2.[5,11] However, subclinical cardiac events have occurred in patients who have received cumulative doses of doxorubicin 240 mg/m^2, which highlights the individual susceptibility to anthracyclines as well as the importance of regular ECHO monitoring during and after therapy.[16] Although no standardized conversion table exists, oncology cooperative groups have investigated anthracycline toxicity equivalence ratios to quantify cumulative doxorubicin lifetime doses and stratify patients who have received multiple anthracyclines based upon risk for HF, which is intended to guide future treatment strategies.[17]

Nonspecific recommendations for LVEF monitoring exist for anthracyclines, with increased frequency of assessments suggested for cumulative doxorubicin doses over 300 mg/m^2. Any clinical sign or symptom of HF warrants discontinuation of anthracycline therapy.[5]

Anti-HER2 Targeted Agents

Although the mechanism of cardiotoxicity is not fully elucidated, HER2 is a protein expressed on the surface of cardiomyocytes and is essential for their survival.[2] Trastuzumab is recognized to be the most cardiotoxic of the four U.S. Food and Drug Administration (FDA)-approved anti-HER2 targeted agents (the others are pertuzumab, ado-trastuzumab emtansine, and lapatinib); however, all have package-label warnings for cardiotoxicity.[6-9] Unlike the anthracyclines, LVEF decline with anti-HER2 targeted agents is not dose related and is normally reversible with termination, with improvements observed in LVEF within 4–6 weeks of discontinuation.[6,18]

Specific intervals of LVEF monitoring are recommended for trastuzumab: every 3 months during therapy, at 4-week intervals if the drug is withheld for significant cardiac dysfunction, and every 6 months for at least 2 years following completion of therapy. An absolute decrease in LVEF of 16% or more from baseline or LVEF below institutional limits of normal and a 10% or higher absolute decrease in LVEF from baseline is an indication for withholding trastuzumab.[6] It is safe to readminister anti-HER2 targeted agents after withholding them for LVEF decreases after heart function has recovered.

Guidance provided for trastuzumab requires that the LVEF return to within normal limits within 4–8 weeks of withdrawal, with an absolute decrease from baseline of 15% or less.[6,18] Trastuzumab should be permanently discontinued for LVEF decline that does not recover within 8 weeks or when trastuzumab has

been discontinued because of cardiomyopathy on more than three occasions.[6]

The use of combination HER2 blockade with trastuzumab and pertuzumab has become routine in treating HER2-positive breast cancer without demonstrating an increased risk of cardiotoxicity.[19,20] LVEF should be monitored every 12 weeks for patients receiving pertuzumab in combination with trastuzumab. Recommendations for withholding and resuming pertuzumab and trastuzumab therapy are stratified by the metastatic or early breast cancer treatment setting and take into account absolute LVEF values as well as LVEF percent decline, allowing lower LVEF measurements in the metastatic setting. Pertuzumab should be discontinued if trastuzumab therapy is terminated. It is important to note that any delays in treatment secondary to withholding for cardiotoxicity require that patients receive a repeat loading dose of pertuzumab if the time between two sequential infusions is 6 weeks or more and of trastuzumab if the dose has been held for longer than 1 week.[6,8] However, when the pharmacokinetics of trastuzumab are taken into account, a repeat loading dose may be necessary only after a dose delay of more than 6 weeks.[21]

Other Chemotherapeutic Agents

Although more robust literature exists on anthracyclines and anti-HER2 targeted agents, other chemotherapeutic agents, including carfilzomib, high-dose cyclophosphamide, and vascular endothelial growth factor (VEGF) inhibitors, are also associated with cardiomyopathy. Carfilzomib is the only proteasome inhibitor with reported cardiac failure events, including LVEF decline and congestive HF, which occurred in 7% of patients.[22] High-dose cyclophosphamide was associated with congestive HF in 28% of patients treated with doses of 180 mg/kg over 4 days within 3 weeks of administration.[23] Although this is a higher administered dose than may be observed in clinical practice in adults, cyclophosphamide package labeling lists cardiotoxicity, including HF, as a warning, with risk factors including high doses, advanced age, and prior radiation when the heart was in the treatment field.[24] Mechanisms of VEGF inhibitor–induced cardiomyopathy include uncontrolled hypertension, which is associated with cardiovascular disease, and impairment of cardiomyocyte survival and proliferation.[2,25]

LVEF decline occurred in 4.1% of patients treated with sunitinib, and development of HF has been reported in 2%–4% of patients treated with bevacizumab.[26-28] VEGF inhibitors have been associated with hypertension in 30%–80% of patients treated with these agents, and blood pressure control may play an important role in mitigating the risk of secondary HF.[28] As with anthracyclines and anti-HER2 targeted agents, symptomatic HF warrants immediate discontinuation of therapy.

"All cardiovascular complications of oncology therapy have the potential to affect the efficacy of cancer treatment, reduce quality of life, and affect long-term survival."

Prevention and Management

Angiotensin-Converting Enzyme (ACE) Inhibitors, Angiotensin II Receptor Blockers (ARBs), and Beta Blockers

ACE inhibitors, ARBs, and beta blockers improve morbidity and mortality rates and are mainstays of traditional HF management.[3] Primary prevention strategies using these agents against anthracycline- and trastuzumab-induced cardiotoxicity are ongoing areas of research. Enalapril initiated 1 month after chemotherapy and continuing for 1 year following initiation of anthracycline-containing chemotherapy regimens demonstrated benefit in preserving LVEF in patients with troponin I elevation after chemotherapy.[29] Evidence on the use of candesartan in the prophylactic setting has been conflicting. Compared to metoprolol and placebo, candesartan demonstrated a benefit in LVEF preservation in females receiving adjuvant anthracycline-containing regimens with or without trastuzumab and radiation, although no benefit was observed in protecting LVEF in a second study in a similar patient population.[30,31]

Prophylactic use of beta blockers has also yielded conflicting evidence in protecting LV function. A small study in patients who received an anthracycline and carvedilol for 6 months demonstrated that patients were able to maintain preserved LVEF.[32] Similarly, patients with hematologic malignancies who received both enalapril and carvedilol at the start of chemotherapy and continued for 6 months maintained preserved LVEF.[33] However, in the largest randomized prospective study to date, treatment-naive breast cancer patients receiving an anthracycline, cyclophosphamide, and a taxane were randomized to receive incremental 3-week dosing of carvedilol or placebo as tolerated until completion of chemotherapy. Carvedilol had no impact on the primary endpoint, an early-onset reduction in LVEF of at least 10% at 6 months.[34]

The current literature highlights a need for further studies to investigate the use of agents known to improve mortality rates in traditional HF so that outcomes for managing cancer therapy–induced HF can be improved. Although both beta blockers and inhibitors of the renin-angiotensin-aldosterone system have demonstrated LVEF protection when initiated at multiple time points in relation to initiation of anthracycline- or trastuzumab-containing regimens, inconsistencies in cardiac benefit seen with these agents show the need to determine the optimal initiation time and duration of use. Further, possible adverse events such as dehydration or weakness secondary to chemotherapy also present a challenge to cancer patients and may limit the initiation of cardiac agents because of blood pressure intolerance. Any presentation of overt symptomatic and asymptomatic HF should be managed according to ACCF/AHA HF guidelines.

Other Prevention Strategies

Other preventive pharmacologic strategies are recommended to reduce the risk of cardiovascular complications prior to initiation of anthracycline therapy and during its administration.[11] Dexrazoxane, an antidote for anthracycline extravasation, is also a cardioprotectant, acting as an intracellular chelating agent to disrupt iron-mediated oxygen free radical generation, a component of anthracycline-induced cardiomyopathy.[35] When administered in a 10:1 ratio of dexrazoxane to doxorubicin or equivalents, dexrazoxane resulted in reduced rates of LVEF decline without compromising antitumor efficacy.[36-39] The FDA-approved indication for dexrazoxane for the prevention of doxorubicin-induced cardiomyopathy specifies its use for patients who have received a cumulative doxorubicin dose of 300 mg/m^2 and will continue anthracycline therapy.[35] Limitations to routine use with anthracyclines outside this setting include package-label warnings for myelosuppression and secondary malignancies; however, clinical evidence has demonstrated that dexrazoxane is associated with reversible myelosuppression, and exposure is not associated with increased risks of secondary malignancies.[35,40] Dexrazoxane has not been shown to affect survival when coadministered with anthracyclines.[40] Guidelines for dexrazoxane use at lower cumulative anthracycline dosing thresholds may be institution specific.

Pegylated liposomal doxorubicin has demonstrated a lower risk of clinical cardiotoxicity compared to conventional anthracyclines without affecting efficacy outcomes, so it is another preventive strategy for mitigating the risk of cardiomyopathy in patients with advanced cancers requiring anthracyclines.[41-43] Adjustment of the rate of anthracycline administration is another preventive strategy; administration of anthracycline via intravenous bolus has been associated with an increased risk of clinical cardiotoxicity, more than four times that seen with continuous infusion.[42]

The most conservative strategy is the avoidance of a potentially cardiotoxic agent in the patient's cancer therapy; however, this decision should recognize the intent of therapy and the possibility that the antitumor efficacy of the alternative agent could compromise cancer-specific outcomes. Considering each individual patient's clinical scenario is vital to ensure that strategies for preventing cardiotoxicity are selected for the patient populations at highest risk. High-risk patients include those receiving high-dose anthracyclines, recognized as doses equivalent to doxorubicin of 250 mg/m^2 and greater.[11]

Conclusion

Management and prevention of cardiotoxicity induced by cancer therapies is an ongoing area of research aimed to balance cancer therapy efficacy with cardiovascular safety. Trastuzumab transformed the landscape of HER2-positive breast cancer treatment, and anthracyclines remain a backbone of hematologic and solid tumor chemotherapy regimens; however, their impact on long-term cancer outcomes can be limited by their cardiotoxicity profiles.[44] LVEF monitoring via ECHO remains the mainstay method for assessing the cardiotoxicity of cancer therapies; however, ongoing research with serum biomarkers and myocardial strain may allow for earlier detection of subclinical HF and intervention to combat cardiotoxicity. Every patient receiving any cancer therapy with cardiotoxic potential must be approached individually, with particular focus on the intent of cancer therapy and pre-existing cardiac risk factors. Institutions fortunate to have providers specialized in cardio-oncology should consider referring high-risk patients early in the treatment course for assistance in cardiac management. All cardiovascular complications of oncology therapy have the potential to affect the efficacy of cancer treatment, reduce quality of life, and affect long-term survival. An integrated approach is therefore necessary to optimize long-term outcomes in this unique patient population. ●●

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Perspectives from Involvement in International Oncology Pharmacy

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Much of the career advice I have read or received over the years has centered on concepts like discovering what you are passionate about and being intentional about setting meaningful goals. Throughout my pharmacy career, one of my goals has been to seek out unique opportunities beyond the traditional clinical setting. Because I am also an avid traveler, I developed a curiosity about how pharmacy is practiced around the world and would often stop at pharmacies or pharmacy museums in other countries if I had the chance. This curiosity also led me to Google *international oncology pharmacy practice*, which is when I came across the International Society of Oncology Pharmacy Practitioners (ISOPP). ISOPP's mission—to advance oncology pharmacy care for patients around the world—struck me as something I wanted to be a part of. The ISOPP membership consists of oncology pharmacists in a wide variety of settings all over the globe; it's a small but close-knit and amazing community. After reading through the materials on the website, I joined the organization that same day and immediately e-mailed to ask how I could become more involved. Since then, I have been able to contribute to the work of multiple committees (including the scientific program committee for the annual symposium, the communications work group, the standards review task force, and the advocacy task force), and I am currently completing a 4-year term on the board of directors.

As with many volunteer experiences, it is amazing how giving can ultimately lead to receiving. The time I have contributed in my work with ISOPP has resulted in so many valuable experiences, networking opportunities, and chances to broaden my perspective. For example, the annual ISOPP International Oncology Pharmacy Symposium is held in a different country every year and provides a wide variety of interesting clinical content in fundamental, clinical, and research tracks as well as exciting new travel and sightseeing opportunities. It has also provided a great way for me to meet oncology pharmacists from all over the world. I now have a network of colleagues in a large number of countries, and I've had the privilege of learning from them as well as returning the favor through invitations to participate in other national conferences. Although specific needs may vary by region, it is fascinating for me to talk with someone halfway around the world who is facing the same challenges I am and then work together to find a solution. For instance, a recent ISOPP initiative is creating a master-class curriculum that covers topics such as supportive care in oncology, oral chemotherapy, and safe handling. It has been wonderful to help develop the content for these programs so they can be shared with oncology pharmacists in China and Turkey and many others planned for the future. Task forces are working to help address challenging topics such as biosimilars and global standards for the role of the oncology pharmacy team.

My involvement with ISOPP also helped me realize how much I enjoy working on a big-picture level. Although I found clinical practice engaging and rewarding, my interests started to shift, and a few years ago I had the opportunity to interview for a position at the National Comprehensive Cancer Network (NCCN). It felt like the perfect fit because of the organization's existing national and expanding international reach, as well as its mission and vision. As the development of new drugs and new data continues to grow at a rapid pace, the mission of NCCN to facilitate high-quality, effective, efficient, and accessible cancer care resonates with me as being particularly relevant and meaningful. At NCCN, I work with a fantastic team of oncology pharmacists and nurses to develop the NCCN Drugs and Biologics Compendium and the Chemotherapy Order Templates, which are both derivative products of the NCCN Clinical Practice Guidelines in Oncology. In addition, we work with many licensees to integrate NCCN compendium and template information into third-party electronic information systems such as electronic medical record clinical decision support and utilization management systems.

My current role gives me a unique perspective because clinical oncology practice at our 28 member institutions helps inform our projects, which then influences clinical oncology practice around the world. It is also exciting to see an increasing global focus with the development of new resources such as translated guidelines, resource-stratified guidelines (guidelines that take into account a country's access to resources like medications or surgical procedures), and harmonized guidelines that are being adapted for specific regions. Working on these projects represents everything that I hope oncology pharmacy as a whole will continue to pursue: collaborating on national and international levels, achieving excellence through team-based innovation, and linking the quality of patient care and outcomes with opportunities for integration and expansion of oncology pharmaceutical care. Aligning my daily work with my personal goals and passions has been one of the most meaningful lessons I have learned so far in the area of achieving career satisfaction.

If you are interested in learning more about ISOPP or NCCN, more information is available at www.isopp.org and www.nccn.org. ●●

Using Digital Patient Engagement to Support the Management of Oral Anticancer Therapy

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The Evolution of Patient Engagement

In the United States, approximately 40 million people suffer from one or more chronic health conditions. Chronic diseases play a major role in healthcare utilization in the United States and are responsible for 75% of total healthcare costs.[1,2] The most common chronic conditions in the United States are heart disease, mental disorders, pulmonary conditions, and cancer.[3] Prevalence of these diseases is projected to increase by an additional 16 million by 2020, accounting for 48% of the population.[4] In oncology, significant advances in cancer treatment have led to prolonged treatment of certain types of cancer, with therapy length comparable to that in the management of patients with hypertension or diabetes. Current care delivery models are not optimized to manage major chronic diseases, primarily because of (1) demands on physicians' time, (2) rapidly expanding medical databases, (3) a large and continuously increasing number of treatment options, and (4) lack of supporting infrastructure.

The Institute of Medicine (IOM) issued a statement in 2013 addressing ways to improve the quality of cancer care. One of the initiatives set forth was to make patients the center of their own care, which reinforces communication and shared decision making. The IOM expressed the need for a system that supports patients in making informed medical decisions according to their needs, values, and preferences in consultation with experts in the field.[6] Several terms assist in defining this concept. *Patient activation* encompasses the knowledge, skills, ability, and willingness to manage one's own health care.[7] However, this definition does not address the effect of external influences on an individual's behavior and decision making. *Patient engagement* is a broader notion that entangles patient activation with modalities aimed at enhancing activation and positive patient behavior.[8] *Patient- and family-centered care* is an even broader term that conveys a vision for what health care should be: "a partnership among practitioners, patients, and their families (when appropriate) to ensure that decisions respect patients' wants, needs, and preferences and that patients have the education and support they need to make decisions and participate in their own care."[9] Patients engaging in their own care have a better understanding of their own health, which leads to fewer complications from treatment, better triaging of complications, and the potential for fewer hospital admissions.[10]

"Patients engaging in their own care have a better understanding of their own health, which leads to fewer complications from treatment, better triaging of complications, and the potential for fewer hospital admissions."

Financial motivation to enhance the current care model has been stimulated by ongoing changes in reimbursement models. As health care transitions from a fee-for-service to a pay-for-performance model, healthcare providers are recognizing that patient engagement is a crucial piece of delivering high-quality health care at a low cost.[11] Additionally, the Centers for Medicare and Medicaid Services (CMS) has proposed the addition of new payment codes for patient engagement and remote patient monitoring (RPM). Some of the projected payment codes include virtual check-in appointments, asynchronous video and image review, and clinical staff allocation for providing virtual patient care.[12]

The evolution of patient engagement is not free of challenges. In 2017, the New England Journal of Medicine (NEJM) Catalyst Insights Council survey regarding patient engagement found that 63% of respondents reported that the time investment required by health teams is the biggest challenge in designing patient engagement into care delivery. Fifty-four percent of providers perceived adoption by patients as another big barrier, and 52% indicate adoption by providers as an obstacle in designing patient engagement into care delivery.[13]

Defining Digital Patient Engagement Platforms

Patient engagement is multifaceted; optimal results cannot be achieved with a single strategy. Incorporating digital technology into the patient-engagement process is an opportunity that is often underutilized. According to a recent patient-engagement survey published by the NEJM Catalyst Insights Council, 63% of responders used team members for patient engagement, 44% of responders used technology (e.g., remote devices), and 24% used patients' social networks. The relatively low use of technology in this setting illustrates a remarkable opportunity for improvement, which can lead to enhancements in patient engagement and make patients the center of their own care.[13,14]

Automated digital patient engagement (DPE) platforms combine remote guidance and telemonitoring to notify the healthcare

team about potential clinical concerns and may assist in bridging the postdischarge or postclinic visit gap. These include mobile applications (e.g., SONIFI Health, HealthLoop) as well as wearable devices (e.g., Proteus Digital Health, Fitbit, Garmin, Apple Watch) that are designed to increase opportunities for education and counseling.[15-17] By detecting developing problems or complications through interaction with the patient, DPE has the potential to increase satisfaction with the healthcare process and avoid hospital admissions and other costly interventions.[10] Employment of such technologies has been shown to improve patients' engagement with their own care as well as improve patients' satisfaction with the healthcare system.[18]

Adaptation of DPE platforms has increasingly been seen in community and academic medical centers over the past 5 years.[19]

DPE platforms can be used simply to provide educational materials, but they can also be used for patient-reported outcomes (PROs) for monitoring adverse events related to medications or procedures. The benefits of using DPE platforms with the sole intent of providing educational materials are demonstrated in a study by Steele and colleagues at MD Anderson Cancer Center, in which patient comprehension of diagnostic imaging information was assessed in 2,226 patients with cancer. Patients were randomized to receive information about diagnostic imaging via a Web-based interactive education platform (HealthLoop, Inc., Mountain View, CA), the same information in document format, or no specialized education (control group). The study concluded that patients using the DPE application had a significantly better understanding of diagnostic imaging information than those who were provided the same information in paper form.[20] DPE platforms deliver information to patients in a sequential manner and in small increments, which reinforces the learning of information.

"The integration [of patient engagement] into the current health system will be necessary in order to provide optimal patient care and receive payment in future reimbursement models."

DPE platforms can further be used with the collection of PROs or adverse event monitoring with medications or procedures. In a study by Basch and colleagues, patients receiving outpatient chemotherapy for advanced solid tumors at Memorial Sloan Kettering Cancer Center were assigned to a PROs group or received usual care consisting of symptom monitoring at the discretion of clinicians. Self-reporting in this study was conducted via Web-based Symptom Tracking and Reporting (STAR). Patients who participated in PROs had better health-related quality of life (HRQoL), fewer emergency room admissions (34% vs. 41%; $p = .02$), and a trend toward fewer hospitalizations (45% vs. 49%; $p = .08$).[21] Post-hoc analysis of overall survival in this study reported significantly improved median overall survival in patients who participated in PRO (31.2 vs. 26 months; $p = .03$).[22] DPE platforms have also been used in pre- and postsurgical patients and have demonstrated that implementation of such tools leads to a significant reduction in avoidable, postsurgery complications (29.6% vs. 7%; $p = .002$) and a trend toward reduction in hospital admissions (7.4% vs. 1.6%; $p = .12$).[10]

Implementing a Digital Patient Engagement Platform

The first and most important step in the implementation of DPE is choosing an appropriate platform. Various DPE platforms offer diverse technologies for follow-up, including automated phone calls, texts, or application alerts. Some applications are automatic in nature; others are not. Some use the voice of the physician and generate check-in notifications over prespecified intervals, and others focus on PROs or HRQoL surveys. DPE platforms can perform a mix of these features, and finding a suitable platform depends on the patient population, physician preference, and current workflows within a practice setting.

A second fundamental step in implementing a DPE platform is to adequately pilot the platform prior to expanding it sitewide. Selecting a patient population to pilot a DPE platform allows for testing the platform and advancing the platform as needed prior to sitewide enrollment. An example patient population is chronic myeloid leukemia (CML). Development of tyrosine kinase inhibitors for treatment of CML has substantially improved the 5-year overall survival rate for this patient population and made it a chronic disease.[23] Additionally, assessing HRQoL and side effects plays a considerable role in managing these patients. At our institution, clinical pharmacists play an integral role in the management of these anticancer agents and perform follow-up via telephone. With a growing number of patients, providing this service is becoming increasingly difficult because of time constraints and limited available resources. It is hypothesized that piloting a DPE platform for use with the CML population may lead to optimal patient care outcomes, cost avoidance as a result of preventing complications, and a decrease in phone call follow-ups made by clinical pharmacists and nursing staff.

On the basis of our institution's experience, other vital steps that can potentially lead to a successful implementation would include (1) creation of a supportive multidisciplinary team of physicians, nurses, and pharmacists, (2) comprehensive education of the staff regarding every step of a DPE platform implementation, (3) use of a specialized DPE team to provide comprehensive education for staff members, and (4) creation of an achievable timeline.

Conclusion and Future Directions

The evolution of patient engagement is inevitable, and its integration into the current health system will be necessary in order to provide optimal patient care and receive payment in future reimbursement models. Nevertheless, the incorporation of patient engagement into care delivery faces several challenges. Consistently, the time investment required by health teams is the biggest challenge. Implementing DPE is one potential way to overcome this

challenge. Choosing a DPE platform that best fits current workflows is important, and piloting the platform in certain chronic oncologic disease states may facilitate implementation in a large oncology facility. In the future, as pilot projects with DPE platforms are completed, comparisons between platforms may help to define the role of DPE platforms in current care models and assist in the evolution of patient engagement. ●●

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Advice from the Experts: Wrapping Up Residency

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We reached out to oncology pharmacists around the country to hear their advice for current postgraduate year-2 (PGY-2) hematology/oncology residents completing the last quarter of residency. We asked them to elaborate on things they wish they had done differently and resources they wish they had used and to offer any tips and tricks to prepare for beginning a career as a clinical oncology pharmacist.

Staying Connected and Up to Date

- Stay involved in organizations by becoming a member, volunteering on committees, and speaking at national conferences.
- Attend national meetings of relevant organizations: Hematology/Oncology Pharmacy Association, American Pharmacists Association, American Society for Blood and Marrow Transplantation, American Society of Clinical Oncology, American Society of Health-System Pharmacists, American Society of Hematology, Society for Immunotherapy of Cancer, Society of Gynecologic Oncology).
- Join local and state pharmacy organizations.
- Join listservs.
- Use social media (Twitter, Facebook, Instagram, hashtags at meetings).
- Subscribe to U.S. Food and Drug Administration (FDA) alerts.
- Subscribe to oncology journals and peruse the new publications each week. Try to read one article each day.
- Sign up for e-mails to receive the tables of contents of selected oncology journals.
- Precept students and residents to keep you on your toes. Use them as a resource for newly published articles (e.g., through a journal club) to teach you new things.
- Complete various continuing education activities to maintain board certification.
- Create and update disease-based pathways and order sets for your providers.
- Sign up to be a journal reviewer.

Secrets to Post-Residency Success

- Continue to grow and challenge yourself daily.
- Never stop learning! Keep that resident's mindset of always looking to gain knowledge.
- Don't take on too much your first year following residency. Focus on getting comfortable in your new role as an independent clinical pharmacist.
- Learn from your mistakes, and don't be afraid to admit when you are wrong. The best practitioners turn mistakes into learning opportunities.
- Find a mentor, and recognize that you may need to find a new mentor depending on your season of life or chosen career track. Most practitioners cannot maintain the same level of achievement that they did in the first 5 years of their career, so you may need to pick a new mentor to keep yourself challenged and progressing even if the pace or rigor is reduced.
- Choose a job you love, but don't be afraid to try a new facet of oncology pharmacy as opportunities arise.
- Surround yourself with good people.
- Stay connected with others in pharmacy.

Avoiding Post-Residency Burnout

- Take advantage of opportunities, but avoid taking on too many tasks at once, and learn how to say no when things do not align with your continuous professional development plan.
- Determine where your niche lies. When you have a feel for what really excites you, let commitments lapse that don't support the path to securing that niche.
- Breathe. Take your vacation time, and truly disconnect from work when possible.
- Protect your time. Plan hobbies or activities for yourself away from the hospital to encourage you to finish work on time.
- Always ask for help when necessary.

#NoRegrets—If You Could Do Anything Differently at the Start of Your Post-Residency Career, What Would It Be and Why?

- I wanted to be very involved and signed up as a resident advisor, research advisory committee member, and research committee member. I found this to be too much too soon and wish I had said no to one of those opportunities. That would have allowed me to focus just on being a pharmacist and establishing my practice.
- I would have traveled more before starting full-time work!
- I regret not being more involved from the get-go as a new practitioner in pharmacy organizations.
- I would have integrated myself into the team more quickly and shown team members how important pharmacy can be for their care team.
- Realize that oncology has many gray areas, and understand that your new institution may practice in different ways than you're used to.

continued on p. 26

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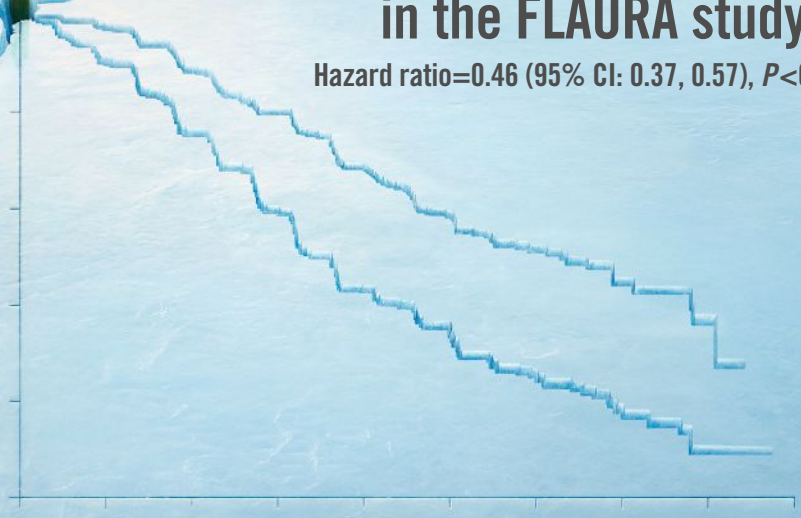
FIRST-LINE TAGRISSO® DELIVERED

AN UNPRECEDENTED 18.9 vs 10.2 months median PFS vs erlotinib/gefitinib in the FLAURA study

Hazard ratio=0.46 (95% CI: 0.37, 0.57), *P*<0.0001



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, once daily). 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 v.1.1). Secondary endpoints included OS, ORR, and DOR.[1,2]

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.

AstraZeneca

GROUNDBREAKING EFFICACY

DOSING

First-line TAGRISSO offers convenient, once-daily dosing, with or without food[1]

ALL SUBGROUPS

Delivered consistent PFS results across all subgroups, including patients with or without CNS metastases[2]

NCCN CATEGORY 1 RECOMMENDED

First-line osimertinib (TAGRISSO) is a National Comprehensive Cancer Network® (NCCN®) Category 1* option[3]

*Category 1 means NCCN has uniform consensus based upon high-level evidence.[3]

SELECT SAFETY INFORMATION

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
- 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: CNS, central nervous system; DOR, duration of response; EGFRm, epidermal growth factor receptor mutation-positive; NSCLC, non-small cell lung cancer; ORR, overall response rates; OS, Overall Survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria In Solid Tumors; TKI, tyrosine kinase inhibitor.

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Please see Brief Summary of Prescribing Information on adjacent pages.

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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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Maintenance Therapy in Ovarian Cancer: Emerging Data on PARP Inhibitors

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Using poly adenosine diphosphate–ribose polymerase (PARP) inhibitors in the treatment of ovarian cancer is not a new concept. The first PARP inhibitor to be used in this setting, olaparib, gained U.S. Food and Drug Administration (FDA) approval in 2014 for the treatment of patients with deleterious or suspected deleterious germline BRCA-mutated recurrent ovarian cancer. Since olaparib's initial approval, PARP inhibitors have become an area of developing research and an attractive option for many patients because it is an oral agent. Multiple PARP inhibitors are now indicated as treatment (olaparib, rucaparib) and as maintenance therapy for recurrent ovarian cancer (olaparib, rucaparib, and niraparib).[1] The role of PARP inhibitors in advanced ovarian cancer will continue to grow as new data emerge.

PARP inhibitors exhibit their clinical effect by arresting PARP proteins involved in several DNA repair processes, including single-strand repair.[2] This action is of particular value in treating BRCA-mutated ovarian cancer because these mutations prevent the repair of double-strand DNA breaks and create reliance on the single-strand repair pathway, which is disrupted by PARP inhibition. This can result in the targeted death of BRCA-mutated cancer cells. BRCA mutation occurs in between 6% and 35% of the population with ovarian cancer, depending on the histology.[3] Additionally, PARP inhibitors have been studied in BRCA wild-type patients. They still have a benefit over placebo in this setting, though the response is less pronounced than that found in BRCA-mutated ovarian cancer.[4-6] Therefore, PARP inhibitors are indicated as maintenance therapy regardless of BRCA-mutation status in platinum-sensitive recurrent ovarian cancer.

In light of these FDA approvals, a large subset of patients with ovarian cancer will qualify for and potentially receive therapy with a PARP inhibitor. Pharmacists are in a unique position to provide education to physicians, patients, and caregivers on appropriate monitoring and side effect management for these agents.

Niraparib

Niraparib's FDA approval in 2017 was based on results from a phase 3 trial, NOVA. This trial randomized 553 patients with platinum-sensitive relapsed ovarian cancer with or without a germline BRCA mutation who had received at least two prior lines of chemotherapy to receive either niraparib (300 mg by mouth [PO] daily) or placebo following platinum-based therapy. Of note, patients were required to start niraparib no later than 8 weeks after completing their last dose of platinum-based therapy. Patients treated with niraparib were demonstrated to have a significant improvement in progression-free survival (PFS), whether BRCA mutation–positive (median PFS 21 vs. 5.5 months; hazard ratio [HR] 0.27; 95% confidence interval [CI] 0.17–0.41; $p <$ .001) or negative (median PFS 9.3 vs. 3.9 months; HR 0.45; 95% CI 0.34–0.61; $p <$ .001).[5] Niraparib was the first PARP inhibitor to be FDA approved for maintenance therapy of recurrent ovarian cancer, and it was the first PARP inhibitor to be approved for use regardless of BRCA-mutation status.

Olaparib

SOLO-2, published in July 2017, was the first phase 3 study to evaluate olaparib as maintenance treatment for recurrent ovarian cancer. This trial randomized 295 platinum-sensitive relapsed ovarian cancer patients with a BRCA mutation who had received at least two prior lines of chemotherapy to receive olaparib (300 mg twice daily) or placebo. PFS was evaluated as the primary endpoint, and it was found that treatment with olaparib resulted in a significantly longer PFS (19.1 months) compared to placebo (5.5 months; HR 0.30; 95% CI 0.22–0.41; $p <$ .0001).[7] These results, along with prior phase 2 results finding benefit regardless of BRCA-mutation status, were the basis of olaparib's FDA approval as a maintenance treatment option for recurrent ovarian cancer regardless of BRCA-mutation status.[8]

In October 2018, a new phase 3 trial, SOLO-1, was published. This trial evaluated newly diagnosed patients with BRCA-mutated advanced ovarian cancer following a response to platinum-based chemotherapy. The trial randomized 391 patients to receive olaparib or placebo. The results showed that after a median of 40.7 months of follow-up, a median PFS was not reached in the olaparib group. Kaplan–Meier estimates of the rate of freedom from disease progression and death at 3 years was significantly higher in the olaparib group compared to placebo (60% vs. 27%; HR 0.30; 95% CI 0.23–0.41; $p <$ .001).[9]

SOLO-1 is one of the first trials to evaluate PARP inhibitor maintenance therapy in newly diagnosed ovarian cancer. Although the data have not yet been given time to mature, maintenance therapy with olaparib introduced earlier in the treatment pathway could reveal a promising new role for PARP inhibitor therapy and a potential replacement to alternative maintenance therapies such as bevacizumab. It also reinforces the importance of identifying a patient's BRCA-mutation status at diagnosis.

Rucaparib

Rucaparib was approved by the FDA for maintenance therapy in April 2018 on the basis of results from the ARIEL3 trial. This randomized double-blind trial enrolled 561 patients with platinum-sensitive recurrent ovarian cancer with or without a BRCA mutation who had been treated with at least two prior lines of therapy to receive either rucaparib (600 mg PO twice daily) or placebo. ARIEL3 demonstrated a statistically significant improvement in estimated PFS in patients receiving rucaparib compared

with placebo (median PFS 10.8 vs. 5.4 months; HR 0.36; 95% CI 0.30–0.45; $p < .0001$).[6] Rucaparib represents the newest option for maintenance therapy in advanced recurrent ovarian cancer.

Safety

PARP inhibitor therapy is administered as an oral tablet either once or twice daily, depending on the agent. Compared to alternative maintenance therapy options such as bevacizumab, an intravenous infusion given every 3 weeks, some patients prefer PARP inhibitor therapy because of convenience. However, using an oral dosage form has specific challenges. Prescribers must be judicious in their selection of an appropriate candidate, given that compliance cannot be monitored as readily as with clinician-administered intravenous therapies. Adverse effects like nausea and fatigue can also increase noncompliance and potentially affect the treatment efficacy of an oral agent. In addition, any recent history of small-bowel obstruction or extensive peritoneal disease creates a concern about malabsorption of oral therapy.

All three available PARP inhibitors have the potential to cause fatigue, myelosuppression, and gastrointestinal side effects. Comparative studies have found that all three PARP inhibitors have similar efficacy when used as maintenance therapy in BRCA-mutated ovarian cancer, but olaparib tends to be better tolerated and is associated with a lower incidence of dose interruption and discontinuation.[10] Olaparib is also a major substrate of CYP3A4 and the only PARP inhibitor with CYP-related drug interactions requiring dose adjustment. It is recommended that patients avoid taking olaparib in combination with moderate to strong CYP3A4 inducers (e.g., rifampin, carbamazepine, phenobarbital, and phenytoin). Olaparib's dose should be reduced to 150 mg twice daily or 100 mg twice daily for moderate to strong CYP3A4 inhibitors (e.g., amiodarone, diltiazem, ketoconazole, ritonavir, and clarithromycin), respectively.

It is imperative that all patients and providers be counseled on how to identify and manage such side effects. Typically, brief dose interruptions and supportive care medications allow the resumption of therapy. However, more severe or recurrent toxicities may require a dose reduction of the PARP inhibitor or its discontinuation.

Gastrointestinal Toxicity

Gastrointestinal (GI) side effects are fairly common, especially in the first few weeks of therapy. Nausea, vomiting, and diarrhea occur in around 70%, 35%, and 25% of patients, respectively. Taking the PARP inhibitor with food or immediately prior to bedtime may help ameliorate some of these side effects. Antiemetics should be prescribed with initiation of treatment and can be taken prophylactically 30–60 minutes prior to the dose. In patients with constipation, low-dose olanzapine has been used as an alternative to ondansetron.[11] However, olanzapine is associated with sedation and may not be an appropriate option for all patients. Some data also suggest that rucaparib can be initiated at a lower dose to improve GI tolerability and then increased to full dosing after 3–4 weeks.[12] If a dose of a PARP inhibitor is missed or vomited, an additional dose should not be taken.

For cases of diarrhea, patients should be counseled to maintain adequate fluid intake to avoid dehydration. Other causes for diarrhea, such as infection or progression of disease, should also be ruled out. In the absence of infection, antimotility agents such as loperamide can be considered in addition to dietary modifications.

Myelosuppression

Anemia, leukopenia, and thrombocytopenia are fairly common side effects. Between 20% and 40% of patients will develop myelosuppression, with the highest incidence occurring in those treated with niraparib, which has a dose-limiting toxicity of thrombocytopenia and more stringent monitoring parameters. Red blood cell or platelet transfusions may be appropriate in certain patients. In addition, underlying causes of anemia, such as iron, folic acid, and vitamin B12 deficiency, should be investigated. Erythropoiesis-stimulating agents are generally not recommended. Instead, treatment can be temporarily interrupted until count recovery. Complete blood cell counts (CBCs) should be checked monthly for rucaparib and olaparib, and weekly monitoring for the first 4–6 weeks is advised for niraparib. Some experts suggest starting niraparib at a reduced dose during the first 4–6 weeks of therapy in patients with baseline myelosuppression.[11] Subgroup analyses have also revealed that patients with a baseline platelet count lower than 150,000 or weight less than 77 kilograms may be at a higher risk of developing thrombocytopenia, and a lower starting dose is warranted in these populations.[5] Bleeding precautions and signs of severe bleeding should be reviewed with patients.

Fatigue

Fatigue is a common side effect that can occur in up to 60% of patients. This side effect warrants evaluation of other underlying causes such as anemia, depression, and sedation from concomitant medications as well as consultation with physical therapy or psychosocial intervention.

Serum Creatinine Elevation

Olaparib and rucaparib are associated with serum creatinine elevations due to an impact on the multidrug and toxin extrusion transporters.[11] A rise in creatinine typically occurs early in treatment, but other causes should still be ruled out, such as administration of concomitant nephrotoxins or hydronephrosis (a fairly common complication in ovarian cancer because of the location of the tumor burden). Dose reduction for renal impairment is required for both olaparib and rucaparib.

Elevations of Transaminase Levels

Elevations in transaminase levels are typically benign and are not associated with organ dysfunction. They more commonly occur with rucaparib treatment, especially in the first 4 months of therapy. Transaminase elevations are often transient and resolve over time. Patients receiving rucaparib should be counseled to avoid hepatotoxic drugs and alcohol.

Hypertension and Palpitations

Treatment with niraparib can result in hypertension (20% of patients) and palpitations (10% of patients).[11] Patients should be advised to obtain a blood pressure monitor and check their blood

pressure at home regularly. Heart rate and blood pressure should also be monitored monthly in the clinic. Caution is advised for patients with preexisting cardiovascular disorders, and they should be closely monitored.

Rash

All PARP inhibitors can cause rash in up to 20% of patients. Rashes induced by rucaparib may be photosensitive, and patients should be counseled to reduce sun exposure and wear sunblock lotion.

Rare but Serious Toxicities

Myelodysplastic syndrome or acute myeloid leukemia can occur in 0.5%–2% of patients treated with PARP inhibitors. The development of a secondary malignancy is postulated to occur as a result of inhibition in compensatory repair pathways, especially in patients with germline BRCA mutations, in addition to prior exposure to cytotoxic agents.[13] Patients with prolonged myelosuppression or a concern for development of a secondary malignancy should have PARP treatment discontinued and be referred promptly to a hematologist for further evaluation.

Pneumonitis has a less than 1% incidence, but it is an adverse event that pharmacists should watch for in patients who present with worsening dyspnea, cough, fever, or associated radiographic changes.

Future Directions

Multiple open studies have included PARP inhibitors. For example, the ongoing phase 3 trial PAOLA-1 is evaluating olaparib in combination with bevacizumab as maintenance treatment for patients with newly diagnosed advanced ovarian cancer, regardless of their BRCA-mutation status. A combination of olaparib and the vascular endothelial growth factor (VEGF) antagonist cediranib is being investigated as a treatment strategy for recurrent ovarian cancer. Trials with veliparib may also eventually establish PARP inhibitors as a front-line treatment option. As the indications for PARP inhibitor therapy expand, clinicians will be able to provide more effective treatment options to their patients, and PARP inhibitor therapy will continue to become more common. Pharmacists can ensure that the prescribing of PARP inhibitor therapy is accompanied by proper monitoring and education. ●●

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FEATURE

Complementary and Alternative Medicine Use Among Cancer Patients and the Role of the Oncology Pharmacist

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As the treatment of various malignancies advances, cancer patients are now living longer than ever before and potentially facing long-term side effects from the therapies used in their treatment. Patients are increasingly seeking new ways to either treat their malignancy with less risk of adverse effects or manage the side effects they are experiencing. One outlet many patients are turning to is complementary and alternative medicine (CAM).[1-5]

To gain a better understanding of the public's opinion on cancer and the care that cancer patients receive, the American Society of Clinical Oncology (ASCO) created an annual Cancer Opinion Survey. The most recent survey took place in July and August 2018, and the results were released in October 2018. Almost 5,000 U.S. adults 18 years of age and older responded to the survey, and of that cohort an astounding 39% reported the belief that cancer could be cured using alternative methods alone in place of standard treatments.[1] That percentage increases to 47% for the youngest cohort who responded to the survey, those 18–37 years of age.

In addition, 75% of survey respondents felt that complementary therapies were a good supplement to standard cancer treatment.[1] These findings highlight the importance of CAM in cancer treatment and the need for providers working in oncology to be knowledgeable about these therapies and willing to discuss them with their patients.

What Is CAM?

It is important to understand the difference between *complementary medicine* and *alternative medicine* because the terms are often mistakenly used interchangeably. According to the National Center for Complementary and Integrative Health (NCCIH), *complementary medicine* refers to "a non-mainstream practice used *together with* conventional medicine," and *alternative medicine* refers to "a non-mainstream practice used *in place of* conventional medicine."[6]

Why Are Cancer Patients Seeking CAM?

Many studies have been conducted to determine why cancer patients are increasingly interested in CAM therapies. When reviewing these studies, one notes a large lack of consistency in the definition of CAM, which somewhat limits the ability to draw generalizable conclusions. One systematic review including 52 such studies reported that the most common reasons cancer patients seek out CAM are a perceived beneficial response or strong belief in CAM, a desire for control over their treatment, and hope in it as a last-resort option.[7] In addition, studies have found that cancer patients and survivors with unmet needs are more likely to turn to CAM to help fulfill what they deem missing from conventional medicine.[8,9] Most often, patients felt that their malignancy was treated well; their unmet need related to their symptoms or to the side effects of treatment.[9] Across several studies, the most common characteristics of users of CAM were younger age, female, higher education level, and higher income.[9-11]

In recent years CAM has received increased media attention, and advertising for CAM products has become more prevalent with advances in instantly accessible technology and increases in social media outlets. Various studies have been conducted to elucidate the accuracy and level of evidence found on CAM websites, and the results are troubling. Misinformation, misleading claims, and a lack of references to peer-reviewed literature abound, which significantly biases cancer patients in favor of these products when no proven benefit exists.[12-14] Moreover, patients approach information about CAM in different ways. Some seek the opinion of their physician or pharmacist, while others find advertisements, testimonials, or personal experience to be more valid.[15] Studies also suggest that the stage of cancer could influence a patient's willingness to try CAM. Those with late-stage disease are often more likely to turn to CAM as a last resort and a way to maintain hope.[15] To complicate things further, these products are easily obtainable without the need for a prescription from a licensed medical provider, which increases the likelihood that patients will self-medicate with these therapies without consulting their medical care team.[9]

Pros and Cons of Using CAM in Cancer Therapy

Again, it's important to separate complementary medicine from alternative medicine. Several studies have documented the negative impact on survival when alternative therapies are used in place of conventional, proven cancer treatments.[16-21] A recent observational study compared outcomes of 281 cancer patients who chose alternative medicine, defined as "other-unproven: cancer treatments administered by non-medical personnel," to that of 560 matched patients who chose to receive conventional treatment. Overall, alternative medicine was associated with poorer 5-year overall survival compared to conventional treatment (54.7% vs. 78.3%; $p < .001$) across all included cancer types. Breast cancer patients had a fivefold increase in the incidence of death with alternative medicine; colorectal and lung cancer patients had a fourfold and twofold increase, respectively.[10]

Even if complementary rather than alternative medicine is used, these agents can still have associated adverse effects, including hepatotoxicity, nephrotoxicity, allergic reactions, and gastrointestinal disturbances.[22-25] Patients may view these therapies as safe because they are believed to be natural, but that is not always the case. As a result of the Dietary Supplement Health and Education Act of 1994 (DSHEA), complementary agents are not considered to be drugs or foods but rather supplements, meaning that the U.S. Food and Drug Administration (FDA) has no oversight concerning their true safety and efficacy.[26-29] Although manufacturers are

required to list the ingredients in their products, the FDA has no authority to test their products before they are brought to market for sale to patients.[29] Product quality therefore may be variable, and instances of contamination with microorganisms, heavy metals, and pesticides have been documented.[22] These contaminants could pose a threat to any consumer but may be especially dangerous to a cancer patient who is also receiving immunosuppressive therapies. DSHEA also prohibits manufacturers of alternative products from making disease-specific claims in reference to their products; however, some manufacturers do so anyway.[29,30]

A concern about drug interactions is legitimate when herbal supplements are used concomitantly with conventional cancer therapies. Robust studies identifying these interactions are largely lacking, although some agents have been better researched than others. Garlic, St. John's wort, echinacea, ginseng, valerian, and kava, for example, have relatively well-documented interactions with commonly prescribed anticancer agents.[31-33] More information exists on interactions between herbals and commonly prescribed medications like antihypertensives, which may also be relevant to cancer patients.[34-36] Drug interactions can occur at any step of the pharmacokinetic process, including absorption, distribution, metabolism, or excretion of an anticancer agent, but most interactions are known to occur as a result of altered metabolism related to cytochrome P450 enzymes.[33] Patients could potentially experience reduced effects of their therapy, negating the therapeutic benefit, or enhanced concentrations of anticancer drugs, resulting in severe toxicities.[9,33,37,38] In either case, the patient would be placed at an increased and unnecessary risk.

CAM is often viewed as consisting exclusively of herbal or natural supplements, but the term refers to much more. Mind-body approaches such as expressive arts, exercise, massage, acupuncture, lifestyle counseling, meditation, and many other activities fall into the realm of CAM as well, and many patients are interested in incorporating these approaches into their overall care. This is likely where the main benefit of CAM lies—as an adjunctive treatment to assist with the palliative or supportive care of cancer patients.[39] Several mind-body approaches have been shown to have beneficial effects on symptoms such as anxiety, insomnia, mood, pain, and gastrointestinal disturbances caused by cancer and its treatments.[40-53] These therapies should be explored with patients interested in incorporating CAM into their overall cancer care as a safe alternative to using potentially harmful herbal products.

How Can Clinical Pharmacists Educate Cancer Patients About CAM?

A key element of assisting in the safe use of CAM is being open to a conversation about these therapies with your patients. You should approach the subject in a nonjudgmental way and make patients feel as comfortable as possible opening up to you and being honest about what they are taking or are considering taking.[54,55] This is especially important because CAM therapies can potentially have harmful adverse effects or cause significant drug interactions, as discussed. An attempt should be made to determine the reason behind the patient's interest in CAM, what the patient's goals are for CAM therapy, whether the patient has had any prior experience or exposure to CAM either personally or via family and friends, and also how the information on CAM is being obtained.

Although many nonreputable websites provide information on CAM, patients can be directed to a handful of reliable online resources for more information (**Table 1**). The NCCIH provides many resources, including a page titled "Herbs at a Glance" with reliable information on selected herbals that patients may be interested in using.[56] In addition, Memorial Sloan Kettering Cancer Center has created a smartphone application called "About Herbs" that can be a helpful resource for both providers and patients. It lists several herbal products, as well as complementary therapies such as acupuncture or tai chi, and when a therapy is chosen, the user may select from "Professional" and "Consumer" versions of the material. Information provided includes a clinical summary, mechanism of action, purported uses, warnings for patients, adverse reactions, and drug interactions.[57]

Because nearly 40% of ASCO survey responders believe that alternative therapies alone can cure cancer, it is critical to share results of the clinical studies that clearly demonstrate that this belief is simply false. The lack of regulation, lack of known clinical data, and, in many cases, lack of clinical data on herbal supplements should be shared with patients in an objective way, and patients should generally be advised to avoid such products during their cancer treatment. Providers should strongly urge patients to undergo conventional treatments, using CAM in a strictly complementary way under the guidance of their oncology medical team.

Conclusion

CAM has existed as a treatment modality for centuries and remains of interest to both the medical community and patients.

Table 1. Selected Online Resources for Complementary and Alternative Medicine

Organization	Website
Memorial Sloan Kettering Cancer Center	www.mskcc.org/cancer-care/treatments/symptom-management/integrative-medicine/herbs
National Cancer Institute Office of Cancer Complementary and Alternative Medicine	https://cam.cancer.gov
National Institutes of Health National Center for Complementary and Integrative Health	www.nccih.nih.gov
National Institutes of Health Office of Dietary Supplements	www.ods.od.nih.gov
University of Texas MD Anderson Cancer Center's Integrative Medicine Center	www.mdanderson.org/integrativemedcenter

Belief in these therapies among cancer patients and their caregivers is on the rise, but evidence supporting their use is not necessarily keeping pace. On the basis of existing data, the use of herbal supplements during cancer treatment is likely ill advised, because the risk of harm is far more proven and documented than the potential benefits. Pharmacists can play a crucial role in broaching the subject of CAM and educating patients about the potential dangers of using these therapies in place of, or along with, conventional treatments.

The mind-body approaches that also fall under the umbrella of CAM likely provide a safer complementary therapy for patients who would like to explore other options for symptom management. In recent years, the more inclusive term *integrative oncology* has been replacing CAM. Unlike alternative therapy, integrative oncology strives to incorporate complementary therapies with a reasonable amount of high-quality scientific evidence on their safety and efficacy into conventional medical therapies.[31,55] The goal is to focus on all aspects of well-being, including physical, mental, emotional, functional, spiritual, social, and communal well-being, and to facilitate the coordination of care between providers to achieve this goal.[6] Most National Cancer Institute–designated comprehensive cancer centers have developed or are developing integrative oncology programs to assist with this initiative, and guidelines are being established to support providers who participate in these programs.[58-63] These centers should serve as resources for cancer patients seeking complementary therapies and represent the future of CAM in this patient population. ●●

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Overview of the Cancer Drug Parity Act

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Cancer treatment is changing at a rapid pace, but the design for insurance coverage of cancer treatment has not changed. Traditionally, intravenous (IV) and injected treatments were the primary methods for delivering chemotherapy. Newer, orally administered chemotherapy medications have become more prominent as treatment choices. Most health plans cover IV therapy through medical benefits and any oral or self-administered medications through retail pharmacy benefits. Although health plans offer affordable copayments for IV therapy, oral chemotherapies are covered at a percentage of the cost. This coverage means that some patients have extremely high costs for their oral medications. As a result, many patients may abandon therapy or choose another treatment that may not be the provider's first choice.

In an attempt to make these medications affordable to patients, efforts to enact insurance design reform are under way. Legislation that directs health plans to extend coverage for cancer treatments to orally administered anticancer medication at a cost no less favorable than the costs for IV or injected cancer medications has been passed in 47 states and the District of Columbia. However, state laws affect only state-regulated insurance plans, which leaves about 100 million people who have federally regulated insurance in need of parity for their cancer treatment. The Cancer Drug Parity Act of 2017 sought to amend the Public Health Services Act and require group and individual health plans that cover anticancer medications to cover oral medications at a no less favorable cost than the cost for coverage of IV or injected treatments. The bill was introduced to Congress in March 2017 but did not receive the support needed to move it through the legislative process in the 115th Congress.

To increase awareness of the Cancer Drug Parity Act and highlight its importance, this first installment of the "Patient Care Stories" column presents stories submitted anonymously by HOPA members featuring a significant moment in which their work had an impact on patient care.

Story 1

A patient with ovarian cancer was in a research study that required taking two oral investigational drugs daily. She was suffering from significant, persistent nausea and vomiting as a side effect of the investigational agents and was on the verge of withdrawing from the study because of these side effects. I met with the patient to discuss potential changes to her antinausea medication regimen, seeking medications that would not interact with her investigational drugs. After reviewing the research protocol and determining which antinausea medications did not interact with her investigational drugs, I met with the patient and developed a plan for adjusting her supportive care medications. The primary change was to switch the patient to a granisetron antinausea patch that she could wear continuously and that would require changing only once every 7 days. The patient found that the antinausea patch dramatically improved control of her nausea and vomiting, and as a result she chose to continue with the research study. The patch was very expensive, but I was also able to find a copay assistance program that brought the cost down to an affordable price.

Story 2

One issue we often deal with as pharmacists is patients' noncompliance with their medication regimens. As a stem cell transplant pharmacist, I monitor a variety of drug interactions and levels, specifically immunosuppression with tacrolimus and sirolimus. In our ambulatory treatment center, a transplant advanced practice registered nurse sees patients independently, and physician visits are held once a week. As part of the transplant team, I noticed that one patient had persistently fluctuating tacrolimus levels, varying from subtherapeutic to therapeutic to supratherapeutic. I suspected that the patient was taking tacrolimus, posaconazole, and other medications incorrectly. However, in patient interviews, the patient insisted that no medication doses had been missed, so we asked the patient to bring in the pillbox filled with the medications. Following weekly reviews and the pharmacist's regular filling of the pillbox, the patient was eventually able to demonstrate appropriate filling of the pillbox with more than 20 medications and was appropriately taking them all.

Generally, clinical pharmacists are heavily involved in patient care. Not only are we focused on therapeutic management (ensuring therapy appropriate to the disease and condition and appropriate medication dosing for renal and hepatic impairment), but we are also able to assess patients and evaluate follow-up. We are meticulous in our workups and have the ability to provide education to patients and caregivers. Although we have made great strides to expand clinical pharmacy practice, we still have a long way to go in advocating for the pharmacy profession.

Story 3

A patient with a germ cell tumor was scheduled to receive chemotherapy with etoposide, vinblastine, and ifosfamide. Unfortunately, his insurance company denied his admission for chemotherapy and approved only an outpatient regimen for him. The patient could not afford a hotel room for 5 nights, so he was going to drive back and forth 1–2 hours from home daily with his wife for outpatient therapy. Given the timing of the chemotherapy and supportive medications, the patient was going to have a chair time of about 11 hours per day. I identified that the main rate-limiting medication for the patient would be the IV mesna that was due at hour 8 after the ifosfamide was started, and I knew that using oral mesna instead would reduce the patient's chair time by 2 hours. The oral mesna was covered under his insurance for a $0 copay, so I updated the treatment plan to reflect administration of the "patient's own supply" of oral mesna instead of IV mesna. The patient was able

to pick up the prescription for oral mesna and tolerated it without any nausea or vomiting beyond that associated with the underlying chemotherapy regimen. This switch saved time for him and his wife each day as they drove back and forth to the infusion center.

Story 4

I was processing a refill request for ibrutinib, and while performing an evaluation of the request, I noticed an important drug interaction with the patient's concomitant medications that could have resulted in increased levels of the ibrutinib. The drug interaction occurred because the patient had been admitted to the hospital for atrial fibrillation. When the patient was prescribed the interacting medication, the problem was not caught by any of the healthcare providers, probably because her oral chemotherapy was withheld during her admission. After identifying the interaction, I communicated the concern to all parties (physicians and coworkers) while working to formulate potential recommendations for alternatives to effectively manage both of the patient's diagnoses. I consulted with the oncologist to create an action plan until an overall plan could be discussed with a cardiologist. Because the patient was having effective disease control with only a minor, nonserious adverse drug reaction, we determined that the patient should not take the ibrutinib for several days until the overall plan could be formulated. I contacted the patient to explain the situation and make the recommendations and then confirmed a follow-up appointment with the oncologist. After discussion between the cardiologist and oncologist, the interacting medication was changed to an alternative, noninteracting medication, and the patient was able to remain on the effective dose of ibrutinib.

Conclusion

As anticancer regimens become more complex, the role of the clinical pharmacist in managing the side effects of oral chemotherapy, modifying supportive care regimens, performing patient counseling, and facilitating medication procurement will become more crucial. We encourage you to add your voice to support for the Cancer Drug Parity Act by writing to your congressional representative and urging him or her to support this important bill. ●●

Advice from the Experts: Wrapping Up Residency *(continued from p. 12)*

Checklists and Planning Goals

- Make a checklist of outstanding projects for the completion of your residency. Put everything on your list, and check them off as you go.
- Don't let missed or rushed deadlines prevent you from taking advantage of your final quarter of learning opportunities.
- Make a list of all the things you want exposure to and experience with before the end of residency. Now is the time to get the experiences you may not have in your new role.
- Become as independent as possible. After you know your job setting and patient population, try rotating in that area, and ask your preceptor to give you autonomy so you know what it will feel like when you start your new job.
- Create a list of career goals for your first 6 months as an initial continuous professional-development plan, and hold yourself accountable.
- Complete your project and submit your manuscript before you are done with your PGY-2 residency.
- You are in the final stretch. All of the work and time you have spent on your education and training is almost finished. Just keep going!

Additional Resources

- Networking
- Chemocare.com for patient education materials
- DailyMed for package inserts
- HOPA alerts for FDA approvals
- Hemonc.org for summarized chemotherapy regimens
- https://drug-interactions.medicine.iu.edu/Home.aspx for drug interactions
- https://www.crediblemeds.org/healthcare-providers/ for drug interactions and QTc-prolonging risk of medications
- Information from pharmaceutical manufacturers (e.g., PowerPoint slides, stability information, unique patients in clinical trials)
- NCCN templates, compendiums, and other resources

A final piece of advice comes from an anonymous source: "Opportunity will knock at random times, so be sure to keep an open ear and not be so hardheaded as to pass it up."

Thanks to all who took the time to send in responses to our survey. We appreciate your participation and enthusiasm for helping guide future oncology pharmacists all over the country! ●●

Pharmacist-Led Oral Chemotherapy Management Program: Improved Adherence Rates and Clinical Outcomes

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Oral anticancer therapies are becoming a main treatment option for many types of cancer. Most of these medications are distributed through a few specialty pharmacies, and most specialty pharmacies remain entities separate from ambulatory care clinics. This stand-alone practice model can lead to operational challenges because of segregated communication channels with patient care teams. To integrate specialty pharmacy into patient care, the University of North Carolina Medical Center (UNCMC) started its own specialty pharmacy. The internal specialty pharmacy filled and dispensed specialty prescriptions, in addition to providing medication assistance. Muluneh and colleagues developed and implemented a closed-loop pharmacist-led oral chemotherapy management program through the specialty pharmacy to manage patients who were prescribed oral chemotherapy by UNCMC oncologists.[1] They recently published their experiences and results of the program in the *Journal of Oncology Practice*.

The oral chemotherapy management program services included patient counseling on oral anticancer therapy, adherence monitoring, and medication management. With this combination of specialty pharmacy and clinical pharmacy services, UNCMC was able to provide a full spectrum of pharmacy services, including dispensing, counseling, refilling, clinical monitoring, and management of patients on oral chemotherapy. The pharmacists who participated in this oral chemotherapy management were credentialed as clinical pharmacist practitioners (CPPs) by the North Carolina Board of Medicine and Pharmacy. This credential allowed licensed pharmacists to provide drug therapy management under a collaborative practice agreement with a licensed physician in the state of North Carolina.

The program was first implemented in the hematology, breast, and gastrointestinal (GI) oncology clinics at UNCMC. The study measured several endpoints, including the impact of a specialty pharmacy and pharmacist-led program on patient knowledge, drug adherence, service satisfaction, and clinical outcomes. Patient knowledge of oral chemotherapy was measured with a 5-question test before and after pharmacist-led counseling. The adherence rates were calculated on the basis of medication possession rate (MPR), a validated scale, with goals of greater than 90% adherence for the hematology clinic and greater than 80% for the breast and GI clinics. Patient and physician satisfaction ratings of the specialty pharmacy and clinical pharmacy services were assessed using a 5-point Likert scale. Last, the study compared molecular response rates of patients with chronic myeloid leukemia (CML) who were treated with oral chemotherapy before and after the implementation of this program.

Research data were collected from September 2014 to June 2015. A total of 107 patients (70 hematology and 37 breast or GI patients) enrolled in the program. The internal specialty pharmacy captured 263 new prescriptions, 257 refills, and 413 clinical interactions (refill follow-up and adherence monitoring). The CPPs counseled 100% of the patients enrolled. The average pretest score was 43% versus 95% for posttest score (p =.0058). In the first 90 days of therapy, each patient had an average of 3.5 encounters with a CPP, including the initial counseling encounter. The CPPs documented 350 follow-up encounters in clinic or by telephone, 318 adverse drug reactions, and 238 total interventions. The most common interventions were management of adverse effects (57%) and dose modification recommendations (16%).

The average self-reported adherence rates for hematology patients and breast/GI patients were 94.7% and 86%, respectively. The MPRs verified for hematology and breast/GI patients were 93.9% and 85%, respectively. According to the patient survey results, 97.8% of the patients reported that the teaching provided at the beginning of therapy was "good" or "excellent." Most patients (97.5%) agreed or strongly agreed that they will continue to use the internal specialty pharmacy in the future. The physician survey had a 45% response rate, and results showed that the physicians valued the education provided by the CPPs and felt that they were knowledgeable. With the CML patients, more patients achieved an early molecular response (EMR) or major molecular response (MMR) at 12 months than the historic preintervention cohort of patients (EMR, 88.9% vs. 54.8%; p = .0138; MMR, 83.3% vs. 57.6%; p = .0575, respectively), indicating a statistically significant improvement in clinical outcome.

A closed-loop pharmacist-led oral chemotherapy management program greatly improved patients' understanding of oral chemotherapy, maintained best-practice adherence rates, and received high satisfaction scores from both patients and physicians. In addition, this study showed a significant improvement in CML patient outcomes for patients enrolled in this program when compared to UNCMC's own historical data. This pharmacist-led model disrupted the traditional stand-alone specialty practice and demonstrated that integration and collaboration within cancer treatment teams led to outstanding results and patient experiences. ●●

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Evolving Role of Immune Checkpoint Inhibitors in Lung Cancer: Combination with Chemotherapy in the First-Line Setting

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Immune checkpoint inhibitors (ICIs) that target the programmed-death ligand 1 (PD-L1)–programmed cell death-1 (PD-1) interaction have transformed the management of many cancers. The initial role of ICIs in the management of lung cancer was in the subsequent-line setting of advanced or metastatic non-small-cell lung cancer (NSCLC) following first-line chemotherapy. Nivolumab, a PD-1 inhibitor, and atezolizumab, a PD-L1 inhibitor, received approval in this patient population regardless of PD-L1 expression on tumor tissue, whereas pembrolizumab, also a PD-1 inhibitor, was approved for patients with PD-L1 expression of 1% or greater.[1-3] Though all three agents demonstrated improved overall survival (OS) when compared to docetaxel in advanced or metastatic disease as second-line therapy, clinicians and investigators aimed to determine whether moving these agents to the front-line setting in combination with platinum-based chemotherapy would be more beneficial. Several trials published in 2018 may answer this question.

Pembrolizumab Plus Chemotherapy in NSCLC

Two large randomized phase 3 trials assessing the role of pembrolizumab in combination with first-line chemotherapy in NSCLC were published in 2018. The first, KEYNOTE-189, included OS analysis of pembrolizumab plus investigators' choice of platinum agent (cisplatin or carboplatin) plus pemetrexed for nonsquamous NSCLC.[4] When the progression-free survival (PFS) data were made available in 2017, some clinicians hesitated to change practice for all patients because of a concern that the significant PFS benefit seen with triple therapy would not correlate with OS and that a change in practice would remove ICI therapy as a viable second-line option.[5] However, the full OS analysis confirms the role of chemoimmunotherapy in the first-line setting. A significant OS benefit was seen in the overall population at 12 months (69.2% vs. 49.4%, hazard ratio [HR] 0.49; 95% confidence interval [CI] 0.38 to 0.64; $p < .001$).[4] This benefit was statistically significant across all subgroups regardless of PD-L1 status or choice of platinum.[4] On the basis of these results, this regimen has been approved by the U.S. Food and Drug Administration (FDA), and the National Comprehensive Cancer Network (NCCN) guidelines for NSCLC list pembrolizumab in combination with pemetrexed and a platinum as a Category-1 preferred regimen for initial systemic therapy in metastatic or advanced nonsquamous NSCLC.[6,7]

Given that KEYNOTE-189 included treatment with pemetrexed, it was limited to patients with nonsquamous histology. KEYNOTE-407, published in September 2018, evaluated pembrolizumab with carboplatin and either paclitaxel or nab-paclitaxel for patients with advanced or metastatic squamous NSCLC.[8] Again, a significant OS benefit was seen in the overall study population: 15.9 months with pembrolizumab plus chemotherapy versus 11.3 months with chemotherapy alone (HR 0.64; 95% CI 0.49 to 0.85; $p < .001$).[8] All hazard ratios in the subgroup analysis favored triple therapy; however, this was not a statistically significant finding in patients 65 years of age or older (HR 0.74, 95% CI 0.51 to 1.07) and those with a PD-L1 expression of 50% or greater (HR 0.64, 95% CI 0.37 to 1.10).[8] When PD-L1 was stratified by expression of less than 1% and 1% or greater, both groups were shown to benefit from chemotherapy plus pembrolizumab. These results were statistically significant.[8] It is worth noting that patients with 50% or greater expression of PD-L1 can receive pembrolizumab alone as first-line therapy and may not receive additional benefit from the combination with chemotherapy.[6] This study was also not powered to detect a difference in OS or PFS for subgroups. Specifically, outcomes stratified on the basis of PD-L1 expression were prespecified exploratory endpoints.[8]

Similar to the results of KEYNOTE-189, these results led to the designation of pembrolizumab plus carboplatin and paclitaxel or nab-paclitaxel as NCCN Category-1 preferred regimens for initial systemic therapy for squamous NSCLC.[6] These are also FDA-approved combinations.[7]

Atezolizumab Plus Chemotherapy and Bevacizumab in NSCLC

The IMpower150 trial, published in June 2018, evaluated the role of atezolizumab for first-line treatment of metastatic nonsquamous NSCLC.[9] This trial had three arms: atezolizumab plus carboplatin and paclitaxel (ACP), bevacizumab plus carboplatin and paclitaxel (BCP), or atezolizumab plus BCP (ABCP).[9] The first analysis available compared ABCP to BCP. This trial examined a new potential biomarker for response to ICI therapy, effector T-cell (Teff) gene signature.[9] Teff gene signature includes expression of PD-L1, CXCL9, and IFN-γ messenger RNA.[9] Previous studies indicated that high Teff-gene-signature expression was a better predictor of response to atezolizumab than PD-L1 expression.[2] Another notable difference with this protocol is that it allowed patients with epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) mutations to be enrolled if they had failed therapy with at least one tyrosine kinase inhibitor (TKI).[9] PFS and OS were assessed in the wild-type (WT) population (those without EGFR or ALK mutations), as well as those patients in the WT group with high Teff gene signature.[9] Median PFS was longer with ABCP when compared to BCP in the WT group (8.3 months vs. 6.8 months; HR 0.62; 95% CI 0.52 to 0.74; $p < .001$).[9] This corresponded to an OS benefit in the same population: 19.2 months versus 14.7 months (HR, 0.78; 95% CI 0.64 to 0.96; $p = .02$).[9] In patients with high Teff-gene-signature expression, PFS was 11.3 months versus 6.8 months (HR, 0.51; 95% CI 0.38 to 0.68; $p < .001$).[9]

Though these results demonstrate the superiority of ABCP over BCP, they do not reveal whether ACP is superior to either ABCP or BCP. The design of IMpower150 did not allow for a direct comparison of ABCP to ACP to assess the benefit of bevacizumab in this regimen.[9,10] When viewed in the context of other trials showing the benefit of chemoimmunotherapy, providers may be more likely to select a three-drug rather than four-drug regimen to avoid additional adverse events and unnecessary healthcare costs. The four-drug regimen has been added as a Category-1 recommendation in NCCN guidelines for advanced or metastatic nonsquamous NSCLC and was recently approved by the FDA.[6,11]

Atezolizumab Plus Chemotherapy in Small-Cell Lung Cancer (SCLC)

Perhaps most encouraging of the chemoimmunotherapy trials was the IMpower133 study. This trial marks the first improvement in OS for patients with extensive-stage SCLC in decades. When compared to carboplatin and etoposide, the addition of atezolizumab lengthened OS, with a median OS of 12.3 months in the atezolizumab plus chemotherapy group versus 10.3 months in the chemotherapy group (HR 0.70; 95% CI 0.54 to 0.91, p = .007).[12] In a patient population with such poor prognosis, a 2-month benefit could be meaningful to patients. However, the value of adding a third drug with potential for immune-mediated side effects for a 2-month survival benefit needs to be discussed openly with providers and patients.

Conclusions and Future Directions

Several trials published in 2018 confirm the role of immunotherapy combined with chemotherapy as first-line treatment for lung cancer. However, several questions have yet to be answered:

- Would some patients benefit more from sequential administration of chemotherapy followed by immunotherapy than from chemotherapy and immunotherapy administered concurrently?
- Is PD-L1 expression the best biomarker to predict response to ICIs, or should we incorporate other markers such as Teff or tumor mutational burden as studied in CheckMate 227[13] in the workup for NSCLC?
- What financial burden will patients, institutions, and the healthcare system overall experience with increasing ICI-combination treatments in the first-line setting?
- What is the optimal second-line treatment for NSCLC following ICI therapy?

As these and other questions are answered, the landscape of NSCLC and SCLC treatment will continue to evolve. ●●

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Board Update

For Everything a Season

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The holidays have come and gone, and winter has set in. I hope that you were able to break away from your busy work life and enjoy some much needed time with those who matter most to you. We all need recharging now and then. As January brings shorter days, less sunshine, and seemingly endless tasks on the to-do-list, you continue to push HOPA forward along a trajectory that has limitless possibilities.

I wanted to take a moment to showcase the amazing HOPA Journal Clubs and the fantastic work our residents have done with these. The Journal Clubs are great educational offerings from residents, and they are free of charge to HOPA members and nonmembers. They give our residents wonderful opportunities to hone their presentation skills and delve deeply into current literature. Our education team has done so well that the schedule for HOPA Journal Clubs is filled through the middle of 2020. If you want to schedule opportunities for your future residents, contact the HOPA education staff at educationsupport@hoparx.org and plan ahead.

HOPA's Board Certified Oncology Pharmacist (BCOP) Recertification Program celebrates its fourth year in 2019. The program currently offers 38 hours of continuing education that meets a range of needs. The program has these components:

- Webinars (5 hours)—covering key abstracts and emerging issues from national hematology/oncology meetings
- Annual Conference Programming (8 hours)—live interactive (and on-demand) presentations showcased at the HOPA Annual Conference
- Self-Study Modules (15 hours)—online reviews of articles in the past year's primary literature covering a range of oncology topics
- BCOP Oncology Pharmacy Updates Course (10 hours)—covering the last 3 years of therapeutic information for oncology pharmacists.

You can purchase individual webinars, multiple sets of programming, or the entire 2019 BCOP Program Bundle. I would like to thank every single member of the BCOP team: members of the BCOP Oversight Committee, BCOP Conference Programming Subcommittee, BCOP Field Testing Subcommittee, BCOP Item Writing Subcommittee, BCOP Self-Study and Webinar Courses Committee, and BCOP Updates Course Subcommittee. If it were not for their hard work and dedication, this anchor of our educational opportunities would not exist for our members and the BCOP-credentialed pharmacists who use this program.

In 2019 HOPA will launch its Mentorship Pilot Program, as announced by the Leadership Development Subcommittee at HOPA's 2018 Practice Management program. The program will focus on professional competencies and leadership skills for practicing oncology pharmacists. The Leadership Development Subcommittee has created a stellar program that will be expanded over the next few years after evaluation of the pilot program. The creative and inventive team that worked on this project was made up of HOPA Past President Phil Johnson (chair), Rebecca Fahrenbruch (vice chair), Matthew Chui, Sandra Cuellar, Raj Duggal, Dave Henry, HOPA Past President Cindy O'Bryant, Alexandra Shillingburg, J. Andrew Orr-Skirvin, and Steve Stricker. This is just one of the great initiatives focusing on leadership development for our members.

As we re-enter our regular routines, we often find ourselves stretched very thin. Our lives are full, as we seek to meet commitments to our families and friends, our workplaces, and the organizations we volunteer for. As pharmacists, we may fill our plate with so many tasks, responsibilities, appointments, and activities that we have to burn the candle at both ends. We may be able to maintain this course for a while, but let's make one New Year's resolution: to take time for ourselves, for the hobbies and activities that refresh and reenergize us. Go to the gym or start taking a kickboxing class. Put on your running shoes and go for a walk or run outside (or use a treadmill if it's bitter cold and snowy outside). Get on a Pilates reformer or work up a sweat in a yoga class. Try meditation. Grab your loved ones or your pets and venture to a park. Go to the movies, read a book, go dancing. Turn off your phone, disengage from the computer and e-mail, and make time for the things you really love. Figure out ways to keep recharging yourself and breaking from the cycle of draining your batteries constantly and limiting your enjoyment. You need breaks and time to recharge, and you deserve it.

Have a wonderful winter! I look forward to seeing you all in Fort Worth, TX, April 3–6, at HOPA's 15th Annual Conference.

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