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Up in Flames: Burnout in Oncology Pharmacy

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FEATURE

Up in Flames: Burnout in Oncology Pharmacy

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Burnout has gained significant attention in recent years, but it is not a new concept. In fact, this phenomenon was originally described by American psychologist, Dr. Herbert J. Freudenberger, in 1974 after he experienced the feeling while working in a free clinic.[1] He identified "the dedicated and the committed" as those most at risk for developing burnout. Dr. Freudenberger suggested that burnout in these individuals is secondary to an internal need to give their time and efforts beyond exhaustion, external pressures from leadership to push forward, combined with boredom of a routine job.[1]

More than four decades later, we have learned the physical and behavioral signs of burnout, developed methods to measure its severity, and identified significant consequences associated with burnout. However, burnout remains highly prevalent. The development of meaningful interventions is imperative to alleviate the negative effects of burnout on individual professionals; institutional performance; and most importantly, quality patient care.

Defining Burnout

The World Health Organization identifies burnout as a "syndrome conceptualized as resulting from chronic workplace stress that has not been successfully managed".[2] It is characterized by feelings of energy depletion or exhaustion, increased mental distance from one's job, feelings of cynicism related to one's job and reduced professional efficacy. The "gold standard" for measuring the extent of burnout is the Maslach Burnout Inventory (MBI).[3] This validated, 22-item questionnaire allows respondents to score each statement on a Likert scale (0 to 6, Never to Every Day) to assess burnout on three scales including emotional exhaustion, depersonalization, and personal accomplishment.

Higher scores on the emotional exhaustion and depersonalization scales represent higher levels of burnout, whereas lower scores on the personal accomplishment scale represent higher burnout. Additionally, the Well-Being Index (WBI) was designed to measure multiple dimensions of distress, including anxiety, stress, depression, and fatigue, and assess the risk of burnout.[4] This nine-item questionnaire is advantageous given its shorter length and it has been validated across many professions, including pharmacists.[5]

Consequences of Burnout

The consequences of burnout in hematology/oncology pharmacy should not be taken lightly. Hematology/oncology pharmacists help to manage critically ill patients receiving highly toxic chemotherapy with a high burden of adverse effects. The longitudinal relationships with patients, coupled with the terminal nature of many disease states may be emotionally challenging. Additionally, the pressure of maintaining competency in a field with the highest rate of new drug approvals among specialties and a proliferative body of literature may confer additional stress.[6,7]

The emotional exhaustion felt by someone suffering from burnout can lead to feelings of workplace apathy. This disinterest may progress to negative feelings about their job, detachment from their responsibilities, decreased efficacy in their position, and may even affect coworkers. At its worst, burnout can result in an individual leaving their position. In hematology/oncology pharmacy, the loss of a highly trained and expert pharmacist can be financially detrimental to an organization as the cost of recruiting, hiring, and training a new pharmacist can be significant.

Healthcare professionals spend a large portion of their lives caring for others, but those with burnout are at increased risk of developing their own mental and physical health conditions. Studies have correlated high levels of burnout with depression, anxiety, insomnia, and use of psychotropic and antidepressant medications.[8] Additionally, those suffering from burnout may be at higher risk for hypercholesterolemia, coronary heart disease, headaches, and gastrointestinal disorders.[9] While it is important to continue caring for patients, it is crucial for healthcare professionals to take care of themselves.

Healthcare professional burnout affects not only the individual and their institution, but also the patients.[10] A recent study of 2,231 pharmacists found nearly a quarter of pharmacists reported concern for having made a major medication error within the past three months.[5] Pharmacists who were concerned about making an error reported higher scores on the WBI, which is associated with an increased risk of burnout. Other studies in pharmacists have demonstrated that increased workload, external job demands and work stress negatively impact medication safety and self-reported medication errors.[11,12]

Seventy percent of studies included in a systematic review of burnout literature demonstrated a significant association with medical errors and potential errors.[13] Similarly, a meta-analysis highlighted physicians with burnout were twice as likely to be involved in a patient safety incident.[10] Even small errors in hematology/oncology pharmacy, such as a miscalculation of body surface area, or missing a decimal point, could result in significant morbidity or even mortality for patients.

Burnout Among HOPA Membership

Given the uptick in discussion around burnout, potential for serious consequences associated with burnout in hematology/oncology pharmacy, and lack of current literature regarding burnout in this population, our team decided to assess burnout among hematology/oncology pharmacists. As the largest organization of hematology/oncology pharmacists, HOPA was chosen as the study population. We developed a survey comprised of the MBI, WBI, and several items assessing sociodemographic and occupational factors to assess the prevalence and risk factors associated with

burnout. This survey was validated by the Mayo Clinic Survey Research Center and sent out to HOPA members in October 2020.

Of the 3,024 pharmacist members of HOPA contacted via email, 550 (18.2%) surveys were able to be scored for burnout and were included in our analysis. Pharmacists who responded worked in a wide variety of settings, including ambulatory clinics (55.2%), hospital/inpatient (47.9%), infusion clinics (41.5%), academic medical center (38.0%), specialty pharmacy (5.9%), administration (5.7%), and academia (5.1%). Respondents had worked on average 12 years as a licensed pharmacist, 8.3 years as a hematology/oncology pharmacist, and five years in their current role.

High Levels of Burnout Among our Colleagues

Overall, our study found that 61.8% of pharmacists were experiencing high levels of burnout based on their emotional exhaustion (≥27) and depersonalization (≥10) scores of the MBI. This rate was consistent with previous studies assessing burnout in pharmacists. It is clear from this data that a majority of our colleagues are struggling with significant symptoms from burnout and mitigating actions are required.

As part of the study, we wanted to assess potential consequences associated with burnout in hematology/oncology pharmacists. One of the most jarring findings was that pharmacists with high burnout were more likely than their counterparts without high burnout to report concern for having made a major medication error in the past three months (27.6% vs 8.1%, $P < 0.001$). Again, it is important to underline the significance of this statistic as even minor errors when working with chemotherapy and other high-risk medications can result in significant, if not fatal, consequences for our already at-risk patients.

Those with Burnout Likely to Leave their Positions

Another potential consequence of burnout we noted was the likelihood of an individual leaving their current position. Of the pharmacists with high burnout based on the MBI, 26.8% responded they were likely or definitely leaving their current position within the next two years for reasons other than retirement compared with 8.1% of pharmacists without high burnout ($P < 0.001$). This correlates with approximately 90 hematology/oncology pharmacists leaving their current position in our cohort of 550 pharmacists. When taking into consideration the incredible amount of expertise and training that could be lost, efforts to minimize the risk of burnout would be valuable to organizations seeking to minimize overhead costs for replacing such a highly trained individual including recruitment and onboarding.

In our multivariable analysis, we identified several factors associated with an increased risk of high burnout. These factors could be used to develop targeted interventions to help mitigate the risk of burnout. First, we found that individuals who were unaware of any wellness programs were over two times as likely to have high burnout. Of those with high burnout, 62.7% felt they would benefit from a wellness program but 30.5% were unaware of any programs available to them. Additionally, pharmacists working more hours overall (per four hours worked, OR 1.22; 95% CI 1.10-1.35) and more administrative hours (≥4 hours versus <4 hours, OR 2.40; 95% CI 1.52-3.78) were at an increased risk of high burnout. We also found that those with decreased wellness secondary to the COVID-19 pandemic were at higher risk for high burnout (OR 1.89; 95% CI 1.24-2.89).

Where Do We Go From Here?

In February 2021, the American Society of Clinical Oncology (ASCO) published a five-year roadmap to address oncology provider burnout.[14] ASCO's framework is threefold: (1) to engage in well-being initiatives across the organization, (2) develop and improve upon well-being resources, and (3) promote research on well-being amongst clinicians. This comprehensive initiative further emphasizes that burnout is a significant problem in oncology. While this plan is intended for our physician and advanced practice provider colleagues, these concepts can be utilized in hematology/oncology pharmacy to develop a framework to tackle this important issue.

Our study identified that pharmacists who were unaware of wellness programs were at an increased risk of burnout. A logical first step would be to ensure institutional wellness programs are open to pharmacists, advertise availability, and educate on resource options. This would ensure equitable access for all provider levels within an institution and may also be emphasized through a national platform such as HOPA with newsletters, email communication, or postings throughout the workplace so the information is readily accessible to those who need it. Hopefully by increasing awareness and access to programs that already exist, more individuals would utilize these resources and the risk and severity of burnout would decrease.

After providing increased awareness, it is important to collect information about the root cause of the problem. A starting point for administrators and organizations would be to identify pharmacists working more hours and those with more administrative responsibilities since we found those were associated with increased risk of burnout. By identifying these pharmacists, we can have open conversations about what they are experiencing, interventions that may be beneficial, and additional resources that are needed to alleviate workplace stress.[15] Hopefully, by starting with those experiencing the most burnout—resources and programs that are initiated would trickle down to those who are experiencing less severe burnout as well.

While these suggestions may serve as a starting point, there is still much to be done to help reduce the incidence and severity of burnout with interventions that are targeted to the needs of hematology/oncology pharmacists. Once interventions are put into place, it will be important to collect follow-up data and determine what types are the most beneficial so efforts can be focused in these areas. In the meantime, it is critical to maintain open dialogue with colleagues, friends, and mentors because simply knowing there is support can alleviate some symptoms of burnout. ●●

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Together as One Voice: Reflection of my Time on HOPA's Board of Directors

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Having recently rolled off as Secretary for the HOPA Board of Directors, I was asked to reflect on the time spent serving our professional organization. I can honestly say it was rewarding, extremely challenging at times, eye opening and fun! Everyone who serves our organization, whether as a Board member, committee leader, or as a volunteer, does so because they are passionate about oncology pharmacy. They are passionate about the role of oncology pharmacists on the care team and the value we bring. And, they are passionate about trying to make sure all cancer patients have access to an oncology pharmacist.

I hope everyone who is interested in volunteering for our organization gets to do so at some at some point. Our organization has grown by leaps and bounds, and we have so many talented individuals. With growth, though, do come challenges, and as a Board, sometimes you have to make hard decisions; sometimes you disagree with each other and sometimes members don't like the decisions you make. But, you learn how to disagree, you learn that there is more than one way to accomplish a goal, and you learn the importance of standing together as one voice.

I have been in oncology pharmacy practice now for almost 23 years and have always prioritized being involved in the many pharmacy organizations that help to train and support our profession. Of course, since its inception, HOPA has been the pharmacy organization where I have chosen to devote my volunteer time. I remember speaking at some of the early conferences; as a new grad, I saw my mentors and teachers out in the audience and felt both scared (I did not want to disappoint), but also proud because they were the ones who helped guide me. I wondered: How could I get involved? And, would I ever be able to do some of the amazing things I saw them doing?

HOPA has given me, and it offers you, all these opportunities. Take advantage of them. Volunteer for small things, committees, anything you can do to be a part of this great organization. Even after all these years, I think part of me feels the same way I did when I was first starting out, still wanting my mentors to be proud of what I had done. But I also wanted to set an example for others to do the same and to encourage younger practitioners to get involved.

When I considered serving on the Board, I thought about many of these same mentors, many whom had served in various volunteer roles within HOPA. I thought of my mother who was always a huge volunteer when I was a child, and I thought of the many other folks who have given of their time. All of these folks set such great examples of volunteerism, and I can only hope that I and every other prior Board member has demonstrated the importance of giving back.

"I thought of my mother who was always a huge volunteer when I was a child, and I thought of the many other folks who have given of their time. All of these folks set such great examples of volunteerism."

I learned a lot about our organization and the people who serve during my time on the Board. It was an honor and privilege to work with the other Board members and many volunteers who give of their time and expertise to move us forward in achieving our mission and vision. We accomplished many things on our strategic plan during my tenure. We transitioned executive directors; transitioned to a new management company; reorganized our committee structure; started the Oral Oncology Collaborative; initiated work in diversity, equity, and inclusion; dealt with the challenges of COVID-19; and I am sure I am forgetting something. But we did it with a great team and I am forever grateful to have been a part of all of it.

I worked with people I knew well, people I only sort of knew and people who I had never met. As in many opportunities in life, it really is the people who made it and the same goes for my time on the Board. The relationships we forged through the good and the bad will stick with us for the long haul, and I am forever grateful for their friendships. It is one of the things I think I miss the most. ●●

An Overview of White Bagging: The Effect on Systems and Potential Strategies

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The distribution of oncology and non-oncology infusion therapies has been rapidly changing over the last several years due to the increased cost of drug therapies and changing trends in the insurance market. Payers have increased the requirements of "white-bagging," which requires an external pharmacy contracted with the payer to deliver a patient's prescription directly to the health care system. The medication is stored at the facility, which requires a separate inventory, and the patient visits the infusion clinic for administration.

This practice is becoming mandatory in some states and, among certain payers and infusion medications, it is increasing at alarming rates. White bagging has increased at, "double digits per year with more than 10% of the annual spend per year being shifted from the medical benefit to the pharmacy benefit for many specialty infusion drugs."[1]

Insurance market trends are focusing on white-bagging or shifting hospital-based care to alternative sites of care, such as a non-hospital based clinic or the patient's home. Commercial plans are primarily the stakeholders requiring this in some capacity and this may differ from state to state depending on the Board of Pharmacy legislation. Payer policies are rapidly changing. Table 1 below provides examples of some restrictions recently required by payers:[2]

Organizational implications from white bagging are multifactorial and directly influence patients and their continuity of care. There are safety and compliance concerns with white bagging as well as substantial financial implications to the organization. Significant delays in patient care of two to four weeks are commonplace. A one to two-week delay in treatment may impact patient outcomes if they are time sensitive infusion therapies and could result in avoidable hospital admissions.[2]

"Organizational implications from white bagging are multifactorial and directly influence patients and their continuity of care."

White-bagging Adds to Complexity of Pharmacy Operations

Delays in treatment for newly diagnosed oncology patients with curative disease have shown a decrease in survival for several solid tumor cancers.[4] Drug shortages add to the difficulty of the situation if the specialty pharmacy cannot procure the medication but the health system can, which could also delay treatment.

Patients may also be required to go to an alternate location for treatment and may not be closely monitored while they are receiving complex therapies.[3] White-bagging creates an additional layer of complexity for pharmacy operations for patient-specific inventory management and significant time for the staff to manage.[3]

The United States Food and Drug Administration (FDA) has requirements for pharmacy to confirm the drug integrity of the product via the Drug Supply Chain Security Act (DSCSA), by tracking all components of procurement and being able to identify drug recalls or other concerns from specific lot numbers of a product. Drug waste is also a consideration in the white-bagging model because the vial cannot be shared for these expensive medications. White-bagging may disrupt the revenue cycle for the health care system; lost revenue generated from specialty infusions could be devastating to the financial health of the organization. Self-referrals to insurance owned or affiliated specialty pharmacies allows the insurance industry to retain the associated revenue, take advantage of rebates from pharmaceutical companies, and negotiate to obtain part of the 340b savings for eligible entities.

Table 1: Commercial Plan Requirements

Commercial Plan	Requirements
Anthem/Blue Cross Blue Shield	Varies by state: Site of Care restrictions for select drugs
Cigna	List of oncology and non-oncology infusions require contracted specialty pharmacy applies only to Hospital Based Fee Schedule, not physician fee schedule
United Healthcare	Apples only to commercial plans, some states excluded
Aetna	Site of care managed program for select oncology drugs

**Updated: December 2020, subject to change.*

Pharmacy Organizations Take Varied Stances

Several pharmacy organizations at the federal and state level are working to address the issues with payers mandating white-bagging. The American Society of Health System Pharmacist (ASHP) has invested significant advocacy efforts and submitted a letter along with 61 health care systems to request a meeting with the FDA to discuss concerns regarding the payer-mandated distribution models and the DSCSA.5

ASHP is "opposed to payer-mandated white-bagging models and lobbying to the federal government" to support this stance.5 ASHP also is against, "payer-mandated distribution models that require clinician-administered drugs and strongly encourages the FDA to consider the patient safety and supply chain security risks of payer-mandated white-bagging models."[5]

Table 2 below provides updates on the current stance of a number of national organizations on white-bagging. Several states are also working aggressively to address payer mandated white-bagging. Louisiana, Virginia, Arkansas, and Indiana passed white-bagging bills in 2021 and several states are in progress, as provided in Table 3.[3,4,5]

Advocacy groups for pharmacy organizations and state boards of pharmacy are actively involved in working with policymakers and educating key stakeholders on the implications of requiring health

Table 2: Current Stance of National Pharmacy Organizations

Organization	Current Stance
American Society of Health System Pharmacists (ASHP)	Opposed to payer-mandated white bagging models for clinician administered drugs dispensed via a third party
American Hospital Association (AHA)	No brown bagging. Prohibitions on certain white bagging, safety criteria when white bagging can apply
National Association Board of Pharmacist (NABP)	White and brown bagging pose legitimate patient protection issues when specialty drug is distributed to an entity other than the patient. State Boards of Pharmacy are left to determine who is accountable
American Society of Clinical Oncology (ASCO)	Does not support white bagging and states practices may "erode quality and access to care and should be addressed immediately." Has developed committee to pursue an in-depth analysis of pharmacy benefit managers and impact on cost and waste, their role and impact on quality of care, and the impact of benefit design on patients' ability to access the care they need.[9]

Table 3: State Legislation Status

State	Legislation	Status and Key Points
Virginia	House Bill 2219	Passed – Plan requires insurers and Pharmacy Benefit Managers (PBM) to allow non-contracted pharmacies to dispense covered drugs and be reimbursed at in-network rates. Bill prevents healthcare plans from imposing unequal cost sharing on patients who select out-of-network pharmacy providers.
Louisiana	Senate Bill 191	Passed – Prevents healthcare plans and PBMs from refusing to pay a participating provider or pharmacy for providing covered physician-administered drugs. This law mandates that all white bagged drugs must meet supply chain security controls set forth by the Drug Supply Chain Security Act.
Indiana	House Bill 1405	Passed – Requires Indiana Department of Insurance, Department of Health, and Board of Pharmacy to conduct a study on the impact of white bagging and issue recommendations for best practices by Dec 21st, 2022.
Arkansas	House Bill 1907	Passed – Healthcare provider and enrollee determine it is in the patient's best interest for the provider to administer any covered prescription medication; the payer must reimburse the provider. Bill prevents the payer from imposing unequal cost sharing or financial penalties on patients or providers.
Texas	House Bill 1586; Senate Bill 1161	Require insurer permit enrollees to obtain clinician-administered drugs from provider or pharmacy and equal reimbursement
Tennessee	Senate Bill 1617	Combined white bagging & 340b reimbursement parity (same as LA and TX)
Massachusetts	Senate Bill 1808; House Bill 3407	Prohibit payer-mandated brown bagging and home infusion; only drugs supplied in "ready-to-administer" dosage can be white bagged
New Jersey	State Board of Pharmacy 13:39-3.10	It shall be unlawful for a pharmacist to enter into an arrangement to provide health care services for the purposes of directing/diverting patients to specified pharmacy
Ohio	State Board of Pharmacy 4729-9-01	"No drugs that has been dispensed and has left the physical premises of the terminal distributor shall be dispensed or personally furnished "

care systems to administer white-bagged drugs. ASHP is working aggressively on this topic and has several white-bagging resources to aid in learning more about this topic and the impact to your health system.[8] Pharmacy leadership should play a major role in educating physicians, managed care contracting, and government relations so that they can be aware of how each of their roles can affect the white-bagging issue.

Health System Engagement: Atrium Health Example

Health systems should actively engage their government relations staff to educate state legislatures on white-bagging's effect on patient care and advocate for legislation to minimize the negative effects on patients and safety net providers.

As an example, Atrium Health in Charlotte, North Carolina took a two-pronged approach to manage white bagging. First, an operational team was assembled, which included clinic and infusion nursing, pharmacy staff, and prior authorization staff. Their purpose was to help develop processes for clinic nurses to setup initial ordering of pharmaceuticals from outside pharmacies, ensure proper notification of in-house pharmacy and infusion staff, track timing of reordering to try to ensure patients had needed doses on hand at the time of their next infusion, and track any changes to therapy that would require starting the ordering process over.

"Health systems should actively engage their government relations staff to educate state legislatures on white-bagging's effect on patient care and advocate for legislation to minimize the negative effects on patients and safety net providers."

They also had to evaluate the additional storage needs, how to best segregate inventories, and how to deal with late shipments and consequent rescheduling of patients. Data was collected and reference materials developed, which could be accessed by staff to help track white-bagged patients and deal with the significantly increased insurance requirements associated with this patient population.

The second prong of the approach was to form a group of physicians, managed care contracting, pharmacy and governmental relations team members to discuss the impacts of white bagging on patients, staff, and the system. Pharmacy leadership engaged this team to help on a more global level to advocate for patients and safety net hospitals via contracting, meeting with state representatives, and supporting state legislation.

Continued Collaboration Moving Forward

ASHP has developed a self-assessment tool available to members on their website.[10] Health systems should work to develop internal policies and procedures to manage white bagging and discuss if white bagging can be implemented into the medical staff bylaws. Other helpful advice is to work with the managed care team to address white-bagging when deciding on the terms of a managed care contract.[2,3] Health care systems should work with their Boards of Pharmacy and national organizations on continued advocacy efforts to support legislation to prohibit white-bagging. ●●

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Pharmacist Contributions to Quality Improvement in Oncology Care Presented at the ASCO Quality Care Symposium 2020

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The virtual fall 2020 American Society of Clinical Oncology (ASCO) Quality Care Symposium showcased methods for measuring and improving the quality and safety of cancer care, including the work of many oncology pharmacists. Quality healthcare domains, as defined by the Institute of Medicine (IOM) include safe, effective, efficient, equitable, timely and patient-centered care.[1] Measurement of quality care should be practical, meaningful, inexpensive and user-friendly. Four abstracts that demonstrate pharmacy leaders measuring and improving quality care for patients with cancer are highlighted.

Organizational Partnership to Expand the ASCO Quality Training Program (QTP) to Oncology Pharmacists[2]

Pharmacists are critical in optimizing medication management and quality care in oncology patients. The Hematology Oncology Pharmacy Association (HOPA) Quality Oversight Committee (QOC) sought to improve educational opportunities in the area of oncology value and quality-based patient care for pharmacists. This led to discussion and a partnership with the ASCO QTP to develop a one-day workshop tailored to oncology pharmacists, aimed to strengthen their knowledge in quality improvement (QI) measures and strategies for practice improvement.

A comparative assessment of attendees pre- versus post-workshop demonstrated a three-point (on a 10-point scale) improvement in knowledge and skills and a 2.8 point increase in competence. A vast majority (93%) of attendees reported as very or extremely likely to use the new skills learned. The authors concluded that the workshop resulted in meaningful training in quality improvement measures for oncology pharmacists. Future partnership plans include additional one-day workshops and a modified ASCO QTP six-month course specifically for HOPA members.

State-wide Quality Improvement Addressing Overutilization of neurokinin-1 receptor antagonists[3]

ASCO's Quality Oncology Practice Initiative (QOPI) SMT28a metric focuses on the overuse of antiemetics, specifically of neurokinin-1 receptor antagonists (NK1-RA) for low or moderate emetogenic regimens. A team including oncology pharmacists created a quality improvement project to provide support to reduce the use of NK1-RA when not indicated. Baseline measurements of performance, prescriber knowledge and beliefs, and pre-populated antiemetic order sets were assessed. A quality improvement intervention was initiated.

Additionally, practice, and state-level performance reporting to the Michigan Oncology Quality Collaborative (MOQC); chemotherapy-induced nausea and vomiting education, and a value-based reimbursement related to measure performance. Initial responses assessing pre-populated antiemetic order sets showed that 23% had NK1-RA or olanzapine in moderate emetic regimens. Post-education, 48% of respondents had plans to or have already rectified their order sets. This ultimately improved performance from 27% to 19% ($p<0.05$) and below the 2020 QOPI mean performance measure of 31%.

Development and Implementation of an Evidence-based Malignant Hematology Clinical Pathway Program[4]

Clinical pathways often include a systemic approach to clinical decision support aimed at providing quality care while decreasing cost. Brahim and colleagues describe their institution's implementation of a clinical pathways program to standardize practice and increase quality of care as measured by pathway adherence. A team consisting of physicians, pharmacists, nurses, a quality manager, and information technology staff worked together to create pathway algorithms and reviewed treatment plans for the treatment of acute myeloid leukemia. This was inclusive of treatments, laboratory testing, supportive care (antiemetics, antimicrobials, and tumor lysis prophylaxis). A retrospective chart review was completed one-year after implementation to assess adherence. The primary objective was to achieve a pathways adherence rate of 80% or higher. Forty-four patient charts pre-pathway implementation utilizing best clinical evidence as a standard were compared to 44 patient charts post-implementation. There were 16 deviations pre-pathway. This included omitted medications, medications added, dose variations, different regimens, and supportive care. There were five deviations in the post-pathway group. Deviations included omitted medications, added medications, and different regimens. Pre- and post-pathway implementation adherence was 64% and 89%, respectively ($p=0.006$). The investigators plan to expand their program to other disease states such as multiple myeloma and ALL while continuing to monitor adherence and program objectives.

Providing Uninterrupted Oral Oncolytic Therapies During the COVID-19 Pandemic[5]

The COVID-19 pandemic has created significant financial and logistic hardship for patients and pharmacies to provide continued oral oncolytic therapy. A team investigated whether the pandemic

impaired access to oral chemotherapy at Tennessee Oncology's medically-integrated specialty pharmacy. In a retrospective analysis, investigators compared medication possession ratios (MPRs) of the five most common medications prior to and during the pandemic (Jan – May), as well as copayments and use of financial assistance resources. Consistent MPRs were demonstrated for the five most common therapies analyzed in 2019 vs 2020 (95.13% vs 94.86%). They also found similar aggregated copay amounts between the study periods and an increase in the use of copay cards (22%) and foundation assistance (12%) from 2019 to 2020. They concluded uninterrupted access to oral oncolytics and financial support services was provided throughout the beginning of the pandemic and attributed maintained MPRs to proactive and strategically-timed patient outreach.

Conclusion

Oncology pharmacists contribute significantly to improving quality and value metrics in the care of patients with cancer. Assessment of quality metrics and engagement in value-based contracts continues to grow and has become applicable to broader populations of patients with cancer in health-systems and oncology clinics. The impact of these to payment models continues to add pressure to meet these goals by the health care team including pharmacists. Publication and presentations regionally and nationally of quality improvement and research aimed at efforts will continue to show the value of the oncology pharmacist within patient-centered care. ●●

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CDK4/6 Inhibition for Adjuvant Treatment of Early Stage Breast Cancer

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Breast cancer is the most commonly diagnosed cancer in the United States accounting for an estimated 281,550 new diagnoses in 2021.[1] The good news is that greater than 90% of those diagnosed with breast cancer have early-stage disease where long-term remissions are possible.[2] Of those diagnosed, approximately 70% have cancers that are hormone receptor positive (HR+) and human epidermal growth factor receptor 2 negative (HER2-) in which standard treatment depends on risk of recurrence and can include surgery, radiation, chemotherapy, and endocrine therapy.[3,4] Despite excellent disease free survival rates with adjuvant endocrine therapy, approximately 20% of patients may experience recurrence within 10 years of starting therapy, and the risk is higher in patients with high risk features.[5] This highlights the importance of identifying patients at highest risk of recurrence and optimizing adjuvant therapy to minimize that risk.

Cyclin-dependent kinases 4 and 6 (CDK4/6) have been shown to be key promotors of tumor growth through the estrogen receptor pathway in HR+ breast cancer.[6] Small molecule inhibition of CDK4/6 plays a significant role in decreasing breast cancer growth and prolonging survival in the treatment of advanced and metastatic HR+, HER2- breast cancer.[7-11] Three CDK4/6 inhibitors (abemaciclib, palbociclib, ribociclib) have been approved for the treatment of metastatic breast cancer based on improvements in progression free survival in large, Phase 3 clinical trials. These agents are now NCCN guideline recommendations as standard of care for first, second, and subsequent lines of therapy either alone or in combination with endocrine therapy for metastatic breast cancer.[4,12] Investigators are now researching whether the incorporation of CDK4/6 inhibitors along with adjuvant endocrine therapy can prevent recurrence and increase disease free survival in patients with early stage breast cancer. A summary of ongoing clinical trials assessing the adjuvant use of CDK4/6 inhibitors are below.

MonarchE Trial

The MonarchE trial is an open-label, randomized, Phase 3 trial aimed to determine the efficacy and safety of the addition of abemaciclib to endocrine therapy for the adjuvant treatment of HR+, HER2- high-risk early breast cancer.[13] The trial enrolled adult patients with HR+ and HER2- early breast cancer with high risk features defined as four or more positive pathologic axillary lymph nodes or one to three positive axillary lymph nodes and at least one of the following: tumor size ≥ 5 cm, histologic grade 3, or centrally assessed Ki-67 ≥ 20%. Patients were randomized (1:1) to receive either abemaciclib 150 mg twice daily continuously plus endocrine therapy or endocrine therapy alone. Abemaciclib was continued for a maximum of two years and endocrine therapy was continued for five to 10 years as clinically indicated. The primary endpoint was invasive disease-free survival (IDFS) and key secondary endpoints included overall survival (OS) and safety.

A total of 5,637 patients were enrolled with a median age of 51 years and the majority being female (99.4%) and postmenopausal (56.5%). Approximately 60% of patients met inclusion criteria of four or more positive lymph nodes and over 95% had received prior chemotherapy and/or radiation therapy. Aromatase inhibitors were used as initial endocrine therapy in 68.3% of patients while 31.4% of patients received tamoxifen. There was a statistically significant difference in IDFS with events occurring in 136 (4.8%) of patients receiving abemaciclib plus endocrine therapy versus 187 (6.6%) of patients receiving endocrine therapy alone (HR 0.75, 95% CI 0.6-0.93; p=0.01). The two-year IDFS rates were 92.2% in the abemaciclib group versus 88.7% in the control group. Overall survival data were immature at the time of data cutoff. Patients receiving abemeciclib commonly developed diarrhea, fatigue, and neutropenia while patients in the control group commonly developed arthralgia, hot flush, and fatigue. Rates of arthralgia and hot flush were significantly reduced in the abemaciclib arm compared to endocrine therapy alone. Interstitial lung disease, venous thromboembolic events, and febrile neutropenia occurred in 2.7%, 2.3%, and 0.3% of patients receiving abemaciclib, respectively. Abemeciclib dose interruptions and reductions occurred in 56.9% and 41.2%, respectively while 16.6% of patients had to discontinue abemaciclib due to adverse effects.

The authors concluded that the addition of abemaciclib to endocrine therapy as adjuvant treatment of early stage breast cancer significantly improves IDFS and should be considered for patients meeting the criteria for high risk of recurrence. The trial is still ongoing with future analyses planned.

PALLAS Trial

PALLAS is an open-label, randomized, Phase 3 trial aimed to determine the efficacy and safety of the addition of palbociclib to endocrine therapy for the adjuvant treatment of early breast cancer.[14] Patients were enrolled within 12 months of being diagnosed with histologically confirmed HR+, HER2- stage II or III invasive breast cancer and within 6 months of initiating adjuvant endocrine therapy. Study participants were randomly assigned (1:1) to receive either palbociclib 125 mg once daily on days 1-21 followed by 7 days off every 28 days for a maximum of two years, plus endocrine therapy or endocrine therapy alone. The choice of endocrine therapy was based on provider and patient choice and consisted of tamoxifen or an aromatase inhibitor for a duration of at least five years. The primary outcome of the study was IDFS with key secondary outcomes being OS and safety.

A total of 5,760 patients with a median age of 52 years, predominantly female (99.4%), and premenopausal (53.5%) were enrolled in the study. Aromatase inhibitors and tamoxifen were used in 67.2% and 32.5% of patients, respectively. One hundred seventy patients in the palbociclib group and 181 patients in the endocrine therapy alone group experienced an IDFS event which did not differ significantly between the two groups. The 3-year IDFS rate was 88.2% in the palbociclib group and 88.5% in the endocrine therapy alone group (HR 0.93, 95% CI 0.76-1.15; p=0.51). Overall survival data were immature at the time of data cutoff. The patients receiving palbociclib plus endocrine therapy most commonly experienced neutropenia, leukopenia, fatigue, and arthralgia while patients receiving endocrine alone most commonly experienced arthralgia, hot flush, and fatigue. Early discontinuation of palbociclib occurred in 42.2% of trials participants with 27.1% due to adverse effects.

The authors concluded that the addition of two years of palbociclib with standard endocrine therapy did not improve IDFS versus endocrine therapy alone and couldn't be recommended for adjuvant treatment of stage II-III, HR+, HER2- breast cancer.

Penelope-B Trial

The Penelope-B trial is a randomized, double-blind, placebo controlled, Phase 3 trial studying the use of palbociclib in combination with endocrine therapy for patients with high risk residual disease following neoadjuvant chemotherapy.[15] Patients were enrolled if they had HR+, HER2- early breast cancer who had residual disease in either the breast or the lymph nodes following neoadjuvant chemotherapy and was considered high risk based on a clinical pathological staging-estrogen receptor grading (CPS-EG) score of ≥ 3 or 2 with ypN+. CPS-EG is a validated prognostic staging system for breast cancer patients with residual disease following neoadjuvant chemotherapy.[16-17] Patients were randomized to receive either palbociclib 125 mg daily on days 1-21 followed by seven days off every 28 days for a maximum of 13 cycles plus endocrine therapy or placebo plus endocrine therapy. Endocrine therapy was continued for at least five years. The primary endpoint of the study was IDFS with key secondary endpoints including OS and safety.

A total of 1,250 patients were enrolled in the study with a median age of 49 years and many patients had a CPS-EG score of ≥ 3 (59.4%) and a Ki-57 ≤ 15% (74.5%). At the time of analysis, there were 152 (24.1%) and 156 (25.2%) IDFS events in the palbociclib and placebo arms, respectively, which didn't demonstrate a statistically significant difference (HR 0.93, 95% CI 0.74-1.17, p=0.525). Overall survival didn't differ significantly between the two groups (HR 0.87, 95% CI 0.61-1.23, p=0.42) with the three-year OS being 93.6% with palbociclib and 90.5% with placebo. The most common adverse effects in the palbociclib group were leukopenia, neutropenia, and fatigue while leukopenia, fatigue, hot flush, and arthralgia were most common in the placebo group. In the palbociclib arm, 47.6% of patients required a dose reduction and 17.5% of patients discontinued early with only 3% discontinuing due to adverse effects.

The authors concluded there was no benefit of the addition of palbociclib for one year to endocrine therapy in patients with residual disease following neoadjuvant chemotherapy based on the IDFS.

Discussion

There is an unmet need for improvements to adjuvant-based therapies based on high rates of recurrence for patients initially treated for HR+, HER- early breast cancer. The CDK4/6 inhibitors have proven highly efficacious and safe in the treatment of advanced breast cancer, so it's reasonable to consider their incorporation into earlier lines of therapy. The conflicting results observed in MonarchE, PALLAS, and Penelope-B make it difficult to determine whether CDK4/6 inhibition combined with adjuvant endocrine therapy provides substantial benefit to incorporate into clinical practice. Differences in the trial design and the CDK4/6 medications themselves may help to explain the differing results.

The PALLAS trial included all patients with stage II-III disease whereas MonarchE utilized lymph node status as well as tumor size, grade, and Ki-67 as a marker of high risk of recurrence and Penelope-B utilized the CPS-EG staging system specific to patients who received neoadjuvant chemotherapy with higher values indicating higher risk of recurrence. This led to more patients in the palbociclib arm of the PALLAS trial having stage II disease (51.1% vs. 25.4%) and node negative disease (12.7% vs. 0.2%) compared to the abemaciclib arm in MonarchE. Patients in MonarchE with stage IIIC disease derived a significant benefit with the addition of abemaciclib though these subgroup analyses need to be interpreted cautiously due to sample size. In Penelope-B, 5.1% of patients in the palbociclib arm had node negative disease while specific staging data was not reported. Another difference in the patient population among trials was that patients in MonarchE had higher Ki-67 proliferation rates compared to Penelope-B (not reported in PALLAS) though the subgroup analysis of Penelope-B didn't suggest a difference in patients with high versus low Ki-67 tumors and Ki-67 was not reported in the subgroup analyses for MonarchE.

Differences observed among the clinical trials in early discontinuation and duration of treatment may also contribute to the differing results. Observed safety profile varied among agents yet no new safety concerns were observed. Notably, diarrhea with abemeciclib, myelosuppression with palbociclib, and the trials had varying rates of discontinuation in intervention arms due to toxicity. The PALLAS study had 42.2% of patients discontinue palbociclib early with 27.1% of the patients discontinuing due to adverse effects. MonarchE and Penelope-B had discontinuation rates due to adverse effects of 16.6% and 3%, respectively. The median follow-up time also differed at the time of reporting. Median follow-up duration was 15.5 months for MonarchE, 23.7 months for PALLAS, and 42.8 months for Penelope-B. Therefore, differences in the time on therapy and the amount of follow up at the time of reporting may contributing to the differing results.

Although these medications are in the same therapeutic class, the specific agents differ in pharmacology and administration. Abemaciclib is dosed continuously and a preclinical study found continuous CDK4/6 inhibition with abemaciclib led to sustained cell-cycle disruption and apoptosis whereas short-term inhibition

led to cell-cycle rebound.[18] Abemaciclib has also shown a 14 times higher affinity for CDK4, which is more highly expressed in breast tumor, compared to CDK6 while palbociclib was found to be equipotent against CDK4 and 6.[19,20] In the absence of head-to-head clinical trials, it's unclear if these differences in pharmacology and administration translate to a difference in clinical outcomes.

The use of CDK4/6 inhibitors in the adjuvant treatment of early stage breast cancer has yet to become standard of care based on the results of these trials. The differing results among these clinical trials may be due to study design, drug pharmacology, or some other factor. Longer follow up on previous trials, and the ongoing NATALEE trial (NCT03701334)[21] which looks at the use of three years of ribociclib with endocrine therapy in HR+, HER2- early breast cancer may shed additional light on the benefit of CDK4/6 inhibition in this patient population.

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"You Want me to Precept?": 5 Tips for Transitioning from a Resident to a Residency Preceptor

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You have done it. You've completed two years of post-graduate training, landed your first "real" job, and are looking forward to your professional future. You meet with your supervisor on your first day and find out…congratulations, you're the newest preceptor-in-training—or full preceptor—for their PGY2 residency program! Don't freak out; nearly all residents will eventually serve as residency preceptors (i.e. co-preceptor, primary preceptor, program director) at some point in their professional careers. I hope this short article provides you with a few helpful tips based on my own personal experience of transitioning from a resident to residency preceptor.

Tip 1: Be Familiar with Accreditation Standards for Residency Preceptors

The American Society of Health-System Pharmacists (ASHP) has published accreditation standards for postgraduate year two (PGY2) pharmacy residency programs, which detail the requirements of residency program directors and preceptors.[1] The standard defines a preceptor as an expert pharmacist who gives practical experience and training to a pharmacy resident and is responsible for the evaluation of a resident's performance. The standard specific to program preceptors (i.e., Standard 4) provides details on preceptor appointment and selection, eligibility, responsibilities, qualifications, and preceptors-in-training; important highlights are below:

- Eligibility
  - Preceptors must be licensed (or equivalent designation for the country conducting the residency) pharmacists who:
    - Have completed an ASHP-accredited PGY2 residency followed by a minimum of one year of pharmacy practice in the advanced practice area; or
    - Have not completed an ASHP-accredited PGY2 residency but have completed a minimum of three years of pharmacy practice in the advanced practice area.
- Responsibilities
  - Preceptors are to serve as role models for learning experiences; they must:
    - Contribute to the success of resident and the residency program,
    - Provide learning experiences that contribute to the residency program's educational goals and objectives to support the achievement of the residency's purpose,
    - Participate actively in the residency program's continuous improvement processes,
    - Demonstrate practice expertise and preceptor skills, striving to continuously improve in both areas,
    - Adhere to residency program and department policies pertaining to residents and services, and
    - Demonstrate commitment to advancing the residency program and pharmacy services.
- Qualifications
  - Preceptors must demonstrate the ability to precept learning experience by meeting at least one qualifying characteristic in each of the following areas:
    - Ability to precept residents' learning experiences using clinical teaching roles (i.e., instructing, modeling, coaching, facilitating) at the level required by residents,
    - Ability to assess residents' performance,
    - Recognition in the area of pharmacy practice for which they serve as preceptors,
    - An established, active practice in the area for which they serve as preceptor,
    - Maintenance of continuity of practice during the time of residents' learning experiences, and
    - Ongoing professionalism, including a personal commitment to advancing the profession.

The majority of pharmacists who graduate from PGY2 residency programs will not meet the qualifications for serving as a residency preceptor immediately following completion of their residency, unless they have previous pharmacy practice in the advanced practice area. ASHP acknowledges this, and created a role specific for this situation, "preceptor-in-training."

- Preceptors-in-Training
  - Pharmacists new to precepting who do not meet the qualifications for residency preceptors must:
    - Be assigned an advisor or coach who is a qualified preceptor, and
    - Have a documented preceptor development plan to meet the qualifications for becoming a residency preceptor within two years.

Tip 2: Identify and Learn From an Expert Advisor/Coach Who is a Qualified Preceptor

It is important to identify an individual within your organization who will contribute to your professional and personal growth as a preceptor for their residency program; this is not a decision to take lightly. In identifying that individual, keep in mind your wants/needs as a preceptor-in-training.

A few questions to ask yourself: "How many years of preceptor experience do they possess (i.e., five years v. 20 years)?", "Do they work in a clinical practice environment that will allow me to learn,

and potentially replicate, relevant preceptor practices to my future learning experience?", "Do they have the time to dedicate to my growth as a future residency program preceptor?" The advisor/coach you choose will be instrumental in providing guidance and feedback as you observe their preceptor style, develop your preceptor development plan, and implement various preceptor practices during your time as a preceptor-in-training.

Tip 3: Utilize Available Preceptor Development Resources

A plethora of preceptor development resources (i.e., continuing education presentations, articles, books, etc.) are available to pharmacists interested in serving as preceptors for both student pharmacists and pharmacy residents. ASHP has residency-specific preceptor resources for members which include general resources, articles, and webinars and presentations all related to preceptor development.

The National Pharmacy Preceptor Conference is an annual event focused on pharmacy precepting which offers great content for preceptors-in-training as they develop their preceptor style.[2] In addition, it's important to check with other various local, state, regional, and national pharmacy organizations for continuing education opportunities related to preceptorship; a lot of organizations have begun to incorporate aspects of preceptor development within their list of presentation topics. Your institution may offer financial assistance in gaining access to these resources so be sure to check with the residency program director or your advisor/coach.

Tip 4: Continue to Refine your Preceptor Style Through Self-Assessment

All residency programs require residents to utilize self-assessment as a way to learn and grow across their learning experiences—remember all of those surveys you've completed over the past two years? The same self-assessment process is necessary and useful for residency preceptors as you continue in your career.

In using self-assessment, reflect on your experiences as a resident or preceptor-in-training, asking yourself what preceptor practices you enjoyed most during your time as a resident. Self-assessment can assist you in identifying areas of improvement in implementing your own preceptor practices (e.g., allowing the resident to develop autonomy too slowly or too quickly, etc.) You will find with continuous self-assessment that there will eventually come a point in time where you feel confident in your preceptor style, making only minor changes along the way.

Tip 5: Elicit Continuous Feedback from Advisors/Coaches and Residents

You are not alone in your transition from resident to residency preceptor. The majority of residency preceptors were once in your shoes, so lean on them to assist you in developing your own preceptor style. If possible, shadow multiple individuals with various preceptor experience during your year as a preceptor-in-training to pick and choose elements of preceptorship that you would like to incorporate into your future learning experiences. In addition, ask other residency preceptors, and your resident trainees, for feedback on your performance as a preceptor. Constructive criticism and feedback can be a wonderful partner in the process of self-discovery as a residency preceptor.

In transitioning from a resident to a residency preceptor, you will have the opportunity to use what you've learned as a resident to benefit your future resident trainees. You will certainly face many challenges as you navigate your new role on the other side, but each challenge will allow you to develop new perspectives and grow into the preceptor you are destined to be. Good luck—you'll do great! ●●

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Updates in Advanced Renal Cell Carcinoma

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Renal cell carcinoma (RCC) is the eighth most commonly diagnosed cancer in the United States, with an estimated number of new cases and deaths of 76,080 and 13,780, respectively, in 2021.[1] Over the past three decades, the treatment for advanced RCC (aRCC) has been transformed with antiangiogenic therapies, including anti-vascular endothelial growth factor (VEGF) tyrosine kinase inhibitors (TKIs), and immune checkpoint inhibitors (ICIs).[2] Both treatment options have improved patient outcomes and modified the natural history of aRCC.[3]

Recently, two phase 3 trials—KEYNOTE-581 (CLEAR) and CheckMate-9ER—were published evaluating ICI and anti-VEGF TKI combinations in the treatment-naive setting.[4,5] Additionally, tivozanib, a potent inhibitor and highly selective anti-VEGF TKI, received US Food and Drug Administration (FDA) approval in March 2021 for treatment of relapsed or refractory aRCC based on the TIVO-3 trial.[6]

To better appreciate how these new trials impact clinical decision making, we summarized the studies in the context of other guideline-recommended treatments. This article reviews the synergistic effect of ICIs and VEGF inhibition, provides a summary of each trial, and reviews investigational therapies that may contribute to the ever-evolving treatment landscape of aRCC.

Synergism of ICI and VEGF inhibition

Aberrations in proangiogenic factors, like VEGF, are a hallmark of RCC.[3] VEGF stimulates blood vessel growth and causes immunosuppression by promoting T regulatory cells and inhibiting T effector cells.[7] It may also induce changes in protein expression on endothelial cells that limit immune-cell tumor infiltration, leading to CD8+ T cells apoptosis, programmed death-ligand 1 or 2 (PD-L1/L2) upregulation, and hypoxia. In hypoxic conditions, cancer cells can recruit regulatory T cells and tumor-associated macrophages differentiate to an M^2 phenotype, which can have immunosuppressive effects.[8]

Antiangiogenic drugs may restore the differentiation of dendritic cells, reducing the level of myeloid-derived suppressor cells and decreasing the levels of regulatory T cells.[7] These agents may also normalize the tumor vasculature and alleviate hypoxia, leading to increased immune-cell infiltration into tumors. As such, combination ICIs and anti-VEGF TKIs have a synergistic antitumor effect.

First-Line Systemic Therapy of Advanced Clear-Cell RCC

Prognostic tools currently used include the Memorial Sloan Kettering Cancer Center (MSKCC) Prognostic Model and the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) Criteria.[3,9,10] Both models are used in clinical practice, but most current clinical trials use the IMDC model. Treatment recommendations are based on risk and are divided into two groups: favorable-risk and intermediate-/poor-risk. Patients without MSKCC or IMDC risk factors are categorized as favorable-risk, whereas those with at least one risk factor are categorized as intermediate-/poor-risk. The majority of patients (70-80%) have at least one risk factor, making them intermediate-/poor-risk.[3]

Per the National Comprehensive Cancer Network (NCCN), the preferred first-line systemic therapy recommendations for favorable-risk aRCC include axitinib plus pembrolizumab, cabozantinib plus nivolumab (category 1), lenvatinib plus pembrolizumab (category 1), pazopanib, and sunitinib.[3] Options for intermediate-/poor-risk aRCC include axitinib plus pembrolizumab (category 1), cabozantinib plus nivolumab (category 1), ipilimumab plus nivolumab (category 1), lenvatinib plus pembrolizumab (category 1), and cabozantinib.

The most recent additions to the first-line treatment armamentarium are lenvatinib plus pembrolizumab and cabozantinib plus nivolumab. Lenvatinib plus pembrolizumab was studied in the phase 3 CLEAR trial and cabozantinib plus nivolumab was studied in the phase 3 CheckMate-9ER trial.

CLEAR: Lenvatinib + Pembrolizumab

CLEAR was a randomized, open-label, phase 3 trial that enrolled subjects with treatment naïve aRCC of clear cell histology.[4] Patients were randomized 1:1:1 to pembrolizumab 200 mg every 21 days plus lenvatinib 20 mg daily (n=355), lenvatinib 18 mg daily plus everolimus 5 mg daily (n=357), or sunitinib 50 mg daily (4 weeks on with two weeks off per cycle) (n=357). The primary endpoint was progression free survival (PFS), and patients were stratified by region and IMDC risk category.

At a median follow up of 27 months, lenvatinib + pembrolizumab demonstrated a significant improvement in PFS, overall survival (OS), and objective response rate (ORR) compared to sunitinib.[4] The median PFS was 2.5 times longer with lenvatinib plus pembrolizumab (23.9 months vs. 9.2 months; hazard ratio [HR] 0.39, 95% confidence interval [CI] 0.32-0.49, $p<0.001$). The median OS was not reached in either arm but favored lenvatinib plus pembrolizumab (HR 0.66, 95% CI 0.49-0.88, $p=0.005$). The confirmed ORR favored lenvatinib plus pembrolizumab over sunitinib (71% vs. 36.1%; HR 1.97, 95% CI 1.69-2.29), as did the complete response (CR) rates (16.1% vs. 4.2%).

Table 1. Pivotal randomized, phase 3 trials for treatment naïve advanced renal cell carcinoma

Year	Trial Name	Agents	Patients, n	ORR (%)	CR (%)	OS (mo)	PFS (mo)	Statistical Benefit
2017	CABOSUN[11]	CABO v SUN	157	33 v 12	1.3 v 0	26.6 v 21.1	8.2 v 5.6	ORR, PFS
2018	CheckMate-214[12]	IPI + NIVO v SUN	1096	42 v 27	9 v 1	NR	11.6 v 8.4	ORR, OS
2019	KEYNOTE-426[13]	AXI + PEM v SUN	861	59.3 v 35.7	5.8 v 1.9	NR	15.1 v 11.1	ORR, OS, PFS
2019	JAVELIN-Renal 101[14]	AXI + AVEL v SUN	886	51.4 v 25.7	4.4 v 2.1	11.6 v 10.7	13.8 v 7.2	ORR, PFS
2021	CheckMate-9ER[5]	CABO + NIVO v SUN	651	54.8 v 28.4	9.3 v 4.3	NR	16.6 v 8.3	ORR, OS, PFS
2021	CLEAR[4]	LEN + PEM v SUN	1069	71 v 36.1	16 v 4.2	NR	23.9 v 9.2	ORR, OS, PFS

Abbreviations: AVEL, avelumab; AXI, axitinib; CABO, cabozantinib; CR, complete response; IPI, ipilimumab; LEN, lenvatinib; NIVO, nivolumab; NR, not reached; ORR, objective response rate; OS, overall survival; PEM, pembrolizumab; PFS, progression free survival; SUN, sunitinib

The CLEAR trial also evaluated lenvatinib plus everolimus in a third arm compared to sunitinib.[4] Lenvatinib plus everolimus statistically outperformed sunitinib in PFS and ORR but showed no difference in OS. Efficacy results were numerically lower in all categories with lenvatinib plus everolimus compared to lenvatinib plus pembrolizumab. While caution should be used comparing results between different studies, the PFS, ORR, and CR were the highest recorded in the lenvatinib plus pembrolizumab group compared to any other trial as seen in Table 1.[4,5,11-14]

Treatment-related adverse events (TRAEs) grade 3 or higher occurred more often with lenvatinib plus pembrolizumab than with sunitinib (71.6% vs. 58.8%).[4] TRAEs leading to dose reduction also occurred more frequently in the lenvatinib plus pembrolizumab arm (67.3% vs. 49.7%). Discontinuation of at least one of the study drugs was seen in 37.2% of the lenvatinib plus pembrolizumab arm compared to 14.4% of the sunitinib arm.

Based on the results of the CLEAR trial, lenvatinib plus pembrolizumab was added to the NCCN guidelines as a preferred, category 1 recommendation regardless of risk categorization.[3] As of June 2021, however, this combination has not received FDA approval for treatment of aRCC.

CheckMate-9ER: Cabozantinib + Nivolumab

CheckMate-9ER was a randomized, open-label, phase 3 trial that enrolled subjects with treatment naïve aRCC of clear cell histology.[5] Patients were randomized 1:1 to receive cabozantinib 40 mg daily plus nivolumab 240 mg every 14 days (n=323) or sunitinib 50 mg daily (4 weeks on with 2 weeks off per cycle) (n=328). The primary endpoint was PFS, and patients were stratified by region, IMDC risk category, and tumor expression of PD-L1.

At a median follow up of 18.1 months, cabozantinib plus nivolumab demonstrated a significant improvement in PFS, OS, and ORR compared to sunitinib.[5] The median PFS was twice as long with cabozantinib plus nivolumab (16.6 months vs. 8.3 months; HR 0.51, 95% CI 0.41-0.64, p<0.001), and the median OS was not reached but favored the cabozantinib plus nivolumab group (HR 0.60, 95% CI 0.40-0.89, p=0.001). The confirmed ORR favored cabozantinib plus nivolumab over sunitinib (55.7% vs. 27.1%, p<0.001), as did the CR rates (8% vs. 4.6%). Survival and response benefits of nivolumab + cabozantinib were noted across all patient subgroups (e.g., IMDC risk status, PD-L1 expression level, bone metastases).

Cabozantinib plus nivolumab was associated with higher rates grade 3 or greater TRAEs (60.6% vs. 50.9%) and treatment discontinuation of at least one drug (19.7% vs. 16.9%).[5] Dose reductions were not allowed with nivolumab but occurred more frequently with cabozantinib than with sunitinib (56.3% vs. 51.6%).

The FDA approved cabozantinib plus nivolumab for aRCC on January 22, 2021.[15] This combination was added to the NCCN guidelines as a preferred, category 1 recommendation regardless of risk categorization.[5]

First-line Treatment Considerations

Many good options exist for first-line systemic treatment of aRCC. However, in some cases, there is not a clear choice regarding which therapy to try first. Clinicians must often weigh adverse event potential, financial toxicity, and patient preference when choosing therapy. Notably, some patients may not need systemic therapy. Many patients with favorable-risk and some intermediate-risk patients can survive for many years with or without therapy.[3] For selected patients, a debulking nephrectomy or active surveillance can be considered.

Clinicians may consider combination ipilimumab plus nivolumab for patients with IMDC intermediate-/poor-risk disease, no significant autoimmune disease, VEGF contraindications, and those who cannot tolerate the chronic adverse events of anti-VEGF TKIs.[3] On the other hand, clinicians may consider combination ICI and anti-VEGF TKI therapy for patients with any IMDC risk disease, those with intermediate-/poor-risk disease who need rapid response, and those who need to avoid the immune-related adverse events associated with dual ICI therapy.

Systemic Therapy for Relapsed/Refractory Advanced Clear-Cell RCC

Second-line treatment options for aRCC may include targeted therapies and ICIs, alone or in combination.[3] Table 2 summarizes

the pivotal randomized trials in aRCC following anti-VEGF TKI therapy.[16-25]

Per NCCN, the preferred regimens for relapsed/refractory aRCC include cabozantinib (category 1), nivolumab (category 1), and ipilimumab plus nivolumab.[3] Other recommended regimens include axitinib (category 1), axitinib plus avelumab (category 1), axitinib plus pembrolizumab, everolimus, lenvatinib plus everolimus (category 1), pazopanib, sunitinib, and tivozanib.

The most recently approved drug for relapsed/refractory aRCC is tivozanib.6 Its approval was based on the results of the phase 3 TIVO-3 trial.

TIVO-3: Tivozanib

TIVO-3 was a randomized, open-label, phase 3 trial that enrolled subjects with aRCC who failed two to three prior systemic regimens, one of which included an anti-VEGF TKI.[24] Patients were stratified by IMDC risk category and type of prior therapy and randomized 1:1 to tivozanib 1.34 mg daily (21 consecutive days every 28 days) (n=175) or sorafenib 400 mg twice daily (n=175). The primary outcome was PFS.

At a median follow up of 19 months, tivozanib demonstrated significantly greater PFS (5.6 months vs. 3.9 months; HR 0.73, 95% CI 0.56-0.94, p=0.016) and ORR (18% vs. 8%, p=0.003; CR rates 0% vs. 0%) versus sorafenib in the intention to treat population, in the subset of patients treated with two prior anti-VEGF TKIs, and in patients treated with a prior anti-VEGF TKI and an ICI.[24,25] Patients with favorable IMDC risk and those with intermediate IMDC risk had longer PFS with tivozanib than with sorafenib, whereas patients with a poor IMDC risk did not. The investigators hypothesized that patients with poor IMDC risk have tumors that are driven less by angiogenesis than their favorable- and intermediate-risk counterparts; therefore, patients with poor-risk disease might derive less PFS benefit from a selective anti-VEGF TKI, like tivozanib. Median overall survival was not significantly different between groups (16.4 months vs. 19.7 months; HR 0.99, 95% CI 0.76–1.29, p=0.95).

The most common grade 3 or higher TRAE was hypertension, occurring in one-fifth of patients in both groups.[24,25] Serious TRAEs occurred in 11% of patients with tivozanib and 10% of patients with sorafenib. Dose interruptions due to TRAEs occurred in 48% of patients treated with tivozanib and 63% of patients treated with sorafenib; TRAEs that led to dose reductions were more common in the sorafenib arm (24% vs. 38%).

The FDA approved tivozanib for relapsed or refractory aRCC following two or more prior systemic therapies on March 10, 2021.[6]

Next-Line Treatment Considerations

Sequencing therapy remains a complicated issue for clinicians. For patients with disease control greater than one year on first-line, single-agent VEGF inhibitor, switching to another single agent anti-VEGF TKI, such as cabozantinib or axitinib, may be appropriate.[3] For patients with brief response to single-agent anti-VEGF TKI, clinicians may consider combination anti-VEGF TKI plus ICI therapy. If patients lack a response to first-line VEGF inhibition, dropping VEGF inhibition and switching to ICI therapy (e.g., ipilimumab plus nivolumab or nivolumab alone) can be considered.

For patients who did not respond to combination anti-VEGF TKI+ ICI therapy, clinicians may consider switching to a second-line anti-VEGF TKI, such as cabozantinib or axitinib, or combination lenvatinib plus everolimus.[3] Notably, phase 3 data support sequential VEGF therapy; however, limited data support sequential ICI therapy.[16-25]

Ongoing Trials

Ipilimumab, Nivolumab, and Cabozantinib

COSMIC-313 (NCT03937219) is a randomized phase 3 trial of ipilimumab plus nivolumab with either cabozantinib or placebo for patients with previously untreated IMDC intermediate-/poor-risk aRCC.[26] PDIGREE (NCT03793166) is also evaluating the combination of ipilimumab, nivolumab, and cabozantinib in the treatment naïve, IMDC intermediate-/poor-risk setting.[27] However, unlike COSMIC-313, PDIGREE has an adaptive protocol. All patients receive up to four cycles of ipilimumab and nivolumab and are assessed at three months. Subsequent therapy is based on response. Patients that achieve a CR receive nivolumab alone. Those with progressive disease receive cabozantinib alone. Patients who achieve either partial response or stable disease are randomized to either nivolumab alone or combination cabozantinib plus nivolumab.

Table 2. Pivotal randomized trials for relapsed/refractory advanced renal cell carcinoma following anti-VEGF TKI treatment

Year	Phase	Trial Name	Agents	Patients, n	Line of Therapy	ORR (%)	OS (mo)	PFS (mo)	Statistical Benefit
2008	3	RECORD[16,17]	EVE v PLA	410	2nd and beyond	1.8 v 0	14.8 v 14.4	4.9 v 1.9	PFS
2011	3	AXIS[18,19]	AXI v SOR	723	2nd	19 v 9	20.1 v 19.2	8.3 v 5.7	ORR, PFS
2015	3	METEOR[20,21]	CABO v EVE	658	2nd and beyond	21 v 5	21.4 v 17.1	7.4 v 5.3	ORR, OS, PFS
2015	3	CheckMate-025[22]	NIVO v EVE	821	2nd or 3rd	25 v 5	25 v 19.6	4.6 v 4.4	ORR, OS
2015	2	NCT01136733[23]	LEN + EVE v EVE	153	2nd	43 v 3	25.5 v 15.4	14.6 v 5.5	ORR, PFS, OS
2020	3	TIVO-3[24,25]	TIV v SOR	350	2nd and beyond	18 v 8	16.4 v 19.7	5.6 v 3.9	ORR, PFS

Abbreviations: AXI, axitinib; CABO, cabozantinib; EVE, everolimus; LEN, lenvatinib; NIVO, nivolumab; ORR, objective response rate; OS, overall survival; PFS, progression free survival; PLA, placebo; SOR, sorafenib; TIV, tivozanib; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor

PDIGREE will help clinicians understand the number of ipilimumab cycles required as the protocol does not require completion of all four cycles of ipilimumab plus nivolumab, as seen with CheckMate-214.[12,27] PDIGREE will also address the feasibility of discontinuing treatment for patients who achieve CR at one year of treatment. To date, no other clinical trials have addressed this question of discontinuing therapy for patients achieving CR.

Belzutifan

Belzutifan (MK-6482) is a novel hypoxia-inducible factor 2 alpha inhibitor that recently received a priority review from the FDA based on a phase 2 trial of patients with Von Hippel-Lindau Disease-associated RCC.[28] This trial showed promising clinical activity for patients with treatment naïve disease (ORR 36.1%). Belzutifan is also being studied in combination with either cabozantinib, everolimus, or lenvatinib for patients with aRCC.[29-31]

Conclusion

Antiangiogenics and checkpoint inhibition have revolutionized the treatment of aRCC. The CLEAR and CheckMate-9ER trials showed promising results in the first-line setting, supporting the use of lenvatinib plus pembrolizumab and cabozantinib plus nivolumab, respectively. Among the first-line treatment options, lenvatinib plus pembrolizumab demonstrated the highest ORR and PFS; however, caution should be used when comparing results between trials. The TIVO-3 trial demonstrated an ORR and PFS benefit with tivozanib in the relapsed/refractory setting and has been added to the treatment armamentarium. Ongoing trials are evaluating the use of combination ICI and anti-VEGF TKI, addressing sequencing of therapies, and investigating the use of novel therapies, such as inhibitors of hypoxia-inducible factor 2 alpha. ●●

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Virtual Patient Advocacy Townhall on Full Display at this Year's Annual Meeting

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Being virtual for this year's Annual Conference did not deter the Patient Outreach Committee from providing a collaborative dialogue across six patient advocacy organizations. HOPA had the honor of hosting: Cancer Care (Sarah Paul, LCSW, OSW-C- Director of Clinical Programs), Cancer Support Community (Elizabeth Franklin, PhD, MSW-President), The Leukemia and Lymphoma Society (Karen DeMairo, MHSA-Vice President—Education, Support & Integration), PAN Foundation (Amy Niles—Executive Vice President), Society for Immunotherapy of Cancer (Peter Intile, PhD—Associate Director of Science & Policy), and Stupid Cancer (Alison Silberman, MUP-CEO). During the hour-long town hall, Dr. Jennifer Powers, HOPA's Patient Outreach Committee Chair, led the participants through a discussion across 3 different topics including: 1) Creating community through the cancer diagnosis, 2) Unique programs and resources for our patients, and 3) Financial and emotional resources to support our patients and families/caregivers. This session was recorded and representatives were available for a live Q&A session.

Creating Community through Cancer Diagnosis

The first topic was creating community through the cancer diagnosis. Stupid Cancer started the conversation with challenges that face the adolescent and young adult (AYA) population such as emotional, financial, and fertility and reproductive health, as well as unique programs that their organization provides. This is accomplished through social environments and events both online and in person. One of these programs is called "CancerCon" which is a weekend long event bringing in patients/caregivers for a fun-filled program for those in the AYA community. Stupid Cancer also recognizes health disparities in people of color, LatinX, and LBGTQ+ communities and provides space for these populations to come together.

The Leukemia and Lymphoma Society (LLS) carried on the conversation to discuss how their organization creates community and impacts healthcare in underserved and unrepresented patients. LLS spoke about their Myeloma Link which strives to increase access to treatment and education to the African American population. Additionally, LLS discussed their new programs reaching the LatinX community and incorporating materials and education in Spanish, similar to what has been accomplished within Myeloma Link.

Lastly, Cancer Support Community (CSC) discussed their focus on health equalities and anti-racist policies within their organization and their outreach to the Navajo nation. CSC is the first patient advocacy organization to help support the Navajo nation both socially and emotionally with support services in the Navajo's first ever cancer care treatment facility.

Unique Patient Resources and Programs

The second component of the town hall addressed some of the unique resources and programs that the participating organizations offer. The Society for Immunotherapy of Cancer (SITC) started the conversation highlighting their commitment to offering education and resources to health care professionals, researchers, patients, and caregivers. One of their main efforts of education dissemination is through their annual meeting where stakeholders can gather to learn the latest information on immunotherapy and research. SITC offers online education through SITC ConnectED for all levels of learners with numerous online resources such as webinars, workshops, and written materials. SITC is also developing a patient survivor panel.

LLS then highlighted resources in their clinical trial support center. This center consists of clinical trial nurse navigators to increase patients' opportunities for clinical trial participation by facilitating informed decision making and minimizing barriers for patients and their family members. Another unique service is their 1-on-1 nutrition consultation with a registered dietician who has experience with oncology patients. Other resources include programs for children with blood cancers on going back to school and ways to facilitate the learning experience during and after treatment.

Financial and Emotional Support

Financial and emotional support was the last topic discussed among the participants. Cancer Care offers an online, searchable database called Online Helping Hand which can connect individuals to financial resources and contact information both regionally and nationally for patients seeking help. Cancer Care also offers programs throughout the continuum of care for the patient from diagnosis through their entire journey. Additionally, they help with government assistance programs, pharmaceutical patient assistance programs, and copay relief groups to assist in alleviating financial burdens for patients. Counseling is a major focus of Cancer Care as they work with the patient from the time of diagnosis through their treatment journey. Counseling is conducted by oncology social workers specifically trained in this area to work with patients, families, and caregivers.

CSC offers a Cancer Support Helpline (available seven days a week) to help connect individuals with short term copay assistance, short term housing needs, treatment decision making support, financial navigation, stress relief and live/video chats. CSC can meet their patients wherever they are in their cancer journey.

Patient Access Network (PAN) Foundation also helps with navigating the process of finding financial assistance for patients. PAN Foundation, which is one of nine national patient assistance programs providing financial support for medications, helps with out-of-pocket expenses, copays, deductibles, and coinsurance costs and they now have additional services targeting other expenses patients are typically faced with when on therapy. They offer

transportation assistance and have created a program entitled, Extra Help that offers financial assistance to Medicare beneficiaries.

FundFinder is a program developed by the PAN Foundation which is updated hourly as funds become available, alerting those who have signed up for notifications for coverage for specific disease states. This helps alleviate stress and time searching individual programs and databases by combining all information in one place. PAN foundation is active on social media to help disseminate this information in a quick manner to patients, caregivers, and providers. Their programs include live support groups, case management services, online support groups, and coping circle communities.

Services are located in New York and New Jersey and other services online are available nationally.

The video recording of the Town Hall will be made available as an on-demand session until the end of November through the meeting platform for registrants of the 2021 HOPA Annual Meeting.

A Town Hall Summary Document is also available on the HOPA Patient Outreach page (https://www.hoparx.org/advocacy-activities/patient-outreach). Within this document there are direct links to these patient advocacy organization resources and materials. The Patient Outreach Committee encourages all HOPA members to check out this great resource to use in your day to day practice.

Managing Immune-Related Adverse Events in an Oncology Clinic

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Immunotherapy has become one of the most important breakthroughs in medicine over the last decade. Specifically, immune checkpoint inhibitors (ICIs) have changed oncology practice with astonishingly robust and durable treatment responses in both the adjuvant and advanced settings.[1] ICIs are now widely used across many treatment indications with an estimated 43% of cancer patients eligible for checkpoint inhibitors based on a 2019 cross-sectional study.[2] ICI therapy can lead to autoimmune toxicities known as immune-related adverse events (irAEs) and early recognition and frequent monitoring of these toxicities are crucial for patients to remain on this immunotherapy. Oncology pharmacists are uniquely positioned to identify and monitor these toxicities.

Development of the irAE Pharmacist Protocol

A team of board-certified oncology pharmacists and a post-graduate year 2 (PGY2) oncology pharmacy resident at Kaiser Permanente Zion Medical Center in San Diego developed an irAE Pharmacy Protocol in accordance with recommendations from National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO), and European Society of Medical Oncology (ESMO).[3-5]

Oncology pharmacists are uniquely positioned to identify and monitor these toxicities known as immune-related adverse events.

The protocol included four irAEs, including immune-mediated dermatologic, hepatic, gastrointestinal and thyroid toxicities. These were chosen as adverse events that were identifiable and manageable within the institution's scope of clinical pharmacy practice. Patients with other toxicities, such as renal and pulmonary toxicities were excluded in the initial study and were to be considered after initial implementation of the protocol. Pharmacist responsibilities under pilot protocol included ordering and assessing laboratory values, prescribing appropriate pharmacotherapy under pharmacist-physician collaboration, scheduling appropriate follow-up, and communicating pharmacotherapy changes with the primary oncologist.

At our institution, an oncology pharmacist reviews and assesses all labs prior to treatment with immune checkpoint inhibitors. Patients were identified to have checkpoint inhibitor toxicities based on abnormal laboratory values or physician workup. Also included in the study were patients 18 years or older who received at least one dose of the immune checkpoint inhibitors ipilimumab, nivolumab, pembrolizumab, durvalumab, atezolizumab or avelumab and who were subsequently identified to have one of the four protocol-listed irAEs between October 1, 2018 and February 28, 2019. Patients with more than one of the four protocol-listed irAEs were still included in the study and managed by the oncology pharmacist.

Patients were excluded from the study if they were determined to have serious or life-threatening toxicities, pre-existing autoimmune disorders, were taking thyroid hormone replacement prescribed by a non-oncology physician, or were currently taking corticosteroids greater or equal to 10mg of prednisone daily or equivalent.

Results:

A total of 17 patients who received an immune checkpoint inhibitor and who were subsequently identified to have an irAE were enrolled into the irAE pharmacy protocol. Oncology pharmacists performed a total of 101 telephone or in-clinic follow-ups with 21 new medications initiated for the treatment of irAE. The most common toxicity managed was hypothyroidism in which thyroid hormone replacement was initiated in seven patients based on abnormal thyroid stimulating hormone (TSH) and free T4 levels. Oral corticosteroids were initiated in six patients, including three patients with hepatotoxicity, two patients with rash and one patient with colitis.

There were a total of 28 medication dose adjustments. Levothyroxine dose was adjusted based on follow-up laboratory values of TSH and free T4 measured every four to six weeks. Steroid doses were tapered or titrated depending on liver function tests in hepatitis or patient symptoms in colitis and dermatitis. Four patients had checkpoint inhibitor therapy held with only one rechallenge. Rechallenge criteria were not analyzed as part of this study.

Pre- and post-pilot physician satisfaction surveys were also distributed to help characterize the pharmacist-physician collaboration. Questions included hours per month managing irAE and physician confidence in pharmacist management rated on a scale of 1 (strongly disagree) to 5 (strongly agree). Through a total of eight physician responses for the pre- and post-pilot surveys, the irAE pharmacist protocol saved an average of one hour physician time per month managing irAEs (3.3 hours pre-pilot to 2.3 hours post-pilot) and increased physician confidence in pharmacist management of irAE.[6]

Conclusion:

Our study demonstrates that pharmacist management of irAEs in an oncology clinic is both feasible and widely accepted by oncologists. Pharmacists performed close follow-up of patient symptoms and laboratory values often contacting patients multiple times per week. The results of this study led to the permanent implementation of this pharmacy service, as well as the addition of

immune-mediated renal toxicity at the time of writing of the original study.

In addition to reducing physician time managing irAEs, a pharmacist-managed irAE protocol may also reduce referrals to specialists. An internal post-graduate year 1 (PGY1) residency project was conducted at the institution two years after the initial study. It found a numerically lower rate of specialist referrals in a pharmacist managed population compared with usual care. Future studies are needed to confirm these findings.

Implementing an irAE pharmacist protocol at your institution is a great way to increase rapport with your oncologists and elevate the oncology pharmacy practice within your team. To start a pharmacist-managed irAE protocol, we would recommend developing a lead oncology pharmacist with a high baseline knowledge of irAEs to create competencies and practical cases for the clinical staff. Then work with other specialties to form an interdisciplinary group to discuss unique cases or cases with severe toxicities. An oncology pharmacist has the knowledge and ability to lead such a group. As the widespread use of immune checkpoint inhibitors continues to increase, pharmacists will remain an important asset in the identification and management of immune checkpoint inhibitor toxicities. ●●

"Implementing an irAE pharmacist protocol at your institution is a great way to increase rapport with your oncologists and elevate the oncology pharmacy practice within your team."

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R2-CHOP in DLBCL: The E1412 and ROBUST Studies

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The most common lymphoid malignancy among adults is diffuse large B-cell lymphoma (DLBCL). DLBCL accounts for approximately 30% of non-Hodgkin lymphomas (NHL).[1] Standard of care treatment for DLBCL is comprised of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone, also known as R-CHOP. The relapse rate after initial therapy is nearly 40% so the target of treatment has been refocused and is directed at the molecular structure of DLBCL.[1-3]

As a heterogenous malignancy, DLBCL can be classified based on cell-of-origin (COO). The major classes of COO consist of germinal center B-cell-like (GCB), activated B-cell-like (ABC), and unclassified subtypes. These subtypes differ in terms of prognosis and response to treatment. ABC-DLBCL has been associated with a worse survival prognosis. Standard of care currently remains the same for all subtypes, but the addition of novel targeted agents to R-CHOP are being investigated to see if outcomes can be improved for ABC-DLBCL.[4-5] Preclinical studies suggested that the addition of lenalidomide provided a direct cytotoxic effect in patients with ABC-DLBCL.[6]

"Standard of care currently remains the same for all subtypes, but the addition of novel targeted agents are being investigated to see if outcomes can be improved for ABC-DLBCL."

Lenalidomide is an analogue of thalidomide with immunomodulatory, antiangiogenic, and antineoplastic properties.[7] In a phase II study, lenalidomide in combination with R-CHOP (R2-CHOP) showed benefit in patients with DLBCL, especially in patients with non-GCB DLBCL.[8] E1412 and ROBUST are two recently published trials that investigated the role of R2-CHOP in ABC-DLBCL.

US Intergroup Study ECOG-ACRIN E1412[9]

E1412 was a prospective multicenter phase II signal-seeking study that compared R2-CHOP versus R-CHOP in newly diagnosed untreated confirmed DLBCL patients who were at least 18 years of age with at least stage II bulky disease. Patients were excluded if they had known central nervous system (CNS) lymphoma, history of deep venous thrombosis or embolism, transformed lymphoma, or primary mediastinal large B-cell lymphoma.

Patients were randomized in a 1:1 fashion to receive R2-CHOP or R-CHOP for six cycles. All patients received R-CHOP21, which consisted of one dose each of rituximab 375 mg/m^2, cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, and vincristine 1.4 mg/m^2 all on day 1, and prednisone 100 mg/m^2 once a day on days 1-5 of each cycle every 21 days for 6 cycles. In the R2-CHOP arm, patients received lenalidomide 25 mg daily days 1-10 of each cycle in addition to the R-CHOP21; the R2-CHOP arm also received pegfilgrastim prophylaxis, while use in the R-CHOP21 was left to provider discretion.

The primary endpoint was progression-free survival (PFS) in all patients with a co-primary end point of PFS in ABC-DLBCL. The secondary endpoints were overall response rate (ORR), complete response (CR) rate, and overall survival (OS).

There were 349 patients enrolled into the study between August 2013 and January 2017. For the efficacy analysis, 280 patients were included: 145 for R2-CHOP and 135 for R-CHOP arm. Of 234 patients with evaluable COO, 122 had GCB-DLBCL and 94 had ABC-DLBCL. The median age was 66 years. Ninety-six percent of patients had stage III or IV disease, 46% had 2 or more extra-nodal sites of involvement, and 24% had International Prognostic Index (IPI) score of 4 or 5; these high-risk features were evenly balanced between arms. The median time from diagnosis to treatment was 21 days. The median follow-up time was 3.0 years.

The results showed R2-CHOP was associated with 34% reduction in risk of progression or death compared with R-CHOP (hazard ratio [HR], 0.66; one-sided P=0.03). The one-year PFS was 84% for R2-CHOP compared to 73% for R-CHOP. R2-CHOP superiority was consistent at the two- and three-year PFS analyses. R2-CHOP had a greater ORR (97% vs 92%; P=0.06) and CR (73% vs 68%, P=0.43) compared to R-CHOP. The 3-year OS was superior in the R2-CHOP group (83% vs 75%; one-sided P=0.05). Based on COO, improved PFS was seen with R2-CHOP over R-CHOP in patients with ABC (HR, 0.64; one-sided P=0.1). Key subgroup analysis of PFS showed a trend favoring R2-CHOP in patients younger than 60 years old, with IPI scores of 2-3.

The safety analysis included 337 treated patients, with 166 for R2-CHOP and 171 for R-CHOP. There were six intended treatment cycles and 86% of R2-CHOP patients and 85% of R-CHOP patients completed all six cycles. The grade 3 or higher adverse events (AE) that significantly differed between the treatment groups were diarrhea (6% v 1%, P=0.005), anemia (29% v 20%, P=0.03), febrile neutropenia (25% v 14%, P=0.003), thrombocytopenia (34% v 13%, P < 0.001), and electrolyte abnormalities (5% v 2%, P=0.06).

Adverse events led to discontinuation in 12 patients in the R2-CHOP arm with cessation of lenalidomide alone in seven of these patients and discontinuation in four patients in the R-CHOP arm. There were nine treatment-related deaths with two in the R2-CHOP and seven in the R-CHOP arm.

ROBUST[10]

ROBUST is a large multicenter, international, double-blind, placebo-controlled phase III trial that compared R2-CHOP to R-CHOP in ABC-type DLBCL. Patients 18-80 years old with CD20 positive ABC-type DLBCL were included. Other inclusion criteria include performance status of two or less, at least stage II disease, and IPI score of two or more. Exclusion criteria consisted of prior lenalidomide exposure, CNS lymphoma, and transformed NHL. Patients were randomized in a 1:1 fashion to receive R2-CHOP or placebo/R-CHOP for six cycles.

(In the ROBUST study), the 2-year PFS was 67% for R2-CHOP and 64% for placebo/R-CHOP.

All patients received R-CHOP21 as defined above, with the exception of prednisone dosed at a flat dose of 100 mg. Patients either received lenalidomide 15 mg oral on days 1-14 of every 21-day cycle if assigned to R2-CHOP, or placebo if assigned to R-CHOP. Additionally, two additional rituximab doses (1 dose/21-day cycle) were permitted at cycles 7 and 8 if prespecified and considered standard of care per local practice. All patients were required to receive primary neutropenia prophylaxis with growth factor.

The primary endpoint was PFS for all randomized patients regardless of receiving study treatment. Secondary end points were event free survival (EFS), OS, response rates, duration of response (DOR), time to next lymphoma treatment, and safety.

There were 570 patients that met eligibility criteria in 21 countries from February 17, 2015 to August 3, 2017. Out of these 570 patients, 285 were randomized to receive either R2-CHOP or placebo/R-CHOP. The median age was 65 years. Eighty-eight percent of patients had stage III and IV disease with 34% having bulky disease. The median time from diagnosis or biopsy date to treatment was 31 days for both arms.

At the median follow-up time of 27.1 months, the primary endpoint of PFS was not met (HR, 0.85; P=0.29). The two-year PFS was 67% for R2-CHOP and 64% for placebo/R-CHOP. In exploratory subgroup analyses, there was a positive trend in two-year PFS for R2-CHOP for patients with IPI three or more, non-bulky disease, and baseline creatinine clearance 30 to < 60 mL/min. The secondary endpoint of EFS was also not met (HR, 1.04; P=0.73) in either arm. OS data was immature, but the estimated two-year OS rates were 79% for R2-CHOP arm and 80% for placebo/R-CHOP arm. ORR was 91% with CR rates of 69% for R2-CHOP arm and 65% for placebo/R-CHOP arm. The other secondary endpoints of time to next treatment and DOR were not reached.

For the safety analysis, patients that received at least one dose of any study treatment were included, which totaled to 283 R2-CHOP and 284 R-CHOP patients. There were 89% of R2-CHOP and 91% of placebo/R-CHOP patients that completed six cycles of R-CHOP. Seventy-five percent of R2-CHOP and 84% of placebo/R-CHOP patients completed both lenalidomide or placebo and R-CHOP.

Serious treatment-emergent AEs occurred in 37% of R2-CHOP and 31% of placebo/R-CHOP. The most common grade 3/4 AEs were neutropenia (60% vs 48%), anemia (22% v 14%), thrombocytopenia (17% v 11%), leukopenia (14% v 15%), febrile neutropenia (14% v 9%), and lymphopenia (11% v 8%) for R2-CHOP and placebo/R-CHOP, respectively. Treatment discontinuation occurred in 17% of R2-CHOP and 11% placebo/R-CHOP, primarily due to neutropenia. There were 119 patients that died during the study (20% R2-CHOP vs 22% placebo/R-CHOP) with the majority being caused by malignant disease or related complications.

CONCLUSION

The E1412 and ROBUST trials conflicted in terms of efficacy results but both showed no new safety concerns with treatment. E1412 showed benefit of R2-CHOP treatment in ABC-DLBCL whereas the larger ROBUST trial did not. However, both trials highlighted the addition of a novel agent to standard of care based on molecular classification. Further studies are warranted to evaluate novel agents in all molecular subsets of DLBCL. ●●

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Board Update

Thanks to Volunteers, Committee Work Shines

Larry Buie, PharmD, BCOP, FASHP
HOPA President (2021–2022)
Manager, Clinical Pharmacy Practice
PGY2 Residency Program Director, Memorial Sloan Kettering Cancer Center
New York, NY

As I write this, it's a beautiful summer day! I hope all of you have been able to enjoy summer, reconnect with family and friends, and relax a bit despite the wrenches that COVID-19 is again throwing our way.

HOPA has been hard at work for you, our members, during this time. During our virtual annual conference in April, I told you that we couldn't accomplish any of our goals for the year without volunteer support. In usual fashion, you all stepped up to the challenge! We have more than 300 volunteers serving on a variety of different committees, subcommittees, and task forces. All of our collective work ladders up to support our four strategic pillars: Education and Professional Development; Professional Tools and Resources; Research; and Advocacy.

In addition, HOPA has been involved with multiple meetings with our supporters and stakeholders to continue to understand ways that we can work together on existing and new programs; collaborative research; patient advocacy; and diversity, equity, and inclusion initiatives. Here are just a few examples:

Chemotherapy Education—Oral and IV

This year, the Oral Chemotherapy Collaborative officially kicked off. And, in addition to our oral chemotherapy education sheets, we are partnering with NCODA, ACCC, and ONS to develop IV education sheets that can be shared with our patients.

Immuno-Oncology Time to Talk™ Campaign

The Time to Talk Immuno-Oncology Toolkits, focused on immune checkpoint inhibitors and cellular therapies, were created and launched last year by a task force led by Dr. Heidi Finnes and can be found on HOPA's website under Patient Education. We recently partnered with iHeart Media to reach diverse populations, including African-American and Latinx patients and their caregivers, through radio broadcast tactics, streaming audio and video placements, and targeted social media.

This campaign will bring important immuno-oncology information into patient homes, cars, and earbuds, and encourage them to speak to their oncology pharmacist—or download a free Time to Talk I-O toolkit from our website. Personally, I think it is awesome that HOPA will be on iHeart Radio!

National Student Committee

Our task force on student engagement has recommended that we establish a National Student Committee. The purpose of this engagement is to advance the professional development of pharmacy students interested in hematology/oncology pharmacy practice, research, scholarship, or advocacy.

We appreciate the efforts of this student engagement task force, led by Drs. Amy Pick and Ginah Nightingale, and we are excited about this opportunity for students moving forward. Watch for additional information about this committee, as well as opportunities to get involved via the volunteer activity center (VAC), in the coming months!

Practice Management: Emerging Trends + Models

Recent concerns about the seriousness of the COVID-19 delta variant prompted us to change the format for Practice Management 2021 from in-person to virtual. The committee, staff, and presenters are all still committed to delivering a full day of *Emerging Trends + Models* in Practice Management on October 7, 2021. There are two learning tracks: investigational drug services and specialty pharmacy. Be sure to attend these sessions to learn about challenges and opportunities, quality improvement, and advocacy in these niche spaces of oncology pharmacy practice.

I know that by the time you see this summer will be fading and fall will usher in busy schedules and a very active HOPA agenda. I hope that you enjoy this issue of HOPA News with a feature on pharmacist burnout, practice management pearls, HOPA member contributions at the ASCO quality care symposium, tips for first time preceptors, and much, much more! Until we can all be together again, take care and stay safe! ●●

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HOPA 2021 PRACTICE MANAGEMENT
EMERGING TRENDS + MODELS

Practice Management 2021 Program is Now Online!

Due to the seriousness of the COVID-19 Delta Variant, HOPA will present Practice Management 2021 (PM21) online on **Thursday, October 7, 2021,** rather than in-person.

Learning and Networking Still Planned
Two learning tracks are still available. Choose Track A: Investigational Drug Service or Track B: Specialty Pharmacy and still earn the corresponding continuing education credits.

Find the latest information about PM21, including speaker topics, at hoparx.org.