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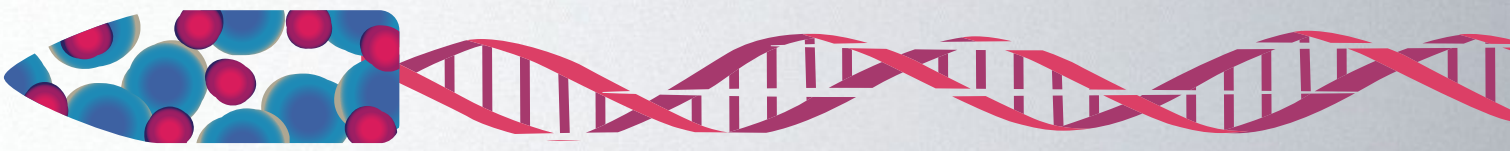

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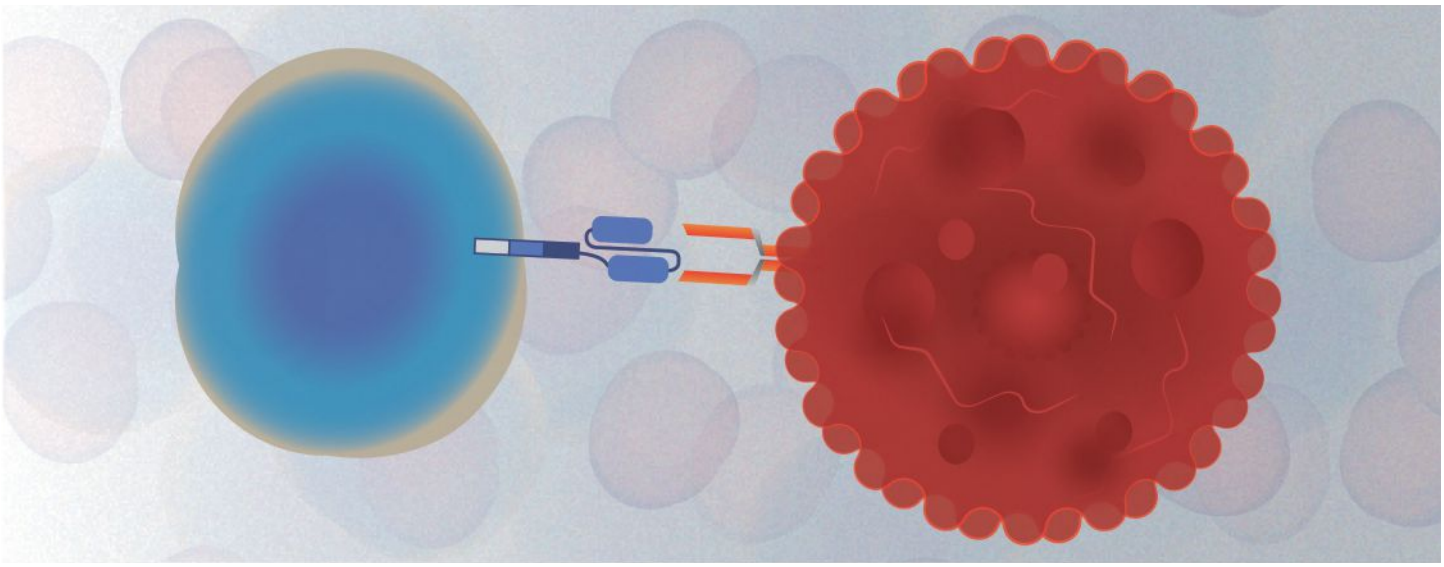

Chimeric Antigen Receptor T-Cell Therapies: A Step Closer to Achieving the Magic Bullet in Cancer Treatment

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August marked a historic milestone for both the oncology and medical communities with the first U.S. Food and Drug Administration (FDA) approval for a gene therapy, tisagenlecleucel (Kymriah).[1] Tisagenlecleucel is the first FDA-approved chimeric antigen receptor T-cell (CAR-T) therapy and has pioneered a new class of "living drugs" in the armamentarium of anticancer therapy. CAR-T cells are T-cells that have been engineered to express antigen-specific receptors and are paired with a costimulatory domain that signals activation of the cell.[2] CAR-T construct design has already undergone significant progress in the short time since the therapy's inception, making possible improvements in both efficacy and safety.[2] First-generation CAR-T cells possessed a ligand-derived extracellular domain and only a single signaling domain, making persistence of the cells a major limitation. The third- and fourth-generation CAR-T cells currently being tested in clinical trials have more sophisticated antibody-derived extracellular domains and three or four signaling domains.[2] Thus far, the therapy has been most heavily studied in B-cell malignancies because, until recently, CAR-T cells could target only extracellular antigens and B-cells express well-established cell surface markers.[2] Additionally, CAR-T cells can easily access the site of disease in B-cell malignancies because these cells are disseminated in areas of the body where T-cells naturally circulate, such as the bloodstream.[2] The early but encouraging results of CAR-T cells in this setting have served as proof of concept for the therapy and incited rapid investigation of its application in a wider variety of cancers.

CD19 has been the most common target for CAR-T therapies developed to date and has been extensively tested in clinical trials. Tisagenlecleucel is a CD19-directed CAR-T product, and its breakthrough therapy approval comes after several years of investigation in relapsed or refractory B-cell acute lymphoblastic leukemia (ALL). The most recent data from the multicenter phase-2 ELIANA trial were presented at the European Hematology Association (EHA) Annual Congress in June 2017. The investigators reported that of the 63 pediatric and young adult patients in the trial evaluable for the primary end point, 83% (95% confidence internal [CI]: 71%–91%) achieved a complete remission (CR) or complete remission with incomplete blood count recovery within 3 months of infusion, with no detection of minimal residual disease at a median follow-up of 6.4 months, which may be suggestive of durability of response.[3] Among responders, there was a 12-month relapse-free probability of 64% (95% CI: 42%–79%) and 12-month survival probability of 79% (95% CI: 63%–89%).[3]

Several other trials conducted in adult and pediatric patients with relapsed or refractory ALL have reported results similar to those of the ELIANA trial, with complete remissions ranging from 70% to 91%.[4-6] One of these studies also demonstrated persistence of the CAR-T cells with sustained remissions and associated B-cell aplasia for up to 2 years following infusion without further therapy.[5] CAR-T therapy has also been shown to be effective in patients who are refractory to the bispecific T-cell engager blinatumomab.[5] In one trial, 3 of the 30 total patients had prior exposure to blinatumomab, and 2 of these patients were able to achieve a CR with CD19 CAR-T therapy. However, one of these patients eventually relapsed with CD19-negative disease.[5]

The authors felt that these results suggest that lack of response to prior CD19-directed therapy does not preclude success with CD19 CAR-T cell treatment. However, it should be noted that all patients included in this trial still had CD19-positive disease at enrollment.[5]

In other relapsed or refractory B-cell malignancies, CD19-directed CAR-T therapy has demonstrated mixed responses. A small number of patients (22%–50%) have achieved complete responses in CD19 CAR-T cell trials in chronic lymphocytic leukemia, mantle cell lymphoma, and follicular lymphoma, with a greater proportion of patients in these studies achieving only partial responses (PR) or stable disease.[7-8] Positive results have also been observed in diffuse large B-cell lymphoma (DLBCL), where CAR-T therapy has demonstrated CR rates of 50% or higher with some durable remissions.[9-11] Data from the interim analysis of the multicenter phase-2 JULIET trial were also presented at this year's EHA Congress. Of the 85 patients included in the trial, 51 patients with multiply relapsed DLBCL were evaluable, and a CR rate of 37% and a PR rate of 8% at a median of 3.7 months postinfusion have been reported.[10] Relapse-free survival at 6 months was 79%, and all patients who achieved a CR at 3 months maintained it until the time of data cutoff for the analysis.[10] The phase-2 ZUMA-1 trial has also shown positive results in DLBCL, with a CR of 39% at a median follow-up of 8.7 months among the 72 patients treated.[11] This trial was also notable in its improvement in manufacturing time for the CAR-T cells, with an average of 17 days between apheresis and return shipment from the manufacturer, which compares to a more typical average time of 28 days in previous CAR-T cell studies.[11] Initial investigations of the application of CAR-T therapy in multiple myeloma (MM) have also used CD19-directed CAR-T, with one case series of 10 patients reporting achievement of a PR or very good partial response (VGPR) in 3 patients who remained free from progression at last follow-up (range 70–222 days). An additional 3 patients in the study were also progression-free, but not yet evaluable for response.[12] The utility of CD19 CAR-T in MM remains to be determined, and additional studies are ongoing.

Cytokine release syndrome (CRS) and neurologic toxicity are the most well documented serious adverse events associated with CAR-T cell therapy and occur during *in vivo* cell expansion. CRS is characterized by fevers, hypotension, and other reversible associated toxicities, such as neurologic disturbances and respiratory dysfunction, and can be life-threatening.[13] However, it has been noted that the occurrence, but not the severity, of CRS is correlated with response rates.[4] Close monitoring, careful management, and use of anticytokine therapy have been used to control these toxicities and maintain both safety and efficacy.[2] Tocilizumab, an interleukin-6 receptor antagonist, is most frequently used for management of grade 3–4 CRS and received FDA approval for this indication with the approval of tisagenlecleucel.[1] It may be necessary for patients to receive multiple doses of tocilizumab for the treatment of CRS; however, if CRS is unresponsive to tocilizumab, steroids (dexamethasone or methylprednisolone) are typically initiated.[14] Other agents that have been used in the second-line treatment of CRS include etanercept and siltuximab, but these have typically been used only in the setting of clinical trials because CRS can usually be effectively managed with tocilizumab and corticosteroids.[14] Recent clinical trials of certain CAR-T constructs have also begun to incorporate administration of a prophylactic dose of tocilizumab 36 hours following CAR-T cell infusion in an effort to reduce the severity of CRS. Preliminary results from one of these trials reported a grade 3 or higher CRS incidence of 13%, compared to the incidence in previous trials ranging from 27% to 53%.[11,13] In addition, other strategies related to cell dose, fractionated administration, thresholds for tumor burden at time of infusion, and incorporation of suicide genes or protein co-expression that can be targeted by commercial depleting antibodies continue to be tested in clinical trials in an effort to identify the safest mode of administration of this therapy.[2]

"CAR-T target selection has quickly evolved into the proverbial space race of cancer immunotherapy."

Other major limitations of CAR-T cells are lack of persistence in some patients, tumor evasion, and resistance. Despite the promising results of initial CD19 CAR-T trials, a subset of treated patients have relapsed with CD19-negative disease or with CD19-positive disease when CAR-T cell levels become undetectable.[2] Strategies currently in clinical testing to overcome resistance include dual antigen targeting (e.g., CD19 and CD123) or antigen and chemokine co-expression, use of CAR-T cells engineered to no longer express immune checkpoint molecules such as programmed cell death protein/ligand 1 (PD1/PDL1), and the co-administration of CAR-T therapy and PD1 monoclonal antibodies.[2] CAR-T cell persistence is highly variable, according to the target antigen, the costimulatory domain, and cell culture systems and manufacturing processes used.[2] CAR-T cell persistence is not the only correlate of durable efficacy, and optimal persistence duration remains an area of active investigation; novel constructs are continuing to be developed to improve this aspect of the therapy.[2,13]

CAR-T target selection has quickly evolved into the proverbial space race of cancer immunotherapy. Current targets under investigation in hematologic malignancies include CD20, CD22, and CD30 for B-cell malignancies; CD33 and CD123 for myeloid malignancies; and CD138, immunoglobulin-κ light chains, and B-cell maturation antigen (BCMA) for MM in hopes of improving both efficacy and disease specificity.[2,13] Encouraging preliminary data of BCMA-directed CAR-T in MM was recently reported, with 33

out of 35 relapsed or refractory patients enrolled in a phase-1 trial demonstrating a clinical remission (CR or VGPR) within 2 months of infusion.[15] Furthermore, 19 of these patients have been followed for more than 4 months, 14 of which have achieved a stringent CR (sCR) without a single case of relapse.[15] Five of these patients have been followed for more than 1 year and remain in sCR and free of minimal residual disease.[15] CAR-T therapy is also beginning to penetrate the world of solid tumors; clinical trials are either currently under way or planned using the following targets: human epidermal growth factor receptor 2 in sarcoma and glioblastoma multiforme, interleukin 13 receptor-α in glioma, disialoganglioside GD2 in neuroblastoma, and carcinoembryonic antigen in lung, breast, colorectal, and gastric cancers.[2,13] Solid tumor application of CAR-T cells will pose unique challenges because these targets are often not expressed uniformly on tumor cells as they are in hematologic malignancies and will likely result in further enhancements in the engineering of this therapy.[2]

A discussion of CAR-T therapy without mention of cost would unfortunately be incomplete. Cost has emerged as a primary concern with the approval of tisagenlecleucel and its associated $475,000 price tag.[16] The product's manufacturer, Novartis, has struck a first-of-its-kind pay-for-performance deal with the Centers for Medicare and Medicaid Services that will fully reimburse the cost of therapy in the event that no response is seen by 1 month after infusion; however, questions and debates regarding reimbursement and pricing still abound.[17] The manufacturer is also providing copay and travel assistance programs, given that the therapy will not be immediately available at all centers.[17] Regulation and practical administration for CAR-T therapy is also uncharted territory because, despite being an engineered human cell product, it is being regulated by the FDA as a drug. This situation will likely create novel challenges for pharmacy departments, with unique considerations related to product labeling and dispensing, budgeting, risk evaluation and mitigation strategies (REMS) program management, and reimbursement. Little guidance is available on these issues, though many institutions are currently navigating their way through them and may be able to share their experiences in the future. The Foundation for the Accreditation of Cellular Therapy (FACT) has created the first set of accreditation standards for programs administering immune effector cell therapy; they provide guidelines and minimum requirements for appropriate management of these therapies from an institutional perspective and are an excellent resource for institutions that will provide this therapy.[18] Creation of standard operating procedures for monitoring and management of toxicities and educational and training requirements of key personnel, including pharmacists, are among the outlined requirements set forth by FACT, and these, when complete, will fulfill the majority of requirements of the tisagenlecleucel REMS program.[18] We are seeing just the tip of the iceberg of CAR-T therapy, and as the technology improves and is used more widely, further questions and challenges will undoubtedly arise. However, for the present, we should all revel in this unique and exciting breakthrough in the war against cancer and all the potential it holds. ●●

REFERENCES

1. U. S. Food and Drug Administration. FDA approval brings first gene therapy to the United States [news release]. August 30, 2017. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm574058.htm
2. Fesnak AD, Levine BL, June CH. Engineered T cells: the promise and challenges of cancer immunotherapy. *Nat Rev Cancer*. 2016;16(9):566-581.
3. Buechner J, Grupp SA, Maude SL, et al. Global registration trial of efficacy and safety of CTL019 in pediatric and young adult patients with relapsed/refractory acute lymphoblastic leukemia: update to the interim analysis. Paper presented at 22nd Congress of the European Hematology Association; June 22-25, 2017; Madrid, Spain. Abstract S476.
4. Lee DW, Kochenderfer JN, Stetler-Stevenson M, et al. T cells expressing CD19 chimeric antigen receptors for acute lymphoblastic leukemia in children and young adults: a phase I dose-escalation trial. *Lancet*. 2015;385:517-528.
5. Maude SL, Frey N, Shaw PA, et al. Chimeric Antigen Receptor T Cells for Sustained Remissions in Leukemia. *New Engl J Med*. 2014;371:1507-1517.
6. Park JH, Riviere I, Xiuyan W, et al. CD19-Targeted 19-28z CAR-Modified Autologous T Cells Induce High Rates of Complete Remission and Durable Responses in Adult Patients with Relapsed, Refractory B-Cell ALL. *Blood*. 2014;124:382.
7. Kochenderfer JN, Somerville R, Lu L, et al. Anti-CD19 CAR T cells administered after low-dose chemotherapy can induce remissions of chemotherapy-refractory diffuse large B-cell lymphoma. *Blood*. 2014;124(21):550.
8. Schuster SJ, Svoboda J, Dwivedy Nasta S, et al. Phase IIa trial of chimeric antigen receptor modified T cells directed against CD19 (CTL019) in patients with relapsed or refractory CD19+ lymphomas. *Blood*. 2015;126(23):183.
9. Kochenderfer JN, Dudley ME, Kassim SH, et al. Chemotherapy-refractory diffuse large B-cell lymphoma and indolent B-cell malignancies can be effectively treated with autologous T-cells expressing an anti-CD19 chimeric antigen receptor. *J Clin Oncol*. 2015;33:540-549.
10. Schuster SL, Bishop MR, Tam C, et al. Global pivotal phase 2 trial of the CD19-targeted therapy CTL019 in adult patients with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL)—an interim analysis. Paper presented at 22nd Congress of the European Hematology Association; June 22-25, 2017; Madrid, Spain. Abstract LB2604.
11. Locke FL, Neelapu SS, Bartlett NL, et al. Clinical and biological covariates of outcomes in ZUMA-1: A pivotal trial of axicabtagene ciloleucel (AXI-CEL; KTE-C19) in patients with refractory aggressive non-Hodgkin lymphoma (NHL). Paper presented at 22nd Congress of the European Hematology Association; June 22-25, 2017; Madrid, Spain. Abstract S466.
12. Garfall AL, Maus MV, Hwang WT, et al. Chimeric antigen receptor T cells against CD19 for multiple myeloma. *N Engl J Med*. 2015;373:1040-1047.
13. Jackson HJ, Rafiq S, Brentjens RJ. Driving CAR T-cells forward. *Nat Rev Clin Oncol*. 2016;13(6):370-383.
14. Lee DW, Gardner R, Porter DL, et al. Clinical concepts in the diagnosis and management of cytokine release syndrome. *Blood*. 2014;124(2):188-195.
15. Fan FX, Zhao W, Liu J, et al. Durable remissions with BCMA-specific chimeric antigen receptor (CAR)-modified T cells in patients with refractory/relapsed multiple myeloma. *J Clin Oncol*. 2017;35(18). doi:10.1200/JCO.2017.35.18_suppl.LBA3001 [Epub ahead of print].
16. Rosenbaum L. Tragedy, perseverance, and chance—the story of CAR-T therapy. *N Engl J Med*. 2017 Sep 13. doi: 10.1056/NEJMp1711886 [Epub ahead of print].
17. Mukherjee, S. The way we treat cancer will be revolutionized as gene therapy comes to the U.S. *Fortune*. 2017(Aug 30). http://fortune.com/2017/08/30/fda-novartis-car-t-kymriah/
18. Foundation for the Accreditation of Cellular Therapy. Immune Effector Cell Standards. www.factwebsite.org/iecstandards/

USP <800>: Strategies for Implementing a Successful Assessment of Risk

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The United States Pharmacopeia (USP) issued General Chapter <800> in February 2016, and institutions that prepare and administer hazardous drugs are expected to be compliant with the guidelines by July 2018.[1] As this issue of *HOPA News* was being prepared, USP released a notice of intent to change the official date of USP <800> to December 1, 2019.[2] This date will align with the next revision of USP <797>. However, USP is still encouraging "early adoption and implementation of Chapter <800> to help ensure a safe environment and protection of healthcare practitioners."[2] Although each state board of pharmacy may require slight variations on USP <800>, the general requirements of the chapter will remain the same, with regard to safe handling of hazardous medications, for all institutions.

USP <800> provides specific guidance for those medications categorized as hazardous by the National Institute for Occupational Safety and Health (NIOSH). NIOSH defines a *hazardous drug* as a medication that has one of these six characteristics:[3]

- carcinogenicity
- teratogenicity
- reproductive toxicity in humans
- organ toxicity in low levels in animals or humans
- genotoxicity
- mimicking of a hazardous drug in structure or toxicity.

NIOSH further categorizes hazardous medications (see Tables 1, 2, and 3 in NIOSH's 2016 publication).[3] Table 1 includes those antineoplastic agents that pharmacists have traditionally viewed as hazardous, with long-standing handling precautions already in place. Agents listed in Tables 2 and 3, on the other hand, may include many drugs for which pharmacists have not implemented strict handling requirements, but all of which now require documented containment strategies under USP <800>.

Under the new USP <800>, many institutions are being challenged to rethink the safety of drugs and dispensing procedures that historically have not required the same stringent containment strategies as the antineoplastic drugs in Table 1. Institutions have two options. The first is to handle each NIOSH drug using all the containment and risk practices listed in USP <800>, a proposition that is likely to affect pharmacy workflow too adversely to be a practical or feasible solution. The second is to perform an assessment of risk to determine alternative containment strategies and work practices. This allows some dosage forms of hazardous drugs to be handled without all of the containment precautions outlined in USP <800>.[1] Most institutions are electing to follow this second option.

"Depending on the number of hazardous NIOSH medications on an institution's formulary, the reality is that the assessment of risk is a large undertaking."

When the assessment of risk is completed for all hazardous drugs on an institution's formulary, engineering controls, personal protective equipment, and workplace practices must be reviewed to ensure appropriate hazardous drug control per USP <800>.[1] Such a succinct summary may make the process sound easy, but depending on the number of hazardous NIOSH medications on an institution's formulary, the reality is that the assessment of risk is a large undertaking, leaving staff at some institutions wondering where to start.

Faced with this conundrum, the Department of Pharmacy at Cincinnati Children's Hospital Medical Center recently spearheaded a Children's Hospital Association collaborative effort between member institutions to complete an assessment of risk for each of the hazardous drugs listed in NIOSH Tables 2 and 3. When asked for some general tips on completing the assessment of risk, Chad Watkins, PharmD, director of pharmacy for Cincinnati Children's Hospital Medical Center–Liberty Campus, recommended first prioritizing those medications that pose the highest risk to healthcare workers and work down the list toward medications that pose minimal risk.[4]

Watkins further advocates "establishing several levels of risk to group NIOSH Table 2 and 3 medications [into], such as: Low Risk, Moderate Risk, and High Risk."[4] In deciding what constitutes low, moderate, or high risk, Watkins recommends establishing criteria that would necessitate an increase in risk category, such as manufacturer's safe handling guidelines, carcinogenicity as defined by the International Agency for Research on Cancer, American Hospital Formulary Service classification, pregnancy category, and chemical characteristics.[3]

Risk factors for exposure to certain hazardous drugs may vary between institutions and will affect whether a drug is categorized as low, medium, or high risk. For example, opening a unit-dose package of a hazardous drug prior to administration poses a lower risk of exposure than crushing a tablet to create a suspension.[5] An institution that purchases

and dispenses tacrolimus only in unit-dose capsules may categorize risk exposure for tacrolimus as lower risk than a facility that purchases tacrolimus capsules in bulk bottles, which necessitates repackaging prior to dispensing. The risk category for tacrolimus would be even higher in a facility where staff members open those capsules to make an oral suspension. Consider the dosage forms and the life cycle of a drug in your institution when completing the assessment of risk.[5] These assigned risk levels will help determine the management of handling and containment precautions under USP <800>.

When the drugs and risk levels have been determined, a standardized worksheet can be used to document the assessment of risk. This worksheet should include, at a minimum, the drug name, the hazardous-drug category, dosage forms, the risk of exposure, packaging, any required manipulation, and documentation of any alternative containment strategies or work practices. Review of this assessment of risk must be documented annually.[1] A worksheet that can be tailored to meet your institution's needs is available in a hazardous drug toolkit published by Joint Commission Resources.[5]

Following completion of the assessment of risk, institutions will need to review their personal protective equipment (PPE) to ensure that it meets the minimum standards outlined in the assessment of risk. NIOSH Table 5 and Section 7 of the USP <800> outline recommend PPE for healthcare workers.[1,2] NIOSH has also published a detailed paper regarding appropriate PPE for the handling of hazardous drugs.[6] Additionally, institutional policies will likely need to be reviewed, a process that Watkins says "poses a huge challenge in maintaining consistency between all hospital services."[4] Finally, all frontline staff must be educated on USP <800> process changes. According to Watkins, this is likely to be the biggest challenge in implementing USP <800>: "Developing a hazardous communication program that effectively reflects the process is essential in achieving compliance. The program must have the capability to direct handling precautions to all staff."[4] Because staff in several service areas will need to comply with USP <800>, training must be specific to each role and completed before staff members handle any hazardous drugs.[1] Some strategies that may be implemented include required orientation on USP <800> practices for new hires, completion of annual competencies by frontline staff, and department-specific training courses. Per USP <800>, reassessment must be completed and documented at least once per year.[2]

Given that implementation of USP <800> will affect several institutional service lines, multidisciplinary involvement in completing the assessment of risk is essential. Watkins recommends that, at a minimum, the task force should include a compounding pharmacist, pharmacy manager/director, nursing manager/director, and staff from pharmacy education, nursing education, occupational safety, and employee health.[4] This multidisciplinary approach to the assessment of risk allows each discipline to provide input based on where in the medication administration process their handling of hazardous drugs occurs. Gathering this information early in the assessment of risk process will allow for identification of potential issues in hazardous-drug handling prior to the transition to implementing USP <800> practices.

Implementing USP <800> will be a work in progress. As institutions complete this massive undertaking, lessons learned will likely necessitate reassessment and changes. Beginning with a focused plan for the assessment of risk, building strong training programs, and including key stakeholders early in the process will help to ensure a smooth rollout. ●●

REFERENCES

1. United States Pharmacopeial Convention. General chapter <800> Hazardous drugs—handling in healthcare settings. USP 40-NF 35; 2017.
2. Notice of intent to revise: General chapter <800> Hazardous drugs—handling in healthcare settings. www.uspnf.com/notices/gc-800-hazardous-drugs-handling-in-healthcare-settings Updated September 29, 2017. Accessed October 3, 2017.
3. Connor TH, MacKenzie BA, DeBord DG, et al. NIOSH list of antineoplastic and other hazardous drugs in health care settings, 2016. Cincinnati, OH: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health; 2016.
4. Chad Watkins, PharmD, e-mail communication, September 19, 2017.
5. Connor TH, Douglass K, Eisenberg S, et al. *Improving safe handling practices for hazardous drugs: toolkit.* Oakbrook Terrace, IL: Joint Commission Resources; 2016.
6. Centers for Disease Control and Prevention. *Personal protective equipment for health care workers who work with hazardous drugs. NIOSH workplace solutions.* Publication no. 2009-106; 2008.

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Is It Business-Savvy for a Pharmacist to Complete an MBA?

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It is humbling and gratifying to serve the patients at the Robert H. Lurie Comprehensive Cancer Center of Northwestern University, a National Comprehensive Cancer Network–designated institution. The spectrum of patients seen at Northwestern Medicine ranges from those with early-stage cancers requiring standard-of-care antineoplastic regimens to those with advanced cancers requiring personalized medicine. Running this vast cancer center requires highly qualified employees across a range of interdisciplinary professions, including financial professionals, physicians, nurses, and pharmacists. My role as the team lead for the operations of our three clinic pharmacies requires me to be more on the front line, handling daily operations, than my colleagues in the coordinator and manager roles, who serve primarily on the back end, tackling higher-level projects. My pursuit of a master's degree in business administration (MBA) with a healthcare focus has opened the door for me to effectively operationalize the work of clinic pharmacies, manage personnel, and become a steward of inventory and resources.

By way of an introduction, after being out of school for 2 years, I started to steer from oncology to emergency medicine, acute and critical care, and outpatient oncology. I knew that to be the oncology pharmacist I aspired to be, I needed to augment my clinical and managerial skills. Rather than completing a PGY-2 oncology or health-system administration residency, I turned my attention to finding an MBA program with a healthcare focus. This program took me on quite a journey—starting with a course on critical thinking, continuing with courses on accounting and finance and then managerial and personnel behavior, and concluding with courses on the healthcare delivery system, healthcare ethics, and healthcare financing.

Whereas hands-on experience and immersion provide very potent and effective learning opportunities, the completion of my MBA degree with a healthcare focus led me to my current position, where I am able to apply the vast majority of my didactic work in my job. For example, the course I took on applied statistics covered a wide array of ways to quantify and apply statistics to real-world situations. This course assisted me in understanding medical journals, particularly the sections on statistics and quantification of results. It also helped me understand how institutions report quantitative results about performance, whether on an individual, departmental, or institutional level. Another course that has had an impact on my career focused on managerial and personnel behavior. All the institutions I have worked in have differed in managerial style and reporting structure, which is not surprising. I received intensive training in this course, but I found that no didactic coursework can truly train and prepare one for handling success and conflict. However, because the course immersed us in many case studies, the real-world examples of success and conflict that I encounter at work are not completely foreign to me.

Two other courses that have paid major dividends in my current role are those on healthcare ethics and healthcare financing. Both courses offered numerous parallels in health care, especially oncology. We dove into the complex topic of medication pricing, which I then applied to oncology. Although we know the amount of research and development that goes into creating medications, the expense of antineoplastic medications presents an obvious ethical dilemma, particularly when we are working with such a vulnerable patient population. On a more objective note, I have found that knowledge of inventory management is imperative in oncology. Outpatient oncology clinic pharmacies operate with a vast budget—in some cases a budget larger than those of entire pharmacy departments. It is therefore crucial that we evaluate our inventory turnover so that we can establish appropriate par levels for both medications and ancillary supplies. We want to do what is right for our patients by having the proper medications on hand, but we also want to do what is right for our department by ensuring that our inventory is turning over appropriately.

My completion of an MBA with a healthcare focus has had a significant impact on my career, allowing me to gain the experience and immersion that I needed to apply my education to my work. However, despite the advantages I have gained by completing an MBA, I see that pharmacists with MBAs are still relatively uncommon. For pharmacists who will not be completing a PGY-2 oncology or health-system administration residency but would like to pursue pharmacy management, augment their supervisory skills, or better understand and apply the complex finances that surround oncology pharmacy, I recommend pursuit of an MBA.

Pembrolizumab in Microsatellite Instability–High or Deficient Mismatch Repair Solid Tumors: The First FDA Approval for a Tissue-/Site-Agnostic Indication

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Houston, TX

The concept of using the host's immune system in the fight against cancer surfaced in the 19th century.[1,2] Historically, however, limited strides have been made in stimulating T-cell immune responses via vaccination or cytokine treatment (interleukin-2 or interferon-alpha).[1-5] Recently, cancer immunotherapy has reemerged in the forefront of oncology investigation, leading to a surge of immune modulation agents approved by the U.S. Food and Drug Administration (FDA).[6-10] The resurgence in oncology care resulted from an investigative shift in targeting tumor immune inhibitory mechanisms, with the identification of key immune checkpoint receptors, cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed cell death-1 (PD-1).[1-5]

Since 2014, five monoclonal antibodies (mAbs) that target the immune checkpoint PD-1 pathway have been approved by the FDA.[4-8] These agents have shown rapid growth in approval accompanied by a vast array of solid tumor indications. Further breakthroughs with these agents are expected, given the substantial number of trials recruiting subjects (a clinicaltrials.gov search for "PD-1" revealed 236 recruiting studies, and a "PD-L1" search showed 166 recruiting studies).[11-12] PD-1 and its respective ligands, programmed cell death ligand-1 (PD-L1) and programmed cell death ligand-2 (PD-L2), when bound cause T-cell exhaustion.[1-5] Tumor cells have an upregulation of PD-L1, allowing these cells to suppress the immune system and avoid elimination. Blocking PD-1/PD-L1 via PD-1 or PD-L1 mAbs allows for T-cell activation. Pembrolizumab, an IgG4 PD-1 mAb, is among these agents.

On May 23, 2017, pembrolizumab achieved a milestone in oncology care when it obtained accelerated FDA approval for a biomarker-specific indication regardless of tumor site origin.[6,13] The tissue-/site-agnostic indication is for the treatment of microsatellite instability–high (MSI-H) or deficient mismatch repair (dMMR) adult and pediatric patients with unresectable or metastatic solid tumors. Patients with solid tumors must have had disease progression following prior treatment and have no satisfactory alternative treatment options; metastatic colorectal cancer (mCRC) patients, specifically, are candidates for pembrolizumab only after disease progression on fluoropyrimidine, oxaliplatin, and irinotecan. The accelerated approval was based on tumor response and the duration of response seen in a pooled analysis, with continued approval contingent upon a confirmatory trial. The prescribing information limits use in pediatric patients with MSI-H central nervous system cancers because safety and efficacy in this population have not been established. Dosing is 200 mg flat dose (adults) or 2 mg/kg (pediatric patients) intravenous (IV) every 3 weeks.

"Pembrolizumab's approval for a tissue-agnostic indication represents an exciting step in oncology care, particularly for rare tumors."

Microsatellites are repetitive sequences of deoxyribonucleic acid (DNA) susceptible to errors during replication.[14-16] The mismatch repair system functions to correct these insertion or deletion errors; however, when a deficient mismatch repair system is present, this leads to microsatellite instability and causes a highly mutated state. MSI-H tumors can be sporadic or can be associated with hereditary nonpolyposis colorectal cancer (HNPCC), known commonly as Lynch syndrome. Lynch syndrome is characterized by inherited defects in MMR proteins (MLH1, MSH2, MSH6, PMS2).[14-17] MSI-H tumors are seen more in the sporadic setting resulting from somatic hypermethylation of the MLH1 promotor (often associated with BRAFV600E mutation in mCRC). MSI-H/dMMR status is tested either by polymerase chain reaction (PCR) DNA testing or via immunohistochemical (IHC) staining to detect the loss of one or more of the mismatch repair proteins.[14-16] A variety of malignancies are associated with MSI-H. Colorectal cancer (15%–20%), endometrial cancer (20%–30%), and gastric cancer (8%–22%) are more frequently reported, but this tumor phenotype can be seen to a lesser degree in many malignancies, including cholangiocarcinoma, pancreatic, esophageal, prostate, small-bowel, thyroid, melanoma, ovarian, cervical, head and neck, and renal cell carcinoma.[14]

Differences between CRC MSI-H/dMMR tumors and microsatellite stable/proficient mismatch repair (MSS/pMMR) CRC tumors have emerged—in clinicopathological features, prediction of immunotherapy response, and prognoses.[18-19] National guidelines recommend MSI or MMR testing for all mCRC patients, given the clear distinction in responses shown with immunotherapy in these two subsets.[18] The immunotherapy

response differences in mCRC were identified by two phase-2 studies with PD-1 inhibitors. Le and colleagues revealed an objective response rate (ORR) of 40%, with 78% progression-free survival (PFS) rate at 12 weeks in the MSI-H/dMMR group who received pembrolizumab compared to 0% ORR and 11% PFS rate in the MSS/pMMR group.[20] Updated results continue to show benefit in only MSI-H/dMMR mCRC patients, with ORR of 50% compared to 0% in the MSS/pMMR group.[21] Disease control was 89% for MSI-H/dMMR mCRC compared to 16% in the MSS/pMMR group. Overman and colleagues studied nivolumab alone or in combination with ipilimumab (a CTLA-4 inhibitor). Preliminary results showed that nivolumab alone resulted in a 27% versus 0% ORR in MSI-H/dMMR and MSS/pMMR, respectively.[22] A recent update on the current results of the nivolumab-alone arm in the MSI-H/dMMR mCRC group showed a 31% ORR and 69% disease control.[23] Diaz and colleagues reported the results of MSI-H/dMMR non-CRC patients from a phase-2 independent tumor histology trial design.[24] Twenty-nine patients (with mostly endometrial, pancreatic, and ampullary cancer) received pembrolizumab. The ORR was 48%, with a disease control rate of 72%. Median overall survival and PFS were not reached at 21 months.

Pembrolizumab's recent tissue-/site-agnostic approval was based on a pooled analysis of five uncontrolled open-label multicenter single-arm trials (KEYNOTE-016, KEYNOTE-164, KEYNOTE-028, KEYNOTE-012, and KEYNOTE-158).[6] Trial design and patient population information is included in **Table 1**. There were 149 total MSI-H/dMMR patients with a median age of 55 years. Patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1. Almost all patients (98%) had metastatic disease. Patients had a median of two prior treatments. Sixty percent had mCRC, with the remainder involving a variety of non-CRC tumors (**Table 2**). MSI or MMR status was determined via local PCR, local IHC, or central PCR. Patients received either 200 mg IV pembrolizumab every 3 weeks or 10 mg/kg IV every 2 weeks. From the pooled analysis the ORR was 39.6% (majority partial response 32.2%), with a duration of response at 6 months of 78%. The rationale for the positive outcomes in MSI-H/dMMR subset compared to MSS/pMMR patients is the concept that MSI-H/dMMR status contains a hypermutated state, increased tumor neoantigens (non-self-recognition by the immune system), and tumor-infiltrating T-cell lymphocytes making MSI-H/dMMR tumors more susceptible to immunotherapy modulating agents.

Pembrolizumab's approval for a tissue-agnostic indication represents an exciting step in oncology care, particularly for rare tumors or entities, which often lack investigational focus and standard-of-care treatment options. MSI-H/dMMR is a rare entity among malignancies. MSI and MMR testing requires tissue; therefore, status determination may present a dilemma for additional testing in rare tumors with a low incidence of MSI-H/dMMR. Regardless of additional testing or biopsy, this pooled analysis allowed for outcomes to be reviewed faster than in traditional tissue-specific trials and was evaluated in patients with refractory cancer who had limited treatment options. Careful considerations and challenges remain, however, in expanding approvals or trial designs based on a targeted characteristic. There remain nonresponders to PD-1 inhibitor monotherapy in MSI-H/dMMR (responses ~ 30%–50%). Future investigation in this tissue-agnostic subset presents a challenge when one is considering immunotherapy-refractory disease and combination therapy trial design because antineoplastics differ in effectiveness across malignancies. Further, oncology investigators must be cautious when extrapolating targeted characteristics across malignancies, as is evident in the study of *BRAF* inhibition. *BRAF* inhibitor outcomes were shown to be vastly different among varying *BRAF* mutated tumors (minimal response in mCRC compared to metastatic melanoma). Targeted therapy and molecular tumor characterization have greatly expanded the way we understand the heterogeneous nature of cancer; however, more steps remain in understanding these targets across malignancies and even in tumor types with the same origin. ●●

Table 1. Five Keynote Trial Designs in Pooled Analysis[6]

Trial Name	Design	Population
KEYNOTE-016	Multicenter phase 2	28 CRC 30 non-CRC
KEYNOTE-164	Multicenter phase 2	61 CRC
KEYNOTE-012	Retrospectively identified	6 non-CRC (gastric, bladder, or triple negative breast cancer)
KEYNOTE-028	Retrospectively identified	5 CRC or non-CRC (esophageal, biliary, breast, endometrial)
KEYNOTE-158	Multicenter phase 2	19 non-CRC

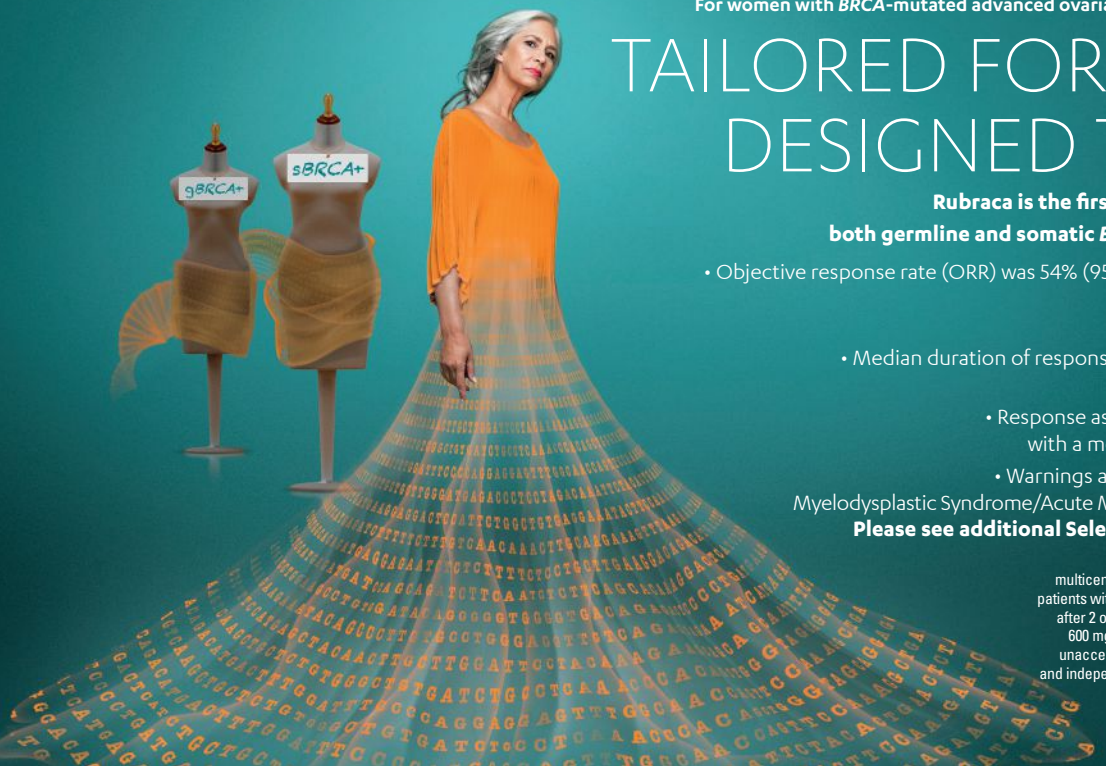
Note. CRC = colorectal cancer.

Table 2. Patients in Keynote Trials by Malignancy[6]

Malignancy	Patients in Five KEYNOTE Trials
Colorectal	90
Endometrial	14
Biliary	11
Gastric or gastroesophageal junction	9
Pancreatic	6
Small bowel	8
Breast	2
Prostate	2
Bladder	1
Esophageal	1
Sarcoma	1
Thyroid	1
Retroperitoneal	1
Small cell lung	1
Renal cell	1

REFERENCES

1. Hoos A. Development of immune-oncology drugs-from CTLA4 to PD1 to the next generations. *Nat Rev Drug Discov.* 2016 Apr; 15(4):235-247.
2. Iwai Y, Hamanishi J, Chamoto K, et al. Cancer immunotherapies targeting the PD-1 signaling pathway. *J Biomed Sci.* 2017 Apr 4;24(1):26.
3. Farkona S, Diamandis EP, Blasutiq IM. Cancer immunotherapy: the beginning of the end of cancer? *BMC Med.* 2016 May 5;14:73.
4. Emens LA, Ascierto PA, Darcy PK, et al. Cancer immunotherapy: opportunities and challenges in the rapidly evolving clinical landscape. *Eur J Cancer.* 2017 Aug; 81:116-129.
5. Ma W, Gilligan BM, Yuan J, et al. Current status and perspectives in translational biomarker research for PD-1/PD-L1 immune checkpoint blockade therapy. *J Hematol Oncol.* 2016 May 27; 9(1):47.
6. Keytruda (pembrolizumab) [package insert]. Whitehouse Station, NJ: Merck Sharp and Dohme Corp.; 2017 July. Accessed September 12, 2017.
7. Opdivo (nivolumab) [package insert]. Princeton, NJ. Bristol-Myers Squibb Co. 2017 September. Accessed September 12, 2017.
8. Tecentriq (atezolizumab) [package insert]. San Francisco, CA. Genentech, Inc.; 2017 April. Accessed September 12, 2017.
9. Bavencio (avelumab) [package insert]. Rockland, MA. EMD Serono, Inc.; 2017 March. Accessed September 12, 2017.
10. Imfinzi (durvalumab) [package insert]. Cambridge, England. AstraZeneca Pharmaceuticals LP. 2017 April. Accessed September 12, 2017.
11. Clinicaltrials.gov. PD-1. Accessed September 12, 2017.
12. Clinicaltrials.gov. PD-L1. Accessed September 12, 2017.
13. U.S. Food and Drug Administration. FDA grants accelerated approval to pembrolizumab for first tissue/site agnostic indication. https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm560040.htm. Accessed September 12, 2017.
14. Colle R, Cohen R, Cochereau D, et al. Immunotherapy and patients treated for cancer with microsatellite instability. *Bull Cancer.* 2017 Jan; 104(1):42-51.
15. Chang L, Chang M, Chang HM, et al. Expending role of microsatellite instability in diagnosis and treatment of colorectal cancer. *J Gastrointest Cancer.* 2017 Jul 11. doi: 10.1007/s12029-017-9991-0. [Epub ahead of print]
16. Lin EI, Tseng LH, Gocke CD, et al. Mutational profiling of colorectal cancers with microsatellite instability. *Oncotarget.* 2015 Dec 8; 6(39): 42334-42344.
17. Koi M, Carethers JM. The colorectal cancer immune microenvironment and approach to immunotherapies. *Future Oncol.* 2017 Aug; 13(18);1633-1647.
18. National Comprehensive Cancer Network. Colon Cancer. Version 2.2017. Accessed September 12, 2017.
19. Van Cutsem E, Cervantes A, Adam R, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. *Ann Oncol.* 27;1386-1422.
20. Le DT, Uram JN, Wang H, et al. PD-1 blockade in tumors with mismatch-repair deficiency. *N Engl J Med.* 2015;372:2509-2520.
21. Le DT, Uram JN, Wang H, et al. Programmed death-1 blockade in mismatch repair deficient colorectal cancer. *J Clin Oncol* 2016;34 abstr 103.
22. Overman MJ, Kopetz S, McDermott RS, et al. Nivolumab +/- ipilimumab in treatment of patients with metastatic colorectal cancer with or without high microsatellite instability: checkmate-142 interim results. *J Clin Oncol.* 2016;34; abstr 3501.
23. Overman MJ, McDermott R, Leach JL, et al. Nivolumab in patients with metastatic DNA mismatch repair deficient or microsatellite instability-high colorectal cancer (checkmate 142): an open-label, multicenter, phase 2 study. *Lancet Oncol.* 2017 Sep;18(9):1182-1191.
24. Diaz LA, Uram JN, Wang H, et al. Programmed death-1 blockade in mismatch repair deficient cancer independent of tumor histology. *J Clin Oncol.* 2016;34; abstr 3003.



For women with *BRCA*-mutated advanced ovarian cancer after two or more chemotherapies,

TAILORED FOR RESPONSE, DESIGNED TO ENDURE

Rubraca is the first FDA-approved PARP inhibitor to treat both germline and somatic *BRCA*-mutated advanced ovarian cancer

- Objective response rate (ORR) was 54% (95% CI [44, 64]) per investigator assessment
  - Complete response rate was 9%
  - Partial response rate was 45%
- Median duration of response (DOR) was 9.2 months (95% CI [6.6, 11.6]) per investigator assessment
- Response assessment by IRR was 42% (95% CI [32, 52]), with a median DOR of 6.7 months (95% CI [5.5, 11.1])
- Warnings and precautions: Rubraca is associated with Myelodysplastic Syndrome/Acute Myeloid Leukemia and Embryo-Fetal Toxicity

Please see additional Select Important Safety Information below.

The efficacy of Rubraca was investigated in 106 patients in two multicenter, single-arm, open-label clinical trials, Study 1 and Study 2, in patients with advanced *BRCA*-mutant ovarian cancer who had progressed after 2 or more prior chemotherapies. All 106 patients received Rubraca 600 mg orally twice daily as monotherapy until disease progression or unacceptable toxicity. ORR and DOR were assessed by the investigator and independent radiology review (IRR) according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

g*BRCA*, germline *BRCA*; IRR, independent radiology review; s*BRCA*, somatic *BRCA*.

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

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

Select Important Safety Information

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

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

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

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

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

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

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

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

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

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

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

CLOVIS ONCOLOGY

Rubraca® (rucaparib) tablets

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PP-RUCA-US-0245 05/2017

RUBRACA™ (rucaparib) tablets, for oral use

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

INDICATIONS AND USAGE

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

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

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Myelodysplastic Syndrome/Acute Myeloid Leukemia

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

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

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

Embryo-Fetal Toxicity

Rubraca can cause fetal harm when administered to a pregnant woman based on its mechanism of action and findings from animal studies. In an animal reproduction study, administration of rucaparib to pregnant rats during organogenesis resulted in embryo-fetal death at maternal exposure that were 0.04 times the $AUC_{0\text{-}24h}$ in patients receiving the recommended dose of 600 mg twice daily. Apprise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment and for 6 months following the last dose of Rubraca *[see Use in Specific Populations (8.1, 8.3) and Clinical Pharmacology (12.1) in the full prescribing information]*.

ADVERSE REACTIONS

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

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

Clinical Trials Experience

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

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

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

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

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

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

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

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

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

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

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

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

Data

Animal Data

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

Lactation

Risk Summary

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

Females and Males of Reproductive Potential

Pregnancy Testing

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

Contraception

Females

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

Pediatric Use

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

Geriatric Use

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

Hepatic Impairment

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

Renal Impairment

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

OVERDOSAGE

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

PATIENT COUNSELING INFORMATION

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

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

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

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

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

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

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Boulder, CO 80301
1-844-258-7662

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Collaborative Drug Therapy Management in the Oncology Setting

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Collaborative practice agreements (CPAs) allow pharmacists to contribute toward a team-based healthcare model, as well as improve medication safety and achieve cost savings.[1,2] The concept of collaborative drug therapy management (CDTM) is not new: the first position statement on the topic was issued by the American College of Clinical Pharmacy in 1997.[3] As the projected shortage of oncologists increases each year, the need for CDTM agreements grows. A 2014 study published by the American Society of Clinical Oncology projects that by the year 2025, about 2,400 fewer oncologists may be practicing than are needed.[4] As the projected shortage of healthcare providers, and specifically oncologists, increases, pharmacists are in a position to help improve access to healthcare in the oncology setting.[5]

Although CDTM is not universally permitted, 48 states currently have laws and regulations in place allowing its implementation. The pharmacy services that are allowed under CPAs vary by state and may include such functions as modifying medication therapy, initiating and discontinuing medication therapy, and ordering and interpreting laboratory studies. Although CDTM agreements traditionally exist between pharmacists and physicians, a number of states have allowed CDTM agreements to expand and include other healthcare providers such as nurse practitioners. The scope of practice of the collaborating pharmacist also will vary depending on each state's laws and regulations. Many states allow the pharmacist to make patient-care interventions according to preselected protocols and guidelines or for specific drug classes or drugs. Some states, however, allow the pharmacist to make patient-care interventions without the use of protocols, providing a more autonomous scope of practice.[6]

Much of the literature on CPAs that has been published to date has focused on chronic disease states, with numerous studies showing clinical benefits in such disease states as diabetes, hypertension, and hyperlipidemia.[7,8] Currently, limited data are available to document the clinical or economic benefits of CDTM in the oncology setting. Hansen and colleagues reported the outcomes of CDTM agreements for the management of chemotherapy-related symptom management in a gynecologic oncology clinic. The CDTM agreements contained treatment algorithms for the management of chemotherapy-induced nausea and vomiting, chemotherapy-induced peripheral neuropathy, vasomotor symptoms, vaginal dryness, and bone health. This CDTM pilot study showed favorable results in patient and physician satisfaction surveys, as well as improvements in patient symptom scores compared to baseline.[9] Valgus and colleagues described the implementation of a pharmacist-led interdisciplinary care model in an outpatient oncology clinic serving gynecologic, radiation, medical, and surgical oncology patients. The majority of medication interventions pertained to pain management, with the other symptoms commonly managed consisting of nausea and vomiting, constipation, and anxiety. Reductions in patient-reported symptoms were seen after the first visit, and reductions were sustained over an average of three visits.[10]

Though numerous studies of the *clinical* outcomes associated with CPAs have been conducted, some studies have detailed their *economic* benefits. Schumock and colleagues conducted a systematic literature review of articles that evaluated the economic impact of clinical pharmacy services. This review identified pharmacy interventions in a wide range of clinical settings, including government clinics, hospital-associated clinics, community hospitals, university hospitals, and physicians' offices. A mean benefit-to-cost ratio of 4.68 to 1 was shown with the addition of clinical pharmacy services.[2] The financial impact of clinical pharmacy services was also reported by Lee and colleagues in a study that evaluated the economic impact of pharmacists' recommendations.[11] This review evaluated 600 medication recommendations by pharmacists in a variety of settings, including inpatient and outpatient facilities and nursing homes. A total of 1,511 recommendations were made, with a physician acceptance rate of 92.4%. The mean medication cost avoidance was increased in the inpatient setting as compared to the outpatient setting or nursing homes, but the mean total medication cost avoidance was $420,155.[11] Although the financial impact will vary depending on the practice setting and clinical scenario, this study shows that pharmacists' interventions can lead to substantial cost savings. A Cochrane Database review of 25 studies showed that pharmacists' collaborative practice resulted in a decrease in the overall use of drugs, as well as the cost.[12] Despite the fact that studies have shown the positive effect of pharmacists' interventions on healthcare costs, reimbursement and funding for these services are limited. Without adequate compensation, the implementation of CDTM may be severely limited, and this limit may be a barrier to optimizing healthcare outcomes.[1]

The documentation of pharmacy services is an important component of CDTM and can help further the development of collaborative agreements. Although not all states have laws and regulations requiring documentation of pharmacists' activities, many require that pharmacists record and track interventions and that collaborating prescribers review these documents at routine intervals.[4] The documentation of activities can allow collaborating prescribers to monitor and approve of interventions, but it also allows tracking to be used for financial and research purposes. Future

research supporting the financial and clinical impact of CDTM on the healthcare system will require thorough records and evaluation of pharmacists' interventions. These documents may be in the form of electronic medical records or in a format tailored to the practice setting and CPA. A study by Sledge and colleagues reported on the use of a daily pharmacy progress note in the surgical intensive care unit. In a 2-month period, 462 daily pharmacy progress notes resulted in 1,055 therapy changes and the avoidance of one sentinel event.[13] This study showed that the documentation of pharmacy services not only provides evidence of the pharmacist's involvement in the multidisciplinary team but also improves patient outcomes.

Despite the many proven benefits of CDTM, many providers are hesitant to sign a CPA. Many reasons for this concern exist, such as not understanding the pharmacist's credentialing, experience level, or scope of practice.[6] Thus, it is important that the pharmacist has established a trustworthy relationship with the providers with whom they request entrance into a CPA. Snyder and colleagues reported on the importance of trustworthiness in the success of CDTM agreements in the community setting. It was shown that physicians scored pharmacists higher on a Pharmacist-Physician Collaborative Index when they had frequent face-to-face communications and when the pharmacist made consistent contributions that improved patient care.[14] Also, healthcare providers who have a strong working relationship with a pharmacist are more likely to have success in improving clinical outcomes.

Although many states require pharmacists to possess specific education and training in order to participate in CPAs, physicians and other healthcare providers may not be familiar with pharmacists' credentials. One way to alleviate this problem would be to educate the prescriber on the credentialing process for pharmacists and explain any experience the pharmacist may have within the given field of practice.

The development of CPAs between pharmacists and healthcare providers has been shown to improve clinical and economic outcomes, increase access to health care, and improve medication safety. Given the projected shortage of physicians, and specifically oncologists, pharmacists are in a position to improve oncology patients' access to the healthcare system. Pharmacists should therefore work closely with their collaborating prescribers to develop trustworthy relationships and limit any potential barriers to CDTM implementation. Routine documentation of pharmacy activities can help demonstrate the clinical and financial impact of CDTM and may provide a basis for reimbursement for services in future healthcare models. ●●

REFERENCES

1. Giberson S, Yoder S, Lee MP. Improving patient and health system outcomes through advanced pharmacy practice. A report to the U.S. Surgeon General. Office of the Chief Pharmacist. U.S. Public Health Service. Dec 2011.
2. Schumock GT, Butler MG, Meek PD, et al. Evidence of the economic benefit of clinical pharmacy services: 1996-2000. *Pharmacotherapy.* 2003;23(1):113-132.
3. Carmichael JM, O'Connell MB, Devine B, et al. Collaborative drug therapy management by pharmacists. *Pharmacotherapy.* 1997;17(5):1050-1061.
4. Yang Y, Williams JH, Hogan PF, et al. Projected supply of and demand for oncologists and radiation oncologists through 2025: an aging, better-insured population will result in shortage. *J Oncol Pract.* 2014;10(1):39-45.
5. Manolakis PG, Skelton JB. Pharmacists' contributions to primary care in the United States collaborating to address unmet patient care needs: the emerging role for pharmacists to address the shortage of primary care providers. *Am J Pharm Ed.* 2010;74(10):S7.
6. Centers for Disease Control and Prevention. *Advancing Team-Based Care Through Collaborative Practice Agreements: A Resource and Implementation Guide for Adding Pharmacists to the Care Team.* Atlanta, GA: Centers for Disease Control and Prevention, U.S. Department of Health and Human Services; 2017.
7. McBane SE, Dopp AL, Abe A, et al. Collaborative drug therapy management and comprehensive medication management–2015. *Pharmacotherapy.* 2015;35(4):e39-e50.
8. Doucette WR, McDonough RP, Klepser D, McCarthy R. Comprehensive medication therapy management: identifying and resolving drug-related issues in a community pharmacy. *Clin Ther.* 2005;27:1104-1111.
9. Hansen EA, Pietkiewicz JM, Blum BL. Evaluation of the feasibility and utility of a pharmacist-centered collaborative drug-therapy management program for oncology-based symptom management. *J Pharmacy Pract.* 2016;29(3):206-211.
10. Valgus J, Jarr S, Schwartz R, et al. Pharmacist-led, interdisciplinary model for delivery of supportive care in the ambulatory cancer clinic setting. *J Oncol Pract.* 2010;6(6):e1-e4.
11. Lee AJ, Boro MS, Knapp KK, et al. Clinical and economic outcomes of pharmacist recommendations in a Veterans Affairs medical center. *Am J Health-Syst Pharm.* 2002;59:2070-2077.
12. Beney J, Bero LA, Bond C. Expanding the roles of outpatient pharmacists: effects on health services utilization, costs, and patient outcomes. *Cochrane Database Syst Rev.* 2000;(3):CD000336.
13. Sledge T, Lonardo N, Simons H, Shipley W. Implementing the use of pharmacist progress notes in the surgical ICU. *Hosp Pharm.* 2016;51(7):577-584.
14. Snyder ME, Zillich AJ, Primack BA, et al. Exploring successful community pharmacist-physician collaborative working relationships using mixed methods. *Res Social Adm Pharm.* 2010;6:307-323.

Evaluating Drug Interaction Databases: Results from an Exploratory Analysis

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Patients are taking an increasing number of medications, including those used to treat cancer and those required for treating comorbidities. Patients and healthcare team members rely on oncology pharmacists to be experts on all these medications. An exciting aspect of oncology practice is the number of new oral antineoplastic (OA) agents coming to the market and the potential for new approvals for existing OAs. Given that many of these drugs may come to market under expedited review through the U.S. Food and Drug Administration (FDA), approval may be granted without a formal drug-drug interaction analysis. With the introduction of these drugs into practice comes a challenge for oncology pharmacists: how to best screen a patient's medications for clinically relevant drug interactions when initiating an OA agent.

Dr. John B. Bossaer and Dr. Christan M. Thomas aimed to shed light on this clinical question through an exploratory evaluation of existing drug interaction databases, a common resource for clinicians. This research, titled "Drug Interaction Database Sensitivity with Oral Antineoplastics: An Exploratory Analysis," was published in March 2017 in the *Journal of Oncology Practice*.[1] Although these databases have been previously evaluated in regard to their sensitivity in detecting drug interactions, those studies did not include OAs. The research team selected 20 drug interactions encountered in actual clinical practice and deemed to be clinically relevant. *Clinically relevant* was defined as a drug interaction that would require a change in therapy, such as selection of a new drug, a change in dose, or more frequent monitoring. This definition is more liberal than those used in the past; however, the authors felt that it more accurately reflected real-world practice. These 20 interactions include a variety of types, as well as newer agents that lack formal drug interaction studies. Examples include the interaction between pazopanib and amiodarone, which results in an increased risk of QTc prolongation, and the interaction between idelalisib and rivaroxaban, which results in an increased risk of bleeding. Well-known interactions, such as that between capecitabine and warfarin, were also included. These 20 interactions were then processed through five electronic databases commonly encountered in clinical practice: four of these were designed for the healthcare professional (Epocrates, Facts & Comparisons, Lexi-Interact, and MicroMedex), and one was oriented toward patients and non–healthcare providers (www.drugs.com). The distribution of sensitivity across groups was assessed using the Cochran Q test.

The authors report that the sensitivities for each database varied. MicroMedex was found to have a sensitivity of 70% (95% confidence interval [CI], .46–.87), Facts & Comparisons, 70% (CI, .46–.87), Epocrates, 90% (CI, .69–.98), Lexi-Interact, 95% (CI, .73–.99), and Drugs.com, 95% (CI, .73–.99). The difference in their detection of clinically significant drug interactions was statistically significant, with a p value of .016. In addition, classification of interactions (major, moderate, not detected, etc.) varied among the databases. Only three interactions (those between idelalisib and phenytoin, bosutinib and voriconazole, and ibrutinib and voriconazole) were classified the same across all five databases. Even if the interactions labeled as major or moderate were considered equivalent, the databases had an agreement rate of 45% (n = 9).

The authors state that these results are not intended to indicate the superiority of one database over another. On the contrary, the variability among the databases, both in detecting an interaction and classifying it, suggests to the researchers that clinicians should use at least two electronic databases when checking a drug interaction. Databases that are transparent in the analysis of a drug interaction (for instance, including links to data supporting the interaction) are preferred. The authors also discuss the need for obtaining a detailed medication history from the patient during clinical encounters rather than relying on a medication list reported in the electronic medical record.

The authors also discuss areas for future research and initiatives and highlight the need for standardization in analysis of drug interactions. The authors note the lack of criteria for defining drug interactions with OAs, which likely contributes to the variability seen in these databases. Furthermore, this study omitted interactions not deemed clinically significant and therefore does not assess the specificity of these databases. Future endeavors that focus on specificity may address alert fatigue, a concern related to the extensive use of electronic resources by those working in the healthcare system. Theoretical drug interactions should also be included in these analyses because they may not come to light until several years after the drugs' introduction into clinical practice.

This exploratory study shows the growing complexity of oral antineoplastics. Clinicians are faced with new agents for which formal drug-drug interaction studies may be lacking. In addition, patients are taking an increasing number of medications for other chronic diseases, and these medications are often prescribed by other providers. Given the high cost and insurance restrictions associated with OAs, patients may be using specialty pharmacies in addition to their preferred local pharmacy, making it difficult for pharmacists to conduct an accurate drug utilization review. Finally, although these databases have the potential to identify many of the clinically relevant drug interactions, the decision about what action to take is patient-specific and is driven by many factors. The work of Dr. Bossaer and Dr. Thomas examining the usefulness of these drug databases in detecting drug-drug interactions, as well as the potential shortcomings of these databases, highlights the need for the clinical expertise of an oncology pharmacist as a member of a patient's cancer care team. ●●

REFERENCE

1. Bossaer JB, Thomas CM. Drug interaction database sensitivity with oral antineoplastics: an exploratory analysis. *J Oncol Pract*. 2017;13(3):217-222.

Highlights of HOPA's 2017 Practice Management Program (September 15–16)

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HOPA's 5th annual Practice Management Program (PMP) was held September 15–16, 2017, in Chicago, IL. The Windy City blew in excellent presenters and an engaged audience for the 2-day conference. Session topics ranged from oncology financial management and oncology care models to intravenous (IV) automation and technology.

A preconference that focused on investigational drug services (IDSs) was held on September 15. Christopher Lowe, PharmD BCPS, spoke about a centralized IDS for each of his health system's entities. Kathy Galus, PharmD BCOP, highlighted the role of clinical pharmacists within the IDS and showed how a proactive approach to services can benefit the research community. Sapna Amin, PharmD BCOP, described the recommendations for IDS best practices made by HOPA and the Association of Dedicated Cancer Centers. Each presentation raised thought-provoking questions and stimulated lively discussion among the attendees.

The conference began with opening remarks from HOPA's president, Susannah Koontz, PharmD BCOP FHOPA. Prior to the keynote address, she introduced a surprise award renaming HOPA's PMP keynote lecture the Niesha L. Griffith Keynote Lecture. Koontz presented a plaque to Niesha Griffith, MS RPh FASHP, vice president of cancer services at West Virginia University Health System. Griffith then introduced the inaugural Niesha L. Griffith Keynote Lecturer, William (Bill) McGivney, PhD, managing principal at McGivney Global Advisors and former CEO of the National Comprehensive Cancer Network.

McGivney spoke about the evolving needs and direction of cancer care and called on HOPA to continue to set the direction for cancer care delivery and take a leadership role in that arena. He commended HOPA's strategic plan as a sturdy framework for these efforts, similar to the path followed by the NCCN in solidifying its place as a leader in cancer care.

The remainder of Friday's sessions centered on oncology care models, white bagging/brown bagging solutions, and oral chemotherapy. Each presentation provided not only excellent information but also practical solutions and examples to help audience members within their own practice sites. The Saturday morning sessions covered a wide array of topics: productivity models, budgeting and managing oncology financials, implementation of USP <800>, and IV technology and automation. The conference ended with sessions on the use of electronic medical records to manage oral chemotherapy and prior authorizations for all infusions and a summary of HOPA's May 2017 Policy Summit on Drug Waste.

All who attended owe a debt of gratitude to those who made the 2017 PMP another fantastic conference and a special thanks to all the presenters, moderators, and the HOPA PMP Committee! We hope to see each of you again and some new faces at next year's Practice Management Program—to be held September 14–15, 2018, in Rosemont, IL (near Chicago). Mark your calendar now, and plan to attend this valuable educational event. ●●

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Deliver superior overall survival vs 7+3[a]

to adults with newly-diagnosed t-AML or AML-MRC[1]

VYXEOS improved overall survival compared to 7+3 in a Phase 3 trial[1]

- Median survival of 9.6 months for VYXEOS vs 5.9 months for 7+3 (*P*=0.005), HR=0.69 (0.52, 0.90)

Study Design[1]

The Phase 3 study was a randomized, multicenter, open-label, active-controlled superiority study of VYXEOS versus cytarabine and daunorubicin (7+3) in patients 60 to 75 years of age with newly-diagnosed t-AML or AML-MRC. There were 153 patients randomized to VYXEOS and 156 patients randomized to the 7+3 arm. 20% of patients had t-AML, 54% had AML with an antecedent hematological disorder, and 25% had de novo AML with MDS-related cytogenetic abnormalities. Efficacy was established on the basis of overall survival from the date of randomization to death from any cause.

VYXEOS 44 mg/100 mg per m^2 (daunorubicin/cytarabine) was given intravenously on Days 1, 3, and 5 for first induction and on Days 1 and 3 for those needing a second induction. For consolidation, the VYXEOS dose was 29 mg/65 mg per m^2 (daunorubicin/cytarabine) on Days 1 and 3. In the 7+3 arm, first induction was cytarabine 100 mg/m^2/day on Days 1-7 by continuous infusion + daunorubicin 60 mg/m^2/day on Days 1-3. For second induction and consolidation, cytarabine was dosed on Days 1-5 and daunorubicin on Days 1 and 2.

INDICATION

VYXEOS (daunorubicin and cytarabine) liposome for injection 44 mg/100 mg is indicated for the treatment of adults with newly-diagnosed therapy-related acute myeloid leukemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC).

IMPORTANT SAFETY INFORMATION

WARNING: DO NOT INTERCHANGE WITH OTHER DAUNORUBICIN AND/OR CYTARABINE-CONTAINING PRODUCTS

VYXEOS has different dosage recommendations than daunorubicin hydrochloride injection, cytarabine injection, daunorubicin citrate liposome injection, and cytarabine liposome injection. Verify drug name and dose prior to preparation and administration to avoid dosing errors.

Contraindications

VYXEOS is contraindicated in patients with a history of serious hypersensitivity reactions to cytarabine, daunorubicin, or any component of the formulation.

Warnings and Precautions

Hemorrhage

Serious or fatal hemorrhage events, including fatal CNS hemorrhages, associated with prolonged thrombocytopenia, have occurred with VYXEOS. The overall incidence (grade 1-5) of hemorrhagic events was 74% in the VYXEOS arm and 56% in the control arm. The most frequently reported hemorrhagic event was epistaxis (36% in VYXEOS arm and 18% in control arm). Grade 3 or greater events occurred in 12% of VYXEOS-treated patients and in 8% of patients in the control arm. Fatal treatment-emergent CNS hemorrhage not in the setting of progressive disease occurred in 2% of patients in the VYXEOS arm and in 0.7% of patients in the control arm. Monitor blood counts regularly and administer platelet transfusion support as required.

Cardiotoxicity

VYXEOS contains daunorubicin, which has a known risk of cardiotoxicity. This risk may be increased in patients with prior anthracycline therapy, preexisting cardiac disease, previous radiotherapy to the mediastinum, or concomitant use of cardiotoxic drugs. Assess cardiac function prior to VYXEOS treatment and repeat prior to consolidation and as clinically required. VYXEOS is not recommended in patients with impaired cardiac function unless the benefit of treatment outweighs the risk.

Total cumulative doses of non-liposomal daunorubicin greater than 550 mg/m^2 have been associated with an increased incidence of drug-induced congestive heart failure. The tolerable limit appears lower (400 mg/m^2) in patients who received radiation therapy to the mediastinum. Calculate the lifetime cumulative anthracycline exposure prior to each cycle of VYXEOS. VYXEOS is not recommended in patients whose lifetime anthracycline exposure has reached the maximum cumulative limit.

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Safety and effectiveness of VYXEOS in pediatric patients have not been established.

IMPORTANT SAFETY INFORMATION, continued

Hypersensitivity Reactions
Serious or fatal hypersensitivity reactions, including anaphylactic reactions, have been reported with daunorubicin and cytarabine. Monitor patients for hypersensitivity reactions. If a mild or moderate hypersensitivity reaction occurs, interrupt or slow the rate of infusion with VYXEOS and manage symptoms. If a severe or life-threatening hypersensitivity reaction occurs, discontinue VYXEOS permanently, treat the symptoms, and monitor until symptoms resolve.

Copper Overload
VYXEOS contains copper. Monitor total serum copper, serum non-ceruloplasmin-bound copper, 24-hour urine copper levels, and serial neuropsychological examinations during VYXEOS treatment in patients with Wilson's disease or other copper-related metabolic disorders. Use only if the benefits outweigh the risks. Discontinue in patients with signs or symptoms of acute copper toxicity.

Tissue Necrosis
Daunorubicin has been associated with severe local tissue necrosis at the site of drug extravasation. Administer VYXEOS by the intravenous route only. Do not administer by intramuscular or subcutaneous route.

Embryo-Fetal Toxicity
VYXEOS can cause embryo-fetal harm when administered to a pregnant woman. Patients should avoid becoming pregnant while taking VYXEOS. Advise females and males of reproductive potential to use effective contraception during treatment and for 6 months following the last dose of VYXEOS.

MOST COMMON ADVERSE REACTIONS

The most common adverse reactions (incidence ≥25%) were hemorrhagic events, febrile neutropenia, rash, edema, nausea, mucositis, diarrhea, constipation, musculoskeletal pain, fatigue, abdominal pain, dyspnea, headache, cough, decreased appetite, arrhythmia, pneumonia, bacteremia, chills, sleep disorders, and vomiting.

Please see following pages for Brief Summary of full Prescribing Information, including BOXED Warning.

Reference: 1. VYXEOS [package insert]. Palo Alto, CA: Jazz Pharmaceuticals.

[a] Cytarabine and daunorubicin.

AML=acute myeloid leukemia; AML-MRC=acute myeloid leukemia with myelodysplasia-related changes; HR=hazard ratio; MDS=myelodysplastic syndromes; t-AML=therapy-related acute myeloid leukemia.

Jazz Pharmaceuticals

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VYX-0036 Rev0817

VYXEOS™ (daunorubicin and cytarabine) liposome for injection, for intravenous use

BRIEF SUMMARY OF PRESCRIBING INFORMATION: Consult the Full Prescribing Information, including BOXED Warning, for complete product information.

Initial U.S. Approval: 2017

WARNING: DO NOT INTERCHANGE WITH OTHER DAUNORUBICIN AND/OR CYTARABINE-CONTAINING PRODUCTS

- **VYXEOS has different dosage recommendations than daunorubicin hydrochloride injection, cytarabine injection, daunorubicin citrate liposome injection, and cytarabine liposome injection. Verify drug name and dose prior to preparation and administration to avoid dosing errors *[see Warnings and Precautions]*.**

INDICATIONS AND USAGE

VYXEOS is indicated for the treatment of adults with newly-diagnosed therapy-related acute myeloid leukemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC).

CONTRAINDICATIONS

The use of VYXEOS is contraindicated in patients with the following:

- History of serious hypersensitivity reaction to cytarabine, daunorubicin, or any component of the formulation *[see Warnings and Precautions].*

WARNINGS AND PRECAUTIONS

Do Not Interchange With Other Daunorubicin And/Or Cytarabine-Containing Products

Due to substantial differences in the pharmacokinetic parameters, the dose and schedule recommendations for VYXEOS are different from those for daunorubicin hydrochloride injection, cytarabine injection, daunorubicin citrate liposome injection, and cytarabine liposome injection. Verify drug name and dose prior to preparation and administration to avoid dosing errors. Do not substitute other preparations of daunorubicin or cytarabine for VYXEOS.

Hemorrhage

Serious or fatal hemorrhage events, including fatal central nervous system (CNS) hemorrhages, associated with prolonged severe thrombocytopenia, have occurred in patients treated with VYXEOS. In Study 1 (NCT01696084), the incidence of any grade hemorrhagic events during the entire treatment period was 74% of patients on the VYXEOS arm and 56% on the control arm. The most frequently reported hemorrhagic event was epistaxis (36% in VYXEOS arm and 18% in control arm). Grade 3 or greater events occurred in 12% of VYXEOS treated patients and 8% of patients treated with 7+3. Fatal treatment-emergent CNS hemorrhage not in the setting of progressive disease occurred in 2% of patients on the VYXEOS arm and in 0.7% of patients on the control arm. Monitor blood counts regularly until recovery and administer platelet transfusion support as required *[see Adverse Reactions].*

Cardiotoxicity

VYXEOS contains the anthracycline daunorubicin, which has a known risk of cardiotoxicity. Prior therapy with anthracyclines, pre-existing cardiac disease, previous radiotherapy to the mediastinum, or concomitant use of cardiotoxic drugs may increase the risk of daunorubicin-induced cardiac toxicity. Prior to administering VYXEOS, obtain an electrocardiogram (ECG) and assess cardiac function by multi-gated radionuclide angiography (MUGA) scan or echocardiography (ECHO). Repeat MUGA or ECHO determinations of left ventricular ejection fraction (LVEF) prior to consolidation with VYXEOS and as clinically required. Discontinue VYXEOS in patients with impaired cardiac function unless the benefit of initiating or continuing treatment outweighs the risk. VYXEOS treatment is not recommended in patients with LVEF that is less than normal.

Total cumulative doses of non-liposomal daunorubicin greater than 550 mg/m^2 have been associated with an increased incidence of drug-induced congestive heart failure. The tolerable limit appears lower (400 mg/m^2) in patients who received radiation therapy to the mediastinum. Calculate the lifetime cumulative anthracycline exposure prior to each cycle of VYXEOS. VYXEOS treatment is not recommended in patients whose lifetime anthracycline exposure has reached the maximum cumulative limit. The exposure to daunorubicin following each cycle of VYXEOS is shown in Table 1.

Table 1: Cumulative Exposure of Daunorubicin per Cycle of VYXEOS

Therapy	Daunorubicin per Dose	Number of Doses per Cycle	Daunorubicin per Cycle
First Induction Cycle	44 mg/m^2	3	132 mg/m^2
Second Induction Cycle	44 mg/m^2	2	88 mg/m^2
Each Consolidation Cycle	29 mg/m^2	2	58 mg/m^2

Hypersensitivity Reactions

Serious or fatal hypersensitivity reactions, including anaphylactic reactions, have been reported with daunorubicin and cytarabine. Monitor patients for hypersensitivity reactions. If a mild or moderate hypersensitivity reaction occurs, interrupt or slow the rate of infusion with VYXEOS and manage symptoms. If a severe or life-threatening hypersensitivity reaction occurs, discontinue VYXEOS permanently, treat symptoms according to the standard of care, and monitor until symptoms resolve.

Copper Overload

Reconstituted VYXEOS contains 5 mg/mL copper gluconate, of which 14% is elemental copper. There is no clinical experience with VYXEOS in patients with Wilson's disease or other copper-related metabolic disorders. The maximum theoretical total exposure of copper under the recommended VYXEOS dosing regimen is 106 mg/m^2. Consult with a hepatologist and nephrologist with expertise in managing acute copper toxicity in patients with Wilson's disease treated with VYXEOS. Monitor total serum copper, serum non-ceruloplasmin bound copper, 24-hour urine copper levels and serial neuropsychological examinations in these patients. Use VYXEOS in patients with Wilson's disease only if the benefits outweigh the risks. Discontinue VYXEOS in patients with signs or symptoms of acute copper toxicity.

Tissue Necrosis

Daunorubicin has been associated with severe local tissue necrosis at the site of drug extravasation. Administer VYXEOS by the intravenous route only. Do not administer by intramuscular or subcutaneous route.

Embryo-Fetal Toxicity

Based on its mechanism of action and findings from animal studies with daunorubicin and cytarabine, VYXEOS can cause embryo-fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of VYXEOS, daunorubicin, or cytarabine in pregnant women. Daunorubicin and cytarabine are reproductive and developmental toxicants in multiple species (mice, rats, and/or dogs), starting at a dose that was approximately 0.02 times the exposure in patients at the recommended human dose on an mg/m^2 basis. Patients should be advised to avoid becoming pregnant while taking VYXEOS. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, apprise the patient of the potential risk to a fetus. Advise females and males of reproductive potential to use effective contraception during treatment and for 6 months following the last dose of VYXEOS *[see Use in Specific Populations].*

ADVERSE REACTIONS

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

- Hemorrhage *[see Warnings and Precautions]*
- Cardiotoxicity *[see Warnings and Precautions]*
- Hypersensitivity Reactions *[see Warnings and Precautions]*
- Copper Overload *[see Warnings and Precautions]*
- Tissue Necrosis *[see Warnings and Precautions]*

Clinical Trials Experience

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

The safety of VYXEOS was determined in a randomized trial for adults with newly-diagnosed t-AML or AML-MRC which included 153 patients treated with VYXEOS and 151 patients treated with a standard combination of cytarabine and daunorubicin (7+3). At study entry, patients were required to have a LVEF of at least 50% and a prior lifetime cumulative anthracycline exposure less than 368 mg/m^2 daunorubicin (or equivalent). On study, the median number of cycles administered was 2 (range, 1–4 cycles) on the VYXEOS arm and 1 (range, 1–4 cycles) on the control arm. The median cumulative daunorubicin dose was 189 mg/m^2 (range, 44–337 mg/m^2) on the VYXEOS arm and 186 mg/m^2 (range, 44–532 mg/m^2) on the control arm.

Nine patients each on the VYXEOS arm (6%) and the control arm (6%) had a fatal adverse reaction on treatment or within 30 days of therapy that was not in the setting of progressive disease. Fatal adverse reactions on the VYXEOS arm included infection, CNS hemorrhage, and respiratory failure. Overall, all-cause day-30 mortality was 6% in the VYXEOS arm and 11% in the control arm. During the first 60 days of the study, 14% (21/153) of patients died in the VYXEOS arm vs. 21% (32/151) of patients in the 7+3 treatment group.

The most common serious adverse reactions (incidence ≥5%) on the VYXEOS arm were dyspnea, myocardial toxicity, sepsis, pneumonia, febrile neutropenia, bacteremia and hemorrhage. Adverse reactions led to discontinuation of VYXEOS in 18% (28/153) of patients, and 13% (20/151) in the control arm. The adverse reactions leading to discontinuation on the VYXEOS arm included prolonged cytopenias, infection, cardiotoxicity, respiratory failure, hemorrhage (GI and CNS), renal insufficiency, colitis, and generalized medical deterioration. The most common adverse reactions (incidence ≥25%) in patients on the VYXEOS arm were hemorrhagic events, febrile neutropenia, rash, edema, nausea, mucositis, diarrhea, constipation, musculoskeletal pain, fatigue, abdominal pain, dyspnea, headache, cough, decreased appetite, arrhythmia, pneumonia, bacteremia, chills, sleep disorders, and vomiting. The incidences of common adverse drug reactions during the induction phase in Study 1 are presented in Table 2.

Table 2: Common Adverse Reactions (≥10% Incidence in the VYXEOS arm) During the Induction Phase

Adverse Reaction	All Grades[a]		Grades 3 to 5[a]	
	VYXEOS N=153 n (%)	7+3 N=151 n (%)	VYXEOS N=153 n (%)	7+3 N=151 n (%)
Hemorrhage	107 (70)	74 (49)	15 (10)	9 (6)
Febrile Neutropenia	104 (68)	103 (68)	101 (66)	102 (68)
Rash	82 (54)	55 (36)	8 (5)	2 (1)
Edema	78 (51)	90 (60)	2 (2)	5 (3)
Nausea	72 (47)	79 (52)	1 (1)	1 (1)
Diarrhea/Colitis	69 (45)	100 (66)	4 (3)	10 (7)
Mucositis	67 (44)	69 (46)	2 (1)	7 (5)
Constipation	61 (40)	57 (38)	0	0
Musculoskeletal pain	58 (38)	52 (34)	5 (3)	4 (3)
Abdominal pain	51 (33)	45 (30)	3 (2)	3 (2)
Cough	51 (33)	34 (23)	0	1 (1)
Headache	51 (33)	36 (24)	2 (1)	1 (1)
Dyspnea	49 (32)	51 (34)	17 (11)	15 (10)
Fatigue	49 (32)	58 (38)	8 (5)	8 (5)
Arrhythmia	46 (30)	41 (27)	10 (7)	7 (5)
Decreased appetite	44 (29)	57 (38)	2 (1)	5 (3)
Pneumonia (excluding fungal)	39 (26)	35 (23)	30 (20)	26 (17)
Sleep disorders	38 (25)	42 (28)	2 (1)	1 (1)
Bacteremia (excluding sepsis)	37 (24)	37 (25)	35 (23)	31 (21)
Vomiting	37 (24)	33 (22)	0	0
Chills	35 (23)	38 (25)	0	0
Hypotension	30 (20)	32 (21)	7 (5)	1 (1)
Non-conduction cardiotoxicity	31 (20)	27 (18)	13 (9)	15 (10)
Dizziness	27 (18)	26 (17)	1 (1)	0
Fungal infection	27 (18)	19 (13)	11 (7)	9 (6)
Hypertension	28 (18)	22 (15)	15 (10)	8 (5)
Hypoxia	28 (18)	31 (21)	19 (12)	23 (15)
Upper respiratory infections (excluding fungal)	28 (18)	19 (13)	4 (3)	1 (1)
Chest pain	26 (17)	22 (15)	5 (3)	0
Pyrexia	26 (17)	23 (15)	1 (1)	2 (1)
Catheter/device/ injection site reaction	24 (16)	15 (10)	0	0
Delirium	24 (16)	33 (22)	4 (3)	9 (6)
Pleural effusion	24 (16)	25 (17)	3 (2)	2 (1)
Anxiety	21 (14)	16 (11)	0	0
Pruritus	23 (15)	14 (9)	0	0
Sepsis (excluding fungal)	17 (11)	20 (13)	n/a	n/a
Hemorrhoids	16 (11)	12 (8)	0	0
Petechiae	17 (11)	17 (11)	0	0
Renal insufficiency	17 (11)	17 (11)	7 (5)	7 (5)
Transfusion reactions	17 (11)	16 (11)	3 (2)	1 (1)
Visual impairment (except bleeding)	16 (11)	8 (5)	0	0

[a]Adverse reactions were graded using NCI CTCAE version 3.0.

During the consolidation phase (both consolidation cycles pooled) the two most common adverse reactions on the VYXEOS arm are the same as those during induction, hemorrhagic events and febrile neutropenia. These occurred at lower rates in the pooled consolidation phase (43% and 29%, respectively), compared to the induction phase. All of the common adverse reactions (≥10% incidence in the VYXEOS arm) seen in the pooled consolidation phase were also seen in the induction phase. These occurred at lower incidence in the consolidation phase, with the exception of chills, dizziness and pyrexia, where the incidences were relatively similar across the induction and consolidation cycles.

Other notable adverse drug reactions that occurred in less than 10% of patients treated with VYXEOS during induction or consolidation included:

- Ear and labyrinth disorders: Deafness, Deafness unilateral
- Eye Disorders: Eye conjunctivitis, Dry eye, Eye edema, Eye swelling, Eye irritation, Eye pain, Ocular discomfort, Ocular hyperemia, Periorbital edema, Scleral hyperemia
- Gastrointestinal disorders: Dyspepsia
- Psychiatric disorders: Hallucinations
- Respiratory, thoracic and mediastinal disorders: Pneumonitis

Laboratory Abnormalities

All patients developed severe neutropenia, thrombocytopenia, and anemia. See Table 3 for the incidences of Grade 3 thrombocytopenia and Grade 4 neutropenia that were prolonged in the absence of active leukemia.

Table 3: Prolonged Cytopenias for Patients in Study 1

	Induction 1		Consolidation 1[b]	
	VYXEOS N=58 n (%)	7+3 N=34 n (%)	VYXEOS N=48 n (%)	5+2 N=32 n (%)
Prolonged thrombocytopenia[a]	16 (28)	4 (12)	12 (25)	5 (16)
Prolonged neutropenia[a]	10 (17)	1 (3)	5 (10)	1 (3)

[a]Platelets <50 Gi/L or neutrophils <0.5 Gi/L lasting past cycle day 42 in the absence of active leukemia.
[b]Patients receiving at least 1 consolidation.

Grade 3-4 chemistry abnormalities occurring in greater than 5% of VYXEOS treated patients in Study 1 are presented in Table 4.

Table 4: Grade 3-4[a] Chemistry Abnormalities ≥5% of VYXEOS Treated Patients in Study 1

	Induction		Consolidation	
	VYXEOS N=153 n (%)	7+3 N=151 n (%)	VYXEOS N=49 n (%)	5+2 N=32 n (%)
Chemistry Abnormalities				
Hyponatremia	21 (14)	20 (13)	3 (6)	0
Hypokalemia	14 (9)	19 (13)	3 (6)	2 (6)
Hypoalbuminemia	11 (7)	19 (13)	1 (2)	4 (13)
Hyperbilirubinemia	9 (6)	6 (4)	1 (2)	1 (3)
Alanine aminotransferase	7 (5)	8 (5)	0	1 (3)

[a]Graded using NCI CTCAE version 3.0.

DRUG INTERACTIONS

Cardiotoxic Agents

Concomitant use of cardiotoxic agents may increase the risk of cardiotoxicity. Assess cardiac function more frequently when VYXEOS is coadministered with cardiotoxic agents *[see Warnings and Precautions]*.

Hepatotoxic Agents

Concomitant use with hepatotoxic agents may impair liver function and increase the toxicity of VYXEOS. Monitor hepatic function more frequently when VYXEOS is coadministered with hepatotoxic agents.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on anecdotal data of cytarabine in pregnant women and results of studies of daunorubicin and cytarabine in animals, VYXEOS can cause embryo-fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of VYXEOS, daunorubicin, or cytarabine in pregnant women. Daunorubicin and cytarabine are reproductive and developmental toxicants in multiple species (mice, rats, and/or dogs), starting at a dose that was approximately 0.02 times the exposure in patients at the recommended human dose on a mg/m^2 basis *[see Animal Data]*. Patients should be advised to avoid becoming pregnant while taking VYXEOS. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, apprise the patient of the potential harm to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. Adverse outcomes in pregnancy occur regardless of the health of the mother or the use of medications. In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies are 2 to 4% and 15 to 20%, respectively.

Data

Human Data

Cytarabine can cause fetal harm if a pregnant woman is exposed to the drug. Four anecdotal cases of major limb malformations have been reported in infants after their mothers received intravenous cytarabine, alone or in combination with other agents, during the first trimester.

Animal Data

A liposomal formulation of daunorubicin was administered to rats on gestation days 6 through 15 at 0.3, 1.0, or 2.0 mg/kg/day (about 0.04, 0.14, or 0.27 the recommended human dose on a mg/m^2 basis) and produced severe maternal toxicity and embryolethality at 2.0 mg/kg/day and was embryotoxic and caused fetal malformations (anophthalmia, microphthalmia, incomplete ossification) at 0.3 mg/kg/day. Embryotoxicity was characterized by increased embryo-fetal deaths, reduced numbers of litters, and reduced litter sizes.

Cytarabine was teratogenic in mice (cleft palate, phocomelia, deformed appendages, skeletal abnormalities) when doses ≥2 mg/kg/day were administered IP during the period of organogenesis (about 0.06 times the recommended human dose on a mg/m^2 basis), and in rats (deformed appendages) when 20 mg/kg was administered as a single IP dose on day 12 of gestation (about 1.2 times the recommended human dose on a mg/m^2 basis). Single IP doses of 50 mg/kg in rats (about 3 times the recommended human dose on a mg/m^2 basis) on day 14 of gestation reduced prenatal and postnatal brain size and permanent impairment of learning ability.

Cytarabine was embryotoxic in mice when administered during the period of organogenesis. Embryotoxicity was characterized by decreased fetal weight at 0.5 mg/kg/day (about 0.02 times the recommended human dose on a mg/m^2 basis), and increased early and late resorptions and decreased live litter sizes at 8 mg/kg/day (about 0.24 times the recommended human dose on a mg/m^2 basis).

Lactation

Risk Summary

There are no data on the presence of daunorubicin, cytarabine, or their metabolites in human milk, their effects on the breastfed infant, or their effects on milk production. Because of the potential for serious adverse reactions in breastfed infants, advise lactating women not to breastfeed during treatment with VYXEOS and for at least 2 weeks after the last dose.

Females and Males of Reproductive Potential

Pregnancy Testing

VYXEOS can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations]*. Verify the pregnancy status of females of reproductive potential prior to initiating VYXEOS.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with VYXEOS and for at least 6 months after the last dose.

Males

Advise males with female partners of reproductive potential to use effective contraception during treatment with VYXEOS and for at least 6 months after the last dose.

Infertility

Based on findings of daunorubicin and cytarabine in animals, male fertility may be compromised by treatment with VYXEOS.

Pediatric Use
Safety and effectiveness of VYXEOS in pediatric patients have not been established.

Geriatric Use
Of the 375 patients who received VYXEOS (daunorubicin 44 mg/m^2 and cytarabine 100 mg/m^2) liposome in clinical studies, 57% were 65 years and over. No overall differences in safety were observed between these patients and younger patients, with the exception of bleeding events, which occurred more frequently in patients 65 years and older compared to younger patients (77% vs. 59%).

Renal Impairment
Dosage adjustment is not required for patients with mild (creatinine clearance [CL_{CR}] 60 mL/min to 89 mL/min by Cockcroft Gault equation [C-G]) or moderate (CL_{CR} 30 mL/min to 59 mL/min) renal impairment. VYXEOS has not been studied in patients with severe renal impairment (CL_{CR} 15 mL/min to 29 mL/min) or end-stage renal disease.

Hepatic Impairment
Dosage adjustment is not required for patients with a bilirubin level less than or equal to 3 mg/dL. VYXEOS has not been studied in patients with bilirubin level greater than 3 mg/dL.

PATIENT COUNSELING INFORMATION

Hemorrhage
Inform patients of the risk of fatal bleeding. Advise patients of the need for periodic monitoring of blood counts and of the importance of keeping scheduled appointments for blood work and necessary transfusions. Advise patients to contact a healthcare provider for new onset fever or symptoms of infection or if they notice signs of bruising or bleeding *[see Warnings and Precautions and Adverse Reactions].*

Cardiotoxicity
Advise patients to contact their healthcare provider if they develop symptoms of heart failure *[see Warnings and Precautions].*

Hypersensitivity Reactions
Inform patients of the risk of hypersensitivity reactions, including anaphylaxis. Describe the symptoms of hypersensitivity reactions, including anaphylaxis, and instruct the patient to seek medical attention immediately if they experience such symptoms *[see Warnings and Precautions].*

Embryo-Fetal Toxicity
VYXEOS can cause fetal harm when administered during pregnancy. Advise females of reproductive potential to use effective contraception during treatment and for 6 months following the last dose of VYXEOS and to inform their healthcare provider of a known or suspected pregnancy before and during treatment with VYXEOS *[see Warnings and Precautions and Use in Specific Populations].*

Lactation
Advise patients not to breastfeed during treatment with VYXEOS and for at least 2 weeks after the last dose *[see Use in Specific Populations].*

Infertility
Advise males of reproductive potential that VYXEOS may cause temporary or permanent infertility *[see Use in Specific Populations].*

Concomitant Medications
Advise patients to speak with their physicians about any other medication they are currently taking *[see Drug Interactions].*

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The Use of Bevacizumab in Treating Cervical Cancer

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The American Cancer Society estimates that about 12,820 new cases of invasive cervical cancer will be diagnosed and about 4,210 women will die from cervical cancer in the United States in 2017.[1] Despite primary prevention measures such as screening and human papillomavirus (HPV) vaccination, cervical cancer remains one of the most common cancers in women and is often diagnosed at advanced stages. Women with recurrent and metastatic cervical cancer have historically had extremely limited treatment options.[2]

It has been the standard of care since 1999 to consider the combination of chemotherapy and radiation for treating stages IB2 to IVA cervical cancer.[3] However, the long-term complications from radiotherapy and poor control of micrometastases raised interest in investigating other approaches. Single-agent cisplatin was widely accepted as the standard for treating late-stage cervical cancer until 2005, when Long and colleagues demonstrated improved overall survival (OS) in patients treated with doublet chemotherapy versus cisplatin alone.[4]

In 2009, the Gynecologic Oncology Group (GOG) 204 study examined four cisplatin-based doublets to assess their efficacy and toxicities. This study found a trend favoring the cisplatin/paclitaxel regimen, although it was not statistically significant. Henceforward, cisplatin and paclitaxel has been considered the standard regimen for patients with stage IVB, recurrent, or persistent cervical carcinoma. However, the investigators in this study concluded that alternative regimens are reasonable and should be considered for individual patients, especially in the setting of pre-existing comorbidities or toxicities.[5] Many patients unfortunately develop recurrence within the first 2 years of completing treatment, and their cases are often not salvageable. Survival for metastatic, recurrent, or persistent cervical cancer is about 12 months.[2]

Vascular endothelial growth factor (VEGF) has emerged as a target to inhibit angiogenesis in many solid tumors because the dysregulation of angiogenesis plays a role in tumor growth and metastasis. Vascularization and increased microvessel density are typically seen on colposcopy in women with invasive cervical cancer; thus, the VEGF receptor seemed a compelling potential target.[6] Bevacizumab is a recombinant humanized monoclonal antibody that binds to VEGF A with potent anti-angiogenic action, and it has been approved for use in treating several types of solid tumors.[7] In 2006, Wright and colleagues conducted a case series that suggested activity of bevacizumab in recurrent cervical cancer, demonstrating a progression-free survival (PFS) extended by 4.6 months.[8] A subsequent phase-2 trial evaluated bevacizumab in patients with persistent or recurrent cervical cancer. This study found that median PFS was extended by 3.4 months and overall survival (OS) by 7.3 months, which compared favorably to historical data. As expected, hypertension, thromboembolism, anemia, cardiovascular side effects, vaginal bleeding, neutropenia, and gastrointestinal fistulas were identified as toxicities, but overall the treatment was considered to be well tolerated.[9] This phase-2 study prompted the development of a phase-3 study with bevacizumab.

GOG 240 was a randomized, open-label phase-3 trial that included patients with metastatic, persistent, or recurrent cervical carcinoma.[10] It included patients with an Eastern Cooperative Oncology Group performance status of 0 or 1 and otherwise healthy patients with a very poor prognosis. Four hundred fifty-two patients were randomly assigned to treatment with either cisplatin plus paclitaxel, with or without bevacizumab, or the non-platinum-containing regimen paclitaxel plus topotecan, with or without bevacizumab. This trial sought to answer two questions: (1) whether bevacizumab was effective in addition to chemotherapy, and (2) whether the non-platinum-based chemotherapy doublet of topotecan/paclitaxel would be effective in circumventing platinum resistance. An interim analysis in 2014 demonstrated no difference in outcomes between the platinum and non-platinum chemotherapy regimens. However, adding bevacizumab to chemotherapy significantly prolonged OS (3.7 months) and PFS (2.3 months) and improved the overall response rate (48% vs. 36%).[10] Primarily on the basis of this interim analysis, the FDA approved bevacizumab for women with advanced cervical cancer. This was the first new drug approved for the treatment of cervical cancer in more than 8 years. In addition to FDA approval, these results also led to the National Comprehensive Cancer Network guidelines listing of bevacizumab as a category 1 recommendation for patients with recurrent or metastatic cervical cancer in combination with either cisplatin/paclitaxel or topotecan/paclitaxel.[11]

In July 2017, the final results from the GOG 240 trial were published. The overall survival curves showed stable separation with a 3.5-month improvement when bevacizumab was added to chemotherapy (16.8 months vs. 13.3 months, $p = .007$). Although this improvement may appear modest, it should be considered that most patients survive only about 12 months at this stage of disease. When the different chemotherapy arms (with and without bevacizumab) were compared, topotecan/paclitaxel was associated with a higher risk of disease progression over cisplatin/paclitaxel (median PFS 5.7 months vs. 7.6 months, $p = .008$), but there was no significant effect on OS (12.5 vs. 15 months, $p = .88$). Adding bevacizumab to the cisplatin/paclitaxel regimen reduced the hazard of death (OS 17.5 months vs. 15.0 months, $p = .04$), but this did not reach significance when added to topotecan/paclitaxel (16.2 vs. 12.0 months, $p = .15$). Interestingly, however, complete and partial responses to topotecan/paclitaxel were almost doubled when bevacizumab was added to the regimen (48% vs. 25%, $p = .0004$), an effect not seen with cisplatin/paclitaxel. Substituting topotecan for cisplatin did not circumvent drug resistance to platinum, which may suggest that cervical cancer does not exhibit

platinum resistance specifically but instead may be resistant to chemotherapy in general. Using topotecan as a non-platinum-based alternative may be advantageous in patients with platinum hypersensitivity or renal insufficiency. After bevacizumab was discontinued, the researchers did not observe a negative rebound effect (i.e., a survival shorter after bevacizumab is stopped than after chemotherapy alone is stopped), which has been observed in other cancers.[10]

Across the literature, bevacizumab is associated with toxicities like hypertension (5%–18%), surgical and wound healing complications (3%–15%), gastrointestinal fistulas (2%–15%), thrombotic events (2.3%–10.6%), gastrointestinal perforation (.3%–3.2%), and nephrotic syndrome (less than 1%).[12] Of these, fistula formation, which occurred in 15% of all bevacizumab-assigned patients in GOG 240, is one of the most concerning toxicities. A clinically significant fistula (grade 3, requiring intervention) occurred in 6% (n = 13) of patients receiving bevacizumab, versus less than 1% (n = 1) in the chemotherapy-alone group.[10] Of note, all patients were previously irradiated. Recurrent or persistent disease in the pelvis following chemoradiation appears to be a risk factor for fistula formation, potentially due to the damage incurred to the microvasculature.[13]

GOG 240 also developed a set of prognostic factors known as the Moore criteria, which identify negative prognostic risk factors that may be used to help guide therapy. Negative prognostic factors included African American race, performance status 1, pelvic disease, prior treatment with cisplatin, and a progression-free interval less than 365 days. Risk categories included low-risk (0–1 factors), mid-risk (2–3 factors), and high-risk (4–5 factors). Patients in the high-risk group obtain the greatest benefit from bevacizumab (hazard ratio [HR] .536) compared to patients in the mid-risk (HR .673) or low-risk (HR .96) groups. Additionally, in low-risk patients treated with chemoradiation prior to recurrence, these criteria can be used to argue against including bevacizumab because the fistula risk is 8.6% with a very small survival benefit.[13]

GOG has now completed nine phase-3 randomized trials over 30 years in the cervical cancer patient population. Although considerable progress has been made, the challenge remains to find tolerable treatments that can further increase survival. Bevacizumab increases the survival of patients with advanced cervical cancer, but significant progress must still be made to cure patients of this devastating disease. ●●

REFERENCES

1. American Cancer Society. 2017. https://www.cancer.org/cancer/cervical-cancer/about/key-statistics.html. Accessed September 9, 2017.
2. Small W Jr., Bacon MA, Bajaj A, et al. Cervical cancer: a global health crisis. *Cancer* 2017; published online May 2.
3. Green JA, Kirwan JM, Tierney JF. Survival and recurrence after concomitant chemotherapy and radiotherapy for cancer of the uterine cervix: a systematic review and meta-analysis. *Lancet*. 2001;358:781-786.
4. Long HJ 3rd, Bundy BN, Grendys EC Jr., et al. Randomized phase III trial of cisplatin with or without topotecan in carcinoma of the uterine cervix: a Gynecologic Oncology Group study. *J Clin Oncol*. 2005 Jul 20;23(21):4626-4633.
5. Monk BJ, Sill MW, McMeekin DS, et al. Phase III trial of four cisplatin-containing double combinations in stage IVB, recurrent, or persistent cervical carcinoma: a Gynecologic Oncology Group study. *J Clin Oncol*. 2009;27:4649-4655.
6. Tewari KS, Monk BJ. New strategies in cervical cancer: from angiogenesis blockade to immunotherapy. *Clin Cancer Res*. 2014;20(21):5349-5358. doi: 10.1158/1078-0432.CCR-14-1099. [Epub 2014 Aug 7.]
7. Ferrara N, Hillan KJ, Gerber HP, et al. Discovery and development of bevacizumab, an anti-VEGF antibody for treating cancer. *Nat Rev Drug Discov*. 2004 May;3(5):391-400.
8. Wright JD, Viviano D, Powell MA, et al. Bevacizumab combination therapy in heavily pretreated, recurrent cervical cancer. *Gynecol Oncol*. 2006;103:489-493.
9. Monk BJ, Sill MW, Burger RA, et al. Phase II trial of bevacizumab in the treatment of persistent or recurrent squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. *J Clin Oncol*. 2009 Mar 1;27(7):1069-1074.
10. Krishnansu TS, Tewari S, Sill MW, et al. Bevacizumab for advanced cervical cancer: final overall survival and adverse event analysis of a randomised, controlled, open-label, phase 3 trial (Gynecologic Oncology Group 240). *Lancet*. 2017;390(10103):1654-1663. http://dx.doi.org/10.1016/S0140-6736(17)31607-0 [Epub ahead of print 27 July 2017]
11. National Comprehensive Cancer Network. Cervical Cancer (Version 1.2017). https://www.nccn.org/professionals/physician_gls/pdf/cervical.pdf. Accessed September 9, 2017.
12. Avastin [package insert]. Genentech, San Francisco, CA; 2016.
13. Tewari KS, Sill MW, Monk BJ, et al. Prospective validation of pooled prognostic factors in women with advanced cervical cancer treated with chemotherapy with and without bevacizumab: a NRG Oncology/Gynecologic Oncology Group Study. *Clin Cancer Res*. 2015 Dec 15;21(24):5480-5487.

The Transition from PGY-1 to PGY-2

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Traveling on a red-eye flight during my move from Los Angeles to Boston was exhilarating. Seventy-two hours after I waved goodbye to my PGY-1 residency, I was sitting in the new-employee orientation at Massachusetts General Hospital (MGH) as a PGY-2 oncology resident. Even before I entered pharmacy school, I knew I wanted to pursue a PGY-2 residency in a specialty. When this moment arrived, I was filled with enthusiasm. I knew that the program at MGH would be rigorous and demanding, but I was thrilled to be able to devote a full year to oncology.

A structured orientation in both the pharmacy department and oncology pharmacy helps transition new residents to the new work environment. Along with all the other incoming PGY-1 and PGY-2 residents, I started out my PGY-2 residency with a month of orientation in the MGH Graduate Pharmacy Education Program. In addition to the general hospital and pharmacy orientation, I had an orientation specifically for PGY-2 oncology residents, which included clinical training and assessments. A series of oncology pharmacology review sessions were also planned to help us build a solid foundation in chemotherapy and targeted therapies. I began shadowing pharmacists in both inpatient and outpatient oncology pharmacies early in the orientation, which helped me learn the oncology pharmacy workflow and provided me the opportunity to work with a number of pharmacists. I felt that this orientation setup helped transition me to the oncology pharmacy work environment.

One of the most important items on the PGY-2 oncology resident's checklist is to communicate with the residency program director (RPD) about short-term and long-term goals. During the orientation month, I met with my RPD several times to develop a customized learning plan that would incorporate both the program's goals and my personal goals. These goals and objectives were translated into specific activities, including clinical rotations, research, operation, leadership, education, and community services. I have found it very useful to have a goal-oriented plan that systematically guides me through the process.

Initially, I felt overwhelmed by the extensive list of activities under each of the objectives and goals set by the American Society of Health-System Pharmacists for completion during this year. Depending on the resident's prior experiences, preceptors or the RPD may need to allocate more time to areas requiring improvement. For example, because I did not have the opportunity to verify chemotherapy orders during my PGY-1 residency, my preceptors provided me one-on-one guidance through professional practice experiences to help me become accustomed to the workflow. I would also like to improve my oral chemotherapy counseling skills and would find mock patient education sessions very helpful.

Though I have a structured schedule for the year, I have been given the flexibility to develop my own research project and select clinical trial pharmacy rotations in my areas of interest. The learning experiences are arranged by disease states, and each preceptor has a subspecialty in that disease state. Unlike the situation in other specialties, most oncology disease states are new to the resident, and didactic lectures can therefore be extremely helpful in building one's knowledge base. For example, my first two rotations were in lymphoma and breast cancer. My preceptors held a number of one-on-one teaching sessions with me, which we spent analyzing patient cases and doing literature reviews, especially during the first week of each rotation. Preparing weekly lectures under the guidance of my preceptors helped me learn in depth about the disease states, treatment options, National Comprehensive Cancer Network guideline recommendations, landmark trials, and agents in the pipeline. In the beginning of the residency I needed more teaching from my preceptors, but I expect that as my oncology knowledge base grows, I will acquire more autonomy.

My learning experiences about clinical trials are incorporated into my core rotations. While providing guideline-based patient care, I will also be learning innovative therapy protocols and witnessing their implementation; MGH has an extensive clinical trials program that is moving oncology practice forward. As the PGY-2 oncology resident at MGH, I feel fortunate to be constantly exposed to the very forefront of oncology practice. In oncology, unlike other specialty practices, numerous clinical trials are conducted; learning how to read a study protocol and search for information in it is a critical skill that every resident must possess. Nevertheless, learning the standard-of-care regimen is the first step before one delves into clinical trials. Preceptors play a pivotal role in helping the resident who is new to the disease state to understand and differentiate among treatment regimens.

Feedback provided by the RPD and preceptors is essential to every resident's growth. Ever since August 1, when my clinical rotations began, I have been receiving constructive feedback and have been asked to provide feedback. I meet with my preceptor weekly to reflect on the positives and negatives of my training so that we can optimize my learning experience and I can continue to achieve the goals set for each rotation. It is important for the resident to document his or her daily and weekly progress and actively seek feedback from the preceptors so that potential problems are addressed immediately. Also helpful is a 10-minute daily recap with the preceptor to discuss what the resident learned that day and identify areas for improvement. Providing and receiving timely feedback allows the resident to reflect on progress and stay on track with the learning objectives.

The field of oncology is changing rapidly. Although what was learned in pharmacy school may become outdated shortly after graduation, pharmacists still need to apply the methodology of providing pharmaceutical care plans to oncology patients. Residency teaches us a framework for approaching patient cases and further refines the skills we already possess. Oncology pharmacy residency builds a solid foundation for our oncology knowledge and equips us to tackle future challenges in our oncology career. ●●

HELP HOPA BUILD ITS RESOURCE LIBRARY!

The HOPA Resource Library is a platform that allows educators, practitioners, and learners to share helpful innovations, materials, and resources with those in the field of hematology/oncology pharmacy practice.

We invite you to submit policies, webinars, podcasts, toolkits, evidence briefs, reports, guidelines and standards, summaries, programs, and materials for patient education to the Library. Resources posted in the Resource Library are not peer reviewed by HOPA but will be vetted by HOPA's Tools and Resources Committee prior to being posted.

Help us make the HOPA Resource Library the "go-to resource" for hematology/oncology pharmacy-related information.

Submit your resources at any time to ***ResourceLibrary@hoparx.org***

Don't forget about your expiring BCOP credits!

Board Certified Oncology Pharmacist (BCOP) recertification education products purchased from HOPA in 2017 will expire at 11:59 pm Pacific Standard Time on December 31, 2017. If you wish to earn BCOP credit for recertification, you must complete all posttests by this deadline.

The following products will expire:

- Updates from American Society of Pediatric Hematology/Oncology (ASPHO)—live and recorded webinar
- Updates from Multinational Association of Supportive Care in Cancer (MASCC)—live and recorded webinar
- 2017 BCOP Self-Study Online Module release II
- Updates from American Society of Clinical Oncology (ASCO)—live and recorded webinar
- 2017 BCOP Conference Repeated Sessions at Practice Management Program
- 2017 BCOP Conference Repeated Sessions—on demand

HOPA

BCOP

Recertification Program

Visit **hoparx.org** for more information on HOPA's BCOP education program, and log in to view the status of your continuing education.

Board Update

A Candle in a Hurricane

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

"You feel like a candle in a hurricane …"

Those words are the opening line of the 2007 hit "Stand," by Rascal Flatts. It's a song about overcoming obstacles in life. We've all had moments when we are challenged by forces seemingly bigger and stronger than ourselves—when our flame flickers to near extinguishment.

This metaphor came to life during the past months for many residents of the Gulf Coast, when Hurricanes Harvey and Irma wrought devastation across the region, most notably in Texas and Florida. Some HOPA members, including me, live and work in those paths of destruction. Our thoughts remain with those still recovering from the damage and loss inflicted by those storms.

HOPA, too, has been a circulating engine of energy, but with productive rather than destructive results. In early June, HOPA attended the annual meeting of the American Society of Clinical Oncology (ASCO), where we accomplished a great deal. HOPA President-Elect Ryan Bookout, Industry Relations Committee Chair Niesha Griffith, our HOPA Professional Relations and Development team of Julie Ichiba and Michael Bourisaw, and I met with several pharmaceutical industry partners to discuss current and potential professional collaborations. At this conference HOPA also participated in the first meeting of ASCO's CancerLinQ Oncology Leadership Council (OLC). HOPA is an inaugural member of the group overseeing this health information technology platform, and we are fortunate to have Amy Seung serving as our representative on the OLC. Not surprisingly, several of our HOPA colleagues also attended ASCO to present their research relating to innovations in the management of cancer patients and delivery of cancer care within the healthcare system.

Also in June, HOPA introduced revisions to our committee structure. The changes made will improve our organizational functionality and facilitate more communication among groups with similar responsibilities for supporting our strategic plan.

June ended with HOPA's participation in a timely meeting on biosimilars, therapeutic agents of importance to us as hematology/oncology pharmacy professionals. Edward Li, a HOPA board member at-large and a renowned authority on these entities, represented our interests at the PDA/FDA [Parenteral Drug Association/Food and Drug Administration] Biosimilars Conference in Bethesda, MD, June 26–27. In these discussions we were able to provide important feedback to regulatory agencies on the strategies required to successfully bring biosimilars to market.

You don't have to be a Washington insider to predict stormy weather buffeting our nation's capital. Each week seemingly brings a new development in the debate on healthcare reform. To help us stay the course through the storms, this summer our Public Policy Committee, chaired by Tim Tyler, issued "Principles of Healthcare Reform" (www.hoparx.org/advocacy-activities/position-statements), a position statement that frames our beliefs and serves as a foundation for our involvement. This group continues to monitor issues of importance to our practice and profession (such as pharmacists' provider status and the 340B drug-pricing program) and ably advises us on advocacy opportunities.

"It's easy for the winds of change to knock us down or dampen our enthusiasm. But responsibly fostering innovation paves the way for meaningful growth and progress."

HOPA's 5th Annual Practice Management Program (PMP), chaired by John Valgus, was held in Chicago, September 15–16 (see Lindsey Amerine's article on p. 19 in this issue for more details). Nearly 300 attendees gathered to hear presentations on issues affecting the implementation and support of pharmacy services, such as the Oncology Care Model, justification of oral chemotherapy services, and strategies to improve medication safety. This year our popular preconference workshop focused on the logistics of investigational drug services. To mark this milestone anniversary of PMP, the keynote lecture was named in honor of Past President Niesha Griffith. Niesha, a hurricane in her own right, has been instrumental in conceptualizing and developing the PMP since its inception in 2013.

At the conclusion of the 2017 PMP, we welcomed Michael Bourisaw as our interim executive director following the retirement of Suzanne Simons. Michael has worked with HOPA for the past 5 years and helped us develop diversified revenue streams and build relationships with other stakeholders. Just a few weeks into his leadership, we are already benefiting from his expertise in nonprofit operations and board governance. Michael has also been an asset to me personally, providing essential wisdom for guiding HOPA during this time of transition.

Finally, at the midpoint of my presidency, I leave you with a reflection on leadership, a pearl of wisdom once shared with me by my mom: blowing out someone else's candle won't make yours burn brighter. Encountering needless obstacles in our work can be challenging, to be sure. And it's easy for the winds of change to knock us down or dampen our enthusiasm. But responsibly fostering innovation paves the way for meaningful growth and progress. As I noted at the end of my remarks as incoming president at our 2017 Annual Conference in March, working hard for something we love is called *passion*. I remain passionate about our organization and dedicated to you as members. We will encounter storms along the way, but I am confident that HOPA's candle is poised to burn more brightly than ever.

HOPA
Hematology/Oncology
Pharmacy Association

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SAVE THE DATE

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14TH ANNUAL CONFERENCE

MARCH 21–24, 2018

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