# HOPA NEWS

*Pharmacists Optimizing Cancer Care*

VOLUME 18 | ISSUE 2

## Vials of Hope: COVID-19 Vaccines for Cancer Patients

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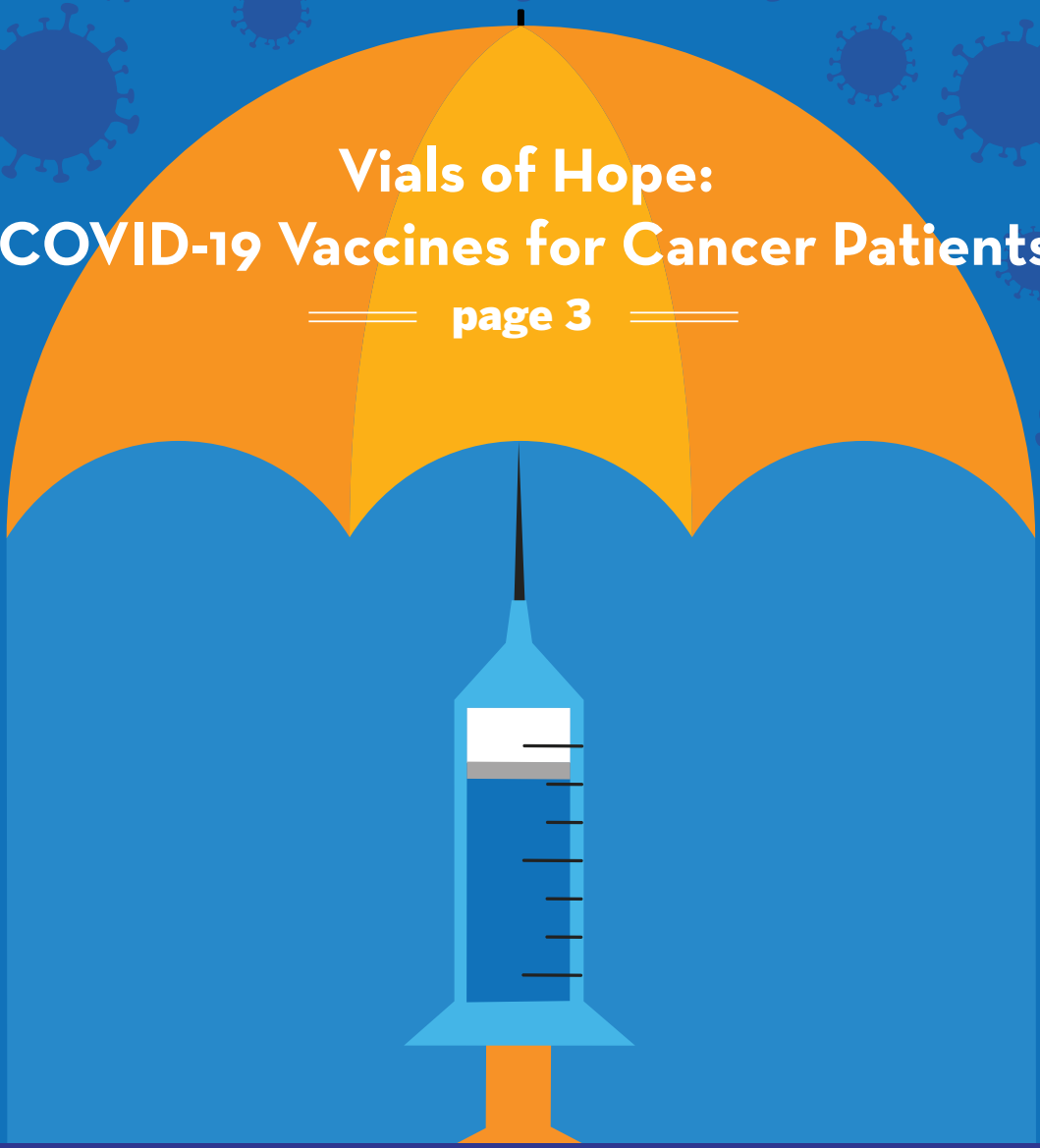

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FEATURE

# Vials of Hope: COVID-19 Vaccines for Cancer Patients

*Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the resulting illness, coronavirus disease 2019 (COVID-19), have emerged as a global pandemic, with over 20 million confirmed COVID-19 cases in the United States.[1] As the death toll for COVID-19 surpasses the 500,000 mark in the United States, there is a clear need for vaccinating cancer patients to avoid excess morbidity and mortality.[1] Large cohort studies have demonstrated that cancer patients are at an increased risk of severe illness from COVID-19.[2-3] Therefore, individuals with active cancer or with active, recent (less than six months), or planned cancer treatment should be considered highest priority to receive one of the COVID-19 vaccines that have been approved by the Food and Drug Administration (FDA) for emergency use authorization (EUA).*

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## How COVID-19 Vaccines Work

Coronaviruses, such as COVID-19, are named for the crown-like spikes on the cell surface, which are called spike proteins and are ideal targets for vaccines. Currently, there are three COVID-19 vaccines that are authorized and recommended in the United States (Table 1). These vaccines work in various ways to offer protection against COVID-19.[4-6]

Messenger RNA vaccines, also called mRNA vaccines, offer a new approach to vaccination. Traditional vaccines put a weakened or inactivated germ into the body to trigger an immune response. In mRNA vaccines, cells are given instructions to make a harmless piece of protein called the "spike protein." These spike proteins are then displayed on the cell surface. This prompts the body to begin building an immune response and making antibodies against COVID-19. There are currently two mRNA vaccines authorized and recommended to prevent COVID-19: Pfizer-BioNTech's COVID-19 vaccine and Moderna's COVID-19 vaccine.[4-5]

Viral vector vaccines offer another mechanism to help patients develop immunity against COVID-19. A viral vector vaccine contains a modified version of a different virus than the one that causes COVID-19. Inside the shell of the modified virus, there is harmless material from the virus that causes COVID-19. This is called a "viral vector" and stimulates the body to build T-lymphocytes and B-lymphocytes that will help fight against COVID-19 if infected in the future. There is currently one viral vector vaccine authorized and recommended to prevent against COVID-19: Janssen/Johnson & Johnson (J&J) COVID-19 vaccine.[6] It is important to emphasize that none of these vaccines can cause infection with COVID-19.

**"These vaccines have been shown to be safe and effective in the general population. However, the safety and efficacy among cancer patients are unknown."**

## Vaccine Safety and Efficacy

These vaccines have been shown to be safe and effective in the general population. However, the safety and efficacy among cancer patients are unknown. For immunosuppressed patients, the vaccines do not pose an immediate safety risk as they do not contain a live virus. Systemic side effects with the COVID-19 vaccine tend to occur within two to three days of the vaccine and may be more pronounced with the second dose. Common side effects include, but are not limited to fever, chills, fatigue, and headache.[4-6] Vaccine safety monitoring systems continue to watch for other potential side effects.

Although each COVID-19 vaccine is unique, all of them may help with herd immunity. Based on the results in clinical trials, the Pfizer-BioNTech vaccine was 95% effective at preventing COVID-19 in people without evidence of previous infection. In addition, the vaccine showed greater than 89% efficacy in preventing people with health conditions, such as diabetes and obesity, from developing symptomatic COVID-19.[4] In clinical trials, the Moderna vaccine was 94% effective at preventing COVID-19 in people who received two doses and had no evidence of being previously infected. The vaccine also exhibited greater than 90% effectiveness in preventing people with health conditions from developing symptomatic COVID-19.[5] Lastly, the Janssen/J&J vaccine was 66% effective at preventing COVID-19 in people who had no evidence of prior infection two weeks after receiving the vaccine. In addition, the vaccine demonstrated to be 100% effective in preventing COVID-19-related hospitalizations and deaths.[6] People

**Table 1. COVID-19 Vaccines Approved by the FDA for Emergency Use[4-6]**

| Manufacturer | Technology | Age Recommendation | Number of Doses |
|---|---|---|---|
| Pfizer-BioNTech | mRNA | ≥ 16 years | Two |
| Moderna | mRNA | ≥ 18 years | Two |
| Janssen/ Johnson & Johnson | Vector vaccine (human adenovirus 26) | ≥ 18 years | One |

are considered fully vaccinated following two weeks after the second dose for the Pfizer-BioNTech and Moderna COVID-19 vaccine and after the single-dose for the Janssen/J&J COVID-19 vaccine.[4-6]

## Considerations in Different Types of Malignancies

The National Comprehensive Cancer Network (NCCN) COVID-19 Vaccination Advisory Committee strongly recommends that COVID-19 vaccines be given to all cancer patients.[7] The rationale of the COVID-19 vaccine in cancer patients is to reduce the risk of COVID-19 morbidity and mortality. Since information on dual vaccination is not available, the COVID-19 vaccine should be prioritized over other needed vaccines. The recommended timeframe between COVID-19 vaccines and other approved vaccines is 14 days.[7]

Considerations for vaccination timing should also be made for patients receiving cancer treatment (Table 2). Currently, there is no available vaccine data for cancer patients receiving active therapy. However, there is a priority to generate data for this population.

### Hematopoietic Stem Cell Transplant (HCT) and Cellular Therapy Recipients

For patients undergoing autologous or allogenic HCT, vaccination may be initiated as early as three months after HCT. In addition, patients who received cellular therapy can be vaccinated as early as three months, if intravenous immunoglobulin (IVIG) independence is demonstrated and B-cell counts ≥ 50 cells/microliter. Patients with controlled graft-versus-host disease (GVHD) should also be considered for the vaccine. There are studies with other vaccines that have shown efficacy in patients with ongoing moderately severe GVHD, without risks of worsening the GVHD. Additionally, there is no data to suggest immune activation from COVID-19 vaccines will exacerbate the GVHD. However, it is reasonable to postpone vaccination in patients with severe, uncontrolled acute GVHD grades III-IV.[8-9]

### Patients with Hematology Malignancies

Patients with hematologic disease, particularly patients on B-cell depleting therapies, should engage with their oncologist in shared decision making related to optimal timing of vaccination. An intact host immunity is necessary to generate optimal protective immunity following vaccination, particularly with respect to B- and T-cell activation and plasma B-cell antibody generation. For patients that have received lymphocyte-depleting therapy (e.g., rituximab, blinatumomab, anti-thymocyte globulin), consideration can be made to defer vaccination until six months after completion of therapy or until there is evidence of lymphocyte reconstitution (absolute lymphocyte count [ALC] ≥ 1.0 x$10^3$/microliter and/or B-cell counts ≥ 50 cells/microliter). This is because patients with B-cell aplasia will likely not mount a humoral immune response.

For asymptomatic chronic lymphocytic leukemia (CLL), the recommendation is to hold B-cell depleting therapy for one month following completion of the vaccination. For symptomatic CLL, vaccination should be postponed for at least one month following completion of cancer treatment. There should be evidence of B-cell recovery prior to the patient receiving the COVID-19 vaccine. If a patient is on chronic CLL therapy and symptomatic, vaccination should still be considered, as a T-cell memory response may still be generated.

Patients who have acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), or an aggressive B-cell lymphoma, such as diffuse large B-cell lymphoma (DLBCL), should not delay induction therapy for vaccination. For ALL patients, vaccination can be given during the maintenance phase if there is evidence of hematopoietic count recovery or during induction if a less intense regimen is given. Vaccination for AML patients can be considered during the consolidation phase or if patients have relapsed disease. In B-cell lymphoma patients, vaccination can be administered following completion of therapy and there is evidence of B-cell recovery.[8-9]

**Table 2. COVID-19 Vaccination Recommendations for Cancer Patients*[7]**

| Cancer and Treatment Type | Timing |
|---|---|
| *Hematopoietic Cell Transplantation/Cellular Therapy* | |
| Allogeneic transplantation<br>Autologous transplantation<br>Cellular therapy (e.g., CAR-T cell) | At least 3 months post-HCT/cellular therapy |
| *Hematologic Malignancies* | |
| Receiving intensive cytotoxic chemotherapy (e.g., cytarabine/anthracycline-based induction regimens for acute myeloid leukemia [AML]) | Delay until absolute neutrophil count (ANC) recovery |
| Marrow failure from disease and/or therapy expected to have limited or no recovery<br>Long-term maintenance therapy (e.g., targeted agents for chronic lymphocytic leukemia or myeloproliferative neoplasms [MPN]) | When vaccine available |
| *Solid Tumor Malignancies* | |
| Receiving cytotoxic chemotherapy<br>Targeted therapy<br>Checkpoint inhibitors and other immunotherapy<br>Radiation | When vaccine available |
| Major surgery | Separate date of surgery from vaccination by at least a few days |

*Adapted from the Preliminary Recommendations of the NCCN COVID-19 Vaccination Advisory Committee

Patients treated with rituximab clearly have diminished humoral responses to vaccination. One of the highest risk groups for COVID-19 morbidity and mortality are patients treated with rituximab and naturally infected with SARS-CoV-2. It is recommended that these patients are vaccinated prior to initiation of therapy when feasible. Since COVID-19 vaccination generates T-cell memory, which may offer partial protection, it is reasonable to offer vaccination even to patients unlikely to mount a B-cell response.[8-9]

**Solid Tumor Malignancies**

Antibody responses to vaccines are generally lower in patients receiving cytotoxic chemotherapy compared with healthy individuals or cancer patients who are not actively receiving treatment. Small studies have yielded conflicting results related to the generation of immune responses, stratified by timing of influenza vaccination in relation to chemotherapy and the nadir period.[10] However, recent reports suggest that timing does not seem to matter.[11-12] Therefore, there is no predefined guidance on the recommended vaccination timing relative to cancer directed medical or radiation therapy. For patients who have planned but not yet initiated cytotoxic treatment, the suggested timing of their first dose of the vaccine is two weeks or more prior to start of therapy.[9]

Patients on immune checkpoint inhibitors (ICI) therapy, specifically for lung cancer, are at a higher risk for severe COVID-19. There is conflicting data, but findings suggest that it may be exacerbated by non-therapy related risks and co-existing medical conditions.[2-3,13-14] Patients receiving ICI have also shown to have a more robust humoral and cell-mediated immune response to the influenza vaccine compared to cancer patients receiving cytotoxic chemotherapy.[15-16] However, there is no data to imply that patients receiving ICI experience more immune-related adverse events (irAE) from vaccination. Therefore, the recommendation for patients receiving ICI therapy is that they should receive the COVID-19 vaccine when feasible and ICI therapy does not need to be held for vaccination.[9]

If a patient is receiving high-dose corticosteroids (20 mg per dose or > 2 mg/kg/day of prednisone or equivalent), the immune response may be attenuated in individuals receiving the vaccine. Doses lower than this are unlikely to significantly affect the immune response to a COVID-19 vaccine. Thus, it is recommended that patients treated with high-dose corticosteroids are vaccinated either prior to therapy or after completion of therapy, if possible.[8-9]

For patients undergoing cancer-related surgery, there are no specific timing recommendations but there are some considerations. It may be desirable to separate vaccination and a major surgery by a few days or a week. If a patient experiences a side effect, such as a fever, it could be difficult to determine whether it is a vaccine side effect or post-surgical complication.[9]

For many people, the COVID-19 vaccine has offered a beacon of hope in a year of despair. In clinical trials, COVID-19 vaccines have been shown to be effective at preventing COVID-19, especially in severe illness and death. However, information about how effective the vaccines are against variants of COVID-19 are still emerging. The goal is that all patients, with or without cancer, will be safe from contracting COVID-19 through vaccination. ●●

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# Disparities in Cancer Care: How Did You Show Up Today?

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I have been on my college's Diversity Committee since joining the University of Rhode Island in 2017. Yet, it wasn't until this past year that I realized I had been largely omitting health disparities from my own lectures. I postulated a few years ago that transgender women might be at an increased risk of breast cancer compared to cisgender men due to the higher use of estrogen therapy. It wasn't until one of my students decided to take it a step further and actually do the literature search that we learned our hypothesis was true.[1]

Why had I never taken the initiative to run the literature search myself? As pharmacists, we are heavily trained in finding, summarizing, and providing information. Why is it that when it comes to health disparities, we don't have the same innate drive to find and amplify the data?

Populations that may be subject to disparities in cancer outcomes include Black, Latinx, and American Indian/Alaska Native populations; people living with a disability; and people with low socioeconomic status.[2] Other groups identified by sexual orientation, gender identity, geographic location, income, education, age, sexual orientation, and national origin may also be affected.

We're starting to witness a shift toward more cultural competence training embedded into both pharmacy education and continuing education at least in part due to the Accreditation Council for Pharmacy Education (ACPE) Accreditation Standards. In 2016, ACPE started requiring graduates to demonstrate cultural sensitivity in its Accreditation Standards.[3,4] In delivering educational content, it is important to be careful to avoid reinforcing stereotypes while also acknowledging how certain factors like social determinants of health and different facets of intersectionality can contribute to health disparities.[5]

As Dr. Vibhuti Arya et al so exquisitely state, "Pharmacists took an oath to protect the welfare of humanity and protect our patients. As such, to practice truly patient-centered care, pharmacists must recognize racism as a root cause of social determinants of health and use their privilege to educate themselves and their colleagues around dismantling structural racism."[6]

**"Pharmacists took an oath to protect the welfare of humanity and protect our patients. As such, to practice truly patient-centered care, pharmacists must recognize racism as a root cause of social determinants of health and use their privilege to educate themselves and their colleagues around dismantling structural racism."**

— Excerpt from "Systemic racism: Pharmacists' role and responsibility," *Journal of the American Pharmacists Association* Vol. 60 Issue 6

The Campinha-Bacote model, which can be shaped like a triangle, describes the necessary components of cultural competence in healthcare.[7] The very bottom of the triangle is desire, describing that the healthcare provider must be self-motivated and committed to engaging in work that will improve cultural competence. Awareness follows, where one explores their own biases and assumptions. Knowledge and skill come afterwards, where a provider must seek and develop knowledge and then practice the skill of collecting necessary data from patients. Finally, putting oneself in situations where they might encounter patients of minoritized populations will allow one to advocate for patients who might be subject to health disparities.

If you are reading this, you have likely surpassed the desire phase. If you haven't had the opportunity to already, I highly encourage you to take implicit association tests (IATs) and to explore options beyond just the race IAT (Table 1).[8] Not unlike the creators of the test, I was upset the first time I took the race IAT and saw my results--a moderate preference for white people. As I looked into this further, I realized I was not alone. Even minoritized groups often test to have a slight or moderate preference toward the "preferred" social group.[9] It's postulated that this is due to the associations we develop from our environments, including the media we consume, the books we read, and the people with whom we interact.

As were many of us, I was grateful for the attention that the resurgence of the Black Lives Matter movement brought to Diversity, Equity, and Inclusion (DEI) work. I began to ask myself, "*how*

## Reflection on Personal Impact and Growth

**Table 1.**

| | Resources | Notes |
|---|---|---|
| Implicit bias | https://implicit.harvard.edu/implicit/takeatest.html | Consider taking multiple different tests |
| Culture Competence and Cultural Humility[a] | Bit.ly/inclusiverx | Free pharmacist CE (0.1 CEU) |
| Implicit Bias in Healthcare[a] | Bit.ly/inclusiverx2 | Free pharmacist CE (0.1 CEU) |
| Inclusive Pharmacy Practices[a] | Bit.ly/inclusiverx3 | Free pharmacist CE (0.1 CEU) |
| Race in Medicine | https://www.nejm.org/race-and-medicine | Collection of articles published by New England Journal of Medicine |
| Cancer Health Disparities | https://www.cancer.gov/news-events/cancer-currents-blog?topic=disparities | National Cancer Institute-funded source for news and commentaries about cancer-related racial, ethnic, and socioeconomic disparities |

a: Modules funded by the American Association of Colleges of Pharmacy
A non-exhaustive table of relevant healthcare provider resources.

*did I show up [for others] today?"* Reflecting on the work I am doing and how it might intersect with health disparities and related topics allows me to adjust my traditional way of thinking. Beverly Daniel Tatum equates systemic and implicit racism as standing on a moving walkway at the airport.[10] Unless we are actively moving against the tide of the moving walkway, faster than it is taking us in the opposite direction, we are not being antiracist. One could say the same about anti-ableism and similar anti-oppression work. It truly needs to be infused into everything we do.

As a Clinical Assistant Professor, I have opportunities to apply a DEI lens both in academia and in clinical practice. Throughout the past year, I have been updating my course material to include social determinants of health and health disparities, infusing this information into patient cases, lectures, and exams. In addition, I have developed a statement surrounding my stance on antiracism and DEI and included it in my syllabi, which has resulted in students feeling more comfortable to approach me surrounding relevant topics. I partnered with a local organization that was already doing antiracism work, and together we are developing a Black in STEMM (science, technology, engineering, math, and medicine) mentorship program. I am lucky that my institution and my college have taken advantage of the same national momentum, so suggestions from our Diversity Committee are being heard and acted upon.

**"Reflecting on the work I am doing and how it might intersect with health disparities and related topics allows me to adjust my traditional way of thinking."**

I have also taken my DEI work beyond the classroom and have advocated for organizations in which I am involved to engage in DEI work and have consulted with those that weren't sure where to start. Finally, I have been more mindful and knowledgeable about which patients may need an advocate and have worked with other likeminded individuals to amplify their voices when their concerns were left unheard.

Perhaps most importantly, in doing this work, we will make mistakes. Being open minded to feedback will allow us to grow. While this work can be taxing for anyone, I recognize that as a cis-white woman, I do not bear the weight of a lifetime of trauma that one with a marginalized identity often does. I am privileged, and I hope to use that privilege to lift some of the weight off of others who have carried it for far too long.

*How did you show up today?* Continually asking yourself this question will allow you to identify new ways that you can help to dismantle structural and systemic oppression and to work towards building a healthcare environment that strives for health equity. ●●

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# Temozolomide Adherence Packaging to Reduce Patient and Caregiver Administration Errors in Primary Brain Tumors

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## Introduction

Primary brain tumors are a diverse group of tumors that vary widely in histology and therefore treatment strategies. The World Health Organization (WHO) classifies primary brain tumors as grade I-IV.[1] WHO grade IV, or glioblastoma, is the most common type of primary brain tumor and accounts for more than half of all malignant tumors in the central nervous system (CNS).[1] Prognosis for glioblastoma is very poor with median survival of just over 1 year.[2] In addition to surgery and radiation, systemic therapy is often needed to prolong survival in patients with primary brain tumors. A challenge when considering systemic treatment of CNS malignancies is the ability for the drugs to cross the blood brain barrier (BBB). Temozolomide is an oral alkylating agent that has good bioavailability, and due to its lipophilicity and small size, can readily cross the BBB. This makes it ideal for brain penetration.[3,4] Temozolomide also has demonstrated a favorable toxicity profile; the most common adverse effects include nausea, vomiting, fatigue and hematologic toxicities.[5]

Temozolomide was first identified to have activity in primary brain tumors when it was studied in relapsed anaplastic astrocytoma in the 1990s. It was shown to have higher objective response rates and progression free survival compared to the standard of care at the time.[6] Stupp et al studied temozolomide in combination with radiotherapy for the first-line treatment of glioblastoma.[7] Temozolomide 75 mg/m$^2$ daily, including weekends, during radiation followed by six cycles temozolomide 150 mg/m$^2$ to 200 mg/m$^2$ on days 1 to 5, every 28 days was compared to radiotherapy alone. Radiotherapy plus temozolomide had a statistically significant survival benefit over radiation alone. Temozolomide is now considered the gold standard for first line treatment of high-grade anaplastic astrocytoma and glioblastoma. In the relapsed setting, temozolomide has been studied using a variety of regimens and doses. The regimens differ by dose and schedule, in addition to the 75 mg/m$^2$ with concomitant radiation and adjuvant temozolomide dosed 150 mg/m$^2$-200 mg/m$^2$ on days 1 to 5 every 28 days, salvage or metronomic regimens include 50 mg/m$^2$ continuously, 75 mg/m$^2$ days 1-21 every 28 days and 150 mg/m$^2$ days 1-7 every 14 days.[8,9,10]

A patient may receive a number of different temozolomide dosing schedules throughout their treatment course, based on their presentation, specifically the disease and number of relapses. Temozolomide is a prescription drug available in several capsule sizes, including 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, and 250 mg; the dose is based on the patient's body surface area.[11] This allows the provider to achieve an individualized dose through a combination of these capsule sizes. The complexity of each of these regimens can be difficult for patients and their caregivers to understand, notwithstanding the regimen changes through the patient's clinical course. An added layer of difficulty for these patients is that cognitive dysfunction is a common complication and can arise from the disease or treatment.[12] Because of these factors, primary brain tumor patients are at a heightened risk for temozolomide dosing errors.

**"Since this process has been fully implemented, no temozolomide related safety reports have been submitted to the internal safety database."**

## Temozolomide patient and caregiver administration errors

A medication error is defined as "any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer."[13] In a 2012 published review of the Institute for Safe Medication Practices (ISMP) and Food and Drug Administration (FDA) MedWatch database, 45 medication errors were attributed to Temozolomide over a fifteen year period.[14] Of these errors, 21 (47%) were attributed to patient or caregiver administration error. Many of these errors were associated with the numerous capsules necessary to develop the patient's personalized dose with the most common error being accidental overdose.[14]

Recognizing the inherent risks to patient safety in oral chemotherapy treatments, the Center for Patient Safety at the Dana-Farber Cancer Institute completed a proactive risk assessment for the oral chemotherapy medication-use process. The assessment identified risk reduction strategies for all stages of the medication-use process, and included four specific recommendations for the administration of temozolomide.[15] These include: utilization of dosing calendars to ensure clarity on intermittent dosing schedule; providing online educational and management tools for addressing adverse effects; maintain high connectivity between the care team

and patients caregivers to ensure safe home administration; and provide temozolomide in prefilled packaging.

After reviewing the risk assessment tool, our pharmacy care team (including both clinic and specialty pharmacy) confirmed the first three recommendations were already in place to minimize the risks associated with temozolomide home administration. Our organization has an integrated care delivery model wherein an embedded pharmacist engages directly with a specialty pharmacy team member who is disease-state focused. Upon prescribing of temozolomide, the pharmacy team ensures patients are provided dosing schedules and receive comprehensive education. Thereafter, follow-up phone calls are made at each subsequent month to evaluate worsening side effects and so that new adherence issues can be identified and addressed. The fourth recommendation was considered, but based on effort versus impact, we decided to hold until we evaluated the impact of the other recommendations.

As of 2019, we continued to receive reports of temozolomide administration errors from both patients and caregivers through our institution specific medication safety reporting system. Reports of both over- and under-dosing were documented. While overdosing is perceived as more severe, given the immediate concerns for toxicity, there is also concern about the clear benefits of receiving a sub-therapeutic treatment of temozolomide in primary brain tumors. Given these reports, our pharmacy team re-evaluated the utility of dispensing temozolomide in prefilled packaging; the current practice at the time was that each strength of temozolomide was dispensed in a separate amber vial.

## Process improvement implementation to reduce errors

Due to the frequency of these patient-reported dosing errors identified within our institution, the specialty pharmacy worked closely with the neurology oncology clinic pharmacist to develop a procedure to dispense all temozolomide prescriptions in adherence packaging. After reviewing our patient safety reports, patients who were dispensed greater than one capsule strength of temozolomide were identified as at the largest safety risk. These patients were placed in the initial adherence packaging pilot. To comply with hazardous drug handling best practices and optimizing the dispensation of prescriptions, a designated filling station was developed, which contains dosing cards, a counting tray and spatula specified for hazardous drugs, and the appropriate personal protective equipment (PPE). During the filling process, all capsules for each dose are placed one compartment. Labels for each prescription are clearly written to include all capsule strengths needed to complete the dose and all are placed on the same dosing card.

To ensure that the process change was effective, patients were called on their last treatment day of their cycle to ensure they had no additional capsules remaining. In addition, the clinical pharmacist continued with clinical follow-up one week, one month and monthly for at least the first six months of therapy. For patients who had to administer multiple strengths per dose of temozolomide, the unique packaging and expected shipped product was discussed in-depth during chemotherapy counseling to the patient and caregivers to ensure understanding.

## Results

Twelve safety events were reported in our internal safety reporting system prior to implementing adherence packaging for patients with multiple strengths (Table 1). Despite success in implementing adherence packaging for this select patient population, patients taking a single strength of temozolomide, either one capsule per dose or multiple capsules per dose, were still at risk for dosing errors. Though less frequent, patient and caregiver administration errors were still reported. Once the process was clearly defined and all staff were trained, all remaining temozolomide prescriptions were dispensed in adherence packaging. Since this process has been fully implemented, no temozolomide related safety reports have been submitted to the internal safety database.

## Conclusion

Temozolomide is an oral alkylating agent commonly used in primary brain tumors. The complexity of the different regimens prescribed and potential cognitive dysfunction in this patient population increases the risk of patient and caregiver administration errors. Adherence packaging for all temozolomide prescriptions proved successful in eliminating administration errors. Since implementation, zero safety events have been reported related to temozolomide administration. However, safety events of this type may be underreported since these errors are generally patient reported and often patients are unaware of their dosing error. In addition, these errors can potentially go unidentified by the clinical team.

While the process for adherence packaging is highly manual, there are clear patient safety benefits. We would strongly recommend communication on the topic of adherence packaging between the clinic-based team and specialty pharmacy filling temozolomide prescriptions. This discussion should begin with completing the proactive risk assessment, followed by an effort versus impact analysis to determine your institution's strategy to enhance safety on dispensing temozolomide. ●●

**Table 1. Safety Events Related to Temozolomide Administration Reported to Safety Database**

| Temozolomide Packaging | Number of Safety Events Related to Administration |
|---|---|
| Standard dispensing in stock bottles or amber prescription vials (2016-2018) | 12 |
| Adherence packaging multiple strengths, standard packaging single strengths (2018-2020) | 2 |
| Adherence packaging all temozolomide prescriptions (2020-Present) | 0 |

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# Pharmacist Impact on Reducing Medication Costs for Patients and Decreasing Medication Waste: Implementation and Expansion of the South Dakota Drug Repository Pilot Program

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## Background on Drug Repository Programs

In the United States, state boards of pharmacy are responsible for establishing rules that dictate how patients can safely and legally access medications. As of 2019, 37 states had laws allowing unused medications to be donated and redispensed to patients through drug repository programs.[1, 2] Drug repository programs are driven by the needs of patient as identified by healthcare providers, patient advocates, pharmacists, nurses, and physicians. Patients who participate must also have a desire to give back in order to decrease the financial burden of medication for others.

In January 2020, the American Society of Clinical Oncology issued a position statement on state drug repository programs. In the statement outlining their support, they noted that widespread use of such programs could lower costs for patients and payers and improve access to treatment for people who are unable to afford high-cost cancer drugs—all while reducing the amount of unused medications in the outpatient setting.[1] Redispensing of unused medication may assist patients in need by offering timely and affordable access to prescription medications, while also saving healthcare dollars from being wasted on things such as hazardous medication disposal. Drug repository programs provide a bridge for patients, allowing them to start therapy immediately, while they await access to medication assistance programs or prior authorizations.

## South Dakota Pharmacy Laws and Rules

In South Dakota, returning unused medications is prohibited based on the following rule, ARSD 20:51.13:02 Return of unused drugs, summarized as pharmacists and pharmacies are prohibited to accept unused drugs or prescribed medications from patients or their proxy.

## Implementation of South Dakota Drug Repository Pilot Program

Noticing the need for a drug repository program in South Dakota, especially with several nearby states having functioning programs in place, oncology clinic pharmacists and specialty pharmacists within Avera McKennan worked with the South Dakota Board of Pharmacy (SDBOP) to propose the development of a drug repository pilot program at the Avera Specialty Pharmacy (ASP)[3, 4, 5]. ASP was originally granted a one-year variance for ARSD 20:51.13:02 to allow the pharmacy to accept the return of unused drugs and redispense the drugs under the following stipulations.

1. Only legend drugs in the original, unopened, sealed or tamper-evident container, which includes lot number(s) and expiration date(s), are eligible for donation
2. Drugs packaged in single-unit doses may be accepted and dispensed if the outside packaging has been opened and the single unit-dose package is unopened

The variance was granted starting July 1, 2019 and extended for an additional year, through June 30, 2021. Policies and procedures were created for accepting, storing, dispensing, and documenting donated legend drugs. The creation of patient donation and receipt forms helped to ensure transparent communication and adequate documentation of all program transactions. The policies dictated what medications would not be accepted, including controlled substances, drugs with REMS requirements, and drugs with temperature sensitive storage requirements. Overall time spent writing policies, protocols, and creating forms amounted to 8-10 hours. For medications that did not meet the donation requirements, pharmacists were able to offer destruction via an onsite MedSafe receptacle. The pharmacists inspected donated medications, and then redistributed to patients in need at no cost to the patient.

Five pharmacists were trained at ASP on donor requirements, the pharmacy acceptance process for donated medications, the storage and dispensing process, and recipient requirements. Time spent training staff and implementing procedures at ASP amounted to two hours. All pharmacists in the hospital and oncology clinics were provided education at a staff meeting. Social workers and patient advocates in the oncology clinic were provided education and reminder e-mails at the initiation of the program.

## Expansion of Pilot Program

The pilot program initially focused on oral oncology specialty medications due to the expensive nature of these medications and frequent therapy changes. During the second year, the goal is to increase the size and scope of the pilot through increased awareness,

education, and advertising. Patient flyers, web pages, and television broadcasts are being distributed across the rural Avera Health footprint.

The focus has broadened to include medications for the specialty disease states of rheumatology, infectious disease, and transplant/hepatology. The program received a grant from the South Dakota Society of Health-System Pharmacists to assist with shipping costs of repository donations and dispensations to and from ASP; this allowed the program to continue to engage the health system outside of the Sioux Falls region and help ensure patients could participate anywhere across the state.

## Statistics on Pilot Program

The program has demonstrated significant cost savings for patients through repurposing of medication that would have otherwise been destroyed. Since implementation, over $2 million in prescription drugs have been donated by over 100 patients. Prescriptions have been dispensed to 103 patients in need, totaling over $1 million in medications dispensed through the pilot program (based on Average Wholesale Price).

| Medications Most Commonly Donated and Dispensed |
|---|
| Abemaciclib 100 mg & 150 mg tablets |
| Abiraterone 250 mg tablet |
| Alpelisib 300 mg (2x150 mg) dose |
| Dasatinib 100 mg tablet |
| Enoxaparin 100 mg/ml syringe |
| Everolimus 5 mg tablet |
| Heparin Lock Flush (100 units/mL) 3 mL |
| Ibrutinib 560 mg tablet |
| Olaparib 150 mg tablet |
| Upadacitinib 15 mg tablet |

Data is currently being collected to identify what type of time savings may be achieved by patients and pharmacies having access to this program. Time is likely saved while patients await medication access or prior authorization approvals; also being studied is the potential time and cost savings for participating pharmacies, including time spent counseling patients, maintaining inventory, and providing community awareness of the program. After two years of program operation, the current time spent maintaining the program donations and dispensations is less than one hour per week.

## Change in Legislature and Advocacy for Pharmacists

The overall goal of this pilot program is to help support a change to the state law to allow pharmacies to create their own drug repository programs within South Dakota, or allow for the creation of a statewide drug repository program. A house bill has been drafted to create an act to provide for the redistribution of donated prescription drugs and medical supplies for this purpose for the 2021 South Dakota legislative session. Data on the pilot program progress, including patients assisted and continued challenges for expansion, will be presented to the SDBOP.

## How to Get Involved

Drug donation programs have been shown to improve access to medications, decrease costs for patients, and lessen prescription drug waste. Pharmacists are critical to the success of programs by ensuring the safety and viability of donated medications, along with dispensing and counseling of patients on their medications. Although numerous states have laws allowing repository programs, several of these have no operational programs. Determining if a state BOP has current rules and regulations allowing or prohibiting drug repository programs is a great first step to get involved.

Pharmacists can reach out to members at their state BOP to determine feasible ways to operationalize a program and request a waiver or variance to a rule, if needed. While obtaining a variance to a state rule, pharmacists can work to create policies and procedures to define the program as described in this article. If a state does not have a law defining a drug repository program, reach out to state legislature members to propose language regarding a change to state law. Working through these steps may help pharmacists grow the number of operational drug repository programs throughout the country. This drug repository pilot program not only helps to assist patients in South Dakota, it promotes pharmacists optimizing overall medication access and care. ●●

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# Belantamab Mafodotin-blmf: Management and Prevention of Ocular Toxicities

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Despite recent advances, multiple myeloma remains an incurable disease, which affects approximately 32,000 patients each year. Multiple myeloma is a plasma cell disorder largely characterized by bone pain, anemia, renal dysfunction, and hypercalcemia. The use of immunomodulatory agents, proteasome inhibitors, monoclonal antibodies, and corticosteroids are the backbone of the management of multiple myeloma, including relapsed/refractory disease. However, the addition of novel agents has begun to change the outlook and management of multiple myeloma. One such agent is belantamab mafodotin-blmf.[1]

Belantamab mafodotin-blmf received accelerated approval from the U.S. Food and Drug Administration (FDA) for use in relapsed or refractory multiple myeloma in patients who have received at least 4 prior therapies, including an anti-CD38 monoclonal antibody, an immunomodulatory agent, and a proteasome inhibitor.[2] The approved dose is 2.5 mg/kg intravenously every three weeks until disease progression or unacceptable toxicity. Belantamab mafodotin-blmf is a B-cell maturation antigen (BCMA)-directed antibody with a microtubular inhibitor conjugate. BCMA is a cell-surface receptor that is expressed on myeloma cells but is largely absent on naïve and memory B-cells. Belantamab mafodotin-blmf is composed of three parts: an afucosylated, humanized immunoglobulin G1 antibody directed against BCMA; a microtubular inhibitor, microtubule-disrupting monomethyl auristatin F (MMAF) which is linked to the antibody via protease-resistant maleimidocaproly linker. Upon binding to BCMA, belantamab mafodotin-blmf is internalized and MMAF is released. The release of MMAF disrupts the microtubules leading to cell cycle arrest and apoptosis. [2-4]

## Clinical Trial

The accelerated approval of belantamab mafodotin-blmf was based on the Phase II trial, DREAMM-2, an open-label, two-arm, randomized, Phase II study, which included 196 relapsed/refractory multiple myeloma patients. Patients were randomized to receive either belantamab mafodotin-blmf 2.5 mg/kg or 3.4 mg/kg intravenously once every three weeks until disease progression or unacceptable toxicity. Patients with corneal epithelial disease were excluded from the study. Additionally, corticosteroid eye drops and preservative free artificial tears were supportive care agents required throughout the study period; the addition of a cooling eye mask was optional during the infusion.

The median lines of therapy prior to study enrollment was 7 (3-21) in the 2.5 mg/kg dosing arm and 6 (3-21) in the 3.4 mg/kg dosing arm. The overall response rate (ORR) was 31% (97.5% confidence interval [CI]: 20.8-42.6) in the 2.5 mg/kg dosing cohort and 34% (97.5% CI: 23.9-46.0) in the 3.4 mg/kg dosing cohort. The most common grade 3 and 4 adverse events were keratopathy (27% in 2.5 mg/kg dosing group and 21% in 3.4 mg/kg dosing group), thrombocytopenia (20% in 2.5 mg/kg group and 33% in 3.4 mg/kg group), and anemia (20% in 2.5 mg/kg group and 25% in 3.4 mg/kg group).[4]

**"The most common adverse effect seen with belantamab mafodotin-blmf was keratopathy; this occurred in 67 patients (71%) in the 2.5 mg/kg dosing cohort and 74 patients (75%) in the 3.4 mg/kg dosing cohort.**

## Safety

Dose reductions due to adverse events occurred in 28 (29%) patients in the 2.5 mg/kg cohort and 41 (41%) in the 3.4 mg/kg cohort. In addition, dose delays occurred in 51 (54%) patients and 61 (62%) patients in the 2.5 mg/kg dosing cohort and 3.4 mg/kg dosing cohort, respectively. Hematologic toxicity, most commonly thrombocytopenia, occurred frequently. All grade thrombocytopenia occurred in 33 (34%) of patients receiving 2.5 mg/kg and 58 (59%) of patients receiving 3.4 mg/kg. Median time to onset of thrombocytopenia was 26.5 days. Dose adjustments and/or treatment delay for thrombocytopenia is recommended for platelets less than 50,000/mcL.[3-4]

Infusion reactions occurred in 20 patients (21%) receiving 2.5 mg/kg and 16 patients (16%) receiving 3.4 mg/kg. Grade 1-2 infusion reactions were the most common and occurred with the first infusion, with the most commonly reported reactions being pyrexia and chills during or within 24 hours of infusion. Pre-medications are not required prior to the first infusion but should be administered for subsequent cycles if reactions occur. For infusion reactions less than or equal to grade 3, belantamab mafodotin-blmf may be paused and resumed at a 50% rate decrease once symptoms resolve. For those patients with grade 4 infusion reactions, belantamab mafodotin-blmf should be permanently discontinued.[4]

The most common adverse effect seen with belantamab mafodotin-blmf was keratopathy; this occurred in 67 patients (71%) in the 2.5 mg/kg dosing cohort and 74 patients (75%) in the 3.4 mg/kg dosing cohort. Keratopathy was the most common adverse event leading to treatment discontinuation and resulted in dose

reductions in 22 patients (23%) and 27 patients (27%) in the 2.5 mg/kg dosing cohort and 3.4 mg/kg dosing cohort, respectively. The most common patient reported corneal symptoms were dry eye and blurred vision. Corneal changes often resolved following discontinuation of treatment; median time to resolution was 71 days (interquartile range [IQR] 57-99) in the 2.5 mg/kg dosing cohort and 96 days (IQR 70-127) in the 3.4 mg/kg dosing cohort. No permanent vision loss was reported. Of note, those patients with a history of dry eye were more likely to develop corneal changes compared to those patients without a history of dry eye.[4]

## Prevention and Management of Ocular Toxicities

The exact mechanism of ocular toxicity is not completely known; corneal events have been reported with other antibody drug conjugates (ADCs) using MMAF or other microtubule-targeting agents. This toxicity might be related to off-target uptake of the ADC into actively dividing epithelial cells which reside in the basal epithelial layer of the cornea. This results in apoptosis of the epithelial cells which then begin to migrate to the center of the cornea resulting in blurred vision and dry eyes.[4-5]

Due to this, ophthalmic examinations should be performed at baseline and prior to each subsequent dose. Baseline exam should be completed within three weeks of beginning treatment. Subsequent examinations should be completed at least one week after the previous dose and within two week prior to the next dose. It is recommended to begin prophylactic preservative-free artificial tears at least 4 times per day beginning with the first infusion and continuing throughout treatment. Contact lenses should also be avoided during belantamab mafodotin-blmf treatment.[3] During DREAMM-2, prophylactic corticosteroid eye drops were administered to a subset of patients in order to evaluate the efficacy in preventing corneal changes. Although it was a small subset of patients, it was found that corticosteroid eye drops were ineffective prophylaxis. There are no recommendations for corticosteroid eye drops throughout treatment due to limited evidence in preventing corneal toxicity.[4]

Other than artificial tears, corneal toxicities can be managed with treatment delays or dose reductions. For those patients who develop grade 2 corneal changes, it is recommended to hold the dose and resume at the same dose once corneal changes resolve to at least grade 1. It is recommended to reduce the dose of belantamab mafodotin-blmf to 1.9 mg/kg upon resolution of toxicity for those patients that develop grade 3 ocular toxicity. For grade 4 toxicity, permanent discontinuation of belantamab mafodotin-blmf should be considered, but if treatment is continued, symptoms should resolve to at least grade 1 before resuming at a reduced dose. Belantamab mafodotin-blmf should be discontinued in patients unable to tolerate 1.9 mg/kg or those with grade 4 ocular toxicity. [3]

**"It is recommended to begin prophylactic preservative-free artificial tears at least 4 times per day beginning with the first infusion and continuing throughout treatment."**

## Belantamab REMS Program

Due to the risk of ocular toxicity, a risk evaluation and mitigation strategy (REMS) program exists; belantamab mafodotin-blmf is only available through this REMS program. The goal of this program is to ensure safe use of belantamab and ensure healthcare providers and patients are informed of the risks associated with belantamab mafodotin-blmf.

In order for prescribers to prescribe belantamab mafodotin-blmf, the provider must review prescribing information and REMS program education. Following review, the provider must complete the knowledge assessment and complete the REMS enrollment form. Prior to initiation of treatment, patients should be counseled on risks and monitoring requirements using the patient guide. Following consent, enrollment of the patient should be completed using the patient enrollment form. Prior to each dose, the results of the ophthalmic exam should be reported via the patient status form. Not only do patients and providers need to be enrolled, but healthcare settings dispensing belantamab mafodotin-blmf must be enrolled as well. The authorized representative, which could be a pharmacist, nurse, advance practitioner, or director of the healthcare setting, should review education materials and submit the enrollment form.

Training of all relevant staff should take place prior to administration of first dose at the health system. Authorization should be obtained with each dose of belantamab mafodotin-blmf; the authorization should include ensuring prescriber is certified and the patient is enrolled and authorized. The dose in milligrams and date of administration should be reported to the REMS program within five days of administration. If the patient discontinues the treatment or transfers care, the REMS program should be notified.[3,6-9]

## Patient Assistance Program

Co-pay assistance is available for commercially insured patients if eligible through the GlaxoSmithKline (GSK) Co-pay program. Eligible uninsured or Medicare patients may receive medication free of charge through GSK's Patient Assistance Program. No cost preservative-free lubricating eye drops are available via GSK's Blenrep eye drop supportive care program after completion and submission of enrollment form.[10, 11]

## Future Directions

Belantamab mafodotin-blmf is currently being studied in combination with other anti-myeloma agents, including proteasome inhibitors and immunomodulatory agents. Due to responses in the relapse/refractory setting, belantamab mafodotin-blmf is also being evaluated for use in upfront, transplant ineligible patients. These studies are also evaluating various dosing intervals in hopes

to decrease toxicity. In order to expand access and provide additional real-world data, belantamab mafodotin-blmf is being studied in renal and hepatic impairment.[12]

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# Take the Stress Out of Responding to Peer Reviews of Your Manuscript

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You have submitted your manuscript and finally received the long-awaited response from the editorial staff… only to find that you have more work to do! Don't worry; nearly all manuscripts require at least some, if not substantial, revisions before they are accepted for publication. So, how do you successfully navigate this scenario? I hope this article supplies you with helpful tips and tricks based on my own and recent personal experience of responding to reviewers' feedback.

## Real-Life Experience Navigating Peer Reviews

My Post-Graduate Year 1 (PGY1) Residency project manuscript was rejected by the first journal I approached for publication. The next journal I approached for publication did not reject it, but they did respond with many suggested revisions. When I received comments from peer reviewers, addressing them all in a timely and complete manner seemed like a daunting task. I was aware the responses I provided would have a major impact on the final acceptance or rejection of my manuscript, which made the process even more intimidating.

The peer review process is simply constructive criticism presented in a way that many are not accustomed to, especially pharmacy residents attempting to publish their first manuscript. Importantly, viewing the experience as a learning opportunity, and even free mentoring, can decrease your anxiety throughout the process. A few highlights from my recent experience responding to peer reviewer comments include:

## Formatting

The first step is to use a standard format, such as a formal letter, which includes an introductory paragraph thanking the reviewers and denoting how changes can be seen (e.g., track changes, journal's online system, etc.) followed by your responses.

- **Don't make more work for yourself!** You can copy each reviewer's comments and suggestions, then bullet your response below each comment/suggestion.
- **Remember to cite the manuscript page(s) and line number(s)** at the start of each response to aid the reviewers in finding your response.
- **Regarding references, try to avoid formatting issues.** If the journal requires you to use track changes, turn this setting off while making changes in auto-referencing (i.e. EndNote, Zotero, Mendeley, etc.) If not, you may run the risk of issues arising in the formatting of your document. Denote these reference changes in your response letter and via the track changes comment function in the manuscript so the reviewers can still follow.

## Timeline

Most journals will specify a turnaround time to respond to comments. If the journal does not specify, give yourself a turnaround time of no more than 3-4 weeks as some journals may not accept responses after that time. If you require additional time, correspond with the editorial team upfront (generally via their online portal "email" function, including your manuscript number).

Once you have determined the final date, set mini deadlines for yourself and be sure to include co-authors to allow ample time for their responses. Send all co-authors the entire reviewer comment list, ideally denoting if a specific co-author should focus on an item in particular (e.g., biostatistician may be tasked to respond to a question on methodology). Some comments may take more time than others to address, and keep in mind that your co-authors are not on the same schedule as you. Peer review can be a disrupting added workload for everyone involved, so do not get frustrated if some cannot respond by your mini deadlines! Reminder emails or deadline appointments on calendars can be helpful to keep everyone on track.

## How to Respond

Determining how to respond can seem overwhelming at first, especially if the reviewers leave many points that need to be addressed in the manuscript. When planning your responses be direct, clear, and concise. If you need to insert statements into your manuscript, there is no need to copy the entire new statement into your response letter. To keep it brief, you can cite the page and lines for that addition. Be respectful in how you respond to the reviewers, but this does not mean that you always have to agree with or change something based on their comments. If this is the case, you MUST justify why you did not agree or chose not to make the change.

How can you politely say no? Here are few examples:

- You no longer have access to the data set or a specific variable → Say "data unavailable, unable to provide requested additional analysis." Consider adding a statement in your limitations on this item, if appropriate, and denoting this in your reply to the reviewer.
- Reviewer asked for something already there → Nicely denote the page and line of its location.
- Reviewer misinterprets and asks for change → Nicely denote why error and location of correct information.
- Reviewer asks for a change which contradicts journal formatting → Denote this discrepancy, decline to change but offer to editorial staff to do so if they agree with reviewer's comment.

- Reviewer makes a comment, but does not ask for a change → Depending on comment, response can be to add to manuscript to address the item (e.g., a limitation comment in discussion) or simply reply to reviewer and ask if a change is recommended, denoting you are willing to make the change, but are unclear about the suggestion. Editors can reach back to the reviewer for clarification if warranted.

## Find Your Process

Overall, establishing a set process will ensure consistency and ease of review throughout your career. If you are stuck or not sure where to begin, start by addressing the easy items first. This can help get your process flowing, provide a sense of accomplishment, and allow you time to figure out how to address other areas without getting behind overall. As you start reaching the more difficult comments, be sure to address any items that are requested outside the main manuscript file (e.g., figures, tables, images, etc.). They can be easy to forget, but very important to include. You may find it helpful to use track changes or the highlight function within your draft response letter when corresponding with co-authors or for pending tasks for you to complete. Lastly, always have all co-authors review the final letter and new documents to "sign off," just like your original manuscript.

Once you find a process that works, stick with it. I hope these things that I learned through my peer review experience make yours easier to navigate. Good luck! ●●

FEATURE

# Intravesicular Chemo for Non-Muscle Invasive Bladder Cancer -to Instill or Not to Instill, That is the Question

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## Background on Non-Muscle Invasive Bladder Cancer

Bladder cancer is the fourth most common malignancy in men in the United States and accounted for 62,100 new cases and 7% of all male malignancies in 2020.[1] In patients with Non-Muscle Invasive Bladder Cancer (NMIBC), a transurethral resection of the bladder tumor (TURBT) should be performed upon diagnosis. At this time, the patient should be clinically staged and risk stratified as "low-," "intermediate-" or "high-risk." Stratification is based on grade (high vs. low), tumor invasion, recurrence, histology, and previous treatment.[2] Post TURBT, intravesicular chemotherapy has been used immediately or, based on patient risk, as an adjuvant treatment to prevent recurrence. Intravesicular chemotherapy is the process of instilling chemotherapy directly into the bladder through a catheter and allowing it to dwell until removal.

**"In a large meta-analysis, BCG was inferior to mitomycin C in preventing recurrence in patients receiving induction only, but superior in those who went on to receive maintenance therapy."**

## Immediate Post-Operative Intravesicular Chemotherapy

In the setting of low-risk NMIBC, a single intravesicular dose of chemotherapy may be given immediately after the TURBT (within 24 hours).[2] The rational for immediate instillation is based on antitumor effects—destroying tumor cells suspended in the irrigation fluid post-TURBT, and the killing of residual tumor cells at the site—and possibly, overlooked tumors.[3,4,5] A systematic review and meta-analysis of immediate intravesicular chemotherapy post-TURBT found a 35% decreased risk of recurrence and a decreased five-year recurrence (from 58.8% to 44.8%) when compared to TURBT alone in patients with a recurrence rate of <1 recurrence per year.[3]

Two Phase III trials have investigated the use of single-dose intravesicular chemotherapy immediately post-TURBT. The use of gemcitabine was investigated in a randomized, double-blind, placebo-controlled Phase III trial of 406 patients with suspected low-grade NMIBC. Immediate instillation of gemcitabine led to a 35% four-year recurrence rate compared to 47% in the placebo group (HR, 0.66; 95% CI, 0.48-0.90; P < 0.001). Adverse events, including voiding dysfunction, voiding pain, and hematuria, were similar in both groups.[6]

Mitomycin C was studied in a Phase III, prospective, multicenter, randomized study investigating recurrence rates in immediate (within 24 hours) versus delayed (two weeks) instillation post-TURBT. Patients were stratified into groups based on risk with the primary endpoints of recurrence as follows: five-year recurrence risk in low-risk group and three-year recurrence risk in the intermediate- and high-risk groups. When stratified by group, recurrence rates in patients who received immediate instillation were significantly lower in the intermediate- and high-risk groups (20% vs. 32%, P=0.037 and 28% vs. 35%, P=0.007, respectively).

As an entire cohort, the recurrence risk was 27% for immediate instillation compared to 36% for delayed instillation (P < 0.001). Adverse events, including exanthema and urinary symptoms, were similar in both groups.[7] When the agents were compared in a systematic review, the rates of adverse events were significantly less with gemcitabine (38.8% vs. 72.2%, P=0.02).[8] It should be noted that immediate post-TURBT intravesicular chemotherapy or immunotherapy should not be administered in patients with a suspected bladder perforation.

## Adjuvant and Maintenance Intravesicular Chemotherapy

In patients with intermediate- to high-risk NMIBC, the use of intravesicular chemotherapy or immunotherapy should be given as a six-week induction regimen.[2] Similar to low-risk patient settings, gemcitabine and mitomycin C are the most common chemotherapy agents for patients in this setting, with gemcitabine also preferred.[8]

In addition to chemotherapy, bacillus Calmette-Guerin (BCG) immunotherapy has also been studied. BCG is a vaccine against tuberculosis and contains a live-attenuated mycobacterium tuberculosis.[9] BCG activates the innate immunity and acquired immunity of the bladder. It directly reacts to tumor cells leading to apoptosis, necrocytosis, and oxidative stress.[10] Aside from eliminating cancer cells, BCG can also induce high expression of PD-L1 on tumor cell surfaces.[11] BCG is most commonly administered weekly for six weeks, followed by a rest period, ending with a re-evaluation at Week 12.[12] BCG induction has been compared to intravesicular epirubicin, gemcitabine, and mitomycin C. Reduced recurrence and improved overall survival were observed in comparison to epirubicin in patients receiving BCG with or without isoniazid.[13] When compared to intravesicular gemcitabine in a Phase II quality of life trial, there were no significant quality of life differences, but there was an increase in mild- to moderate-adverse events in the BCG group. It should be noted that this trial utilized a 1/3 BCG dose and both arms received maintenance therapy for a year (monthly instillations of gemcitabine or three weekly BCG instillations at 3, 6, and 12 months).[14] With similar quality-of-life outcomes, the frequency of administration should be considered when weighing options.

Lastly, when compared to mitomycin C, the use of maintenance therapy weighed heavily on the outcomes. In a large meta-analysis, BCG was inferior to mitomycin C in preventing recurrence in patients receiving induction only, but superior in those who went on to receive maintenance therapy.[15]

Maintenance therapy remains somewhat controversial. Maintenance intravesicular chemotherapy is generally given monthly, whereas BCG regimens may differ. A Phase III trial compared the long-term efficacy of intravesical epirubicin, BCG, or BCG with isoniazid, in which patients received three weekly instillations at months 3, 6, 12, 18, 24, 30, and 36. Regardless of isoniazid, BCG demonstrated superiority to epirubicin in time to first recurrence, time to distant metastases, disease-specific survival, and overall survival in intermediate- and high-risk patients.[16]

There is still some debate regarding the length of maintenance therapy, as data has shown benefits for both one and three year BCG maintenance regimens, stratified by risk catergory.[17,18] Based on the results of a randomized trial investigating outcomes of 1/3 dose BCG compared to full dose BCG, and one year versus three years of maintenance, full dose BCG for one year may be more appropriate for intermediate-risk patients, whereas three-year maintenance may be beneficial for high-risk patients.[18] These recommendations are contingent on patient tolerance and BCG toxicities. Due to the immunogenicity of BCG, patients may experience flu-like symptoms for up to 72 hours after dosing.[19] Other side effects, such as localized discomfort and dysuria, are also common.[19,20] When comparing patients on 1/3 dose BCG and full dose BCG, toxicity outcomes were similar, leading to recommendations for full dose BCG in patients that can tolerate it.[18]

**"When comparing patients on 1/3 dose BCG and full dose BCG, toxicity outcomes were similar, leading to recommendations for full dose BCG in patients that can tolerate it."**

## Intravesicular Use After Recurrence

In patients with recurrence after initial intravesicular treatment, further intravesicular treatment may be appropriate. Following an initial 12-week course of intravascular treatment, intermediate- or high-risk patients with persistent or recurrent disease may receive an additional course of BCG therapy followed by a repeat TURBT.[2] A Phase II trial evaluating the use of intravesicular gemcitabine in patients with NMIBC who failed two courses of BCG, including 89% with high-risk NMIBC, demonstrated activity and may be reasonable for those not eligible for cystectomy. In this trial, 47% of patients remained disease free at three months and 28% at one year.[21] In intermediate- to high-risk patients with persistence or recurrence after two courses of BCG, further intravesicular chemotherapy is only recommended in the instance of no available clinical trials.[2] Patients with carcinoma in situ (CIS) that is refractory to BCG may be offered intravesicular valrubicin.

A single-arm study evaluated the efficacy of valrubicin in patients with CIS refractory to multiple courses of intravesical therapy, including at least one course of BCG. Valrubicin was given as six weekly instillations of 800 mg. Complete response, defined as no evidence of recurrence for at least six months, was achieved in 21% of patients, with a median time to failure of greater than 18 months in patients with complete responses. In the trial, no complete responders or patients who underwent cystectomy following valrubicin died during the 30-month follow-up period.[22] Toxicity wise, local bladder symptoms were observed during the trial. Additionally, systemic pembrolizumab was recently approved for BCG-unresponsive patients based on the results of the Phase II, Keynote-057 trial.[23] Cystectomy is still the preferred treatment for patients in this setting, if eligible.[2]

## Upper Tract Urothelial Carcinoma (UTUC)

Upper Tract Urothelial Carcinoma (UTUC) is a malignant process that occurs in the urothelial cells lining the urinary tract. These can occur anywhere from renal calyces, renal pelvis, or ureter down to the ureteral orifice.[24] A much less common genitourinary malignancy, these account for 5% of urothelial cancers and less than 10% of renal tumors.[25] While surgery is the primary treatment of choice, mitomycin for pyelocalyceal solution (mitomycin gel) may be used for adult patients with low-grade UTUC.

In a Phase III, single-arm trial of patients with treatment-naïve or recurrent low-grade noninvasive UTUC with at least one measurable papillary tumor above the ureteropelvic junction, six weekly instillations of mitomycin gel was administered to the renal pelvis or calyces. Mitomycin gel was dosed based on patients' volume of renal pelvis and calyces, and capped at 60 mg. Complete response, defined as a negative three-month ureteroscopic evaluation, negative cytology, and negative for-cause biopsy, was achieved in 59% of patients who received at least one instillation of mitomycin gel. The most common adverse effects reported were ureteric stenosis, urinary tract infection, hematuria, and flank pain.[26] As surgery is the primary treatment, this should be reserved for patients who are not interested in or eligible for a nephroureterectomy.

## Recap

Intravesicular chemotherapy has become a mainstay of therapy for patients with NMIBC. In low-risk patients, the immediate single instillation of chemotherapy has significantly prolonged time to recurrence. Gemcitabine is preferred in these patients due to the more benign toxicity profile and lower cost. In the intermediate- to high-risk group, the use of intravesicular BCG with maintenance has been shown to be favorable compared to intravesicular chemotherapy on outcomes including overall survival. Intermediate- and high-risk patients may receive a repeat course of BCG at time of first recurrence or persistent disease if they are not eligible for a cystectomy, with limited data for subsequent intravesicular che-

motherapy. The development of localized intravesicular therapy has prolonged disease-free intervals in patients regardless of risk category in NMIBC. Finally, when it comes to patients with low-risk UTUC, the approval of mitomycin gel has given patients who are not interested in or eligible for a nephroureterectomy an effective option for treatment.

## Drug Preparation and Clinical Pearls (American Urological Association Recommendations)[27]

### Handling Chemotherapy

- Follow institutional policies for the preparation of all hazardous medications
- Chemotherapy should be prepared utilizing aseptic technique with proper chemotherapy safety precautions
- All equipment and supplies used to handle cytotoxic agents are disposed of as chemotherapy waste

### *Gemcitabine (Not FDA-approved)*[27]

A. Preparation
   1. Use gemcitabine powder for injection 1 gm or 2 gm vials
   2. Reconstitute gemcitabine with normal saline to 1000 mg/50 mL or 2000 mg/50-100 mL, or use premixed gemcitabine with closed system administration set
   3. Containers should be clearly marked "For irrigation only" to avoid accidental intravenous administration

B. Clinical Pearls[27]
   - Instruct patient not to void for one to two hours post-procedure
   - Gemcitabine should be instilled via gravity flow
   - Male patients should sit when voiding to avoid splashing post-procedure
   - Instruct patient to wash perineum or glans after voiding to decrease irritation

### *Mitomycin C (Conventional, Not FDA-Approved)*[27]

A. Preparation
   1. Dosing: Mitomycin 40 mg reconstituted in 20 mL sterile water

B. Clinical Pearls[27]
   - Oral sodium bicarbonate 1.3 g may be recommended to take the night before, morning of, and 30 minutes prior to treatment to help improve effectiveness[28]
   - Instruct patient not to void for one to two hours post-procedure
   - Male patients should sit when voiding to avoid splashing post-procedure
   - Instruct patient to wash perineum or glans after voiding to decrease irritation
   - Mitomycin is a vesicant

### *Bacillus Calmette-Guerin (BCG)*[27]

A. Preparation
   1. Dosing: one vial suspended in 50 mL preservative free 0.9% sodium chloride injection
   2. BCG must be used within two hours of reconstitution; unused solution is discarded as biohazardous waste after two hours
   3. To avoid cross contamination, parental drugs are not prepared in areas where BCG has been prepared
   4. All equipment, supplies, and receptacles in contact with BCG are handled and disposed of as biohazards
   5. If preparation cannot be performed in a biocontainment hood, then a mask, face shield, and non-permeable gown should be worn to avoid inhalation and inadvertent exposure to broken skin
   6. Do not use a filter with BCG instillation
   7. Syringe Method[19]
      a. Draw 1 ml of sterile, preservative-free saline into a small syringe (~3 mL) and add to one vial of TICE® BCG to resuspend
      b. Gently swirl the vial until it forms a homogenous suspension; avoid forceful agitation which may cause clumping
      c. Dispense suspension into the top of a catheter-tip syringe containing 49 mL of saline. Total volume is 50 mL. Swirl gently to combine
   8. Reconstitution accessories may be provided with a BCG order. In this case, refer to specific instruction for use with the accessories
   9. Avoid exposing BCG to direct sunlight

B. Clinical Pearls[19,27]
   - Patients should not drink fluids for four hours before treatment and should void their bladder prior to administration
   - Instruct patient not to void for one to two hours post-procedure
   - The reconstituted BCG should be administered by gravity flow only, with no pressure applied to the plunger to force the flow of BCG
   - BCG is retained in the bladder for two hours then voided. If patient cannot retain BCG for two hours, they may be allowed to void sooner
   - While BCG is intra-bladder, the patient should be repositioned from left side to right side and also lie on their abdomen and back. Rotate and reposition every 15 minutes to maximize bladder surface exposure
   - Acetaminophen or ibuprofen may be used to help reduce/treat fever and body aches
   - Antispasmodic medications may be warranted to help with frequency and urgency
   - If sexually active, condoms should be worn during intercourse throughout treatment

### *Valrubicin (FDA-Approved)*[29]

A. Preparation
   1. Dosing: 800 mg diluted in 75 mL of 0.9% sodium chloride
   2. Allow four 5 mL vials (200 mg/5 mL vials) to slowly warm to room temperature

3. Withdraw 20 mL from the four vials and dilute with 55 mL of 0.9% sodium chloride injection to provide 75 mL of diluted valrubicin
4. Diluted valbucin in 0.9% sodium chloride is stable for 12 hours at room temperature (25°C, 77°F)
5. Valrubicin should be handled and disposed of like other cytotoxic drugs. Please use goggles, gloves, and protective gowns during preparation and administration

B. Clinical Pearls

- Valrubicin (Valstar®) contains polyoxyl castor oil, which may cause leaching of di(2-ethylhexyl) phthalate (DEHP) from PVC bags. Prep and store in glass, polypropylene, or polyolefin containers and tubing
- Temperatures less than 4°C (39°F) may cause the polyoxyl castor oil to form a waxy precipitate. If this occurs, gently warm vial in the hand until solution is clear. Do not warm by other forms of heat
- Valrubicin should be instilled by gravity over several minutes
- Valrubicin is retained in the bladder for two hours before voiding. If patient cannot retain valrubicin for two hours, they may be allowed to void sooner
- Patients should maintain adequate hydration post-instillation
- In patients undergoing a Transurethral Resection of the Bladder (TURB), bladder evaluation is warranted. Administration should be delayed at least two weeks after transurethral resection and/or fulguration
- Caution should be used in patients with severe bladder symptoms. Bladder spasms and spontaneous discharge of the instillate may occur; it is not advised to clamp the urinary catheter

***Mitomycin for Pyelocalyceal Solution (Jelmyto®, FDA-Approved)[30]***

A. Preparation

1. Dosing: The volume administered is based on volumetric measurements using pyelography. Maximum dose is 15 mL (60 mg of mitomycin)
2. The preparation of Jelmyto® (mitomycin) is a tedious and complex process that requires initial steps one day prior to planned administration. The pharmacy preparation is broken into six sections: freeze the chilling block, prepare supplies, create pre-wetting solution, mix the admixture, prepare the admixture, and dispense the admixture. These instructions can be found in a supplemental section of the Jelmyto® package insert, titled *Instructions For Pharmacy*. Due to the length of complexity of this process, it is best to strictly follow the Jelmyto® package insert

B. Clinical Pearls

a. Patients should receive 1.3 gm of oral sodium bicarbonate the evening prior to, the morning of, and 30 minutes prior to instillation
b. Reconstituted Jelmyto® should be instilled as soon as possible after reconstitution, but if not possible, may be stored at 20°C to 25°C (68°F to 77°F) for 8 hours
c. Once chilled to -3 to 5°C (27°F to 41°F) Jelmyto® will convert to a viscous liquid for instillation that is stable for one hour and must be instilled within one hour of viscous conversion
d. General anesthesia, local anesthesia, sedation, prophylactic antibiotics and/or antihistamines may be used
e. Diuretics may be held one day prior to instillation and until four hours after instillation
f. Entire syringe must be instilled within one minute
g. Jelmyto® may turn urine a violet to blue color post-instillation. Patients should avoid contact with urine for a least six hours post-instillation
h. Advise patients to sit when voiding and to flush toilet several times after each use
i. Myelosuppression may occur with Jelmyto® and should be withheld for Grade 2 or 3 thrombocytopenia or neutropenia. Jelmyto® should be permanently discontinued for Grade 3 or greater thrombocytopenia or neutropenia ●●

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# A Complex State of Mind: "Is this going to cure me?"

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I was in the clinic room with a patient while the oncologist explained that the recommended therapy was not a cure but a way to prolong life. After a week, the patient's oral oncolytic was approved and I was doing the initial counseling when he asked me, "Is this going to cure me?" I repeated what the oncologist explained at the prior visit. This example was my first experience with this scenario, and it has happened various times since. It never gets easier and sits heavy on my mind every time.

Upon first hearing the news of incurable disease, patients may find themselves not fully comprehending what is happening. It's not a failure to deliver the news; it's also the shock that the patient has to come to grips with his or her own mortality.

## We Have All Had These Days

We have all had these days, and worse. I had one of those worse days a week ago, where I said goodbye to one of my favorite families because the patient was transitioning to hospice. The oncologist had to deliver similar news to the next three patients. It takes a toll.

Death is the natural order of life. We will all reach it one day, but we never want to think about it. Yet, as oncology pharmacists, we come face-to-face with it on a daily basis, which bodes the question: how do we cope with this?

One of my greatest fears working as an oncology pharmacist is that I will become desensitized to death and the struggles that the families are going through. They are losing a father, mother, son, daughter, or friend. It hurts… a lot. We care deeply about these people and want to see them at peace. Often in our quest to heal others, we forget to care for ourselves.

## When One of Those Days Becomes Burnout

In an American Society of Clinical Oncology professional development article by McFarland DC and colleagues, burnout was found to be prevalent amongst oncologists: 25%–35% among medical oncologists, 28%–36% among surgical oncologists, and 28% among radiation oncologists.[1] I venture to believe that these statistics are similar for oncology pharmacists and also other medical professional colleagues who practice in oncology. Often this burnout is related to situations like the ones listed previously. If left unchecked, burnout can lead to more serious issues, mainly depression and in some unfortunate cases, suicide. To prevent these, we have to become more adept at recognizing and addressing these feelings and thoughts, whether it be in ourselves or those with whom we work closely.

It is difficult to talk about. It is awkward at times. It is draped in stigma. Some feel it makes them weak. I, personally, struggle with my mental health regularly. I often do not talk about it because of the aforementioned perceptions; however, I have learned that in order to live a full, healthy life I have to have an outlet to express my emotions. Mine is writing my emotions and thoughts on paper so that I have a physically tangible copy of something that was previously an abstract thought.

The question I struggle with most that reverberates in my mind when I am speaking with my cancer patients and their family members is why is this happening to them and not me? I feel guilty that I am currently getting to live a healthy, wonderful life while the ones I'm helping are living a physical and emotional nightmare.

## We Need Outlets for Coping

When this question reappears, I look to the words of an oncologist with whom I work closely that I have pinned to my desk: "I know it is often hard to understand what can seem futile when it comes to what therapy we have available for cancer, a lot of what we are doing is trying to shepherd people along this path. I am thankful and very proud of all." These words allow me to reset and focus on what drives me on a daily basis: helping others less fortunate.

I write this in hopes that if you are struggling with these issues such as I am, you will reach out for help; you are not alone. I encourage you to find an outlet, an oasis where you can regularly go for help. Because we are the ones trained in providing care, we can often feel extra stress by thinking we are burdening others because we cannot "fix" ourselves. We do not need fixing because we are not broken. We are human, and we need to lean on one another at time.

Find your peace whatever it may be. As I mentioned before, mine is writing, so I will leave you with this poem:

Challenging it is
My own complex state of mind
Yet, we will prevail ●●

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# Impact of an Oral Anticancer Medication Program on Patient Adherence

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Administration of oral anticancer medications (OAMs) associated with improved clinical outcomes and quality of life, often decrease the burden of cancer care. However, OAMs present unique challenges with regard to safety, toxicity management, and adherence to treatment.[1] Adherence, a widespread obstacle in patient care, is a dynamic process governed by both patient and socioeconomic factors.[2,3,4] The number of OAMs in clinical practice has increased significantly, but strategies for toxicity monitoring and adherence tracking remain limited. Ambulatory oncology clinical pharmacists are uniquely positioned to play a key role in the provision of care.[1, 5-8]

The Georgia Cancer Center for Excellence (GCCE) at Grady Health System in Atlanta, Georgia, treats a patient population that is economically underserved and which has low health literacy. In collaboration with the American Society of Clinical Oncology's (ASCO) Quality Training Program (QTP), the GCCE initiated a quality improvement project to increase adherence to oral anticancer medications. A team consisting of a physician, clinical pharmacist, nurse and two cancer center administrators was created. Adherence barriers were identified through cause and effect analysis and patient and provider surveys. Potential adherence interventions were categorized using a priority/pay-off matrix.

## First, a Baseline Adherence Rate was Established

A retrospective chart review was then performed to establish a baseline adherence rate. The GCCE has an onsite pharmacy with access to specialty OAMs that is utilized by the majority of patients with cancer, allowing for easy tracking of prescriptions and refill history. Randomly selected patients (n=54) who filled an OAM prescription at least three times in the Cancer Center Pharmacy were included in the analysis. Adherence was calculated using the medication possession ratio (total days of medication supplied/ total days in all cycles evaluated) on the basis of prescription refill history and was defined as having drug available ≥80% to <120% of days evaluated. Overall, twenty patients had a medication possession ratio ≥80% to <120% of days evaluated, resulting in a baseline adherence rate of 37% (20/54).[9]

## Program Aims to Increase Adherence

An ambulatory OAM adherence program was developed and implemented with the goal of increasing adherence by 30 percentage points within six months. The primary outcome was the change in adherence rate before and after the program implementation. The adherence program was led by a board-certified oncology clinical pharmacist. The main study focus was to improve adherence using low-cost adherence tools (pillbox and calendar), patient education, and toxicity monitoring. The pharmacist counseled patients, provided a treatment calendar, and prepared color-coded pillboxes to align with days of treatment. For three cycles, a mid-cycle follow-up pharmacy visit was scheduled for toxicity monitoring and supportive care management.

The adherence program intervention period ranged from October 2016 to November 2017, during which 52 patients were prescribed a new OAM. The most common OAMs were similar pre- and post-intervention and included immunomodulatory agents, tyrosine kinase inhibitors, antiandrogens, and antimetabolites. At the end of the 13-month study, 85% of patients (n=44/52) met the definition of adherence, exceeding the study goal of a 30-percentage point increase compared to the historical data (85% vs. 37%, $P<0.0001$). The clinical pharmacist collected data on 204 patient encounters, including dedicated clinic visits and informal encounters. Interventions were most commonly related to treatment counseling, drug acquisition, supportive care management, and filling pillboxes. Overall, 655 adherence-based (n=331; counseling, pillbox, treatment plan) and/or treatment-based (n=324; drug acquisition, supportive care, coordination of care) interventions were documented.

As part of the OAM clinic development plan, surveys were distributed to both patient (n=24) and healthcare professional (n=23) focus groups to identify barriers to adherence. Respondents were asked to rank the importance of various barriers. The two groups had contradictory results. Healthcare professionals ranked patient-related issues, financial support, and medication access as the main barriers affecting adherence. In contrast, patients' top barriers included medication adverse events (AEs), lack of support, and challenges with transportation. Surprisingly, patients reported less emphasis on medication access. This could be explained in part by access to manufacturer medication assistance and state-sponsored programs for uninsured and underinsured patients with cancer. Such programs aim to alleviate obstacles and curtail the economic barriers to OAM access in the GCCE patient population.

Our pharmacist-led OAM adherence program targeted individual patient needs to improve adherence using low-cost adherence tools. Adherence improved by more than 48 percentage points during the study period and positively impacted clinical care. As previously demonstrated, low-cost tools do not improve patient adherence independently, thus highlighting the role of patient education and monitoring for these high-risk medications.[7] Education has become more pertinent in light of studies indicating underreporting of AEs by patients which can lead to early medication discontinuation and nonadherence.[10,11] In this study, OAM counseling and toxicity monitoring delineated AEs warranting an Emergency Department visit versus outpatient toxicity management. Because of the established relationship and pharmacist accessibility, patients often felt comfortable communicating toxicity concerns throughout the treatment cycle. The specialized role of clinical pharmacists in the overall provision of oncology care continues to demonstrate the

impact of collaboration, personalized education and close monitoring on adherence to anticancer treatment.[1,8]

## Study Strengths & Limitations

Strengths of this study included open access to a clinical pharmacist during clinic hours, limiting serious AEs in multiple cases. Additionally, nurses triaged telephone calls regarding toxicity and supportive care and directed them to the pharmacist as appropriate, a service that was not previously available. Furthermore, the cancer center pharmacy is onsite, allowing the pharmacist to easily follow up on insurance authorizations and communicate with outside specialty pharmacies.

Limitations of the study include that prescription refill history is an indirect measure of adherence and it does not account for outside factors, including insurance delays or doses held due to toxicity. Patient interactions outside of clinic encounters were not always captured in pharmacist notes, possibly underestimating interventions, treatment delays, and AEs.

## Conclusion

In conclusion, this clinical pharmacist-led adherence program combined with low-cost adherence measures exceeded the goal of this initiative, suggesting that a multidisciplinary collaborative approach to OAM adherence can have a significant impact on outcomes. To sustain this improved OAM adherence, a full-time clinical pharmacist was hired to assist with treatment initiation and follow up. The pharmacist leads the adherence clinic and continues to expand the program. ●●

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# HOPA ANNUAL CONFERENCE 2022

## *We'll See You in Boston!*

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# The BELLINI Trial

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Multiple myeloma (MM) is the second most common hematologic malignancy and is responsible for about 1% of all cancers and 10% of all hematologic malignancies.[1-3] In this plasma cell dyscrasia, proliferation of cytogenetically defective malignant plasma cells leads to eventual end-organ dysfunction.[4-6] Standard treatment of MM is comprised of different cocktails of agents with activity against plasma cells, including monoclonal antibodies, immunomodulatory drugs, proteasome inhibitors and corticosteroids.[7]

## BELLINI Trial Attempts to Define the Role of Venetoclax in Patients with Relapsed or Refractory MM

The treatment landscape has evolved substantially over the past 15 years with the development of new, more effective targeted agents and regimens that possess a high level of anti-tumor activity.[4,8] In spite of this progress, nearly all MM patients ultimately relapse, even those who experience a response to initial therapy, rendering the disease incurable at this point in time.[8-9]

Venetoclax is a potent, small molecule inhibitor of the B-cell lymphoma-2 (BCL-2) protein. BCL-2 is an anti-apoptotic protein, which can be overexpressed in cancers, promoting cell survival.[10-11] Inhibition of BCL-2 has shown significant activity in the treatment of acute myeloid leukemia, gaining venetoclax Food and Drug Administration (FDA) approval in 2018.[12] BCL-2 overexpression is a potential driver of malignant proliferation and is a pathway for survival in MM cells.[13] In vitro studies demonstrated the apoptotic activity of venetoclax in certain MM cells, particularly in those with t(11;14) translocation.[14-15] The recently published BELLINI trial attempts to define the role of venetoclax in patients with relapsed or refractory MM.

The BELLINI trial was a randomized, double-blind, placebo-controlled, multicenter, Phase III trial that evaluated the efficacy and safety of venetoclax in combination with bortezomib and dexamethasone for the treatment of relapsed or refractory MM. Adult patients with MM who received one to three previous lines of therapy, had an Eastern Cooperative Oncology Group performance status of 2 or less, and were sensitive or naïve to proteasome inhibitors were included. Patients were excluded if they had previous treatment with BCL-2 inhibitors, allogeneic transplant within 16 weeks or autologous transplant within 12 weeks, grade 3 or worse peripheral neuropathy or grade 2 or worse peripheral neuropathy with pain. Patients were randomized 2:1 to receive venetoclax or placebo in combination with dexamethasone and bortezomib.

Venetoclax 800 mg was administered by mouth daily, bortezomib 1.3 mg/m$^2$ subcutaneously or intravenously was administered days 1, 4, 8 and 11, and dexamethasone 20 mg was administered days 1, 2, 4, 5, 8, 9, 11 and 12 of a 21-day cycle for eight cycles. From cycle nine, venetoclax administration ceased, bortezomib was administered days 1, 8, 15 and 22 and dexamethasone was administered days 1, 2, 8, 9, 15, 16, 22 and 23 of a 35-day cycle. Venetoclax was dose reduced by 50% in patients receiving concomitant moderate CYP3A inhibitors, and by 75% in patients receiving strong CYP3A inhibitors. There was no venetoclax dose ramp-up per the protocol. All patients received herpes zoster prophylaxis.

The primary end point was progression-free survival (PFS). Secondary endpoints included overall survival (OS), overall response rate (ORR), duration of response, and rate of minimal residual disease negativity. Safety analysis was conducted in patients who received at least one dose of therapy.

Between July 19, 2016 and October 31, 2017, 291 patients were included in the study: 194 randomized to the venetoclax arm and 97 patients to the placebo arm. Fifty-four percent of the population had received at least two lines of prior therapy, 41% had previous exposure to proteasome inhibitors and immunomodulatory drugs and 60% had a previous stem cell transplant. High-risk disease was present in 17% of the population and 44% had International Staging System Stage I disease.

Median PFS was significantly longer in the venetoclax arm (22.4 months vs 11.5 months; HR 0.63 [95% CI 0.44-0.90] p=0.010). Median OS was not reached in either arm; however, there were twice as many deaths in the venetoclax arm than in the placebo arm (21.1% vs 11.3%; HR 2.03 [95% CI 1.04–3.94]). Duration of response was longer in the venetoclax arm (not reached vs 12.8 months) and ORR was significantly higher with venetoclax compared to placebo (82% vs 68%, p=0.0081). The proportion of patients who achieved a minimal residual disease negative response ($10^{-5}$) was also significantly higher in the venetoclax arm than in the placebo arm (13% vs 1%, p=0.00066).

Of the total population, 35 patients were positive for t(11;14) translocations: 20 patients in the venetoclax arm and 15 patients in the placebo arm. Prespecified analysis showed that median PFS (not reached vs 9.5 months, p=0.004) was longer and ORR (90% vs 47%, p=0.0038) was higher in the venetoclax arm compared to placebo in patients with t(11;14) translocation. However, median OS was not significantly different (not reached in either group). A total of 177 patients had BCL-2 expression data, with high expression in 140 patients. Amongst those with high BCL2 expression, post-hoc analysis showed median PFS was significantly longer in the venetoclax arm compared to placebo (22.4 months vs 9.9 months). However, neither ORR (85% vs 75%) nor median OS (not reached in either group) were significantly different between arms.

In the safety analysis, 63% of patients in the venetoclax and 78% of patients in the placebo arm discontinued treatment. The most common grade 3 or higher treatment-emergent adverse events (TEAEs) were neutropenia (18% in the venetoclax arm vs 7% in the placebo arm), pneumonia (16% vs 9%), diarrhea (15% vs 11%), thrombocytopenia (15% vs 30%), and anemia (15% vs 15%). TEAEs led to dose reductions in 57 (30%) patients in the venetoclax arm and 15 (16%) patients in the placebo arm. Forty (21%) of

193 patients in the venetoclax arm and 11 (11%) of 96 patients in the placebo arm died. Of these deaths, 13 (7%) patients in the venetoclax arm and one (1%) patient in the placebo arm died within 30 days of the last dose of study drug and were considered treatment-emergent. Causes of death include disease progression (5% in the venetoclax arm vs 1% in the placebo arm), sepsis or septic shock (5% vs 1%), multiple myeloma (3% vs 3%) and cardiac arrest (2% vs none). In March 2019, the FDA placed a partial clinical hold of trials investigating venetoclax in multiple myeloma based on the interim analysis of the BELLINI trial.[16] A protocol amendment to the BELLINI trial required patients receiving venetoclax to receive antimicrobial and *Pneumocystis jiroveci* pneumonia prophylaxis, in addition to influenza and pneumococcal vaccinations.

## Previous Observations Confirmed; More Studies Underway

The BELLINI trial confirmed previous observations that the addition of venetoclax to bortezomib and dexamethasone provides a high overall response rate in certain patients with relapsed or refractory MM. Despite increases in response and PFS, the increased mortality rate raises questions regarding the safety of this combination.

The authors postulate this may be due to increased immunosuppressive effects of the regimen, leading to higher rates of infections. Longer PFS in patients with t(11;14) translocations or high BCL-2 expression demonstrate a potential role for venetoclax in the MM treatment algorithm. However, the lack of mortality difference observed may place this below the multiple alternative treatment regimens available in relapsed or refractory MM. While this regimen did not make its way into the NCCN guidelines, venetoclax and dexamethasone are listed as a treatment option for relapsed or refractory multiple myeloma in patients with t(11:14) translocation based on phase one data.[17] Further studies are underway (NCT03314181, NCT03539744 and NCT02899052) to identify the true role of venetoclax in the treatment of MM. ●●

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## Thank You for attending HOPA Annual Conference 2021.

HOPA's Board of Directors, Executive Team and Staff, would like to express our extreme gratitude to all who made HOPA's Annual Conference 2021 an amazing success.

Though we were not able to meet in person, it was our pleasure to bring you the great science, CE credits and networking events you've come to expect from HOPA.

THANK YOU to our attendees, sponsors and presenters. We look forward to seeing you in Boston, during HOPA's Annual Conference 2022, March 30-April 2.

# Board Update
## Springing into Action

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

The winter was long and hard. We have all been battered by COVID-19, politics, and social injustice. We remain resilient; we are full of hope and energized for change.

**A Note of Thanks**

I want to thank David DeRemer, Immediate Past-President, and the 2020-2021 HOPA Board of Directors for their leadership through unprecedented times in our history. I also want to thank board members who have completed their terms: Susie Liewer, Past-President; Sally Barbour, Secretary; and Jeremy Whalen, At-Large Member, for their years of service to HOPA. You will be missed, but your legacy will be continued in the work we do.

At the time of this writing, spring is in full bloom and we just completed our 17th Annual Conference. The energy was evident, even within a virtual platform. We had more than 1,400 registrants, making it the largest HOPA attendance ever! For many of us, the Annual Conference was an opportunity not only for education, but also to be able to "see" our friends and colleagues for the first time in a very, very long time.

**Mission, Vision, Growth**

As we look ahead, I want to remind everyone of our mission, which is to support pharmacy practitioners with tools and resources that allow them to optimize the care provided to cancer patients; and also our vision, which is that all cancer patients have access to a pharmacist who serves as integral member of their care team.

HOPA as an organization is strong and our membership continues to expand as the "care team" continues to evolve. We now have more than 4,000 Members! Over the next year, HOPA will continue to expand its reach. A student task force is already meeting to talk about opportunities for enhanced student engagement between schools of pharmacy and HOPA.

HOPA should be the professional home for all pharmacists taking care of patients with cancer, including those working in specialty pharmacies and with oncology investigational drugs. HOPA is committed to serving pharmacists who work in these areas and these topics will be the focus of our fall practice management meeting (Save the date: October 7, 2021!)

In addition, HOPA will move forward next year in creating a collaborative research framework. HOPA will sponsor projects focused on quality improvement and pharmacist-led research that will ultimately show the value of the hematology/oncology pharmacist. HOPA will use this information to develop standards and publish best practices; we have a real opportunity to lead in this space!

We are kicking off this effort with the creation of the Oral Chemotherapy Collaborative, which will bring together experts in oral chemotherapy, quality, advocacy, and research. This collaboration will be led by Drs. Karen Ferris and Benyam Muluneh.

**"Our ultimate goal is inclusive excellence within HOPA. Ours should be an organization where everyone can thrive, regardless of our differences or orientation."**

**Equity Embedded in All We Do**

Not only did we suffer through a pandemic this past year, we have also seen racial and social injustice highlighted in unimaginable ways. The Annual Conference Keynote by Dr. Lakesha Butler, entitled "Dismantling Structural Racism in Pharmacy," set the stage for much of our diversity, equity and inclusion (DEI) work to come. This is only the beginning of our efforts to better understand structural racism and disparities in healthcare.

A new DEI Task Force is being led by Drs. Maurice Alexander and Britny Brown. Under their leadership, HOPA will approve a DEI statement and the task force will recommend how to best weave DEI into all of our strategic pillars. Goals will be set and metrics will be used to measure our progress moving forward. Our ultimate goal is inclusive excellence within HOPA. Ours should be an organization where everyone can thrive, regardless of our differences or orientation.

**Honored to Serve**

Post-COVID, the world and our profession will be different. HOPA will continue to do all it can to advocate for oncology pharmacists and cancer patients. It really is the honor of a lifetime to serve as the 18th HOPA President, to work with and for you all. As our committees begin their work for the next year, know how much you are appreciated for all you do for HOPA and your patients. I hope you have a wonderful summer and that you are able to spend quality time with those that matter most in your lives!

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# EMERGING TRENDS + MODELS IN PRACTICE MANAGEMENT

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