HOPA NEWS

Pharmacists Optimizing Cancer Care

VOLUME 14 | ISSUE 3

To Try or Not to Try: The Impact of Right-to-Try Laws

page 3

HOPA
Hematology/Oncology Pharmacy Association

VOLUME 14 | ISSUE 3

Send administrative correspondence or letters to the editor to HOPA, 8735 W. Higgins Road, Suite 300, Chicago, IL 60631, fax 847.375.6497, or e-mail info@hoparx.org.

HOPA News is published by the Hematology/Oncology Pharmacy Association.

HOPA
Hematology/Oncology Pharmacy Association

Pharmacists Optimizing Cancer Care®

COLUMNS

FEATURE

To Try or Not to Try: The Impact of Right-to-Try Laws

Melissa Gamble, BA
PharmD student, Skaggs School of Pharmacy and Pharmaceutical Sciences
University of Colorado Anschutz Medical Campus
Aurora, CO

Right-to-try laws, currently approved in 37 states, allow terminally ill patients who have exhausted all other options to try experimental agents that have successfully passed phase 1 drug trials.[1] In oncology, phase 1 trials generally test novel therapies in patients with cancer who have exhausted standard-of-care treatment options in order to gather data on general safety and toxicity and recommended drug dosing for phase 2 studies. Efficacy is not a focus of phase 1 studies. Right-to-try legislation bypasses important government safety measures, including the Food and Drug Administration (FDA) expanded-access application process and institutional review board (IRB) review. Reporting of adverse drug events and evaluating use in patients is not mandatory, according to these laws. The laws restrict liability to the patients alone and do not require manufacturers to provide access to drugs. At most, they can shorten the time to drug acquisition in exchange for reduced patient protection and a disregard of societal well-being. In short, right-to-try laws, including the recently proposed federal legislation, the Trickett Wendler Right to Try Act (H.R. 878/S. 204), do not add any new material to the FDA's expanded-access program already in place for these patients (**Table 1).** (See also the update in "Legislative News," p. 10.)

Impact on Patients

The right-to-try laws provide little benefit to patients for whom experimental agents are warranted. Proponents of these laws, citing the need for greater patient autonomy, do not believe that patients should need government permission for access to drugs that may save

Table 1. Comparison Between Proposed Trickett Wendler Right to Try Act and the FDA's Expanded-Access Program for Investigational Drug Access As It Applies to Individual Patients[2]

	Right to Try Act	FDA's Expanded-Access Program
Oversight	None	FDA and IRB
Eligible patient	Patient who has a terminal illness with unfavorable prognosis and no known cure	Patient who has a serious or immediately life-threatening disease or condition
Product requirements	Recommendation by a physician after all other current treatment options have been considered No FDA involvement	Recommendation by a physician after determination that the investigational drug risk is not greater than the probable risk from the disease or condition FDA determines that the potential benefit justifies the use and is reasonable for the disease or condition
Informed consent	Required	Required with IRB review and approval
Timeframe	No delay; bypasses FDA or IRB oversight Manufacturer must still grant access	Emergency: hours to days; 30-day window on IND but often shorter Manufacturer must still grant access
Duration	No duration limits addressed	Treatment limited to single course of specified duration unless otherwise approved
Liability	Medical licensing boards are prohibited from acting against a physician	Not addressed
Drug availability	Determined by manufacturer; not mandated	Determined by manufacturer; not mandated
Costs	Manufacturers may charge without approval Insurers are not compelled to provide coverage	Manufacturer may charge if parameters are met; FDA approval required Insurers are not compelled to provide coverage
Impact on future research	Not addressed	Investigational drug use should not interfere with initiation, conduct, or completion of clinical investigations

Note. FDA = Food and Drug Administration; IND = investigational new drug; IRB = institutional review board.

their lives. Though respect for patient autonomy is a fundamental concept of medicine, it is not as simple as allowing patients to make their own decisions. Autonomy should also include the provision of medical guidance for patients so that they understand the situation adequately for informed decision making.[3] Physicians must provide this autonomy in balance with their duty to do no harm. If a physician determines that treatment with an experimental agent is appropriate and applies for the FDA's expanded-access program, two safety measures are in place. Also, the denial of experimental agents by the FDA is rare, with more than 99% of patients getting approved.[4] However, if the benefit of an experimental drug does not outweigh the calculated risk, a physician may deny the patient's request to use it. Patients have the right to seek out a physician willing to provide them the opportunity, even if it is not in their best interest. With FDA regulatory processes in place, an unethical request would be denied. Elimination of these processes could lead to an increased risk of harm to the patient.

Supporters of right-to-try laws argue that bypassing government approval reduces the patient's time to drug acquisition. Though the process was cumbersome when these laws were first suggested, the FDA recently sped up the processing of expanded-access applications with a new form (FDA form 3926) to an average time of 4 days in non-emergent cases and within hours for emergent cases.[5] The second component of government approval includes the IRB review, which can take longer for non-emergent cases but can be circumvented in emergent cases.[6] Still, the reality is that the drug manufacturer approval is what lengthens the time to experimental treatment after the expanded-access application has been approved. Right-to-try laws do nothing to shorten this amount of time. The benefit of reducing days to treatment by 2 days may not outweigh the risks associated with a lack of patient protection normally provided by FDA oversight, especially in emergent situations.

Access to experimental drugs remains a major barrier for patients, even with right-to-try laws. First, the laws do not guarantee that the manufacturer will provide the drug to the patient. Therefore, these laws do not ensure the right to try but instead allow the right to petition. In the current FDA regulatory process, patients are already allowed the right to petition with oversight. Laws are already in place to help patients gain access to medications. The 21st Century Cures Act, a federal law enacted in December 2016, requires drug companies to be more transparent about how they decide which patients get access and the approximate time needed before attaining the investigational agent.[7] The right-to-try laws are not set up to augment access from the drug manufacturers regarding time or cost. Also, these laws do not require health insurance providers to cover the cost or provide assistance for experimental agents.[5] Without the means to afford or reduce the inevitably high drug cost, most patients cannot access these medications anyway. In fact, an unintended consequence of right-to-try laws could include a disparity between those who can and those who cannot afford experimental agents. Therefore, right-to-try laws do not introduce any new component to compensate for the lack of access or the affordability of drugs and could potentially increase the inequality between the wealthy and the poor.

Impact on Providers

Providers are also affected by proposed right-to-try laws. Currently, physicians must take the time to apply on behalf of the patient to the FDA and IRB. Right-to-try laws aim to reduce physicians' effort, time, and liability by eliminating the need to report to the FDA and IRB. They allow a physician in good standing to request access to experimental medications, assuming all other options have been exhausted, without government intervention or follow-up. The belief is that physicians will be able to recommend experimental treatments for patients without fear of repercussions from the state medical board if complications occur.[8] However, this freedom and lack of liability are not harmless. Although advocates for these laws view the regulatory processes that physicians must adhere to as obstacles, those against the laws consider them safety measures. Providers, whether unintentionally or not, may not be as rigorous in their efforts to provide the safest care to their patient. Their integrity may falter if they do not have to answer to anyone.

In addition to FDA and IRB approval, physicians must inform these entities about adverse drug reactions that a patient may experience while on the medication. According to the right-to-try laws, physicians would no longer have to follow up on the adverse effects that a patient may experience because of experimental agents.[5] This could have major implications for future patients. Reporting of adverse drug events is a major way to gather safety information that would otherwise not be available for informed decision making. Pertinent information could be excluded from discussions surrounding the use of a drug that could cause avoidable harm. Providers would have to make recommendations in the absence of more complete safety data that could affect their decision to treat a patient or not. Right-to-try laws may claim to improve patient autonomy, but they certainly can interfere with providers' foremost goal of beneficence.

Impact on Society

Right-to-try laws may be detrimental to society as well. Although these laws attempt to foster individual patient autonomy, they pose an indirect threat to randomized controlled trials. Patients may choose to obtain an investigational drug directly from the drug company without enrolling in clinical trials in order to avoid receiving a placebo and to reduce the time commitment. This choice could slow down the clinical trial process, especially for diseases or conditions that affect a small patient population.[6] The progress

of phase 2 and 3 clinical trials that will show proof of efficacy and safety for these drugs will be compromised. It will take longer to develop products that could benefit larger patient populations and may even cost more in the end to produce effective agents. Such a result would have a large impact on public health, effectively undermining future medical developments.

Right-to-try laws were not created to balance individual risk with societal risks. Supporters argue that certain individuals may be excluded from randomized controlled trials, which prohibits them from receiving a drug that could save their life. If patients can get the medication directly from the drug company, they will not have to waste time trying to enroll in clinical trials that the FDA may recommend prior to using the expanded-access program. As previously stated, bypassing the FDA program means that reports of adverse drug events will not be available. The gathering of important safety and efficacy data is not guaranteed. These laws allow potentially harmful events that occur when an individual uses an investigational drug to go unreported. Proponents argue that representatives of drug companies worry that reporting adverse events associated with their experimental agents will diminish use by other patients or even lead to denial of the agent for the market.[5] Yet these drugs have very serious side effects that should be made known to the public. Permitting vital knowledge to go unreported neglects public well-being. The advocates of right-to-try laws do not account for actions that put the rest of society at risk.

Conclusion

The FDA's current expanded-access program is still the most appropriate available option for patients seeking investigational agents. The FDA considers the likelihood of effectiveness and risk of harm on an individual basis without compromising public health. It requires reporting of adverse drug events to consolidate safety data on the experimental agents. The application process has been expedited to simplify the form and reduce the time burden. Furthermore, more than 99% of patients are given permission to proceed with investigational drug use.[4] The current process preserves the progression of investigational agents within clinical trials and the quality of medical care. The FDA prohibits drug companies from charging more than the manufacturing cost, and manufacturers rarely charge for compassionate-use medications under the expanded-access programs for fear of criticism. In conclusion, right-to-try laws do not break down the main barrier to access from the drug manufacturers, may impede medical progress, and raise concerns about proper oversight. The Trickett Wendler Right to Try Act would offer no added benefit to patients in comparison with the FDA's expanded-access program. ●●

REFERENCES

1. FAQ—Right to Try National Movement for Terminal Patients. Available from http://righttotry.org/faq/
2. Holbein, ME, Berglund JP, Weatherwax K, Gerber DE, Adamo JE. Access to investigational drugs: FDA expanded access programs or "right-to-try" legislation? *Clin Transl Sci.* 2015;8(5):526-32.
3. Newman E, Kaloupek D. Overview of research addressing ethical dimensions of participation in traumatic stress studies: autonomy and beneficence. *J Trauma Stress.* 2009;22(6):595-602.
4. Expanded Access to Investigational Drugs for Treatment Use—Questions and Answers: Guidance for Industry. Available from www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM351261.pdf
5. Yang YT, Chen B, Bennett C. "Right-to-try" legislation: progress or peril? *J Clin Oncol.* 2015;33(24):2597-99.
6. Lurie P. 2016. Committee on Homeland Security and Government Affairs Hearing Testimony, US Food and Drug Administration. Available from https://www.fda.gov/NewsEvents/Testimony/ucm522044.htm
7. Hudson KL, Collins FS. The 21st Century Cures Act—a view from the NIH. *New Engl J Med.* 2017;376(2):111-13.
8. Feibel C. 2017. Patients demand the 'right to try' experimental drugs, but costs can be steep. Available from www.npr.org/sections/health-shots/2017/03/03/517796956/patients-demand-the-right-to-try-experimental-drugs-but-costs-can-be-steep

Maintaining Competence for Pharmacists Practicing in Oncology

Maxwell A. Brown, PharmD
Clinical Pharmacy Manager, Stem Cell Transplantation
New York-Presbyterian/Weill Cornell Medical Center

The American Cancer Society estimates that the number of cancer survivors will increase from 15.5 million in 2016 to more than 20 million in 2026.[1] This improvement in cancer survivorship creates a significant demand for oncology services, one that the American Society of Clinical Oncology predicts will be unmet by 2020, because of a shortage of qualified oncologists.[2]

Recent publications advocate for the use of oncology clinical pharmacy services to mitigate the effects of the impending shortage of oncologists.[3-6] However, the current number of postgraduate year-2 (PGY-2) oncology trained and board-certified oncology pharmacists (BCOPs) is insufficient to fill the growing number of oncology pharmacist positions.[7] Consequently, many pharmacists without advanced training in oncology are being tasked with providing clinical services to cancer patients. These services may include chemotherapy counseling, comprehensive medication reviews, management of adverse effects and drug interactions, and supportive care services. Given that the management of patients with cancer is becoming increasingly complex, it is crucial for pharmacists who are caring directly for patients with cancer to maintain a high level of competence.

Competence can be broadly defined as the possession of knowledge and skills across multiple domains required for one to perform adequately in a given setting.[8] The development of a standardized framework of competencies that must be completed by individuals within an organization can serve as a guide for recruiting qualified personnel, training existing employees, and maintaining knowledge of the ever-expanding list of cancer medications.

In 2010, Carrington and colleagues published an article describing the development of a competency framework for pharmacists providing cancer services in Australia. The authors stated that "practitioners may be considered competent when they are able to successfully apply their knowledge and skills to complete a framework of defined activities associated with their role."[9] The framework consisted of clusters of competencies in three basic categories: pharmaceutical care of oncology patients, knowledge of oncology, and practice management. Assessment of the degree of competence in each of these areas allows for designation of oncology pharmacists at varying levels of clinical practice and can inform managers about what responsibilities are appropriate for their staff. For example, pharmacists with less experience may benefit from the mentorship of a more seasoned pharmacist if they wish to specialize further in oncology, while oncology pharmacists with a high degree of competence may be able to independently engage in direct patient care.

The development of a competency framework for oncology pharmacists should be considered a best practice, and assessment of pharmacists' competence should be tailored to experience level as described by Carrington and colleagues.[9] The use of self-paced electronic modules, clinical in-service trainings, and team-based skills labs may be sufficient for assessing pharmacists who possess either extensive experience or specialty training in the care of patients with cancer.[10] However, opportunities for advanced on-the-job training should be offered to pharmacists without specialty training in oncology, who are involved in the care of oncology patients, to allow for professional development, career advancement, and safe, effective patient care. Strategies for improving knowledge in oncology will allow pharmacists without residency or equivalent training to help fill gaps in the care of oncology patients.

"The establishment of a standardized competency framework within an institution paves the way for continuous training and professional development for pharmacists practicing in the field of oncology."

In 2016, Saylor and colleagues described the implementation of an oncology pharmacy training course (OPTC) for pharmacists in oncology positions within their institution who did not possess PGY-2 training or BCOP certification. The OPTC employed bimonthly didactic education sessions led by PGY-2 trained pharmacists over the course of 1 year on a variety of oncology topics, including the basics of chemotherapy, supportive care in cancer, and disease state overview and management. Pharmacists participating in the OPTC were evaluated with the use of written examinations derived from the Oncology Pharmacy Preparatory Review and Recertification Course. Preliminary results reported at 3 months postimplementation demonstrated a significant improvement in oncology knowledge scores among the 29 pharmacists enrolled (29.6% to 52.2%, $p < .01$).[7] These results demonstrate that a formalized training course in oncology can effectively improve oncology knowledge among pharmacists who lack specialized training in the care of patients with cancer.

The implementation of a competency framework and training program for pharmacists within an organization is not without its challenges. Especially within larger institutions, it can be difficult to ascertain where to focus educational effort to ensure maximum impact. A thorough needs assessment should be conducted to determine where existing knowledge gaps exist. If available, medication adverse-event reporting systems within an institution can also be used to guide competency development through identification of commonly reported events.

(continued on p. 32)

Navigating Personal Finances

David Cecere, PharmD MBA
Assistant Director of Pharmacy
WVU Medicine
Morgantown, WV

Now that you have graduated from a pharmacy program and are beginning your professional career, what is your plan for financial stability? How do you pay down debt? How do you save for the future? Where do you start?

The purpose of this article is to offer some ideas on establishing a strong financial footing. We will review how to pay down debt, how to manage your current finances, and how to plan for future needs.

The Ghost of Financials Past

I have worked with many graduates from various programs, and I am amazed at the amount of debt that they have incurred. Over the past 30 years, the amount owed postgraduation has ballooned, depending on the loan program. It has been reported that 70% of the students who graduate this year will have loans averaging $37,172. This is a staggering amount of debt for someone beginning a new career, and the amount of debt owed by graduates increases yearly.

Not all school loans are created equally. Each has its own terms and interest assessment. Interest rates can vary from 4.6% to 7%, on average, with repayment terms of 10–20 years. To determine what you will actually pay back over the life of a loan, you can use one of the many online amortization calculators. Amortization calculators are helpful in showing you how much of your payment is allotted to the loan interest and how much to the principal payment. Early in the life of a loan, the interest owed makes up most of the payment. The percentage of your payment that goes toward interest decreases over the life of the loan, with a subsequent increase in the amount that is applied to your principal balance. For example, for a $30,000 loan at 4% interest over 20 years, the payment would be $181.79 per month. For the first month, $100 of the $181.79 would go to interest.

If you are able, commit to paying more than the minimum payment each month. The extra money will go toward your principal balance. By doing this, you will pay off the loan more quickly and pay back less interest over the life of the loan. Treating the extra payment as part of the loan makes this easier to accomplish. For example, if the payment is $181.79, consider paying $200. This is not a significant additional amount, but it does add up over the life of the loan. By paying an extra $18.21 per month, you will decrease the life of the loan by 31 months and save approximately $1,830 that would have gone toward interest.

"Now that you have graduated from a pharmacy program and are beginning your professional career, what is your plan for financial stability?"

The Ghost of Financials Present

Ideally, your new position has come with an increase in wages. It is time to consider what to do with your salary. Paying monthly bills is the first priority, but you will also want to consider the following areas:

Credit Cards

Credit cards are a necessity. The interest rate on your card is based on your credit rating. As a result, credit cards have different interest rates. The average credit card interest rate is approximately 16%. When you are selecting a credit card, select one with a low interest rate, one with a rewards program, or one that has both features. As a rule of thumb, I recommend charging on a credit card only what you can pay off at the end of the month so that you avoid paying interest charges. This takes some discipline but is well worth the effort.

Budget

Create a personal budget. The best way to do this is to take 1–3 months of expenses and determine where your salary is going. In addition to tallying monthly payments you make on bills, consider saving all your receipts. At the end of the month, record all your expenditures. Not only will this exercise make you aware of where you are spending your money, but it may also give you an idea of where you can cut costs in order to free up extra money.

Emergency Fund

Emergency funds are kept to prepare for an unexpected loss in wages, such as illness or a job loss. Most experts recommend that you have 3–6 months of savings to cover expenses until the emergency is resolved. The amount you need depends on the expenses that you have.

It may take some time to save enough to cover your expenses. For example, if you need $2,000 per month for expenses, then you would need $6,000 in your emergency fund for 3 months of unemployment. If you saved $600 per month, it would take you 10 months to create enough in your emergency fund to cover 3 months of expenses.

The key is to get into the habit of saving regularly. If possible, automate a monthly transfer to your savings account. Stay on top of your expenses. Keep accurate expense records, including accurate checking account records. After analyzing your spending, do you see things you could do without? Can you bring a lunch from home instead of eating out? Can you make your morning coffee at home instead of buying that expensive flavored coffee? It's okay to reward yourself once in a while if it's done in moderation, but try to be conscious of your spending habits.

The Ghost of Financials Future

Even though you may have just graduated and are entering the workforce, time flies. It is never too early to start saving for retirement. Here are some tips:

Selecting a Financial Advisor

Getting financial advice from an expert is a good idea, but where do you start? It's best to interview a potential financial advisor before enlisting the person's help. You may want to consider these questions when selecting a financial advisor:

- Has the person been recommended by someone whose judgment you trust?
- Is the advisor independent, or does he or she work for a firm?
- Is the person's work done on commission or for a flat fee?
- Does the advisor have references?
- Do you think you will like working with the person?

Retirement Plans

When investing for the future, ask yourself "Am I a risk taker, or do I have a low tolerance for risk?" The answer to this question will help guide you on how to invest.

Many organizations offer retirement plans that you can contribute to through a payroll deduction. This makes it easy to automate retirement savings. The most common type of retirement account is a tax-sheltered annuity plan, known as a 401(k). Nonprofit organizations offer a 403(b), which is equivalent to a 401(k). If you are a risk-averse investor, the money in your account can be used to purchase funds according to the year you plan to retire. If you plan to retire in 40 years, these funds weigh the amount of risk your account can tolerate over the course of its lifespan and adjust your investments accordingly. These funds are designed to offer higher risk with greater return (i.e., more stock investments) in the beginning and less risk with less return (i.e., bonds) as you get closer to retirement. If you are willing to tolerate more risk in your investments, you can formulate your own plan from a variety of offered funds. The Internal Revenue Service specifies upper limits to how much you can contribute to your account each year, and you will need to determine what that ceiling is when contributing.

Many different plans exist, and you may want to work with your financial advisor to select the one that works best for your current situation. In addition, your financial advisor can help you estimate how much you will need in your account when you retire. Typically, you can move your retirement savings in these plans between employers when you change jobs.

Conclusion

New graduates entering the work force may want to consider the basic financial principles discussed above and begin implementing these recommendations:

- Start with formulating a budget. Determine how much you can save each month.
- Make a plan to start paying down your student loan debt.
- Apply for a credit card, but select and use one wisely.
- Create an emergency fund.
- Start saving for retirement.
- Consider hiring a financial advisor to help you meet your financial goals. ●●

HELPFUL RESOURCES

Compiled by Sarah Newman, Section Editor

Amortization Calculators

- Bankrate—http://www.bankrate.com/calculators/mortgages/amortization-calculator.aspx
- FedLoan Student Loans Repayment Plan Calculator—https://myfedloan.org/borrowers/repayment-plans/

Books

- *Personal Finance for Dummies*, by Eric Tyson—As expected with the Dummies series, this book breaks down the basics of personal finance into easy to manage chunks. Expect lessons on all areas of personal finance: budgeting, saving, getting out of debt, timely investments, and retirement.
- *Debt-Free by 30*, by Jason Anthony and Karl Cluck—This book helps you rework your personal finances and find additional money each month to put toward your debt. It also helps you to prioritize your debt and create a debt payment plan that doesn't leave you overwhelmed by how much money you owe.
- *I Will Teach You to Be Rich*, by Ramit Sethi—Written with a sense of humor that will appeal to millennials, this book presents a practical approach to personal finance for the "materially ambitious but financially clueless" among us. The book is separated into a 6-week program centered around the four pillars of banking, saving, budgeting, and investing.
- *A Random Walk Down Wall Street*, by Burton Malkiel—This book is a classic for those who want a deeper understanding of investing. It breaks down all things investment related from index funds to derivatives. A must-read for anyone who wants to manage their own investment portfolio.

Making the Financial Transition from Resident to New Practitioner: An Insider's Perspective

Morgan Belling, PharmD
Clinical Hematology/Oncology Pharmacist
The University of Kansas Health System
Kansas City, KS

When you finish your residency, your life acquires some new features: more independent practice, additional preceptor responsibilities, more sleep, maybe a vacation (or two), and an increase in salary. So how do you successfully manage your money, or at least get off to a good start? The following are some tips and principles that I have learned from mentors:

It is imperative to create a budget. An objective assessment of how you spend your money will make you more aware of how you're allocating funds and whether you should be cutting back in some areas and saving in others. Remember how PharmAcademic™ prompted you to set specific, measurable, objective goals so that you could establish a roadmap and plan to improve your skills as a pharmacist? A budget serves the same purpose for your financial fitness, and several apps can help you track this. What's important is to establish a system that *works for you*, whatever that may be.

Save 10%–20% of what you earn. Having this done automatically every time you're paid is a smart move and trains you to work with your budget.

Start saving for retirement early! When I started my new position, I met with a financial advisor affiliated with the institution and determined a set percentage of my paycheck that I wanted to direct automatically toward my retirement. If you can, and depending on your student loan obligations, *definitely* try to maximize your retirement contributions (the federal government determines this maximum amount every year). This is a good way to reduce your taxable income, especially if you have few other qualifications to do so (no dependents, no mortgage, etc.). If contributing this maximum amount is not feasible, know that saving *early* is more important than the *amount* that you save because you're taking advantage of that compounded interest *over time*. Many employers offer a contribution match. Be sure to take full advantage of this—it's essentially "free money."

Listen to podcasts or read books from reputable financial advisors. These resources cover a variety of topics from mortgage strategies, ways to pay down debt, and stocks and bonds investments to saving for your children's college tuition. Focus on finding programming that is straightforward—the simplest principles can often take you a long way if you abide by them. Then your financial advisor (ideally, a fee-only advisor, someone who does not earn a commission for encouraging you to invest in certain mutual funds) can help you build on that solid foundation of principles and help you navigate more complex terrain.

Remember that not only does being a pharmacist bring us professional fulfillment; we are also fortunate enough to be in a position to pay back our loans, save for our future, and enjoy the life we build outside of work.

HELPFUL RESOURCES

Compiled by Sarah Newman, Section Editor

Apps

- Mint—Best all-around personal finance app. This app lets you create budgets, keep track of your accounts, create financial goals, and pay bills, all in one app. You also get a free monthly credit score update, with recommendations for ways to improve it.
- You Need a Budget (YNAB)—Best for someone who finds it difficult to stick to a budget. But let's be honest: who doesn't occasionally? If you get off track with your budget during the month, YNAB helps you rebalance your budget around your remaining funds.
- Acorns—Best for automating savings. This app invests your money using your spare change. For every purchase made using a linked account, Acorns rounds up the purchase to the next dollar and funnels that money to a "micro investing" account.
- Stash—Best for beginner investors. With as little as $5 to get started, you can buy, sell, and monitor investment funds from the Stash app. It's an easy way to start learning the basics of investing without the need for a lot of investment capital.

Podcasts

- You Need a Budget—The companion podcast for the YNAB app. Episodes focus around YNAB's four rules of budgeting: give every dollar a job; save for a rainy day; roll with the punches; and live on last month's income.
- Feed the Pig—This podcast features financial teachings from the experts at the American Institute of Certified Public Accountants and covers all the basics of personal finance.
- Freakonomics Radio—The offshoot of the popular productivity books of the same name, this podcast teaches listeners how to think more productively, rationally, and creatively—all of which can help you better manage your personal productivity and your finances.

Update on HOPA's Health Policy Activities

Jordan Wildermuth, MSW
HOPA Health Policy and Advocacy Manager

Various attempts to repeal and replace the Affordable Care Act (ACA) delayed deliberation on all other healthcare legislation for most of the summer. Although the House managed to pass legislation to repeal the ACA in May, the Senate was unsuccessful in its efforts. Before leaving for summer recess, the Senate introduced a scaled-down repeal bill (dubbed the "skinny repeal"), which would roll back the ACA's individual and employer mandates as well as the tax on medical devices. The measure did not receive enough votes to pass, leaving the future of the repeal–and-replace effort up in the air. Although conversation about next steps in the effort is continuing, Congress has pivoted from health care to the issues of tax reform and appropriations for fiscal year (FY) 2018.

FDA Reauthorization Act of 2017

On August 3, Congress passed the FDA [Food and Drug Administration] Reauthorization Act of 2017, reauthorizing the prescription drug, generic drug, medical device, and biosimilar user-fee programs through 2022. The Congressional Budget Office estimates that the new bill will generate $9 billion in fees—$8 billion for drugs and $1 billion for devices—between 2018 and 2022. The fees collected through the program are used to pay for the regulatory review of new medicines, with the intent of speeding up the approval process. HOPA has been monitoring the progress of the bill because it includes provisions pertaining to user fees for biosimilars. The final bill

- eliminates fees for supplements to biosimilar applications and biosimilar manufacturing facilities
- assesses holders of approved applications for biosimilars with an annual fee
- sets the annual amount of revenue that must be generated by fees
- extends through FY 2022 programs, policies (including Critical Path Public-Private Partnerships), and support for the development of medical products for rare conditions.

Right-to-Try Legislation

The Trickett Wendler Right to Try Act (H.R. 878/S. 204) sponsored by Senator Ron Johnson (R-Wis.), which allows people facing life-threatening diseases access to unapproved experimental drugs, was passed on the same day that the FDA Reauthorization Act was passed. The legislation prohibits the government from restricting access to medications that have undergone only preliminary testing in humans. Patients first would have to try all other available treatments and be unable to participate in clinical trials. The final version of the bill incorporates compromises made following a previous version, which faced scrutiny because it barred the FDA from considering any information on safety problems as part of its approval process for a drug falling under the right-to-try rubric. The latest version was modified to allow the agency to consider such information if it is critical to determining whether the drug meets the agency's safety standards.

FY 2018 Appropriations

The House Appropriations Committee has passed a FY 2018 Labor, Health and Human Services, and Education (LHHS) spending measure, which contains funding for programs of interest to HOPA. Funding includes $35 billion for the National Institutes of Health (a $1.1 billion increase), $5.77 billion for the National Cancer Institute (an $82 million increase), and $300 million for the Cancer Moonshot Initiative. The Senate is expected to release its FY 2018 LHHS bill when it returns in September from the summer recess. HOPA continues to work with the entire cancer community to maintain and expand U.S. investments in research for cancer treatment to ensure that new innovations are possible.

Cancer Drug Coverage Act

In early July 2017, HOPA joined members of the Patients Equal Access Coalition and met with staff members in 18 Senate offices to solicit support for a Senate companion oral parity bill. The House bill was reintroduced in March and requires any health plan that provides coverage for cancer chemotherapy treatment to provide coverage for self-administered anticancer medication at a cost no less favorable than the cost of intravenous, port-administered, and injected anticancer medications.

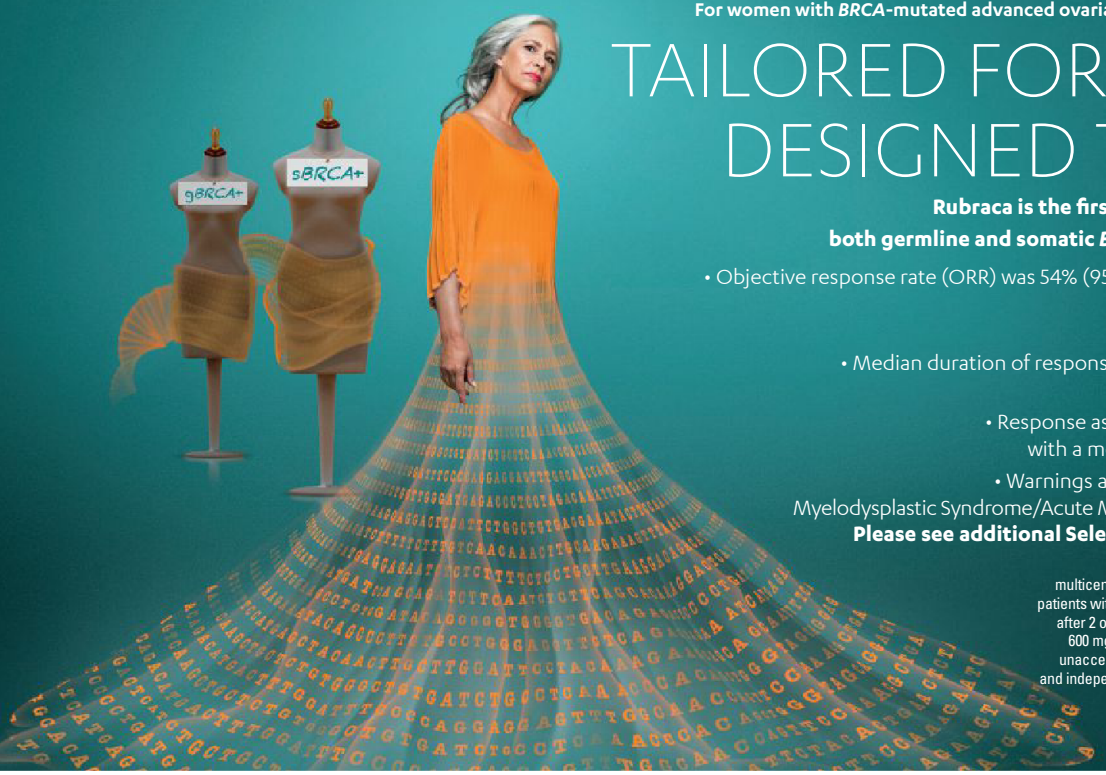
HOPA has also initiated a state advocacy program working with the State Patients Equal Access Coalition. To date, 43 states have passed and implemented oral parity laws. HOPA is continuing its work to mobilize members in Michigan, North Carolina, and Tennessee to participate in these efforts and is working with HOPA members in New Jersey to support a bill that caps out-of-pocket spending on prescription drugs.

Provider Status

The number of House and Senate cosponsors of the Pharmacy and Medically Underserved Areas Enhancement Act (H.R. 592/S. 314) continues to grow. HOPA's visits with legislators on HOPA Hill Day in May garnered 11 additional cosponsors in the House and 1 in the Senate. The number of cosponsors has now crossed the two-thirds threshold among Republicans on the House Committee on Energy and Commerce that is required to bring a bill up for consideration. The Patient Access to Pharmacists' Care Coalition implemented a summer media strategy consisting of digital and radio advertising.

Looking Ahead

HOPA will continue to monitor activity relating to repeal and replacement of the Affordable Care Act and to thoughtfully assess any legislation and coalitions that bear directly on HOPA's mission and public policy agenda. HOPA has decided not to prioritize taking a position on repeal-and-replace legislation but instead to remain focused on securing provider status for pharmacists and seeing that patients have access to oral chemotherapy at a rate no less favorable than that for intravenous chemotherapy. ●●



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

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]*.

Distributed by:
Clovis Oncology, Inc.
Boulder, CO 80301
1-844-258-7662

Issued: February 2017
PP-RUCA-US-0252 07/2017

Outcomes and Logistics of Cancer Treatment in the Intensive Care Setting

Bryan Do, PharmD BCOP
Clinical Pharmacy Specialist, Lymphoma/Myeloma
The University of Texas MD Anderson Cancer Center
Houston, TX

Shilpa Paul, PharmD BCOP
Clinical Pharmacy Specialist, Leukemia
The University of Texas MD Anderson Cancer Center
Houston, TX

Jeff Bruno, PharmD BCPS BCNSP BCCCP FCCM
Director, PGY-2 Critical Care Pharmacy Residency
Clinical Pharmacy Specialist, Critical Care/Nutrition Support
The University of Texas MD Anderson Cancer Center
Houston, TX

The prevalence of cancer was an estimated 14,738,719 cases in the United States in 2014, with 1,688,780 new cancer diagnoses in 2017.[1] Up to 10% of patients with cancer may develop a severe or life-threatening complication requiring intensive care, and approximately 5% will receive cancer treatment in the intensive care unit (ICU).[2,3] Advances in the management of hematologic malignancies and solid tumors and improvements in comprehensive critical care for patients with cancer have been shown to improve survival.[4-6] This review discusses the outcomes and logistical considerations of cancer treatment in critically ill patients.

Cancer and Critical Illness

In general, in-hospital mortality is high (up to 60%) among cancer patients admitted to the ICU for medical complications (e.g., respiratory failure requiring mechanical ventilation).[5,7,8] Recent studies suggest that the short-term prognosis (ICU mortality or hospital mortality) of critically ill cancer patients may be more strongly associated with severity of illness and extent of organ dysfunction present upon ICU admission and developing during ICU stay than with the malignancy itself.[7,9-12] In addition, mortality appears to be influenced by time to intervention following the patient's deterioration. Retrospective analyses revealed that time to patient intervention by a medical emergency team was independently associated with in-hospital mortality (adjusted odds ratio [OR], 1.445; 95% confidence interval [CI], 1.217–1.717, per 1-hour delay) and crude 1-year mortality (adjusted hazard ratio [HR], 1.027; 95% CI, 1.017–1.037, per 1-hour delay).[13,14] Similarly, ICU admission within 24 hours of the patient's deterioration has been associated with improved in-hospital survival.[5]

Allocation of ICU resources for critically ill cancer patients has recently been revisited in the 2016 Society of Critical Care Medicine (SCCM) guidelines for ICU admission, discharge, and triage (ADT).[15] The SCCM ADT guideline task force suggests that "ICU access of cancer patients be decided on the basis established for all critical care patients, with careful consideration of their long-term prognosis" (ungraded recommendation/best-practice statement). Essentially, ICU resources should be afforded on the basis of severity of illness (is the patient sick enough to benefit?) and long-term prognosis (i.e., lower priority for ICU admission would be given in the setting of terminal illness with no further oncologic treatment options), rather than solely on the basis of having malignancy with or without metastatic disease. A 2005 publication revealed that metastatic cancer was independently associated with critical care providers' refusal of ICU admission (OR, 5.82; 95% CI, 2.22–15.28).[16] The SCCM ADT guidelines also suggest that the status of all critically ill patients, "in particular, cancer patients with advanced disease," be reassessed and discussed with all major stakeholders, including the patient, at regular intervals (ungraded recommendation/best-practice statement). This statement is in line with ICU time trials suggested in the literature. Based on their 2007 investigation, Lecuyer and colleagues recommended a 6-day full-code ICU treatment trial for critically ill cancer patients who have stable disease, are not bedridden, and have options for lifespan-extending cancer treatment.[10] A more recent investigation revealed that the optimal ICU trial duration may be as short as 1–4 days in patients with poor-prognosis solid tumors, but as long as 10 or more days in patients with hematologic malignancy or low severity of illness (sequential organ failure assessment score less than 5) regardless of malignancy type.[17] Such findings appear to be in line with perceived prognosis (i.e., good short-term prognosis associated with a low severity of illness or good long-term prognosis in hematologic malignancy with perceived curability) and the provision of aggressive and sustained interventions in an attempt to overcome the acute insult.

Outcomes of Administering Chemotherapy in the ICU

Historically, little was known about the impact of administering chemotherapy to cancer patients in the ICU, but recent studies have shed some light on this topic. In a retrospective observational study, outcomes of intravenous chemotherapy administration in ICU patients with hematologic malignancies were evaluated.[18] This tertiary referral center was staffed by three full-time intensivists, of which two had hematology/oncology training. Of the 345 patients evaluated, 54 required chemotherapy, but only 37 went on to receive treatment. Intracranial bleeding, severe uncontrolled infection, septic shock with and without multiple organ failure, and pregnancy constituted reasons for withholding chemotherapy in 17 patients. Extensive disease resulting in upper airway obstruction and tracheal compression, leukostasis or leukemic infiltration of organs, severe disseminated intravascular coagulation (DIC), severe diseases with associated hemolysis, and acute promyelocytic leukemia were reasons provided for chemotherapy initiation. The majority of patients who received chemotherapy (86%) had high-grade malignancy identified as acute myeloid and lymphoblastic leukemia or non-Hodgkin lymphoma, 30% of patients had relapsing disease, and 41% had concomitant infection. Patients with lower severity of illness and lower rate of relapses were more

likely to receive chemotherapy than those with severe illness and higher number of relapses (acute physiology and chronic health evaluation II [APACHE II] score, 23±7 vs. 29±5, p = .007; 30% vs. 76%, p = .002, respectively). The only association with in-hospital mortality was mechanical ventilation (OR, 9.3; 95% CI, 1.7–52, p = .007). The 6-month mortality of mechanically ventilated and nonventilated ICU patients was 48% and 7%, respectively (p = .013). Overall, 16 patients died, and of the 21 that survived, a few continued to require renal replacement therapy or vasopressor support or both. This study concluded that initiating chemotherapy early can save lives of those in critical condition; however, it is important to assess each patient individually for the severity of their illness and disease status and to have an agreement between the intensivist and hematologist/oncologist.

Darmon and colleagues conducted a prospective observational study of 100 patients who had organ failure due to newly diagnosed, untreated cancer and required ICU admission and immediate treatment.[19] Patients were assessed for overall survival at 30 and 180 days. The majority of the patients had acute leukemia (48) and lymphoma (37). Patients were managed by a multidisciplinary team consisting of a hematologist/oncologist and intensivists. Median age was 47 years (range 32–61 years), and 84 patients had advanced disease (leukocytosis, stage 3/4 lymphoma, or metastatic or locally extensive solid tumor). Fifty patients had documented infection at time of admission, 5 patients had superior vena cava syndrome, and 5 patients had leukemic pulmonary infiltrates or leukostasis. Anticancer treatment was given within 1 day of initial diagnosis (range 0–11.5 days). Chemotherapy dose adjustment for organ failure occurred only in nonleukemic patients. Thirty patients needed to be dialyzed, 42 patients required vasopressors, and 23 patients required both interventions. The overall survival rate after 30 days and 180 days was 60% and 49%, respectively. The independent factors that negatively impacted 30-day outcomes were need for mechanical ventilation (OR, 6.36; 95% CI, 1.76–22.94), need for vasopressors (OR, 6.01; 95% CI, 1.86–19.4), and hepatic failure (OR, 7.76; 95% CI, 1.25–48.27). The study also found that outcomes were directly correlated to number of organ failures, rather than the malignancy itself.

In a retrospective study conducted by Wohlfarth and colleagues, critically ill cancer patients who received chemotherapy in the ICU were assessed for long-term survival.[6,20] Fifty-six patients were identified with mostly acute leukemia (n = 13) and aggressive non-Hodgkin lymphoma (n = 25). The investigators noted that 88% of the patients who started chemotherapy in the ICU continued to receive treatment and that one in three patients was alive at 1 year, of whom 69% are in complete remission.[20] The reduction in mortality is primarily a result of better triage, better supportive care, better understanding and acknowledgment of oncologic emergencies, and better identification of high-risk malignancies (e.g., acute promyelocytic leukemia).[6] The purpose of providing chemotherapy to cancer patients in the ICU can vary from being curative to being palliative or simply a means to provide for symptom management (e.g., to manage tumor lysis syndrome or to reduce mediastinal tumor mass to improve breathing). With increased awareness and knowledge of this subset of patients among nurses, pharmacists, and physicians in the ICU, safe administration of chemotherapy can lead to improvement in short-term and long-term survival.

Logistical Considerations for Management of Critically Ill Cancer Patients

Comprehensive cancer centers, large academic institutions, and community hospitals face common logistical issues in the care of patients with cancer who require both intensive care and chemotherapy. These patients may be admitted to the ICU prior to, during, or after receiving chemotherapy because of cancer-related complications or treatment-related toxicities.[3,19] A multidisciplinary approach, with communication between medical, nursing, and pharmacy staff, is crucial to providing appropriate care to critically ill cancer patients. Although a basic understanding of oncologic emergencies or common disease-related complications is helpful in initial management, an intensivist may not have the specialized training necessary to recognize, diagnose, and treat various hematological malignancies and solid tumors. Likewise, a hematologist or oncologist may not be able to optimally manage a patient exhibiting acute deterioration. ICU nurses and pharmacists may lack familiarity with chemotherapy and its unique monitoring parameters and adverse effects. All team members must therefore work together to define the goals of care in order to stabilize the patient and determine the need for anticancer therapy.[3,19,21]

Several considerations must be made on an individual basis before chemotherapy is initiated in critically ill patients. The healthcare team should determine whether the patient has a confirmed diagnosis of malignancy, consider patient-specific issues (e.g., prognosis, patient wishes), and determine whether safe administration of chemotherapy in the ICU is feasible.[3] Confirmed pathology is important because comparisons of postmortem findings have revealed inaccurate or missed diagnoses in up to 25% of patients. Obtaining a diagnosis in critically ill patients, however, can be challenging because they may not be able to undergo diagnostic testing or may receive medications that either confound or delay the workup. For example, early initiation of corticosteroids may treat and alter an underlying lymphoid malignancy, affecting the ability to establish a precise diagnosis. Recent administration of anticoagulants can cause the postponement of some procedures (e.g., biopsies) because of an increased risk of bleeding. The administration of dextrose-containing intravenous fluids, including antibiotics and heparin, may lead to inaccurate positron emission tomography/computed tomography imaging studies. In addition, patients who present with oncologic emergencies such as tumor lysis syndrome, hypercalcemia, spinal cord compression, or DIC may require immediate intervention without a confirmed diagnosis.[19,22,23]

Initiating chemotherapy in the ICU is often necessary in patients with

extensive disease and major organ involvement or high tumor burden with systemic complications.[18] Risk versus benefit of a treatment must be weighed on an individual basis. Patients may have pre-existing comorbidities, impaired organ function, immunodeficiency, or secondary metabolic complications that can make treatment decisions challenging. On the other hand, organ dysfunction and various disease-related complications may improve after anticancer treatment is initiated. Many chemotherapy agents and their metabolites are hepatically or renally eliminated, and doses must be adjusted accordingly because of pharmacokinetic and pharmacodynamic changes.[24,25]

Patients with end-stage renal disease present an added challenge because of the effects of intermittent hemodialysis and continuous renal replacement therapy on drug clearance, dosing, and timing of chemotherapy.[25,26] Available literature is limited; however, antimicrobial and chemotherapy dosing recommendations in patients requiring renal replacement therapies have been summarized.[25,27] A comprehensive medication review is especially important in critically ill patients because these patients may be on multiple agents that interfere with the metabolism, elimination, or stability of chemotherapy agents (e.g., sedatives, analgesics, antimicrobials, antiepileptic drugs). Lack of oral access, limited data for enteral tube administration, and concerns regarding impaired enteral absorption may impede the safe administration of oral chemotherapy agents. Safe and effective chemotherapy administration in the critically ill requires careful patient selection, multidisciplinary treatment planning, and close monitoring of toxicities.[3]

The American Society of Clinical Oncology and the Oncology Nursing Society established four domains for safety standards concerning chemotherapy administration: (1) staffing and general policy; (2) treatment planning, patient consent, and education; (3) ordering, preparing, dispensing, and administering chemotherapy; and (4) monitoring and assessment.[28] Although these recommendations serve as the basis for chemotherapy policies and standards at many institutions, barriers still exist because of the lack of appropriate knowledge, training, and experience; the lack of integrated computer systems or electronic health records; and limited staffing or support systems. Critical care providers do not have enough exposure or frequent opportunities to become familiar with various antineoplastic or targeted therapies. Although the decision to treat in the ICU may be the result of an interdisciplinary effort, it is important that the critical care team is able to execute the treatment plan. These limitations may lead to medication errors, including underdosing or overdosing; scheduling, timing, and infusion rate errors; and omission or improper administration of drugs. Moreover, obtaining informed patient consent and conducting education in the ICU are problematic when patients are sedated or intubated and when caregivers are unavailable or have differing perspectives.

Effective communication between all parties is important to prevent inappropriate care and exclusion in treatment decisions.[3] Because of the advent of new therapies that may require ICU admission, the demand for additional resources to help educate and train medical staff and patients and their caregivers regarding safe administration of anticancer therapies and recognition of signs and symptoms of their toxicities is increasing. For example, T-cell engaging therapies such as blinatumomab and chimeric antigen receptor (CAR) T-cells can have severe treatment-related toxicities (e.g., cytokine release syndrome, hemophagocytic lymphohistiocytosis, and neurotoxicity) that require intensive care.[29,30] Modalities to optimize continuity of care include formalizing a critical care–oncology collaboration system, developing shared continuing education programs, scheduling periodic reviews to discuss initiatives and improvements, and enhancing training programs.[31]

Bedside Execution of the Above Principles

The University of Texas MD Anderson Cancer Center (MDACC), a National Cancer Institute–designated comprehensive cancer center with 600-plus beds, houses a 36-bed medical ICU (MICU) and an 18-bed surgical ICU, with a proposed expansion in the near future. In addition, a medical emergency response incident team (MERIT) provides 24/7 prompt, hospital-wide evaluation of patients exhibiting signs of decompensation. MERIT works closely with the ICU triage team to coordinate timely transfer and interventions for patients requiring ICU admission. All ICUs within MDACC are open units, with patients comanaged by critical care teams and the primary hematology/oncology teams (e.g., stem cell transplant, leukemia, and lymphoma/myeloma teams). Teams comprising an attending physician, physician trainees, advanced practice providers (nurse practitioners or physician assistants), and clinical pharmacy specialists with 2 years of postgraduate or equivalent training conduct daily patient care rounds using an academic model. Ancillary care members including respiratory therapists, dietitians, and social workers participate daily in ICU patient care rounds; consultant teams (e.g., from the areas of infectious diseases, cardiology, and nephrology) are available as needed and are used often. Though respective teams may round separately, daily communication occurs between providers to coordinate plans of care and to help optimize achievement of patient-specific goals. Accordingly, the oncology clinical pharmacy specialist and the critical care clinical pharmacy specialist work closely together to address pharmacotherapy-related issues.

Between July 1, 2016, and June 30, 2017, 1,592 patients were admitted to the MICU, and 186 patients (12%) received chemotherapy (excluding investigational agents and CAR T-cell therapy). A total of 1,047 doses of chemotherapy were administered to these 186 patients: 516 oral/enteral, 511 intravenous, and 20 intrathecal doses. Patients with leukemia accounted for the majority (62%) of chemotherapy doses administered (67% oral/enteral, 55% intravenous, 80% intrathecal doses), followed by lymphoma/myeloma (16% of all chemotherapy, 0.2% oral/enteral, 33% of intravenous, 20% of intrathecal doses). Other populations

that received chemotherapy in the MICU during this period included genitourinary oncology, gynecologic oncology, melanoma, sarcoma, thoracic medical oncology, and neuro-oncology.

Given the relative infrequency of chemotherapy administration in our MICU, it is imperative that the ICU bedside nursing staff receive adequate training and support. Therefore, all newly hired ICU nurses first participate in a mandatory 3-week didactic lecture series as part of their orientation, which includes general ICU topics (e.g., hemodynamics, renal replacement therapy, end-of-life care) and specific presentations on the principles and general pharmacology of chemotherapy and biotherapy. A second component of the training is a required case study, with simulated chemotherapy administration using our intravenous pumps and respective medication library. Both the didactic portion and the case simulation are facilitated by ICU nurse educators and guest lecturers with expertise on the selected topics. Third, to help solidify training, all ICU nurses spend 1 experiential day on a stem-cell-transplant patient care floor, where they are assigned to an established oncology nurse and must demonstrate proper chemotherapy administration, documentation, and monitoring procedures according to MDACC policies. Finally, the institution's oncology charge nurses and nurse educators are available to help troubleshoot chemotherapy-related administration concerns; similarly, the oncology clinical pharmacy specialists are available to triage questions regarding chemotherapy treatment plans.

Conclusion

Outcomes of critically ill cancer patients requiring admission to the ICU were once thought to be dismal; however, recent data suggest that hospital survival may be more reflective of severity of illness than the malignancy itself. Accordingly, critically ill cancer patients who have a reasonable prognosis should be considered for ICU admission. Chemotherapy administration in the ICU appears feasible, but treatment should be carefully considered and individualized for each patient. Coordinated efforts among multidisciplinary critical care and hematology/oncology providers are crucial in managing the critically ill cancer patient. Institutions are encouraged to develop an appropriate infrastructure and staff educational plan to facilitate safe and prompt management of cancer patients experiencing acute decompensation. ●●

REFERENCES

1. National Cancer Institute. SEER Cancer Stat Facts: Cancer of Any Site. http://seer.cancer.gov/statfacts/html/all.html
2. Bos MM, Verburg IW, Dumaij I, et al. Intensive care admission of cancer patients: a comparative analysis. *Cancer Med*. 2015;4(7):966-976.
3. Shimabukuro-Vornhagen A, Boll B, Kochanek M, Azoulay E, von Bergwelt-Baildon MS. Critical care of patients with cancer [published online ahead of print on June 27, 2016]. *CA Cancer J Clin*. doi: 10.3322/caac.21351
4. Azoulay E, Soares M, Darmon M, Benoit D, Pastores S, Afessa B. Intensive care of the cancer patient: recent achievements and remaining challenges. *Ann Intensive Care*. 2011;1(1):5.
5. Azoulay E, Mokart D, Pene F, et al. Outcomes of critically ill patients with hematologic malignancies: prospective multicenter data from France and Belgium—a groupe de recherche respiratoire en reanimation onco-hematologique study. *J Clin Oncol*. 2013;31(22):2810-2818.
6. Moors I, Pene F, Lengline E, Benoit D. Urgent chemotherapy in hematological patients in the ICU. *Curr Opin Crit Care*. 2015;21(6):559-568.
7. Soares M, Caruso P, Silva E, et al. Characteristics and outcomes of patients with cancer requiring admission to intensive care units: a prospective multicenter study. *Crit Care Med*. 2010;38(1):9-15.
8. Bos MM, de Keizer NF, Meynaar IA, Bakhshi-Raiez F, de Jonge E. Outcomes of cancer patients after unplanned admission to general intensive care units. *Acta Oncol*. 2012;51(7):897-905.
9. Staudinger T, Stoiser B, Mullner M, et al. Outcome and prognostic factors in critically ill cancer patients admitted to the intensive care unit. *Crit Care Med*. 2000;28(5):1322-8.
10. Lecuyer L, Chevret S, Thiery G, Darmon M, Schlemmer B, Azoulay E. The ICU trial: a new admission policy for cancer patients requiring mechanical ventilation. *Crit Care Med*. 2007;35(3):808-814.
11. de Montmollin E, Tandjaoui-Lambiotte Y, Legrand M, et al. Outcomes in critically ill cancer patients with septic shock of pulmonary origin. *Shock*. 2013;39(3):250-254.
12. Xia R, Wang D. Intensive care unit prognostic factors in critically ill patients with advanced solid tumors: a 3-year retrospective study. *BMC Cancer*. 2016;16:188.
13. Song JU, Suh GY, Park HY, et al. Early intervention on the outcomes in critically ill cancer patients admitted to intensive care units. *Intensive Care Med*. 2012;38(9):1505-1513.
14. Lee DS, Suh GY, Ryu JA, et al. Effect of early intervention on long-term outcomes of critically ill cancer patients admitted to ICUs. *Crit Care Med*. 2015;43(7):1439-1448.
15. Nates JL, Nunnally M, Kleinpell R, et al. ICU admission, discharge, and triage guidelines: a framework to enhance clinical operations, development of institutional policies, and further research. *Crit Care Med*. 2016;44(8):1553-1602.
16. Garrouste-Orgeas M, Montuclard L, Timsit JF, et al. Predictors of intensive care unit refusal in French intensive care units: a multiple-center study. *Crit Care Med*. 2005;33(4):750-755.
17. Shrime MG, Ferket BS, Scott DJ, et al. Time-limited trials of intensive care for critically ill patients with cancer: how long is long enough? *JAMA Oncol*. 2016;2(1):76-83.
18. Benoit DD, Depuydt PO, Vandewoude KH, et al. Outcome in severely ill patients with hematological malignancies who received intravenous chemotherapy in the intensive care unit. *Intensive Care Med*. 2006;32(1):93-99.
19. Darmon M, Thiery G, Ciroldi M, et al. Intensive care in patients with newly diagnosed malignancies and a need for cancer chemotherapy. *Crit Care Med*. 2005;33(11):2488-2493.
20. Wohlfarth P, Staudinger T, Sperr WR, et al. Prognostic factors, long-term survival, and outcome of cancer patients receiving chemotherapy in the intensive care unit. *Ann Hematol*. 2014;93(10):1629-1636.
21. Schellongowski P, Sperr WR, Wohlfarth P, et al. Critically ill patients with cancer: chances and limitations of intensive care medicine—a narrative review. *ESMO Open*. 2016;1(5):e000018.
22. McCurdy MT, Shanholtz CB. Oncologic emergencies. *Crit Care Med*. 2012;40(7):2212-2222.
23. Pi J, Kang Y, Smith M, Earl M, Norigian Z, McBride A. A review in the treatment of oncologic emergencies. *J Oncol Pharm Pract*. 2016;22(4):625-638.
24. Floyd J, Mirza I, Sachs B, Perry MC. Hepatotoxicity of chemotherapy. *Semin Oncol*. 2006;33(1):50-67.
25. Niscola P, Vischini G, Tendas A, et al. Management of hematological malignancies in patients affected by renal failure. *Expert Rev Anticancer Ther*. 2011;11(3):415-432.

(continued on p. 32)

PARP Inhibitors: Current Approvals and Future Directions

Renee K. McAlister, PharmD
Genitourinary/Melanoma Clinical Pharmacist
Vanderbilt-Ingram Cancer Center/Vanderbilt University Medical Center
Nashville, TN

Overview of PARP Inhibitors

The poly ADP-ribose polymerase (PARP) enzymes are a family of 18 proteins that repair single-stranded deoxyribonucleic acid (DNA) damage via base-excision repair and via inhibition of the nonhomologous end-joining DNA repair pathway, a method of double-strand break repair.[1,2] Inhibition of the PARP1 and PARP2 enzymes results in the accumulation of double-stranded breaks, which are normally repaired by the homologous recombination double-stranded DNA repair pathway. The *BRCA1* and *BRCA2* enzymes function to repair double-stranded DNA breaks via homologous recombination. A germline or somatic mutation in one *BRCA1/2* allele is compensated for by the wild-type allele, and double-stranded break repair function is maintained. However, subsequent loss of the wild-type allele, known as loss of heterozygosity (LOH), renders the homologous recombination pathway ineffective. Tumor cells that have LOH are therefore most susceptible to PARP inhibition because they have essentially no way to fix double-stranded breaks. Ovarian and breast cancers are the most common malignancies associated with *BRCA1/2* mutations; however, prostate and pancreatic cancers have been associated with *BRCA1/2* mutations as well.[3] PARP inhibition represents a new class of chemotherapeutic agents, and three PARP inhibitors have been approved by the Food and Drug Administration (FDA). All approvals to date have been for treatment of ovarian cancer, though several other PARP inhibitors are currently in development.

Currently Approved PARP Inhibitors

Olaparib

Olaparib (Lynparza), the first PARP inhibitor on the market, was granted accelerated approval on December 19, 2014, as monotherapy in patients with deleterious or suspected deleterious germline *BRCA* (*gBRCA*) mutated advanced ovarian cancer who had been previously treated with three or more lines of chemotherapy.[4] BRACAnalysis CDx, a diagnostic test that detects *BRCA* mutations, was included in this approval. Accelerated approval was based on a multicenter single-arm phase 2 study that enrolled patients with a *gBRCA1/2* mutation and recurrent ovarian, breast, pancreatic, or prostate cancer.[3] Patients received olaparib 400 mg (supplied as 50-mg capsules) twice daily until the disease progressed or an unacceptable level of toxicity was reached. Of the 298 patients enrolled, 193 patients had a diagnosis of ovarian cancer resistant to prior platinum-based therapy, defined as relapse within 6 months of platinum therapy, or were unsuitable candidates for further platinum chemotherapy. Tumor response rate was 26.2% overall (95% confidence interval [CI], 21.3–31.6) and 31.1% in patients with ovarian cancer (95% CI, 24.6–38.1) and did not differ according to *BRCA1* versus *BRCA2* mutation. Median progression-free survival (PFS) was 7 months, and median overall survival (OS) was 16.6 months for patients with ovarian cancer. The most common adverse event (AE) greater than grade 3 was anemia (18.7% in the ovarian cancer group).

Recent data from the SOLO2 study have led to granting of FDA priority review status for use of olaparib in the maintenance setting for ovarian cancer.[5] SOLO2 was a randomized double-blind phase 3 study that evaluated maintenance olaparib in patients with platinum-sensitive relapsed ovarian cancer with a *BRCA1/2* mutation who were in response to the most recent platinum-based chemotherapy after at least two lines of treatment.[6] A total of 295 patients were randomized in a 2:1 ratio to receive olaparib 300 mg (supplied as a 150-mg tablet) twice daily or placebo. Pharmacokinetics of the new tablet dosage form were also studied in this trial, and the 300-mg dose was found to provide similar concentrations to the 400-mg dose administered as 50-mg capsules. This tablet dosage form has not yet been approved by the FDA. Median PFS in the olaparib group was 19.1 months versus 5.5 months in the placebo group ($p < .0001$). OS data have not yet been published. Grade 3 or greater anemia was observed in 19.5% of patients.

Rucaparib

Rucaparib (Rubraca) was granted accelerated FDA approval on December 19, 2016, for the treatment of patients with deleterious *BRCA* mutation (germline or somatic) associated advanced ovarian cancer who had been treated with two or more chemotherapies. The FoundationFocus CDx_{BRCA}, a next-generation sequencing diagnostic that detects alterations in the *BRCA1/2* genes, was approved by the FDA at the same time.[7] Approval was based on the results of two multicenter single-arm open-label clinical trials that included a total of 106 patients at the time of approval. The first trial was a phase 1/2 study of rucaparib for relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer with *gBRCA* mutations.[8] This study enrolled 41 patients who had received 2–4 prior chemotherapy regimens and had a progression-free interval 6 months after administration of their last platinum agent. Patients received rucaparib 600 mg twice daily in 21-day cycles until disease progression. The overall objective response rate (ORR) was 67%, with 15 of 22 responses ongoing at time of publication. The ORR was 65% for patients with a *BRCA1* mutation and 70% for patients with a *BRCA2* mutation. Grade 3–4 AEs included asthenia or fatigue (16%), anemia (22%), and alanine aminotransferase (ALT)/aspartate aminotransferase (AST) elevations (11%).

The second trial was ARIEL2, from which the final results of part 1 were just recently published. ARIEL2 was a two-part phase 2 open-label study that enrolled patients with recurrent platinum-sensitive high-grade ovarian carcinoma on the basis of the presence or absence of *BRCA* mutation (deleterious germline or somatic *BRCA* mutant, *BRCA* wild-type and high loss of heterozygosity [LOH], or *BRCA* wild-type and low LOH).[1] Two hundred six patients were enrolled and received oral rucaparib 600 mg twice

daily for continuous 28-day cycles. Median PFS was 12.8 months in the *BRCA* mutant group (95% CI, 9–14.7, $p < .0001$, compared to low LOH), 5.7 months in the high LOH group (95% CI, 5.3–7.6, $p = .011$, compared to low LOH), and 5.2 months (95% CI, 3.6–5.5) in the low LOH group. The most common grade 3 or greater AEs were anemia (22%) and AST/ALT elevations (12%).

Niraparib

Niraparib (Zejula), the third FDA-approved PARP inhibitor, was approved on March 27, 2017, for the maintenance treatment of patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who had had a complete or partial response to platinum-based chemotherapy.[9] Niraparib approval was based on the ENGOT-OV16/NOVA trial, a randomized double-blind phase 3 trial that included 553 patients with platinum-sensitive, recurrent ovarian cancer.[10] Patients who had had a complete or partial response following platinum-based therapy were enrolled into cohorts on the basis of the presence or absence of a *gBRCA* mutation as well as the type of non-*BRCA* mutation (homologous recombination deficiency [HRD] vs. non-HRD), and were randomized in a 2:1 ratio to receive niraparib 300 mg or placebo once daily. The primary end point, PFS, was longer in the niraparib group versus the placebo group in all cohorts (21.0 vs. 5.5 months in the *gBRCA* cohort [$p < .001$], 12.9 vs. 3.8 months in the non-*gBRCA* with HRD cohort [$p < .001$], and 9.3 vs. 3.9 months in the overall non-*gBRCA* cohort [$p < .001$]). Grade 3-4 AEs were reported in 74.1% of patients receiving niraparib versus 22.9% receiving placebo. The most common grade 3-4 AEs were hematologic: thrombocytopenia (33.8%), anemia (25.3%), and neutropenia (19.6%).

Currently Approved PARP Inhibitors: A Summary

All three FDA-approved PARP inhibitors are approved in the setting of recurrent disease, though they are approved at different stages of therapy. As noted, niraparib is approved for patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who have had a complete or partial response to the most recent platinum-based chemotherapy. The National Comprehensive Cancer Network (NCCN) guidelines recommend the use of niraparib for patients in this setting.[11] Rucaparib is approved for patients with deleterious *gBRCA*- or somatic *BRCA*-mutated advanced ovarian cancer who have progressed after two or more lines of therapy. The NCCN guidelines include rucaparib as an acceptable agent for treatment of recurrent disease.[11] Olaparib is approved for patients with deleterious *gBRCA*-mutated advanced ovarian cancer who have progressed after three or more lines of therapy, but it has also received priority review for use in the maintenance setting. The NCCN guidelines also include olaparib as an acceptable targeted therapy for treatment of recurrent disease.[11]

Future Directions for FDA-Approved PARP Inhibitors

As noted above, PARP inhibitors are also being studied in several other oncologic diagnoses, particularly those with *BRCA1/2* mutations. Results of the OlympiAD study were presented at the American Society for Clinical Oncology (ASCO) Annual Meeting in June 2017. OlympiAD was a randomized open-label phase 3 trial studying olaparib versus chemotherapy (capecitabine, vinorelbine, or eribulin) in 302 patients with HER2-negative (50% of whom had triple-negative breast cancer [TNBC]) *gBRCA*-positive metastatic breast cancer (MBC).[12] PFS was significantly longer in the olaparib group versus the chemotherapy group (7 vs. 4.2 months, respectively, $p = .0009$). ORRs were 59.9% and 28.8% for the olaparib and chemotherapy arms, respectively. Olaparib is also being studied for use in non–small cell lung cancer (NSCLC), small cell lung cancer (SCLC), head and neck cancer, sarcomas, and other malignancies.[13]

Ongoing studies for rucaparib use in ovarian cancer include ARIEL3, which is studying the use of rucaparib as maintenance therapy for platinum-sensitive high-grade serous or endometrioid epithelial ovarian, primary peritoneal or fallopian tube cancer, and ARIEL4, a confirmatory phase 3 randomized study of rucaparib versus chemotherapy for patients with relapsed *BRCA* mutant high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer.[14,15] Rucaparib is also being studied for use in metastatic castrate-resistant prostate cancer (mCRPC), pancreatic cancer, ovarian cancer in combination with atezolizumab, and MBC.[16]

Niraparib is currently being studied for use in mantle cell lymphoma, endometrial cancer, TNBC or ovarian cancer in combination with pembrolizumab, recurrent ovarian cancer, and mCRPC.[17]

Additional studies have shown that the presence of a mutation in the isocitrate dehydrogenase *(IDH) 1* or *IDH2* genes may increase susceptibility to PARP inhibitors, as mutations in *IDH1/2* render the homologous recombination DNA damage repair pathway ineffective in a manner similar to mutations in *BRCA1/2*.[18] *IDH1* and *IDH2* mutations are common in malignancies such as gliomas, acute myeloid leukemia, and cholangiocarcinoma.[19] Olaparib is currently being studied in *IDH1* and *IDH2* mutant solid tumors, and niraparib is being studied in DNA double-strand break repair deficient malignancies.[20]

New PARP Inhibitors on the Horizon

Two PARP inhibitors that have yet to gain FDA approval, talazoparib and veliparib, are currently being studied in clinical trials as well. Results of the ABRAZO trial, a two-stage, phase 2 study of talazoparib in 84 patients with locally advanced breast cancer or MBC and a *gBRCA1/2* mutation previously exposed to platinum-based chemotherapy (cohort 1) or at least three prior non-platinum-based cytotoxic regimens (cohort 2), were presented at the 2017 ASCO Annual Meeting. The primary end point, ORR, was 24% for patients with a *BRCA1* mutation and 34% for patients with a *BRCA2* mutation.[21] The ORR was 26% for patients with TNBC and 29% for patients with hormone receptor–positive disease. Grade 3 or greater AEs were anemia (35%), thrombocytopenia (19%), and neutropenia (15%). EMBRACA, a phase 3 study to evaluate talazoparib versus physician's choice of treatment in *gBRCA1/2*-mutated MBC, is currently under way.[22]

The results of several trials that evaluated the use of veliparib were also presented at the 2017 ASCO Annual Meeting. Studies evaluated veliparib for disease states such as SCLC (in combination with cisplatin and etoposide), NSCLC (in combination with

carboplatin and paclitaxel-based chemoradiation), pancreatic cancer (in combination with modified FOLFIRI [folinic acid, fluorouracil, irinotecan], prostate cancer (in combination with abiraterone and prednisone), and TNBC (in combination with carboplatin).[23]

Conclusion

In summary, three PARP inhibitors are currently approved by the FDA for the treatment of ovarian cancer. The currently approved PARP inhibitors are also being studied in other disease states, particularly in the setting of *BRCA1/2* and *IDH1/2* mutations. Several additional PARP inhibitors are being studied in clinical trials in a variety of settings. It remains to be seen whether the use of PARP inhibitors will result in favorable response rates and survival data in malignancies other than breast or ovarian cancer. ●●

REFERENCES

1. Swisher EM, Lin KK, Oza AM, et al. Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ARIEL2 Part 1): an international, multicentre, open-label, phase 2 trial. *Lancet Oncol.* 2017;18(1):75-87.
2. Dziadkowiec KN, Gąsiorowska E, Nowak-Markwitz E, Jankowska A. PARP inhibitors: review of mechanisms of action and BRCA1/2 mutation targeting. *Prz Menopauzalny.* 2016;15(4):215-219.
3. Kaufman B, Shapira-Frommer R, Schmutzler RK, et al. Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. *J Clin Oncol.* 2015;33(3):244-250.
4. Lynparza (olaparib) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; January 2017.
5. AstraZeneca shares progress on LYNPARZA™ (olaparib) tablets in the US [press release]. AstraZeneca; March 28, 2017. https://www.astrazeneca-us.com/media/press-releases/2017/astrazeneca-shares-progress-on-lynparza-olaparib-tablets-in-the-us-03282017.html. Accessed August 7, 2017.
6. Pujade-Lauraine E, Ledermann JA, Penson RT, et al. Treatment with olaparib monotherapy in the maintenance setting significantly improves progression-free survival in patients with platinum-sensitive relapsed ovarian cancer: results from the phase III SOLO2 study [abstract LBA2]. *Gynecol Oncol.* 2017;145(suppl 1):219-220.
7. Rucaparib. US Food and Drug Administration Web site. https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm533891.htm. Updated May 18, 2017. Accessed August 7, 2017.
8. Shapira-Frommer R, Oza AM, Domchek SM, et al. A phase 2 open-label, multicenter study of single-agent rucaparib in the treatment of patients with relapsed ovarian cancer and a deleterious BRCA mutation [abstract 2746]. *Eur J Cancer.* 2015;51(suppl 3):S545.
9. Niraparib (Zejula). US Food and Drug Administration Web site. https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm548487.htm. Updated May 30, 2017. Accessed August 7, 2017.
10. Mirza MR, Monk BJ, Herrstedt J, et al. Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. *N Engl J Med.* 2016;375(22):2154-2164.
11. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology (NCCN guidelines): ovarian cancer including fallopian tube cancer and primary peritoneal cancer [version 2.2017]. https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf. Published June 27, 2017. Accessed August 7, 2017.
12. Robson ME, Im SA, Senkus E, et al. OlympiAD: phase III trial of olaparib monotherapy versus chemotherapy for patients (pts) with HER2-negative metastatic breast cancer (mBC) and a germline BRCA mutation (gBRCAm) [abstract LBA4; published online ahead of print June 2017]. *J Clin Oncol.* 2017; 35(18)(suppl). doi: 10.1200/JCO.2017.35.18_suppl.LBA4.
13. ClinicalTrials.gov [database online]. Bethesda, MD: US National Institutes of Health; https://clinicaltrials.gov/ct2/results?cond=&term=olaparib&cntry1=&state1=&Search=Search. Accessed August 7, 2017.
14. Clovis Oncology, Inc. A study of rucaparib as switch maintenance following platinum-based chemotherapy in patients with platinum-sensitive, high-grade serous or endometrioid epithelial ovarian, primary peritoneal or fallopian tube cancer (ARIEL3). https://clinicaltrials.gov/ct2/show/NCT01968213. NLM Identifier: NCT01968213. Accessed August 7, 2017.
15. Clovis Oncology, Inc. ARIEL4: a study of rucaparib versus chemotherapy BRCA mutant ovarian, fallopian tube, or primary peritoneal cancer patients. https://clinicaltrials.gov/ct2/show/NCT02855944. NLM Identifier: NCT02855944. Accessed August 7, 2017.
16. ClinicalTrials.gov [database online]. Bethesda, MD: National Institutes of Health. https://clinicaltrials.gov/ct2/results?cond=&term=rucaparib&cntry1=&state1=&Search=Search. Accessed August 7, 2017.
17. ClinicalTrials.gov [database online]. Bethesda, MD: National Institutes of Health. https://clinicaltrials.gov/ct2/results?cond=&term=niraparib&cntry1=&state1=&Search=Search. Accessed July 11, 2017.
18. Sulkowski PL, Corso CD, Robinson ND, et al. 2-Hydroxyglutarate produced by neomorphic IDH mutations suppresses homologous recombination and induces PARP inhibitor sensitivity. *Sci Transl Med.* 2017;9(375): eaal2463.
19. IDH-mutant tumors vulnerable to PARP inhibition. *Cancer Discov.* 2017;7(4):OF4.
20. ClinicalTrials.gov [database online]. Bethesda, MD: National Institutes of Health. https://clinicaltrials.gov/ct2/results?cond=&term=PARP%2C+IDH&cntry1=&state1=&Search=Search. Accessed August 7, 2017.
21. Turner NC, Telli ML, Rugo HS, et al. Final results of a phase 2 study of talazoparib (TALA) following platinum or multiple cytotoxic regimens in advanced breast cancer patients (pts) with germline BRCA1/2 mutations (ABRAZO) [abstract 1007]. *J Clin Oncol.* 2017;35(15)(suppl):1007.
22. Pfizer. A study evaluating talazoparib (BMN 673), a PARP inhibitor, in advanced and/or metastatic breast cancer patients with BRCA mutation (EMBRACA Study) (EMBRACA). https://clinicaltrials.gov/ct2/show/NCT01945775?term=NCT01945775&rank=1. NLM Identifier: NCT01945775. Accessed August 7, 2017.
23. American Society of Clinical Oncology. 2017 ASCO annual meeting abstracts. http://abstracts.asco.org/199/IndexView_199.html. Published May 17, 2017. Accessed August 7, 2017.

HOPA Members Present Research at the 2017 American Society of Clinical Oncology Annual Meeting

Alissa Karr, PharmD BCOP
Oncology Clinical Pharmacist
Markey Cancer Center
University of Kentucky HealthCare
Lexington, KY

HOPA members had the opportunity to highlight their research during poster sessions at the 2017 American Society of Clinical Oncology (ASCO) Annual Meeting held in Chicago, IL, June 2–6. Featured in this article are excerpts from research and e-published abstracts from HOPA members who were the primary author. Additional members, listed at the end of the article, were secondary authors on posters and e-published abstracts. This article does not provide a comprehensive list; the authors had to self-report their presentations.

Abstract types: late-breaking abstract (LBA), trials in progress abstract (TPS), abstracts selected for publication but not for presentation at the annual meeting (e).

Dr. Edward Li and colleagues presented "Spending on Antineoplastic Agents in the United States: 2011–2016" (*J Clin Oncol*. 35, 2017 [suppl; abstr 6618]). Little information on trends in actual antineoplastic expenditure since the introduction of costly novel antineoplastic therapies is available. The objective of Dr. Li's study was to describe antineoplastic expenditures by year and healthcare sector in the United States. Quintiles IMS National Sales Perspective data for the years 2011–2016 were evaluated to describe antineoplastic agent expenditures. After they were grouped by healthcare sector and calendar year, actual expenditures were adjusted for U.S. medical-cost inflation to 2016 dollars. Growth was calculated as the percentage increase from previous years. Results of the study showed a total increase in antineoplastic expenditures from $26.8 billion in 2011 to $38.9 billion in 2016. Rituximab, bevacizumab, nivolumab, trastuzumab, and pertuzumab accounted for the top five antineoplastic expenditures in the study period, with $3.7 billion, $3 billion, $2.6 billion, $2.6 billion, and $0.9 billion expenditures in 2016, respectively. Hospitals and clinics showed an increase in spending on biologics by 80% from 2011 to 2016. Cytotoxic drug spending remained flat during the time studied because of the availability of multiple generic products. Dr. Li and colleagues concluded that antineoplastic expenditures increased significantly from 2011 to 2016. Expenditures are expected to continue rising with the anticipated approval of additional costly novel antineoplastic agents and an aging population.

Drs. Michael Kane, Paul Auriemma, and colleagues presented "Financial Impact of Flat Dosed (FD) Monoclonal Antibodies (MABs) at a Single Institution in 2016" (*J Clin Oncol*. 35, 2017 [suppl; abstract 6617]). Immuno-oncology agents are important breakthrough treatments in cancer. Some agents were adjusted after initial Food and Drug Administration (FDA) approval to flat dosing instead of weight-based dosing. Flat dosing (FD) may be thought to simplify prescribing, dispensing, inventory, and billing. Nivolumab and pembrolizumab are FDA approved for several malignancies. Original studies established weight-based dosing of nivolumab 3 mg/kg every 2 weeks and pembrolizumab 2 mg/kg every 3 weeks. The FDA approved FD of nivolumab 240 mg in melanoma, renal cell carcinoma, and non–small cell lung cancer. The FDA approved FD of pembrolizumab 200 mg in melanoma and non–small cell lung cancer as well as other indications. Dr. Kane and colleagues looked at the financial impact of this FD methodology compared to weight-based dosing of nivolumab (3 mg/kg, capped at 240 mg), as well as weight-based dosing of pembrolizumab (2 mg/kg, capped at 200 mg). Availability of pembrolizumab in 50-mg vials was also assessed. The electronic medical record was used for applicable dispensed dose and patient's weight. Wholesale acquisition costs (WAC) at the end of the year were used for financial comparison (**Table 1**).

Table 1. Cost Comparison for Nivolumab and Pembrolizumab by Dosing Method

Nivolumab: 54 patients, 510 doses (mean 77.3 kg; 33 patients less than 80 kg [302 doses])					
2016 WAC	All weight-based doses (3 mg/kg)	Flat dose (240 mg)		Weight-based dose (3 mg/kg, capped at 240 mg)	
Cost	$3,147,460.20	$3,069,225.90		$2,870,628.51	
Pembrolizumab: 103 patients, 605 doses (mean 80.14 kg; 89 patients less than 100 kg [528 doses])					
2016 WAC	All weight-based doses (2 mg/kg)	Weight-based dose if 50 mg vials were available	Flat dose (200 mg)	Weight-based dose (2 mg/kg capped at 200 mg)	Weight-based dose capped at 200 mg if 50-mg vials were available
Cost	$5,615,929.50	$4,811,113.00	$5,380,265.00	$5,300,228.00	$4,619,913.50

Note. WAC = wholesale acquisition costs.

In conclusion, weight-based dosing with a cap (nivolumab, 240 mg, pembrolizumab 200 mg) versus flat dosing would have saved $198,567 and $80,037, respectively. In addition, Dr. Kane and colleagues found savings of $760,351 if pembrolizumab in 50-mg vials was available. Wide-scale adoption of flat dosing for immune-oncology monoclonal antibodies may result in higher drug costs. FDA labeling to include weight-based and flat-dose options as well as appropriate multidose vial sizes would restrain the costs of care.

Drs. Samantha Reiss, Prakirthi Yerram, Lisa Modelevsky, and colleagues presented "Retrospective Review of Safety and Efficacy of Checkpoint Inhibition in Refractory High-Grade Gliomas" (J Clin Oncol 35, 2017 [suppl; abstr 2033]). Limited treatment options are available for refractory high-grade gliomas (HGGs). Programmed cell death ligand-1 (PD-L1) expression has been reported in 0%–61% of HGGs and therefore may be a suitable target. The study objective was to describe the safety and efficacy of PD-1 inhibition in patients with refractory HGGs. This was a retrospective single-center study. Adult patients who had pathologically confirmed HGG who had received a PD-1 inhibitor between September 2014 and October 2016 outside a clinical trial were included. Twenty-five patients were identified who had received pembrolizumab as compassionate use. The median age was 49 years, 44% were men, 52% had glioblastoma, and the median baseline Karnofsky Performance Status was 80 (range 50–100). Patients had received a median of four prior lines of therapy, with 19 (76%) having failed therapy with bevacizumab. Concurrent treatment included bevacizumab in 17 patients (68%) or bevacizumab and temozolomide in 2 patients (18%). The median number of doses was 3 (range 1–14). Treatment toxicity and response were assessed in 24 patients. Pembrolizumab-related adverse events (AEs) included liver function test elevations (33%), hypothyroidism (17%), diarrhea, (17%), myalgias and arthralgias (13%), and rash (8%). Other common AEs were hyperglycemia, fatigue, thrombocytopenia, lymphopenia, headache, and nausea in the setting of concomitant therapy and additional supportive care (dexamethasone). Grade 3 AEs included seizure (4%), headache (4%), nausea (4%), and vomiting (4%). Response rates were partial response (n = 2), stable disease (n = 50), and progressive disease (n = 17). Median progression-free survival (PFS) was 42 days (range 7–282), and median overall survival was 121 days (range 15–415). Three patients (12%) had a PFS >90 days; of these, two received single-agent pembrolizumab. Dr. Reiss and colleagues concluded that patients with refractory HGG had low response rates, with a small number having prolonged PFS. Patients, even those receiving concomitant therapy, tolerated pembrolizumab with few serious AEs.

Dr. R. Donald Harvey and colleagues presented "Enrollment into Molecular Selection Trials and Impact on Patient Disposition" (*J Clin Oncol* 35, 2017 [suppl, abstract e14035]). Optimal use of molecularly targeted therapies is achieved by pairing agents with driver mutations present in tumor tissue. Enrollment in clinical trials to demonstrate this objective requires obtaining informed consent prior to tumor molecular analysis. Delays can occur in tissue acquisition, testing results, and treatment initiation. Dr. Harvey and colleagues reviewed their experience and patient disposition with studies where assignment to treatment required mutation data. Trials were identified that required consent prior to tissue mutational analysis. Review included time intervals between landmark events, starting with trial presentation to patient, consent, tissue shipment, mutation analysis results, and if and when treatment was initiated. Demographic data, change in Eastern Cooperative Oncology Group performance status (PS), and subsequent therapy were also collected. Patients were included if they signed consent forms. The median age was 60 years (range 32–87); gender: 56% female; race: 72% White, 24% African American, 4% Asian. Most common cancers were lung (35%), colorectal (18%), parotid (7%), and sarcoma (7%). Nineteen patients required new biopsies; 15 patients (22%) discontinued participation before the molecular results were available. Reasons for discontinuation included insufficient archival tissue, loss to follow-up, initiation of other treatment, and death. For the 53 patients who continued: overall mediation time from consent to test results received was 41 days (range 12–149); with median time from consent to obtaining tissue of 22 days (range 0–121), and tissue sent to results received was 13 days (range 1–77). In those with advanced disease (*n* = 36), PS worsening occurred in 28%. Three patients were matched to therapy; 1 received more than one cycle. In those not matching (*n* = 50), 46% received approved therapies, 22% were lost to follow-up, 18% enrolled in another trial, and 14% died. In conclusion, enrolling patients into molecular-based treatment trials requires additional time and resources, and many patients do not have driver mutations. The long intervals between decision points can delay therapies and impair the ability to explore alternative treatment.

Additional research by HOPA members reported in conjunction with the 2017 ASCO Annual Meeting is listed below.

Dr. Lisa M. Cordes

"A Phase I Study of Cabozantinib plus Nivolumab (CaboNivo) and CaboNivo plus Ipilimumab (CaboNivoIpi) in Patients (pts) with Refractory Metastatic (M) Urothelial Carcinoma (UC) and Other Genitourinary (GU) Tumors" (*J Clin Oncol.* 35, 2017 [suppl: abstr 4562]

"Avelumab in Metastatic Castration-Resistant Prostate Cancer (mCRPC)" (*J Clin Oncol*. 35, 2017 [suppl: abstr 5037])
"Preliminary Results from a Phase 1 Trial of M7824 (MSB0011359C), a Bifunctional Fusion Protein Targeting PD-L1 and TGF-β, in Advanced Solid Tumors" (*J Clin Oncol.* 35, 2017 [suppl; abstr 3006])

Dr. R. Donald Harvey

"Phase IB Study of Induction Chemotherapy with XELOX, Followed by Radiation Therapy, Carboplatin, and Everolimus in Patients with Locally Advanced Esophageal Cancer (EC)" (*J Clin Oncol.* 35, 2017 [suppl; abstr e15607])

"GCT1021-01, a First-in-Human, Open-Label, Dose-Escalation Trial with Expansion Cohorts to Evaluate Safety of Axl-Specific Antibody-

Drug Conjugate (HuMax-Axl-ADC) in Patients with Solid Tumors (NCT02988817)" (*J Clin Oncol.* 35, 2017 [suppl; abstr TPS2605])

Dr. Patrick Kiel
"Clinical Implementation of Whole Genome Multi-Omics Analyses for Patients with Refractory Cancers" (*J Clin Oncol.* 35, 2017 [suppl; abstr 1531])

Dr. John G. Kuhn
"Metformin to Treat Prostate Cancer (PCa) and Prevent Metabolic Syndrome Associated with Androgen Deprivation Therapy (ADT): Results of A Randomized Double-Blind Placebo-Controlled Study of Metformin in Non-Diabetic Men Initiating ADT for Advanced PCa" (*J Clin Oncol.* 35, 2017 [suppl; abstr e 16502])

Dr. Cindy O'Bryant
"Safety and Pharmacokinetics of Crizotinib in Patients (pts) with Hepatic Impairment (HI) and Advanced Cancer" (*J Clin Oncol.* 35, 2017 [suppl; abstr 2552])

Dr. Ming Poi
"Phase Ib Study of Heat Shock Protein 90 Inhibitor, Onalespib in Combination with Paclitaxel in Patients with Advanced, Triple-Negative Breast Cancer (NCT02474173)" (*J Clin Oncol.* 35, 2017 [suppl; abstr TPS1127])

Dr. Hai T. Tran
"Local Consolidation Therapy (LCT) after First Line Tyrosine Kinase Inhibitor (TKI) for Patients with EGFR Mutant Metastatic Non-Small Cell Lung Cancer (NSCLC)" (*J Clin Oncol.* 35, 2017 [suppl; abstr e20654])

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***

NOW APPROVED

The first dual-drug liposomal encapsulation of daunorubicin and cytarabine shown to...

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.

Vyxeos™
daunorubicin and cytarabine
liposome for injection

Learn more at vyxeos.com

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

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].*

Paradigm Shift in Cancer Research Development: The NCI ALMANAC (A Large Matrix of Antineoplastic Agent Combinations)

Hetalkumari Patel, PharmD BCOP
Pharmacy Clinical Coordinator, Hematology/Bone Marrow Transplant
University of Texas Southwestern-Simmons Comprehensive Cancer Center
Dallas, TX

Stefanie Conley, PharmD
Pharmacy Clinical Coordinator, Oncology-Investigational Drug Service
University of Texas Southwestern-Simmons Comprehensive Cancer Center
Dallas, TX

The National Cancer Institute (NCI) Developmental Therapeutics Program started more than 50 years ago with a mission to discover and develop novel anticancer agents. It makes several resources available to researchers to assist in drug discovery and development. Two such resources are the NCI-60, which has been available for about 25 years, and now the NCI ALMANAC. The NCI-60 contains human tumor cell lines and has been pivotal in helping create the NCI ALMANAC. Without the NCI-60, the ALMANAC might not have been created.[1,2] The ALMANAC database contains information based on the testing of these cell lines with various combination drug therapies and is a tool that expedites the discovery of combination therapies. Two phase 1 trials have been developed so far using the ALMANAC database, one for triple negative breast cancer and the other for relapsed solid tumors.[3]

The emergence of resistant subpopulation clones are due in part to the inherent heterogeneity of tumors, and therefore it is imperative to discover new combination therapies.[4] Investigators have been testing combinations of drugs for the treatment of cancer since the late 1950s, when drug combinations were first used for treatment of testicular cancer and other tumors.[5] Because of the numerous Food and Drug Administration (FDA)–approved drugs available for various cancers, the rate at which an investigator can successfully find a novel therapeutic combination that is considered safe and effective is hindered by lack of time, money, and intellectual property rights. The ALMANAC database should allow investigators to accelerate their search for potential combination therapies for cancers like leukemia and solid tumors including melanoma, and those of the lung, brain, breast, ovary, prostate, and kidney.[1,2]

For example, a patient newly diagnosed with acute myelogenous leukemia with an FLT3 mutation may initially respond to therapy but may develop another mutation that did not exist at the time of the initial diagnosis. This second mutation may cause the growth of a different clone that becomes the predominant type in a relapsed or refractory setting. After the new mutation has been identified, one must question whether the mutation can be targeted and whether treatment with a combination therapy would decrease the chance of resistance or development of another mutation.

Using a database containing multiple combinations of FDA-approved oncology drugs that have been tested with a certain type of cell line could be the answer. If combinations of drugs that target cancer cells at different pathways within the same tumor can be identified, that regimen may overcome the mutated pathway, leading to a treatment response. The NCI ALMANAC, which became available to the public in May 2017, contains more than 5,000 combinations of 104 FDA-approved anticancer drugs that potentially have a therapeutic effect on cancer cell lines in vitro.[6]

The NCI-60 consists of 60 different human tumor cell lines that can be used to test novel compounds that can either kill the tumor cell line or inhibit growth. The cell lines include leukemia, melanoma, and cancers of the lung, colon, brain, breast, ovary, prostate, and kidney.[1,2] Each cell line has been characterized extensively at the molecular level. These cell lines also examine multiple mechanisms for drug resistance; these include, but are not limited to, mutations or amplifications of the gene-encoding target, enhanced drug efflux or metabolism, activation of signaling networks that bypass the target, changes in deoxyribonucleic acid damage response or epigenetic pathways, and alterations in tumor microenvironment.[7]

When a single compound is tested against these tumor cell lines, a biologic response, if one exists, can be ascertained. By testing pairs of drugs, researchers have been able to create a database that shows activity of the FDA-approved drugs. Each drug in each pair was tested at different concentrations, producing more than 3 million data points.[6]

The NCI ALMANAC database tests novel drug combinations or drug combinations that have already been used in a subtype of cancer. The activity of the combination therapy is reported as a ComboScore. A positive ComboScore indicates strong activity in the tested pair as compared to each individual drug activity against the cell line. This is reported as a heat map where one can quickly visualize results to dose-response graphs.[3]

The decision to proceed with testing in vivo depended on three factors: clinical utility, ability for the cell lines to grow in xenograft implants, and the ComboScore. Hence in-vitro combination testing did not always result in in-vivo testing because of the sheer volume of combinations. Twenty novel combinations were chosen for greater than single-agent efficacy in one or more xenograft models derived from the NCI-60.[3]

One combination that showed increased activity in vivo has led to a phase 1 clinical trial. Clofarabine and bortezomib given in combination are being studied in adults with relapsed solid tumors (NCT02211755). These drugs have already gained FDA approval for hematologic malignancies individually but have not shown significant activity as monotherapy for solid tumors in previous testing.[3]

The NCI ALMANAC can be found on the NCI website and is available to the public.[8] The database can be searched in four ways: using the heat map with results from all pairs tested, selecting two specific drugs tested, selecting a specific drug and a specific modifier mechanism, or generating a heat map for a particular drug against all tested specific modifier mechanisms.[8]

The NCI ALMANAC is a good example of what collaboration between government and private organizations can achieve for the advancement of cancer treatment. Easy access to the resource should expedite bench to bedside research for cancer patients. ●●

REFERENCES

1. Holbeck SL, Collins JM, Doroshow JH. Analysis of Food and Drug Administration-approved anticancer agents in the NCI-60 panel of human tumor cell lines. *Mol Cancer Ther*. 2010; 9(5):1451-1460.
2. National Cancer Institute. NCI-60 Human Tumor Cell Lines Screen. Available from https://dtp.cancer.gov/discovery_development/NCI-60.
3. Holbeck S, Camalier R, Crowell JA, et al. The National Cancer Institute ALMANAC: A comprehensive screening resource for the detection of anticancer drug pairs with enhanced therapeutic activity. *Cancer Research*. 2017;77(13):3564-3576.
4. Chen S-H, et al. Two is better than one: toward a rational design of combinatorial therapy. *Curr Opin Struc Biol*. 2016;41:145-150.
5. Devita V, et al. The use of drugs in combination for the treatment of cancer: rationale and results. *N Engl J Med*. 1973;288:998-1006.
6. Doroshow J, Collins J. (2017, May 12). NCI ALMANAC: A new tool for research on cancer drug combinations [Blog post]. Retrieved from https://www.cancer.gov/news-events/cancer-currents-blog/2017/nci-almanac-drug-combinations.
7. Rebucci M, et al. Molecular aspects of cancer cell resistance to chemotherapy. *Biochem Pharmacol*. 2013;85:1219-1226.
8. National Cancer Institute. NCI ALMANAC Study Results. Available from https://dtp.cancer.gov/ncialmanac/initializePage.do

Maintaining Competence *(continued from p. 6)*

Learner fatigue can also become problematic with expansion of the number of required annual competencies. Every effort should be made to streamline the process of competency evaluation to avoid lack of engagement on the part of the learner.

As the scope of practice of oncology pharmacists grows in depth and complexity, it is our professional responsibility to maintain expertise in the provision of care to patients with cancer. The establishment of a standardized competency framework within an institution paves the way for continuous training and professional development for pharmacists practicing in the field of oncology. ●●

REFERENCES

1. American Cancer Society. Cancer Treatment and Survivorship: Facts and Figures 2016-2017. Atlanta: American Cancer Society; 2016.
2. Erikson C, Salsberg E, Forte G, Bruinooge S, Goldstein M. Future supply and demand for oncologists: challenges to assuring access to oncology services. *J Oncol Pract*. 2007;3(2):79-86.
3. Sessions JK, Valgus J, Barbour SY, Iacovelli L. Role of oncology clinical pharmacists in light of the oncology workforce study. *J Oncol Pract*. 2010;6(5):270-272.
4. Ignoffo R, Knapp K, Barnett M, et al. Board-certified oncology pharmacists: their potential contribution to reducing a shortfall in oncology patient visits. *J Oncol Pract*. 2016;12(4):e359-368.
5. Dobish R, Chambers C, Iwaasa K, Hubley B, Brigden M. Expanding the role of clinical pharmacists in community oncology practice. *Oncology Exchange*. 2014;13(4):24-28.
6. Merten JA, Shapiro JF, Gulbis AM, et al. Utilization of collaborative practice agreements between physicians and pharmacists as a mechanism to increase capacity to care for hematopoietic stem cell transplant recipients. *Biol Blood Marrow Transplant*. 2013;19(4):509-518.
7. Saylor MS, Blanchette LM, Smith MB, Cambron K, Andricopulos K, Brown MJ. Initiation and preliminary evaluation of an oncology pharmacy training course for staff pharmacists. *J Oncol Pharm Pract*. 2016;22(4):611-617.
8. Koster A, Schalekamp T, Meijerman I. Implementation of competency-based pharmacy education (CBPE). *Pharmacy*. 2017;5:1-16.
9. Carrington C, Weir J, Smith P. The development of a competency framework for pharmacists providing cancer services. *J Oncol Pharm Pract*. 2011;17(3):167-178.
10. Lapointe S, Philip L. Implementing pharmacist training and annual competencies. *Pharmacy Today*. 2015;1:52-53. Available at http://pharmacytoday.org/article/S1042-0991(15)30548-X/pdf

Outcomes and Logistics of Cancer Treatment *(continued from p. 17)*

26. Nolin TD, Aronoff GR, Fissell WH, et al. Pharmacokinetic assessment in patients receiving continuous RRT: perspectives from the Kidney Health Initiative. *Clin J Am Soc Nephrol*. 2015;10(1):159-164.
27. Heintz BH, Matzke GR, Dager WE. Antimicrobial dosing concepts and recommendations for critically ill adult patients receiving continuous renal replacement therapy or intermittent hemodialysis. *Pharmacotherapy*. 2009;29(5):562-577.
28. Neuss MN, Gilmore TR, Belderson KM, et al. 2016 Updated American Society of Clinical Oncology/Oncology Nursing Society Chemotherapy Administration Safety Standards, Including Standards for Pediatric Oncology. *J Oncol Pract*. 2016;12(12):1262-1271.
29. Maude SL, Barrett D, Teachey DT, Grupp SA. Managing cytokine release syndrome associated with novel T cell-engaging therapies. *Cancer J*. 2014;20(2):119-122.
30. Shank BR, Do B, Sevin A, Chen SE, Neelapu SS, Horowitz SB. Chimeric antigen receptor T cells in hematologic malignancies. *Pharmacotherapy*. 2017;37(3):334-345.
31. Hull CS, O'Rourke ME. Oncology-critical care nursing collaboration: recommendations for optimizing continuity of care of critically ill patients with cancer. *Clin J Oncol Nurs*. 2007;11(6):925-927.

SAVE THE DATE

HOPA

14TH ANNUAL CONFERENCE

MARCH 21–24, 2018

COLORADO CONVENTION CENTER

DENVER, CO

HOPA
Hematology/Oncology
Pharmacy Association

Board Update

The Duty of Care

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

"Leadership is not about being in charge. Leadership is about taking care of those in your charge."

If you had the opportunity to hear my incoming president's remarks at HOPA's 13th Annual Conference in March 2017, you know that I'm a big fan of leadership guru Simon Sinek (https://startwithwhy.com/simon-sinek/). His observation quoted above is one of my favorites. Sinek explains that leadership doesn't necessarily entail being the person with all the answers or knowledge, but rather being able to empower and nurture those around us to achieve things thought to be out of reach. A few HOPA events and initiatives that have occurred since I became president come to mind in this connection.

On May 8, 2017, at the National Press Club in Washington, DC, HOPA hosted its first policy summit. The topic was drug waste in the care of cancer patients—something that we all routinely grapple with in our practices. Though identifying the problem is easy, bringing diverse stakeholders together in the same room to discuss the issues and identify potential solutions is quite challenging. But that's exactly what HOPA did this spring. Our Industry Relations Council (IRC) work group labored tirelessly to organize this daylong meeting, in which leaders in the field presented data and professional accounts of cancer-drug waste to a roomful of colleagues, industry partners, patient advocates, and policy professionals.

The conversation at the Drug Waste Summit was both educational and productive. And although we didn't leave the room with all the answers, together we identified meaningful next steps to address the issues. This policy summit on drug waste was the first time HOPA has played such a visible leadership role in directing a national conversation on a topic of recognized importance. As your president, I am committed to making sure it will not be the last.

The following week, on May 16, HOPA took to Capitol Hill to advocate for our profession as oncology pharmacists. Fourteen HOPA members from nine states visited more than 50 Congressional offices to seek cosponsorship of legislation concerning the provider status of pharmacists. This HOPA Hill Day targeted congressional members who have not yet supported H.R. 592 or S. 109, the Pharmacy and Medically Underserved Areas Enhancement Act.

For nearly all the HOPA Hill Day participants, this was their first time to meet with a member of Congress or to visit a congressional office. Conventional wisdom might say that such an exercise would be futile—asking novice advocates to convince their busy representatives to develop enough interest in the bill to support it. But our efforts were actually extraordinarily fruitful. In the weeks following HOPA Hill Day, we obtained 11 additional cosponsors for these bills, and we expect this number to rise in the weeks ahead.

So how did HOPA execute two successful events in close succession, where the odds were not necessarily in our favor? One simple reason: because everyone involved cared deeply about the work to be done. As pharmacy professionals, we care about the impact that drug waste has in our institutions and on our patients. By the same token, your HOPA directors and fellow members care enough about this issue for our association to take ownership of it. We can look forward to the outcomes of this first HOPA policy summit as well as future HOPA-led forums tackling other issues that we as pharmacists care deeply about.

And what about those first-time advocates who were so successful on Capitol Hill? They invested time and care in reading up on the pending legislation and actively participated in briefings conducted by our excellent policy consultants—Jeremy Scott and Jerrica Mathis of the District Policy Group—before their meetings.

"We can look forward to the outcomes of this first HOPA policy summit as well as future HOPA-led forums tackling other issues that we as pharmacists care deeply about."

Please join me in saluting the stellar efforts of our HOPA colleagues to move our profession forward.

Of course we all care about HOPA—why else would we be members? But beyond this, what else can we be doing to invest in our association? A few ideas occur to me, some of which you probably are already carrying out:

Spread the word. You gave us feedback on how to improve the initial expansion of our Board Certified Oncology Pharmacist (BCOP) programming. Our team of dedicated volunteers listened, and the improvements are noticeable. So please encourage your colleagues to participate in the 38 hours of BCOP education that HOPA offers each year—available on demand to fit your schedule (www.hoparx.org/education/bcop-course-offerings). HOPA is the premier provider of BCOP recertification credits—let's keep it that way.

Share the benefits. Don't forget that you can invite your coworkers, trainees, and students to become members of HOPA (hoparx.org/member-get-a-member). You need not be a pharmacist to reap the rewards of an extensive network of pharmacy professionals, exceptional programming at our annual conference (hoparx.org/annualconference) and Practice Management Program (hoparx.org/pmp), and a growing library of professional tools and resources. Our next membership milestone—3,000 members—is within close reach. Make sure that you and your associates don't miss out in joining us to optimize the care of cancer patients.

Support your association. One way to support your association is by making a donation to HOPA or the HOPA Research Fund beyond your regular dues. Although this is important and, frankly, quite easy to do (go to hoparx.org/home/donate), you can also support HOPA with your energy, service, and ideas. Examples include answering the call to participate in one of HOPA's programs, voting in the upcoming HOPA Board of Directors election in November, providing feedback to me and the rest of the HOPA board via member surveys, and presenting your research at HOPA meetings. And, of course, just showing up at meetings—either in person or virtually—is a great way to participate. It's not too early to start thinking about HOPA's 14th Annual Conference taking place March 21–24, 2018, in Denver, so mark your calendar!

Finally, your board of directors is committed to fulfilling our duty of care as a vital part of our fiduciary responsibility to HOPA and its members. We are therefore continuing to evaluate the performance of our organization and programs. As directors, we would be remiss in carrying out our fiduciary duty if we did not regularly review HOPA's business relationships and insist on high standards of performance in each one.

Serving as HOPA president is a unique honor, and I feel a profound sense of humility in being called to be your president and chair of your board of directors. Most of all, I have a deep commitment to caring for HOPA over the coming year. I'm glad we are on this journey together. ●●

HOPA
Hematology/Oncology
Pharmacy Association

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

TIME TO TALK CINV™

HOPA Hematology/Oncology Pharmacy Association | Eisai | HELSINN Building quality cancer care together

A TOOLKIT OF RESOURCES

to Help You Communicate with Your Patients About Chemotherapy-Induced Nausea and Vomiting (CINV)

TimeToTalkCINV.com