HOPA NEWS

Pharmacists Optimizing Cancer Care

VOLUME 17 | ISSUE 2

Cannabidiol Oil for Cancer Patients: Nature's Best Remedy?

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FDA ACCELERATED APPROVAL

Now approved for adult patients with locally advanced or metastatic urothelial cancer who have previously received a PD-1 or PD-L1 inhibitor, and a platinum-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced or metastatic setting[1]

SET A COURSE FOR RESPONSE

INDICATION

PADCEV (enfortumab vedotin-ejfv) is indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer (mUC) who have previously received a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor, and a platinum-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced or metastatic setting.

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

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hyperglycemia occurred in patients treated with PADCEV, including death and diabetic ketoacidosis (DKA), in those with and without pre-existing diabetes mellitus. The incidence of Grade 3-4 hyperglycemia increased consistently in patients with higher body mass index and in patients with higher baseline A1C. In one clinical trial, 8% of patients developed Grade 3-4 hyperglycemia. Patients with baseline hemoglobin A1C ≥8% were excluded. Closely monitor blood glucose levels in patients with, or at risk for, diabetes mellitus or hyperglycemia. If blood glucose is elevated (>250 mg/dL), withhold PADCEV.

Peripheral neuropathy (PN), predominantly sensory, occurred in 49% of the 310 patients treated with PADCEV in clinical trials; 2% experienced Grade 3 reactions. In one clinical trial, peripheral neuropathy occurred in patients treated with PADCEV with or without preexisting peripheral neuropathy. The median time to onset of Grade ≥2 was 3.8 months (range: 0.6 to 9.2). Neuropathy led to treatment discontinuation in 6% of patients. At the time of their last evaluation, 19% had complete resolution, and 26% had partial improvement. Monitor patients for symptoms of new or worsening peripheral neuropathy and consider dose interruption or dose reduction of PADCEV when peripheral neuropathy occurs. Permanently discontinue PADCEV in patients that develop Grade ≥3 peripheral neuropathy.

Ocular disorders occurred in 46% of the 310 patients treated with PADCEV. The majority of these events involved the cornea and included keratitis, blurred vision, limbal stem cell deficiency and other events associated with dry eyes. Dry eye symptoms occurred in 36% of patients, and blurred vision occurred in 14% of patients, during treatment with PADCEV. The median time to onset to symptomatic ocular disorder was 1.9 months (range: 0.3 to 6.2). Monitor patients for ocular disorders. Consider artificial tears for prophylaxis of dry eyes and ophthalmologic evaluation if ocular symptoms occur or do not resolve. Consider treatment with ophthalmic topical steroids, if indicated after an ophthalmic exam. Consider dose interruption or dose reduction of PADCEV for symptomatic ocular disorders.

Skin reactions occurred in 54% of the 310 patients treated with PADCEV in clinical trials. Twenty-six percent (26%) of patients had maculopapular rash and 30% had pruritus. Grade 3-4 skin reactions occurred in 10% of patients and included symmetrical drug-related intertriginous and flexural exanthema (SDRIFE), bullous dermatitis, exfoliative dermatitis, and palmar-plantar erythrodysesthesia. In one clinical trial, the median time to onset of severe skin reactions was 0.8 months (range: 0.2 to 5.3). Of the patients who experienced rash, 65% had complete resolution and 22% had partial improvement. Monitor patients for skin reactions. Consider appropriate treatment, such as topical corticosteroids and antihistamines for skin reactions, as clinically indicated. For severe (Grade 3) skin reactions, withhold PADCEV until improvement or resolution and administer appropriate medical treatment. Permanently discontinue PADCEV in patients that develop Grade 4 or recurrent Grade 3 skin reactions.

Infusion site extravasation Skin and soft tissue reactions secondary to extravasation have been observed after administration of PADCEV. Of the 310 patients, 1.3% of patients experienced skin and soft tissue reactions. Reactions may be delayed. Erythema, swelling, increased temperature, and pain worsened until 2-7 days after extravasation and resolved within 1-4 weeks of peak. One percent (1%) of patients developed extravasation reactions with secondary cellulitis, bullae, or exfoliation. Ensure adequate venous access prior to starting PADCEV and monitor for possible extravasation during administration. If extravasation occurs, stop the infusion and monitor for adverse reactions.

EV-201 TRIAL: PRIMARY (ORR) AND SECONDARY (DOR) ENDPOINTS[1-3]*

ORR 44%
(n=55/125; 95% CI: 35.1%, 53.2%)

12% CR (n=15/125)

32% PR (n=40/125)

7.6-month median DOR
(95% CI: 6.3, NE; range: 0.95, 11.3+ months; 10.2 months median follow-up)

- PADCEV™ is an **antibody-drug conjugate** that requires **no biomarker testing**[1-3]

*The EV-201 trial is a single-arm, multicenter trial of 125 patients with locally advanced or metastatic urothelial cancer who had previously received a PD-1 or PD-L1 inhibitor and a platinum-containing chemotherapy. Patients received 1.25 mg/kg of PADCEV via IV infusion over 30 minutes on Days 1, 8, and 15 of every 28-day cycle and continued to receive treatment until disease progression or unacceptable toxicity. The major efficacy outcome measures, confirmed ORR and DOR, were assessed by BICR using RECIST v1.1. Median duration of follow-up was 10.2 months.[1]

Embryo-fetal toxicity PADCEV can cause fetal harm when administered to a pregnant woman. Advise patients of the potential risk to the fetus. Advise female patients of reproductive potential to use effective contraception during PADCEV treatment and for 2 months after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with PADCEV and for 4 months after the last dose.

ADVERSE REACTIONS

Serious adverse reactions occurred in 46% of patients treated with PADCEV. The most common serious adverse reactions (≥3%) were urinary tract infection (6%), cellulitis (5%), febrile neutropenia (4%), diarrhea (4%), sepsis (3%), acute kidney injury (3%), dyspnea (3%), and rash (3%). Fatal adverse reactions occurred in 3.2% of patients, including acute respiratory failure, aspiration pneumonia, cardiac disorder, and sepsis (each 0.8%).

Adverse reactions leading to discontinuation occurred in 16% of patients; the most common adverse reaction leading to discontinuation was peripheral neuropathy (6%). Adverse reactions leading to dose interruption occurred in 64% of patients; the most common adverse reactions leading to dose interruption were peripheral neuropathy (18%), rash (9%) and fatigue (6%). Adverse reactions leading to dose reduction occurred in 34% of patients; the most common adverse reactions leading to dose reduction were peripheral neuropathy (12%), rash (6%) and fatigue (4%).

The most common adverse reactions (≥20%) were fatigue (56%), peripheral neuropathy (56%), decreased appetite (52%), rash (52%), alopecia (50%), nausea (45%), dysgeusia (42%), diarrhea (42%), dry eye (40%), pruritus (26%) and dry skin (26%). The most common Grade ≥3 adverse reactions (≥5%) were rash (13%), diarrhea (6%) and fatigue (6%).

LAB ABNORMALITIES

In one clinical trial, Grade 3-4 laboratory abnormalities reported in ≥5% were: lymphocytes decreased, hemoglobin decreased, phosphate decreased, lipase increased, sodium decreased, glucose increased, urate increased, neutrophils decreased.

DRUG INTERACTIONS

Effects of other drugs on PADCEV Concomitant use with a strong CYP3A4 inhibitor may increase free MMAE exposure, which may increase the incidence or severity of PADCEV toxicities. Closely monitor patients for signs of toxicity when PADCEV is given concomitantly with strong CYP3A4 inhibitors.

SPECIFIC POPULATIONS

Lactation Advise lactating women not to breastfeed during treatment with PADCEV and for at least 3 weeks after the last dose.

Hepatic impairment Avoid the use of PADCEV in patients with moderate or severe hepatic impairment.

Please see Brief Summary of full Prescribing Information on adjacent page.

BICR=blinded independent central review; CI=confidence interval; CR=complete response; DOR=duration of response; FDA=US Food and Drug Administration; IV=intravenous; NE=not estimable; ORR=objective response rate; PD-1=programmed death receptor-1; PD-L1=programmed death-ligand 1; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors.

References: 1. PADCEV [package insert]. Northbrook, IL: Astellas Pharma US, Inc. **2.** Rosenberg JE, O'Donnell PH, Balar AV, et al. Pivotal trial of enfortumab vedotin in urothelial carcinoma after platinum and anti-programmed death 1/programmed death ligand 1 therapy. J Clin Oncol 2019;37(29):2592-600. **3.** Seattle Genetics, Inc. and Astellas. PADCEV. Data on File.

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PADCEV™ (enfortumab vedotin-ejfv) for injection, for intravenous use

The following is a brief summary of full Prescribing Information. **Please see the package insert for full prescribing information.**

INDICATIONS AND USAGE

PADCEV is indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer (mUC) who have previously received a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor, and a platinum-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced or metastatic setting.

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

DOSAGE AND ADMINISTRATION

Recommended Dosage

The recommended dose of PADCEV is 1.25 mg/kg (up to a maximum of 125 mg for patients ≥100 kg) administered as an intravenous infusion over 30 minutes on Days 1, 8 and 15 of a 28-day cycle until disease progression or unacceptable toxicity.

Dose Modifications

Adverse Reaction	Severity*	Dose Modification*
Hyperglycemia	Blood glucose >250 mg/dL	Withhold until elevated blood glucose has improved to ≤ 250 mg/dL, then resume treatment at the same dose level.
Peripheral Neuropathy	Grade 2	Withhold until Grade ≤1, then resume treatment at the same dose level (if first occurrence). For a recurrence, withhold until Grade ≤1 then, resume treatment reduced by one dose level.
	Grade ≥3	Permanently discontinue.
Skin Reactions	Grade 3 (severe)	Withhold until Grade ≤1, then resume treatment at the same dose level or consider dose reduction by one dose level.
	Grade 4 or recurrent Grade 3	Permanently discontinue.
Other nonhematologic toxicity	Grade 3	Withhold until Grade ≤1, then resume treatment at the same dose level or consider dose reduction by one dose level
	Grade 4	Permanently discontinue.
Hematologic toxicity	Grade 3, or Grade 2 thrombocytopenia	Withhold until Grade ≤1, then resume treatment at the same dose level or consider dose reduction by one dose level.
	Grade 4	Withhold until Grade ≤1, then reduce dose by one dose level or discontinue treatment.

*Grade 1 is mild, Grade 2 is moderate, Grade 3 is severe, Grade 4 is life-threatening.

WARNINGS AND PRECAUTIONS

Hyperglycemia

Hyperglycemia occurred in patients treated with PADCEV, including death, and diabetic ketoacidosis (DKA) in those with and without pre-existing diabetes mellitus. The incidence of Grade 3-4 hyperglycemia increased consistently in patients with higher body mass index and in patients with higher baseline A1C. In EV-201, 8% of patients developed Grade 3-4 hyperglycemia. In this trial, patients with baseline hemoglobin A1C ≥8% were excluded. Closely monitor blood glucose levels in patients with, or at risk for, diabetes mellitus or hyperglycemia. If blood glucose is elevated (>250 mg/dL), withhold PADCEV.

Peripheral neuropathy (PN)

Peripheral neuropathy, predominantly sensory, occurred in 49% of the 310 patients treated with PADCEV in clinical trials; 2% experienced Grade 3 reactions. In study EV-201, peripheral neuropathy occurred in patients treated with PADCEV with or without preexisting peripheral neuropathy. The median time to onset of Grade ≥2 was 3.8 months (range: 0.6 to 9.2). Neuropathy led to treatment discontinuation in 6% of patients. At the time of their last evaluation, 19% had complete resolution, and 26% had partial improvement. Monitor patients for symptoms of new or worsening peripheral neuropathy and consider dose interruption or dose reduction of PADCEV when peripheral neuropathy occurs. Permanently discontinue PADCEV in patients that develop Grade ≥3 peripheral neuropathy.

Ocular disorders

Ocular disorders occurred in 46% of the 310 patients treated with PADCEV. The majority of these events involved the cornea and included keratitis, blurred vision, limbal stem cell deficiency and other events associated with dry eyes. Dry eye symptoms occurred in 36% of patients, and blurred vision occurred in 14% of patients, during treatment with PADCEV. The median time to onset to symptomatic ocular disorder was 1.9 months (range: 0.3 to 6.2). Monitor patients for ocular disorders. Consider artificial tears for prophylaxis of dry eyes and ophthalmologic evaluation if ocular symptoms occur or do not resolve. Consider treatment with ophthalmic topical steroids, if indicated after an ophthalmic exam. Consider dose interruption or dose reduction of PADCEV for symptomatic ocular disorders.

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Skin reactions occurred in 54% of the 310 patients treated with PADCEV in clinical trials. Twenty-six percent (26%) of patients had maculopapular rash and 30% had pruritus. Grade 3-4 skin reactions occurred in 10% of patients and included symmetrical drug-related intertriginous and flexural exanthema (SDRIFE), bullous dermatitis, exfoliative dermatitis, and palmar-plantar erythrodysesthesia. In study EV-201, the median time to onset of severe skin reactions was 0.8 months (range: 0.2 to 5.3). Of the patients who experienced rash, 65% had complete resolution and 22% had partial improvement.

Monitor patients for skin reactions. Consider appropriate treatment, such as topical corticosteroids and antihistamines for skin reactions, as clinically indicated. For severe (Grade 3) skin reactions, withhold PADCEV until improvement or resolution and administer appropriate medical treatment. Permanently discontinue PADCEV in patients that develop Grade 4 or recurrent Grade 3 skin reactions.

Infusion Site Extravasation

Skin and soft tissue reactions secondary to extravasation have been observed after administration of PADCEV. Of the 310 patients, 1.3% of patients experienced skin and soft tissue reactions. Reactions may be delayed. Erythema, swelling, increased temperature, and pain worsened until 2-7 days after extravasation and resolved within 1-4 weeks of peak. One percent of patients developed extravasation reactions with secondary cellulitis, bullae, or exfoliation. Ensure adequate venous access prior to starting PADCEV and monitor for possible extravasation during administration. If extravasation occurs, stop the infusion and monitor for adverse reactions.

Embryo-Fetal Toxicity

Based on the mechanism of action and findings in animals, PADCEV can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of enfortumab vedotin to pregnant rats during the period of organogenesis caused maternal toxicity, embryo-fetal lethality, structural malformations and skeletal anomalies at maternal exposures approximately similar to the clinical exposures at the recommended human dose of 1.25 mg/kg.

Advise patients of the potential risk to the fetus. Advise female patients of reproductive potential to use effective contraception during PADCEV treatment and for 2 months after the last dose of PADCEV. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with PADCEV and for 4 months after the last dose.

ADVERSE REACTIONS

Clinical Trial Experience

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

The data in the **WARNINGS AND PRECAUTIONS** section reflect exposure to PADCEV as a single agent at 1.25 mg/kg in 310 patients in EV-201, EV-101 (NCT02091999), and EV-102 (NCT03219333). Among 310 patients receiving PADCEV, 30% were exposed for ≥ 6 months and 8% were exposed for ≥12 months.

The data described in this section reflect exposure to PADCEV from EV-201, a single arm study in patients (n=125) with locally advanced or metastatic urothelial cancer who had received prior treatment with a PD-1 or PD-L1 inhibitor and platinum-based chemotherapy. Patients received PADCEV 1.25 mg/kg on Days 1, 8 and 15 of a 28-day cycle until disease progression or unacceptable toxicity. The median duration of exposure to PADCEV was 4.6 months (range: 0.5-15.6).

Serious adverse reactions occurred in 46% of patients treated with PADCEV. The most common serious adverse reactions (≥3%) were urinary tract infection (6%), cellulitis (5%), febrile neutropenia (4%), diarrhea (4%), sepsis (3%), acute kidney injury (3%), dyspnea (3%), and rash (3%). Fatal adverse reactions occurred in 3.2% of patients, including acute respiratory failure, aspiration pneumonia, cardiac disorder, and sepsis (each 0.8%).

Adverse reactions leading to discontinuation occurred in 16% of patients; the most common adverse reaction leading to discontinuation was peripheral neuropathy (6%). Adverse reactions leading to dose interruption occurred

in 64% of patients; the most common adverse reactions leading to dose interruption were peripheral neuropathy (18%), rash (9%) and fatigue (6%). Adverse reactions leading to dose reduction occurred in 34% of patients; the most common adverse reactions leading to dose reduction were peripheral neuropathy (12%), rash (6%) and fatigue (4%).

The most common adverse reactions (≥20%) were fatigue, peripheral neuropathy, decreased appetite, rash, alopecia, nausea, dysgeusia, diarrhea, dry eye, pruritus and dry skin. The most common Grade ≥3 adverse reaction (≥5%) were rash, diarrhea, and fatigue.

Table 1 summarizes the all grade and Grade ≥3 adverse reactions reported in patients in EV-201.

Table 1. Adverse Reactions Reported in ≥15% (Any Grade) or ≥5% (Grade ≥3) of Patients Treated with PADCEV in EV-201

Adverse Reaction	PADCEV n=125	
	All Grades %	Grade ≥3 %
Any	**100**	**73**
General disorders and administration site conditions		
Fatigue*	56	6
Nervous system disorders		
Peripheral neuropathy†	56	4
Dysgeusia	42	0
Metabolism and nutrition disorders		
Decreased appetite	52	2
Skin and subcutaneous tissue disorders		
Rash‡	52	13
Alopecia	50	0
Dry skin	26	0
Pruritus§	26	2
Eye disorders		
Dry eye¶	40	0
Gastrointestinal disorders		
Nausea	45	3
Diarrhea#	42	6
Vomiting	18	2

*Includes: asthenia and fatigue

†Includes: hypoesthesia, gait disturbance, muscular weakness, neuralgia, paresthesia, peripheral motor neuropathy, peripheral sensory neuropathy and peripheral sensorimotor neuropathy.

‡Includes: dermatitis acneiform, dermatitis bullous, dermatitis contact, dermatitis exfoliative, drug eruption, erythema, erythema multiforme, exfoliative rash, palmar-plantar erythrodysesthesia syndrome, photosensitivity reaction, rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash papular, rash pustular, rash pruritic, rash vesicular, skin exfoliation, stasis dermatitis, and symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) and urticaria.

§Includes: pruritus and pruritus generalized

¶Includes: blepharitis, conjunctivitis, dry eye, eye irritation, keratitis, keratopathy, lacrimation increased, limbal stem cell deficiency, Meibomian gland dysfunction, ocular discomfort, punctate keratitis, tear break up time decreased.

#Includes: colitis, diarrhea and enterocolitis

Other clinically significant adverse reactions (≤15%) include: herpes zoster (3%) and infusion site extravasation (2%).

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or other enfortumab vedotin products may be misleading. A total of 365 patients were tested for immunogenicity to PADCEV; 4 patients (1%) were confirmed to be transiently positive for anti-therapeutic antibody (ATA), and 1 patient (0.3%) was confirmed to be persistently positive for ATA at any post-baseline time point. No impact of ATA on efficacy, safety and pharmacokinetics was observed.

DRUG INTERACTIONS

Effects of Other Drugs on PADCEV

Strong CYP3A4 Inhibitors

Concomitant use with a strong CYP3A4 inhibitor may increase free MMAE exposure, which may increase the incidence or severity of PADCEV toxicities. Closely monitor patients for signs of toxicity when PADCEV is given concomitantly with strong CYP3A4 inhibitors.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on the mechanism of action and findings in animals, PADCEV can cause fetal harm when administered to a pregnant woman. There are no available human data on PADCEV use in pregnant women to inform a drug-associated risk. In an animal reproduction study, administration of enfortumab vedotin-ejfv to pregnant rats during organogenesis caused maternal toxicity, embryo-fetal lethality, structural malformations and skeletal anomalies at maternal exposures approximately similar to the exposures at the recommended human dose of 1.25 mg/kg. Advise patients of the potential risk to the fetus.

Lactation

Risk Summary

There are no data on the presence of enfortumab vedotin-ejfv in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in a breastfed child, advise lactating women not to breastfeed during treatment with PADCEV and for at least 3 weeks after the last dose.

Females and Males of Reproductive Potential

Pregnancy testing

Verify pregnancy status in females of reproductive potential prior to initiating PADCEV treatment.

Contraception

Females

PADCEV can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during PADCEV treatment and for 2 months after the last dose.

Males

Advise male patients with female partners of reproductive potential to use effective contraception during treatment with PADCEV and for 4 months after the last dose.

Infertility

Males

Based on findings from animal studies, PADCEV may impair male fertility.

Pediatric Use

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

Geriatric Use

Of the 310 patients treated with PADCEV in clinical studies, 187 (60%) were 65 years or older and 80 (26%) were 75 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

Hepatic Impairment

Avoid the use of PADCEV in patients with moderate or severe hepatic impairment. PADCEV has not been studied in patients with moderate or severe hepatic impairment. In another ADC that contains MMAE, the frequency of ≥Grade 3 adverse reactions and deaths was greater in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment compared to patients with normal hepatic function. No adjustment in the starting dose is required when administering PADCEV to patients with mild hepatic impairment.

Renal Impairment

No dose adjustment is required in patients with mild (CrCL >60-90 mL/min), moderate (CrCL 30-60 mL/min) or severe (CrCL <30 mL/min) renal impairment.

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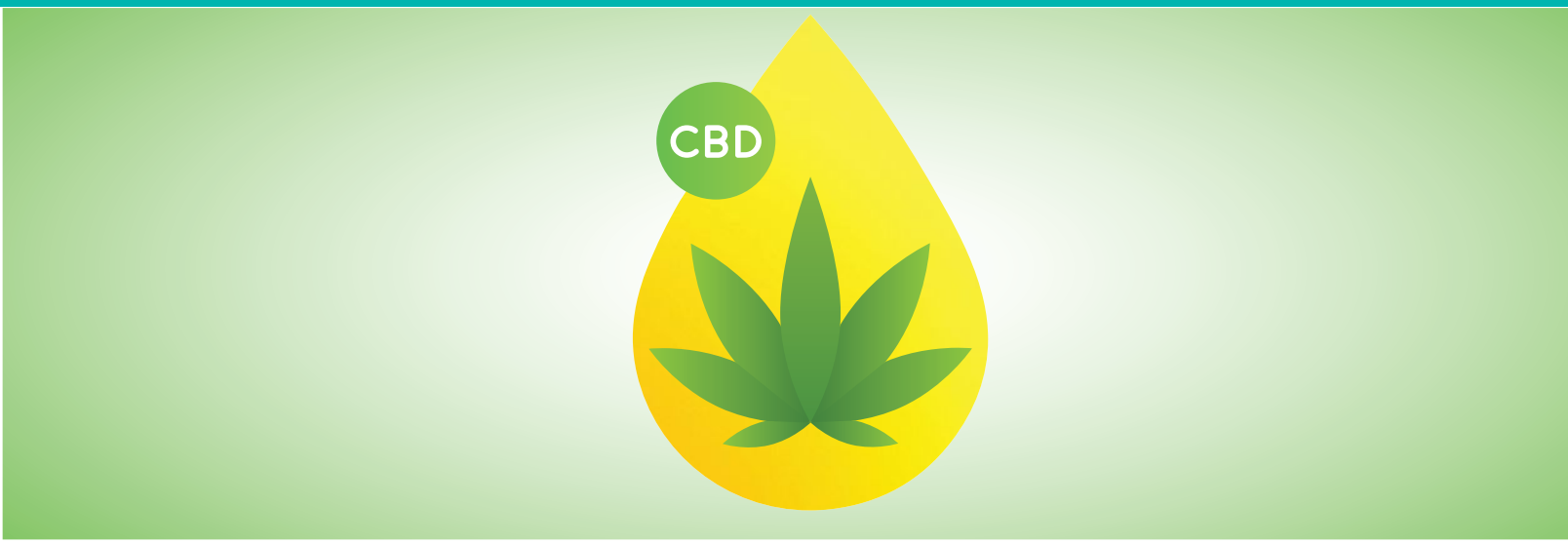

Cannabidiol Oil for Cancer Patients: Nature's Best Remedy?

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Cannabidiol (CBD) oil is a supplement that has gained tremendous popularity over the past few years. The compound is marketed for numerous indications and sold across the United States by various shops, gas stations, and online retailers. CBD is produced in a variety of formulations, one of the more prevalent being CBD oil.[1] One area in which CBD oil is gaining interest is the cancer setting, and because of its wide availability, it is likely that many cancer patients are turning to this alternative medicine to help manage their disease or symptoms. It is therefore important for healthcare professionals to educate themselves regarding the efficacy, safety, and legality of this compound.

"As evidenced by the widespread use and current availability of cannabidiol oil products, patients are likely to consume these products despite a lack of efficacy or safety data."

CBD is a compound derived from the cannabis plant. Cannabis is the source of one of the oldest plant-based medicines known to man, and for thousands of years it has been cultivated by humans for various purposes.[2] Two common strains of the plant are marijuana, cultivated for its medicinal purposes, and hemp, cultivated for its use in food, clothing, and paper.[3] The cannabis plant contains various active components, two of which are cannabinoids and terpenes.[2] Researchers have identified up to 113 different cannabinoids and 120 different terpenes in cannabis.[4] The two cannabinoids delta-9-tetrahydrocannabinol (THC) and CBD are the most prevalent and well-known cannabis components. However, terpenes have also been shown to bind to receptors in animal studies, suggesting that they may play a role in the overall pharmacologic profile of cannabis.[2] Many people likely associate cannabis with marijuana and the "high" effect that it elicits. This psychoactive effect is a result of the action of THC on cannabidiol (CB)1 and CB2 receptors.[5] CBD does not act in the same way; in fact, it is thought to have antagonistic effects on the CB receptors. As a result, it does not produce the psychoactive effects seen in THC-containing cannabis.[5] CBD has a long list of proposed benefits, including potential antiepileptic, anxiolytic, antipsychotic, anti-inflammatory, and neuroprotective effects.[6] Medicinal marijuana products often contain a combination of THC and CBD but may also be pure THC or CBD alone. CBD oil, however, primarily contains the CBD, with minimal (<0.3%) THC content.

The legal status of cannabis and cannabis-related products in the United States can be difficult to understand. Federally, the Controlled Substances Act (CSA) of 1970 placed cannabis and its components into schedule I, the most restrictive category.[7] As of January 1, 2020, 33 individual states, along with Washington, DC, Puerto Rico, and Guam, have implemented laws that allow for medicinal cannabis use. Of these, 11 states plus Washington, DC, and Guam allow for recreational use.[8-10] These states can sell all types of cannabis products with varying contents of active ingredients (e.g., THC, CBD) and dosage forms. The 2018 Farm Bill removed hemp, defined as cannabis-derived product with less than 0.3% THC, from the CSA.[7] This has allowed for widespread commercial sales of CBD products outside of medical marijuana dispensaries.[11] The extracts that are produced from cannabis can range widely in their composition and effects, depending on which part of the plant

is used. Hemp seed oil contains no THC and minimal CBD and is extracted from cannabis seeds. CBD oil and cannabis oils, which are extracted from the flower or plant material, contain CBD at variable levels; the difference is that CBD oil can contain only up to 0.3% THC.[3] The sale of these products is legal in all states but Idaho, Nebraska, and South Dakota, where no cannabis access laws currently exist. Because these CBD oils do not contain psychoactive levels of THC, they can be purchased and consumed without the recommendation or certification of a provider.[3]

In 2018, the U.S. Food and Drug Administration (FDA) approved CBD oral solution (Epidiolex) for the treatment of seizures in Lennox-Gastaut and Dravet syndrome.[7] Epidiolex, a purified CBD oral solution that contains less than 0.1% THC, was placed into schedule V (low-abuse potential) by the U.S. Drug Enforcement Agency (DEA) in 2018.[12,13] This is currently the only FDA-approved CBD product, and it has not been evaluated in cancer patients. According to the DEA, all non-FDA-approved CBD products are still considered schedule I controlled substances.[13] The 2018 Farm Bill allows for exceptions to this status under certain conditions. In order for hemp-derived CBD to be considered legal, it must be produced by a licensed grower under specific conditions set forth by the Farm Bill, state regulations, and federal regulations.[14] This, along with the implementation of state laws on cannabis access, has made the regulation of CBD products a difficult task.[8] A 2016 study investigated the labeling accuracy of online-purchased CBD products. Researchers purchased 84 non-FDA-approved CBD products and tested their CBD and THC content. The alarming findings were that only 31% were accurately labeled within 10% of the reported CBD content, and 21% of the products contained unlabeled THC at a low level.[15] The FDA has issued warnings regarding mislabeling to dozens of firms that market CBD products and has warned the public to beware of these products.[16]

Cannabinoids have been used to treat patients with cancer since 1985, when dronabinol (Marinol), a synthetic THC product, was approved by the FDA to treat chemotherapy-induced nausea and vomiting.[17] The specific role of CBD in cancer treatment is still unclear. In vitro and in vivo studies have shown some evidence for CBD's efficacy as an anticancer agent through mechanisms such as induction of apoptosis or inhibition of tumor growth and metastasis.[18,19] In vitro data supports the ability of CBD to induce tumor cell death in patients with glioblastoma.[20] Furthermore, case reports have been published showing a potential anticancer effect in lung cancer and ovarian cancer patients.[21,22] Regarding supportive care for cancer patients, the role of CBD is again unclear. Evidence exists for the use of cannabis for chemotherapy-induced nausea and vomiting, cancer pain, anorexia and cachexia, and appetite stimulation; however, most studies were poorly designed and evaluated products that also contained THC.[2] Until more human trial data become available, the appropriateness of using CBD oil in these indications remains uncertain. Several studies are investigating the use of CBD in patients with cancer for indications such as palliative care in cancer patients to reduce symptom burden; as standard-of-care treatments in patients with multiple myeloma, glioblastoma multiforme, and gastrointestinal malignancies; and for prevention of graft-versus-host disease in patients undergoing allogeneic hematopoietic stem cell transplantation.[23-25] Continuing research is necessary to understand CBD's usefulness in treating cancer patients.

As noted, CBD lacks the psychoactive effects that are found with other cannabinoids. This does not mean that it can be used without concern. Epidiolex has been associated with hepatocellular injury, sedation, and suicidal behavior and ideation, in addition to more common side effects of decreased appetite (16–22%), diarrhea (9–20%), fatigue (11–12%), and insomnia (5–11%). It is important that patients using CBD be made aware of the possibility that they will test positive in a cannabis drug screen.[12] It should be noted that rigorous safety studies have been performed only with prescription Epidiolex, not with over-the-counter or other CBD oil products. Given that the strengths of CBD oil products vary greatly, it is difficult to fully understand the side-effect profile of CBD. Emerging evidence has also indicated the potential carcinogenicity of CBD, with one study finding that CBD can cause chromosomal damage in human-derived cell lines.[26] Also of note, CBD interacts with a number of common medications. CBD is a substrate for cytochrome (CYP) p450 enzymes CYP3A4 and CYP2C19; a dose reduction should therefore be considered when a patient is concomitantly using moderate or strong inhibitors of these enzymes, and a dose increase should be considered when a patient is using moderate or strong inducers. In addition, when CBD is used concomitantly with substrates of UGT1A9, UGT2B7,

Table 1. Considerations for Selecting a High-Quality CBD Oil Product[3]

- Ensure that the product is certified as organic by the U.S. Department of Agriculture, has been extracted by carbon dioxide (rather than solvents), and has been tested for pesticides/herbicides.
- Ensure that the product meets quality standards for certification, as defined by the U.S. Food and Drug Administration; European Union, Australian, or Canadian organic certification; or National Science Foundation International certification.
- Ensure that the company has an independent adverse event reporting system.
- Ensure that laboratory tests confirm a THC level <0.3%.
- Ensure that the product contains CBD oil and not just hemp oil, which contains little or no cannabinoids.

Note. Imported European products have more stringent requirements for low THC than are required in the United States and a more stringent regulatory system for hemp.

CYP2C8, CYP2C9, CYP1A2, or CYP2B6, a dose reduction of the substrate should be considered.[12] The combination of potential side effects and drug interactions, along with the regulatory issues highlighted above, raises concerns about patient safety. As evidenced by the widespread use and current availability of CBD oil products, patients are likely to consume these products despite a lack of efficacy or safety data. Because of this likelihood, healthcare providers should provide guidance to their patients on selecting the safest product possible. **Table 1** lists considerations for choosing high-quality CBD oil products.[3]

Overall, very little evidence exists to support the medical use of CBD oil for patients with cancer. Although some case reports have demonstrated benefit, the lack of data from well-designed human trials presents the single largest barrier to acceptance and routine use of CBD by medical professionals. In addition to the lack of evidence, CBD's questionable legality also presents an obstacle to be overcome before providers can comfortably recommend it to their patients. In the meantime, as the CBD craze sweeps across the nation, providers should focus on educating themselves about the risks and benefits of CBD oil in order to manage expectations and avoid adverse effects and drug interactions in their patients who are curious about CBD. ●●

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Firstborn Turned 18: The Twin Cities Oncology Journal Club

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In the fall of 2001, I successfully completed the second of my two postdoctoral residencies—they were in pharmacy practice and specialty hematology/oncology—and moved to Minnesota to start my first job as oncology clinical coordinator at Abbott Northwestern Hospital. As a young and ambitious pharmacist in the oncology/hematology field, I looked for many ways to get involved and make an impact in the profession. Luckily, I met Pam Jacobson, PharmD FCCP, a distinguished professor and associate department head in the department of experimental and clinical pharmacology at the University of Minnesota College of Pharmacy (COP). We worked collaboratively on the idea of an oncology journal club (OJC) and began to co-coordinate this meeting.

Our goals were simple: to get pharmacists interested in oncology/hematology together for a journal club and foster an environment for networking and education. Our first meeting was held on January 10, 2002. We had 17 pharmacists and 6 pharmaceutical company representatives in attendance and discussed a review titled "Epoetin Alfa Therapy Increases Hemoglobin Levels and Improves Quality of Life in Patients with Cancer-Related Anemia Who Are Not Receiving Chemotherapy and Patients with Anemia Who Are Receiving Chemotherapy." Wow, have times changed! To date, we have had 108 journal club meetings and average around 70 attendees at each meeting.

OJC, an evening dinner program, begins in January and occurs in alternate months throughout the year. The program consists of a 30-minute presentation by a speaker or program representative from a pharmaceutical company, followed by 10 minutes for questions, and then a 60-minute presentation developed for pharmacists' continuing education (CE). A pharmaceutical company sponsor provides the educational speaker and the meal. The location of the meeting rotates among Minneapolis, St. Paul, and other suburbs in the Twin Cities area.

Attendees are pharmacists, University of Minnesota COP students, residents, drug representatives, and medical science liaisons. For the past 5 years, 1 hour of CE credit has been available for pharmacists via this program through the Minnesota Board of Pharmacy. We are very fortunate to have a wide variety of speakers, including pharmacists, pharmacy residents (postgraduate year-1 and year-2 [PGY-1 and PGY-2]), University of Minnesota COP students, and industry speakers (doctors, medical science liaisons, pharmacists, nurse practitioners, etc.). Without our volunteer CE speakers and industry support, OJC would not be sustainable.

Over the past 18 years, topics across a wide range have been discussed at OJC, and varying formats have been used:

- Overview of practice sites (patient population, number of beds/chairs, staffing, etc.)
- "How We Do It" discussions (on topics like febrile neutropenia, nausea and vomiting, and mucositis)
- Clinical Pearls articles from *HOPA News*
- New drug updates
- Case studies
- Disease overviews
- Major projects conducted by PGY-1 and PGY-2 residents
- Pharmaceutical company presentations ranging from supportive care to unbranded disease education.

With such a longstanding program, change was inevitable. OJC was established with pharmaceutical company education grants, and an industry speaker was not required. This quickly changed when the Pharmaceutical Research and Manufacturers of America (PhRMA) Code on Interaction with Health Care Professionals was implemented in January 2009. OJC adapted its programming to the requirements of speakers from drug companies. In 2016, we began using Google to create a Gmail account, update contact lists, and create Google Forms to streamline the RSVP process. Beginning in 2020, OJC will be coordinated through the Upper Midwest Oncology Education Network (UMOEN), with the current board working on programming and CE credits. UMOEN may be considered my first-born grandchild, because it was born out of OJC. But that's a story for another day, and honestly, I am far too young to be a grandmother! Luckily, I am on the board of UMOEN and will continue to be involved in this endeavor.

I have learned many things since starting OJC. First, surveys sent to the participants asking for topics of interest and suggestions of volunteers to speak at future meetings has helped ensure the longevity of OJC. Using a wide variety of speakers and choosing discussion topics from across various disease states in inpatient and outpatient practice help engage our diverse audience of pharmacy professionals. Every pharmaceutical company has different regulations, so establishing guidelines upfront can help prevent any issues arising with industry sponsorship and speaker roles. On the practical side, keeping people informed about upcoming dates so they can request certain work shifts has allowed

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Women in Oncology Pharmacy Leadership: Strides to Close the Gap—A Review of HOPA's 2019 White Paper

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In August 2019, *The Journal of Oncology Pharmacy Practice* published HOPA's white paper on the issue of women in oncology pharmacy leadership.[1] The publication highlights the current disparity between women and men in oncology pharmacy leadership in the United States: women represent 58.1% of pharmacy professionals, but only 25% of those women hold leadership roles.[2] In an effort to understand how this disparity is affecting female oncology pharmacists, HOPA's Leadership Development Committee held a summit in 2017 to deliberate on this issue and discuss the results of a national HOPA membership survey assessing the barriers that prevent female oncology pharmacists from assuming leadership roles. The authors of the white paper identify common sentiments expressed by survey respondents, describe key barriers, and provide suggestions to institutions and individuals on how the profession can encourage and promote female representation in oncology pharmacy leadership.

An online survey distributed to the HOPA membership through its e-mail discussion group in the summer of 2017 was returned by 160 respondents; the group was made up of men and women who had a range of experiences and years of service in oncology pharmacy practice. Opinions on resources available for leadership training were divergent. Approximately half of the respondents perceived a lack in leadership training resources, whereas the other half believed that numerous opportunities existed and that creating more leadership training experiences was unnecessary. However, there was a consensus among respondents about the benefit of providing more formal leadership training through educational efforts. The Leadership Development Committee noted that schools of pharmacy have already begun to add these leadership development practices to their foundational curricula and that the American Society of Health-System Pharmacists has integrated similar efforts into the goals and objectives for accredited residency programs. However, the implementation of these experiences varies greatly across residency programs. In the future, HOPA can support leadership development training programs by constructing a HOPA-sponsored leadership fundamentals course for postgraduate year-2 oncology residency programs and by encouraging engagement by trainees in HOPA.

The analysis of the survey results identified and described six main barriers affecting female oncology pharmacists. Two of the six were institutional barriers: a lack of succession planning by superiors and a lack of emphasis on formalized leadership training for continued career growth in the pharmacy profession. In a 2018 survey carried out by the American College of Healthcare Executives, succession planning was not reported as a priority for executives.[3] In addition, 70% of executives polled in another survey by the American College of Healthcare Executives denied having formalized succession plans in their workplaces.[4] The HOPA committee infers that if more workplaces were to develop formalized succession plans and consider female internal hires for leadership roles, internal talent would be nurtured and the proportion of women assuming leadership roles would increase. Regarding the lack of formalized professional development training, the Leadership Development Committee states that in some cases professional organizations are deficient in providing training courses that would help establish foundational leadership skills. Professional organizations like HOPA should continue to organize leadership workshops and mentorship programs with current leaders to help enhance leadership skills and support female leaders whose goals change throughout dynamic careers. Although these steps will help in the future, the immediate need is for opportunities in the workplace for professional training and managerial roles for women who have a strong bent toward leadership.

Another set of barriers identified were interpersonal: the problem of women bullying other women and the existence of sexual harassment. The Leadership Development Committee noted that a commonly expressed perception was a lack of support for other women among female leaders. This lack of support may be manifested as bullying behavior. The Leadership Development Committee members offer possible reasons for such behavior, but they emphasize the need for women to support other women in the field. By encouraging each other, opposing bullying, and creating supportive environments, women can help each other succeed and overcome discrimination in the workplace. HOPA has a large proportion of women in leadership roles, so HOPA leaders hope to set the precedent for other disciplines and professional organizations.

Unfortunately, sexual harassment remains an issue in the workplace and threatens affected employees' sense of safety and value. Not only do such violations cause personal suffering, but they have an adverse impact on professional aspirations. Members of HOPA's Leadership Development Committee believe that even though national stories of abuse have shed light on these occurrences, the eradication of sexual harassment will occur only when the broader culture changes. HOPA plans to include leadership training program strategies for addressing harassment and constructing supportive, respectful workplace environments. Although these efforts will not eradicate sexual harassment, they can provide tools to help leaders combat this societal epidemic, protect those who have been harmed or who are at risk, and prevent future occurrences.

The last two barriers identified were concerns about work-life balance and perceived self-worth and confidence. Challenges in maintaining work-life balance are certainly faced not just by women: a 2015 study reported that 70% of women felt "unable to take

any time off work" compared with 60% of men.[5] Balancing personal time and obligations with professional responsibilities can be a challenge. Endorsing the belief that work-life prioritization is a personal decision, the Leadership Development Committee advocates that female oncology pharmacists find a balance for themselves and seek continued professional involvement while taking time away from work. Workplace environments should provide equal opportunity for both job and personal satisfaction without allowing perceptions about gender roles to influence career placement decisions. HOPA also plans to provide resources to women throughout their career trajectories for maintaining their credentials while they choose to use family- or personal-leave time.

By creating more professional development programs for members, encouraging early involvement of trainees in HOPA, and developing training tools to fight discrimination in the workplace, HOPA demonstrates its commitment to the advancement of women in pharmacy leadership roles and to the reduction and elimination of disparities between men and women in pharmacy leadership. However, the HOPA Leadership Development Committee cannot be successful in these efforts without the involvement of members and cooperation from institutions. HOPA places the responsibility of creating cultural change on institutions and current women pharmacists. With members and healthcare institutions uniting to support changes that will facilitate progress, these efforts can be successful in the future. ●●

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Firstborn Turned 18: The Twin Cities Oncology Journal Club

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more pharmacists to attend. And holding our meetings in a great location with easy parking has been helpful for an after-work evening program.

Finally, having more than one person involved in the planning of OJC has allowed us to continue to provide this education in Minnesota. I would like to thank Pam Jacobson, PharmD FCCP, and past OJC CE education coordinator Sara Smith, PharmD BCOP, of University of Minnesota Health for all their help. As they say, it takes a village.

Last September I presented on the Twin Cities OJC at HOPA Practice Management during the Practice Management Pearls session. Shortly afterward, I received a LinkedIn tag post from Sarah Francis, PharmD BCOP, thanking me for the presentation. Hearing about our OJC motivated Dr. Francis and her colleagues to schedule the first South Florida Oncology Pharmacy Journal Club! I was honored and happy to have helped start another OJC in the United States.

I have two children, ages 12 and 14, but my professional firstborn is OJC! I may be a bit biased, but I believe this is the oldest and largest specialty pharmacy OJC in the nation. I am so proud of having been able to provide oncology/hematology education in Minnesota for the past 18 years. The journal club has allowed for the flourishing of a fantastic professional networking group of pharmacists, students, residents, and industry representatives.

If you are interested in starting an OJC in your area, please contact me at bjnowak1@gmail.com with any questions. ●●

Pharmacists-in-Training Implementing Quality Initiatives in Oncology Care

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Demonstrating the ability to provide high-quality and cost-efficient care by using process, outcome, and patient-reported metrics is now an essential part of health care and is linked to reimbursement and star ratings. The Centers for Medicare and Medicaid Services (CMS) created the Merit-Based Incentive Payment System and alternative-payment Oncology Care Model with the goal of promoting high-quality patient-centered care. CMS has approved the American Society of Clinical Oncology (ASCO) Quality Oncology Practice Initiative (QOPI) as a quality assessment program that can increase the potential for reimbursement by focusing on patient care and measuring quality in areas such as symptom management, evidence-based medicine, and cost mitigation. Oncology pharmacists are in an ideal position to influence the quality of care through financial stewardship by developing policies, improving patient outcomes through therapeutic management, and enhancing patient perceptions through direct education and enhanced supportive care.[1] Pharmacists-in-training make it possible to expand the services offered by a pharmacist. The impact of pharmacy residency training programs on quality improvement initiatives has been documented since at least 1996.[2] Although many projects remain unpublished and are being used solely for internal quality improvement, various publications demonstrate the involvement of pharmacy residents and students in efforts to improve quality metrics such as medication reconciliation, discharge follow-up, patient education, and patient engagement.

"Focusing on developing new services and activities to address quality metrics and using pharmacy trainees in the process is an essential responsibility and next step for oncology pharmacists to further improve patient care while also ensuring that reimbursement is optimized."

Leveraging Layered Learning to Expand Patient Care and Meet Quality Metrics for Oncology Patients

A study by Bates and colleagues published in 2016 evaluated the impact of leveraging pharmacists-in-training to expand care by conducting discharge medication reconciliation and counseling for malignant hematology and medical oncology patients.[3] The advanced pharmacy practice experience (APPE) student was focused on obtaining admission medication histories and counseling, while the resident was responsible for discharge medication reconciliation, patient education, documentation, order verification, and providing support for obtaining medications. The clinical pharmacist assisted and coordinated team activities. During the 60-day study period, 61 patients (51%) received discharge medication reconciliation and counseling. The number of medication-related problems (MRPs) identified at discharge (mean of 1.26 for malignant hematology patients; mean of 2.1 for medical oncology patients) was captured and showed that the majority of problems involved coordination of specialty medications for the malignant hematology group and the need for an additional drug in the medical oncology group. The pharmacy team made recommendations to resolve all MRPs; the acceptance rates were 89.7% and 78% for the malignant hematology and medical oncology teams, respectively. This study demonstrated that pharmacists-in-training can be integrated into efforts to expand pharmacist care and improve patient outcomes.

Student Pharmacist–Driven Medication Reconciliation

A number of studies have evaluated the impact of pharmacy student–led medication reconciliation in the ambulatory care setting, such as in the infusion center of a comprehensive cancer center. A study by Ashjian and colleagues involved students in their introductory pharmacy practice experiences who completed medication histories for 510 hematology/oncology patients and found that 88% had at least one discrepancy.[4] In a separate study, Phan and colleagues utilized APPE students to complete medication histories for 60 patients and found a similar rate of at least one discrepancy (83%), with 21% of those discrepancies involving a high-risk medication.[5] Pharmacists-in-training can add significant value to patient care by correcting discrepancies and reducing the likelihood of medication errors.

Pharmacy Resident and Clinical Pharmacist Postdischarge Follow-Up Telephone Program

Discharge planning and follow-up are essential components of patient care and the prevention of avoidable hospital readmissions and complications. Patients with cancer are at an increased risk of transitions-of-care errors because of the complexity of their medication regimens. Pharmacists at the University of Texas MD Anderson Cancer Center teamed up with a PGY-1 resident and an

educational specialist to develop a pilot program for postdischarge telephone calls to assess medication adherence, provide education, and address medication-related concerns with patients.[6] Two hundred and six calls were made within 72 hours following discharge, and 150 (73%) of patients were successfully reached; 20 of the 206 patients who were contacted (9%) declined the call. Of the patients reached, 87 (58%) were found to have one or more discrepancies with their medications. Although it is known that scheduled follow-up with patients after hospitalization is beneficial, time and resources are a limiting factor. Pharmacists are well positioned to improve continuity of care and have a positive impact on medication-related issues, both of which are measures endorsed by the National Quality Forum and are National Patient Safety Goals, according to the Joint Commission.

Increased Patient Engagement Following Chemotherapy Consultation by a Pharmacist and Trainees

The literature is replete with evidence suggesting that patients who are engaged in their care have better outcomes and a lower cost of care. *Patient engagement*, or *patient activation*, refers to a patient's knowledge, skills, and confidence to manage their own health and can be measured using the patient activation measure (PAM)-10 tool, with a higher score indicating improved outcomes. One study demonstrated this through a first-cycle chemotherapy consultation service, which was completed by a pharmacist or pharmacist-in-training.[7] This service included patient education, medication therapy management, and the addressing of MRPs. After administering a baseline PAM-10 survey, pharmacists or trainees called the patient within 2 days of discharge for a second PAM-10 survey. Of the 36 patients analyzed in this study, the PAM-10 scores were significantly improved following the intervention (68.5 vs. 75, pre- and postintervention, respectively; $p = .001$). This study highlights the effectiveness of using pharmacy residents and students to positively affect patient care and encourage patient involvement in the care process.

Conclusion

Oncology pharmacists have demonstrated their abilities to influence patient care and positively affect quality metrics endorsed by ASCO QOPI as part of their current scope of practice. Pharmacy residents and students are able to assist in this process and can be called upon to supplement quality care given by the team. They can help implement and expand on established pharmacy services. Although pharmacists and pharmacy trainees have made significant contributions to enhancing the quality of oncology care, additional opportunities for pharmacy involvement remain. Areas of well-established pharmacist-led impact on quality include patient education, symptom management, medication reconciliation, discharge follow-up, transitions of care, and increasing patient engagement and activation. Focusing on developing new services and activities to address quality metrics and using pharmacy trainees in the process is an essential responsibility and next step for oncology pharmacists to further improve patient care while also ensuring that reimbursement is optimized. ●●

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Toxicity Management for Immune Checkpoint Inhibitors

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Programmed death-1 (PD-1) and programmed death-ligand 1 (PD-L1) inhibitors have become the mainstay of therapy for numerous oncologic indications (**Table 1**). Most U.S. Food and Drug Administration approvals pertain to treatment of advanced or metastatic cancers; however, agents such as atezolizumab have gained approval in the first-line setting (IMpower133).[1] An increasing number of patients are exposed to these therapies; therefore, it is imperative for healthcare providers in community and academic medical center settings to recognize and appropriately manage these unique toxicities. The purpose of this article is to provide an overview of immune checkpoint inhibitor (ICI) toxicity management while also highlighting resources available for clinicians managing these therapies in various clinical settings.

Checkpoint inhibitor–based immunotherapies have varying toxicity profile incidence and timing, which are often related

Table 1. FDA-Approved PD-1/PD-L1 Inhibitors[3-8]

Class	Medication Name (Generic, Brand)	FDA-Approved Indication(s)*
PD-1 Inhibitors	pembrolizumab (Keytruda)	• Cervical cancer (recurrent or metastatic) • Endometrial cancer (advanced) • Esophageal cancer (recurrent locally advanced or metastatic) • Gastric cancer (recurrent locally advanced or metastatic) • Head and neck, SC (unresectable/recurrent or metastatic) • HCC • HL, classical (relapsed or refractory) • Melanoma (adjuvant and unresectable or metastatic) • Merkel cell carcinoma (recurrent or metastatic) • MSI-high cancer (unresectable or metastatic) • NSCLC • Primary mediastinal large B-cell lymphoma (relapsed or refractory) • RCC (advanced) • SCLC (metastatic) • Urothelial carcinoma (locally advanced or metastatic)
	nivolumab (Opdivo)	• CRC, MSI-high, or mismatch repair deficient (metastatic) • Head and neck, SC (recurrent or metastatic) • HCC • HL, classic (relapsed or refractory) • Melanoma (adjuvant and unresectable or metastatic) • NSCLC • RCC (advanced) • SCLC (metastatic) • Urothelial carcinoma (locally advanced or metastatic)
	cemiplimab (Libtayo)	• Cutaneous squamous cell carcinoma (locally advanced or metastatic)
PD-L1 Inhibitors	atezolizumab (Tecentriq)	• Breast cancer, triple negative (locally advanced or metastatic) • NSCLC (metastatic) • SCLC, extensive stage • Urothelial carcinoma (locally advanced or metastatic)
	avelumab (Bavencio)	• Merkel cell carcinoma (metastatic) • RCC (advanced) • Urothelial carcinoma (locally advanced or metastatic)
	durvalumab (Imfinzi)	• NSCLC, stage III unresectable • Urothelial carcinoma (locally advanced or metastatic)

*As of February 17, 2020; detailed information on the specific place in therapy in these indications can be found in the drugs' prescribing information.
Note. CRC = colorectal cancer; FDA = Food and Drug Administration; HCC = hepatocellular carcinoma; HL = Hodgkin lymphoma; MSI-high = microsatellite instability-high cancer; NSCLC = non-small-cell lung cancer; PD-1 = programmed death 1; PD-L1 = programmed death-ligand 1; RCC = renal cell carcinoma; SC = squamous cell; SCLC = small-cell lung cancer.

to their unique mechanism of action, setting them apart from traditional cytotoxic chemotherapies. Toxicities can be divided into three categories: infusion reactions, immune-related adverse events (irAEs), and adverse events of special interest. The skin, colon, endocrine organs, liver, and lungs are the organs most frequently affected by irAEs.[2]

Infusion-Related Reactions

Most infusion-related reactions are mild and are typically associated with low-grade fever, chills, headaches, or nausea (**Table 2**). Severe reactions are reported in less than 1% of patients. Infusion-related reactions have most commonly been reported with avelumab, with any-grade reactions occurring in 25% of patients. Recommendations for the management of infusion-related reactions are summarized in Table 2. The National Comprehensive Cancer Network (NCCN) guidelines recommend that clinicians refer to each product's prescribing information for premedication recommendations.[9] Mild reactions are generally transient and do not require therapy interruption or any other interventions. Moderate reactions are generally managed by withholding the infusion or slowing down the rate of infusion per institutional guidelines. Treatment with antihistamines, acetaminophen, nonsteroidal anti-inflammatory drugs, narcotics, or intravenous (IV) fluids may be used but typically isn't required for longer than a 24-hour period. Severe reactions require urgent management and permanent discontinuation of the ICI.

"The role of PD-1/PD-L1 inhibitors in the treatment of various cancers is rapidly expanding, and it is important for clinicians and patients to understand the unique toxicities associated with these therapies."

Immune-Related Adverse Events

Successful management of irAEs begins with toxicity recognition and grading. Some of the most common toxicities and their management are highlighted in **Table 3**. Clinicians should refer to national or institution-specific clinical guidelines to determine when withholding immunotherapy may be an appropriate management option for irAEs. Early recognition of symptoms is crucial for prompt intervention and treatment; counseling of patients regarding symptom recognition is therefore important before initiation of ICI therapy. Immunosuppression with corticosteroids is the mainstay of therapy, except in the case of selected endocrine irAEs, which may be managed with hormonal supplementation.[9]

Dosing for systemic steroids such as prednisone or methylprednisolone depends on the toxicity grade or severity and can range between 0.5 and 2 mg/kg/day. Myocarditis is a rare but potentially severe adverse event of ICI therapy. Its symptoms are nonspecific, and management requires pulse-dose methylprednisolone administration at 1,000 mg IV daily for 3–5 days.[9] Steroid therapy is generally administered until symptoms resolve to grade 1 or lower (unless otherwise specified), followed by a taper over a 4- to 6-week period. Important considerations with high-dose or prolonged steroid therapy include the following: hyperglycemia, opportunistic fungal or bacterial infections, osteoporosis, and gastritis. Additional immunosuppression may be required for severe irAEs not responding to initial corticosteroid therapy in 48–72 hours. Consultation with any appropriate and relevant medical specialist is recommended at this point.[10]

Tumor necrosis factor inhibitors such as infliximab can be used in steroid-refractory cases by means of targeting and inhibiting proinflammatory cytokines (IL-1 and IL-6).[11] These agents are particularly effective for immune-mediated colitis and inflammatory arthritis. Duration of therapy is not well defined in the setting of irAEs but is typically a single dose. Vedolizumab is a monoclonal antibody that binds and inhibits the interaction of α4β7 integrin with mucosal addressin cell adhesion molecule-1 (MAdCAM-1).

Table 2. Management of Infusion-Related Reactions[9]

Infusion-Related Adverse Event(s)*	Assessment and Grading	Management
Fever, chills, rigors Urticaria or pruritus Angioedema Flushing or headaches Hypertension or hypotension Shortness of breath Coughing or wheezing Hypoxemia Dizziness or syncope Sweating Arthralgia or myalgia	Mild or transient	• Withhold infusion until symptoms resolve; resume infusion as tolerated. • Consider premedications with future infusions.**
	Moderate (symptoms respond to symptomatic treatment)	• Treat per institutional guidelines. • Consider rate decrease and continue immunotherapy. • Consider premedications with future infusions.** • Consider steroids as last resort.
	Severe (symptoms are prolonged; symptoms recur following initial improvement)	• Treat per institutional guidelines. • Permanently discontinue immunotherapy.

*Prescribing information for each immunotherapy agent should be consulted for recommendations regarding premedication(s).

**Premedications: acetaminophen, famotidine, diphenhydramine

A multicenter study evaluating vedolizumab in 28 patients with steroid-refractory enterocolitis found favorable outcomes and yielded good safety data.[12] Mycophenolic acid and mycophenolate mofetil (MMF) are immunosuppressive agents that decrease the proliferation of B and T cells, induce T-cell apoptosis, and suppress dendritic cells and IL-1. These agents have been used in steroid-refractory irAEs involving the liver, kidney, pancreas, and eyes.[9,13] Intravenous immunoglobulin (IVIG), with its immunomodulatory mechanism, can be used to manage neurologic inflammatory or autoimmune conditions.[9] Plasmapheresis or IVIG may be considered for severe or steroid-refractory neurological irAEs.[14,15] Additional therapies cited in the NCCN guidelines include rituximab, tacrolimus, tocilizumab, cyclosporine, cyclophosphamide, methotrexate, and antirheumatic agents.[9,16,17]

Table 3. Management of Immune-Related Adverse Events[9]

Adverse Event(s)	Assessment, Grading, and Monitoring	Management
Fatigue	Mild (G1) (relieved by rest)	• Continue immunotherapy and consider consultation based on abnormalities.
	Moderate (G2) (not relieved by rest; limiting ADLs)	• Do all of the above. • Consider administering low-dose steroids.
	Severe (G3-4) (not relieved by rest; limiting self-care)	• Withhold or consider withholding immunotherapy. • Arrange consultation or carry out treatment based on abnormalities.
Dermatologic Adverse Events		
Maculopapular Rash	Mild (G1) (<10% BSA affected, with or without symptoms)	• Continue immunotherapy. • Apply topical emollient and/or administer oral antihistamine. • Apply moderate-potency topical steroids to affected areas.
	Moderate (G2) (10%–30% BSA affected, with or without symptoms; limiting instrumental ADLs)	• Do all of the above and/or • Administer prednisone 0.5–1 mg/kg/day.
	Severe (G3-4) (>30% BSA affected, with or without symptoms; limiting ADLs)	• Withhold immunotherapy. • Apply high-potency topical steroids to affected areas. • Administer prednisone 0.5–1 mg/kg/day; consider increasing to 2 mg/kg/day if no improvement is seen. • Arrange dermatology consultation and consider inpatient care.
Pruritus	Mild (G1) (mild or localized)	• Continue immunotherapy. • Administer oral antihistamines. • Apply moderate-potency topical steroids to affected areas or lidocaine patches.
	Moderate (G2) (intense or widespread; intermittent; skin changes from scratching; limiting instrumental ADLs)	• Continue immunotherapy with intensified antipruritic therapy. • Administer oral antihistamines. • Consider GABA agonists (e.g. gabapentin, pregabalin). • Apply hgh-potency topical steroids to affected areas. • Arrange dermatology consultation.
	Severe (G3) (intense or widespread; constant; limiting self-care or sleep)	• Withhold immunotherapy. • Administer oral antihistamines. • Administer prednisone/methylprednisolone 0.5–1 mg/kg/day. • Arrange dermatology consultation. • Consider GABA agonists, aprepitant, omalizumab for refractory cases.
Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis	Urgent dermatology consultation and/or consider skin biopsy	• Permanently discontinue immunotherapy and inpatient urgent care. • Administer prednisone/methylprednisolone 1–2 mg/kg/day. • Consider IVIG (1 g/kg/day for 3–4 days). • Arrange urgent dermatology, ophthalmology, and urology consultations.

(continued)

Table 3. Management of Immune-Related Adverse Events *(continued)*

Gastrointestinal Adverse Events			
Diarrhea Colitis	Mild (G1) (<4 BMs above baseline per day; no colitis symptoms)		• Consider withholding immunotherapy. • Administer loperamide or diphenoxylate/atropine for 2–3 days (pursue infectious workup if no improvement in symptoms). • Check hydration and perform close monitoring. • If symptoms or PD, check lactoferrin; if positive, treat as Grade 2 (see below); if negative and no infection, add mesalamine or cholestyramine.
	Moderate (G2) (4–6 BMs above baseline per day; no colitis symptoms)		• Withhold immunotherapy. • Administer prednisone/methylprednisolone 1–2 mg/kg/day. • Consider infliximab or vedolizumab if no response in 2–3 days.
	Severe (G3-4) (>6 BMs above baseline per day; colitis symptoms interfering with ADLs, hospitalization, other serious complications*)		• Permanently discontinue agent. • Consider inpatient care. • Administer methylprednisolone IV 1–2 mg/kg/day. • If no response in 2 days, continue steroids and add infliximab or vedolizumab.
Endocrine Adverse Events			
Asymptomatic/ Subclinical Hypothyroidism	Monitor TSH, free T4 every 4–6 weeks	TSH between 4 to <10; normal free T4; asymptomatic	• Continue immunotherapy. • Continue to monitor TFTs.
		TSH >10; normal free T4	• Continue immunotherapy. • Consider levothyroxine.
		Normal or low TSH; low free T4	• Follow treatment for central hypothyroidism (see below).
Clinical, Primary Hypothyroidism	Monitor TSH, free T4 every 4–6 weeks		• Continue immunotherapy. • Consider endocrine consultation. • Exclude concomitant adrenal insufficiency (morning cortisol level). • Supplement thyroid hormone based on TSH level.
Central Hypothyroidism	Evaluate TFTs Estradiol testing in females and testosterone testing in males Consider MRI of pituitary		• Consider withholding immunotherapy until symptoms resolve. • Treat as hypophysitis.
Pulmonary Adverse Event			
Pneumonitis	Mild (G1) (asymptomatic; confined to one lobe of the lung or less than 25% of lung parenchyma)		• Consider withholding immunotherapy. • Reassess in 1–2 weeks (history, physical, and pulse oximetry). • Consider chest CT with contrast.
	Moderate (G2) (presence of new or worsening symptoms**)		• Withhold immunotherapy. • Consider pulmonary consultation. • Consider infectious disease workup, infectious evaluation, empiric antibiotics if infectious disease has not yet been fully excluded. • Consider bronchoscopy with BAL and CT chest with contrast. • Administer prednisone/methylprednisolone 1–2 mg/kg/day; if no improvement after 48–72 hours of corticosteroids, treat as Grade 3. • Monitor every 3–7 days (history, physical, and pulse oximetry).
	Severe (G3-4) (G3 = symptoms involve all lung lobes and more than 50% of lung parenchyma; limiting self-care ADLs; oxygen indicated. G4 = life-threatening respiratory compromise)		• Permanently discontinue immunotherapy. • Give inpatient care. • Arrange pulmonary and infectious disease consultation. • Perform infectious disease workup and give empiric antibiotics if infectious disease has not yet been fully excluded. • Administer methylprednisolone IV 1–2 mg/kg/day; reassess in 48 hours. • If no improvement within 48 hours consider adding the following: infliximab 5 mg/kg IV, IVIG, mycophenolate mofetil 1–1.5 g BID.

Cardiovascular Adverse Event		
Myocarditis	Severe (G3) (arrhythmia, significant ECHO findings without hypotension, cardiac markers > upper limit of normal) or Life-threatening (G4) (arrhythmia, hemodynamic instability, cardiac markers > 3 times upper limit of normal)	• Arrange immediate cardiac consultation. • Perform ICU-level monitoring. • Transient pacemaker in patients with arrhythmia • Permanently discontinue immunotherapy. • Consider methylprednisolone pulse dosing 1,000 mg/day for 3–5 days; treat until cardiac function returns to baseline, then taper over 4–6 weeks. • If no improvement within 24 hours on steroids, consider adding other immunosuppressive agents: antithymocyte globulin, infliximab, IVIG, mycophenolate.

*Ischemic bowel perforation, toxic megacolon

**Shortness of breath, cough, chest pain, fever, and increasing oxygen requirement

Note. ADLs = activities of daily living; BAL = bronchoalveolar lavage; BID = twice daily; BMs = bowel movements; BSA = body surface area; CT = computed tomography; ECHO = echocardiogram; G = grade; GABA = gamma-aminobutyric acid; ICU = intensive care unit; IV = intravenous; IVIG = immune globulin; kg = kilogram; mg = milligram; MRI = magnetic resonance imaging; PD = progressive disease; TFTs = thyroid function tests; TSH = thyroid stimulating hormone.

Conclusion

The role of PD-1/PD-L1 inhibitors in the treatment of various cancers is rapidly expanding, and it is important for clinicians and patients to understand the unique toxicities associated with these therapies. Prompt symptom reporting and toxicity identification is imperative for appropriate toxicity management. To date, three clinical guidelines discuss the differences and similarities in the management of ICI toxicities: those of the National Comprehensive Cancer Network, the American Society of Clinical Oncology, and the European Society of Medical Oncology.[2,9,15] Understanding the available guidelines and resources is an important step for institutions as they develop and practice site-specific protocols for the management of irAEs.

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Establishing a New Practice Site in the Ambulatory Setting

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The role of the oncology pharmacist on the care team continues to expand, and this growth is especially apparent in the ambulatory setting. Our training, skills, and pharmacotherapy knowledge place us in a unique position to care for this patient population, and other healthcare providers and administrators are seeing the potential for pharmacists to improve the quality of care for patients with cancer. Given this expanding role in the ambulatory setting, many current postgraduate year-2 (PGY-2) oncology residents find themselves applying and interviewing for positions that involve establishing a new practice site. But how does a brand-new graduate go about carrying out this task?

After completing my PGY-2 oncology residency at University of Wisconsin Health in Madison, WI, I took a position at Augusta University (AU) Health in Augusta, GA, in the ambulatory oncology setting. My mission: (1) to establish a new practice site in the solid tumor clinics that would enhance patient care and be successful enough to justify more positions in other oncology clinics and (2) to create a new learning experience for PGY-2 oncology residents, PGY-1 pharmacy residents, and advanced pharmacy practice experience students. Sounds simple enough, right? Having just completed my PGY-2 at an institution that launched new pharmacist positions in the oncology clinic at the beginning of my residency year, I had seen some of the challenges my preceptors faced as well as the projects that had been successful and well received. I had also once been a student and resident, so I felt confident that I could develop learning experiences while also establishing myself as an independent practitioner. I thought that I had set realistic expectations for myself and that I could reasonably achieve my goals during my first year at AU Health. Reflecting on my first year out of residency and the subsequent experiences I have had in my position has shown me that my expectations were not as realistic as I had hoped. I want to share what worked well for me, what was not successful, and what I recommend to anyone creating a new practice site.

"Pharmacists feel a significant amount of pressure to make interventions and justify their position, but it is okay to take time to create and learn the system, modify workflows, and establish boundaries."

First, the Dos

Do learn about the pharmacy department and oncology pharmacy service line.

Your initial onboarding is a key step in being successful in your clinic. This is your chance to see the priorities of the institution and pharmacy department in action. It is also an opportunity to see what initiatives other pharmacists are working on and what they struggle with in carrying out their daily duties. How do your goals for your position help the department? What can you do for your pharmacy team members? After completing a PGY-2 residency in oncology, you will be very familiar with the challenges involved in transitions of care. What initiatives are the inpatient oncology pharmacists working on? Can your role in the clinic help them be more successful in their jobs, and vice versa? The answer is yes, and when you are observing the inpatient practice site during your orientation, you will start to see how you can enhance their practice from the clinic.

Make sure your initial orientation to your position includes the opportunity to shadow pharmacists in other service lines. Even if the clinic position is new for oncology, the institution may have pharmacists in other clinics, such as those for internal medicine or infectious diseases. If this is the case, ask that your orientation schedule includes time in those clinics. How are those pharmacists integrated into the healthcare team? What clinical services do they provide? What challenges do they face in their clinics? Although the disease states are different, I have found that many of my ambulatory pharmacist colleagues face the same issues I do, and they can be great sounding boards for new ideas.

Finally, spend time in your infusion pharmacy to understand the operational opportunities in the cancer center. How can you improve the safety and efficiency of the production process? What challenges do the infusion pharmacy staff members face? Having a pharmacist in the ambulatory clinics will improve the communication between the infusion pharmacy and the providers, and improvements in this area will enhance patient care.

Do learn about your clinic.

When you are establishing a new *pharmacy* practice site, it is important to remember that the *clinical* practice site was likely already in existence. It has been successful enough to still be in operation and to expand services to include its own clinical pharmacist! One of the best pieces of advice I can give is to begin by listening and observing. You will be eager to provide several services: among them, patient education, supportive care management, cancer therapy optimization, and therapeutic drug monitoring. Make a list of services you think a pharmacist should be providing in clinic. Are these services being offered? Most likely, the answer is yes. Who is currently performing these duties? For example, in my practice site, the nurse navigators were responsible for patient education on new regimens. I wanted to learn the following from them:

- How do you fit patient education into your workflow?
- What resources do you use and provide to patients?
- How do you document that education has been conducted?

Asking about their process taught me that, although they loved speaking with patients about their treatment plans, they had to balance that task with many other duties, such as receiving referrals for new patients and triaging calls from existing patients. Having this information, I realized that offering to help educate patients on medications meant I was doing something I was passionate about and that patients would benefit from, while also helping with the overall workflow of the clinic. Make it a collaborative decision and seek out their ideas on how a pharmacist can improve patient care.

Do find a mentor.
As a new graduate from residency, you are going to have a wealth of knowledge and experiences to call upon during difficult times in your position, but you (or anyone, for that matter) cannot know everything. Having someone who either practices in the same area you do or understands the challenges you are facing will be invaluable during your transition to becoming an independent practitioner. Seek out advice from other pharmacists and stay in touch with your preceptors from residency! This is something I wish I had recognized earlier in my career.

Do delegate, and say no if you need to.
This is a lesson I learned the hard way—you cannot do everything on your own. In addition, you do not have to take on every project offered to you. In my experience, many people were excited to have a pharmacist in their clinics and wanted to involve me as much as possible, but it is okay to tell someone you are not able to participate in a project if you truly feel you will not be able to dedicate the effort needed for it to be successful. Maybe you are not the right person for the project. Colleagues would much prefer that you be honest than overcommit and underdeliver. The transition from residency is tough, and it takes practice learning to say "no" when you want to help. Lean on your mentors and supervisor in these instances—they can help you navigate the process of establishing boundaries and prioritizing.

Now, the Don'ts

Don't set unrealistic timelines.
You will have just completed residency, where everything needs to be achieved in 1–2 years. This is not the case in your first job as an independent practitioner, especially if it is a new practice site. It takes time to develop your job, and changes will be small at first. Pharmacists feel a significant amount of pressure to make interventions and justify their position, but it is okay to take time to create and learn the system, modify workflows, and establish boundaries. A strong foundation in these will help you be a more effective and efficient pharmacist.

Don't take on learners too early.
I am a strong advocate for having protected time in your practice before taking on learners. You are still doing a considerable amount of learning yourself—about your institution, clinic, and the disease state(s) in which you are practicing. One thing we all love about oncology is the fast pace at which it changes, but this is also a challenge. It is difficult to teach and figure out how to integrate learners of all levels into your workflow when that workflow is not yet established. Ask when you will be expected to precept students and residents and be honest about your ability to effectively precept when that time comes.

Don't get burned out.
This advice may seem like a given, but new pharmacy residency graduates are at particularly high risk of burnout, regardless of the position they take. Your institution likely has resources, such as employee assistance programs, to help with this transition. Be upfront and honest with your supervisor and your teammates if you are struggling or sense that you are getting burned out.

Establishing a new practice site can be daunting and will inevitably involve challenges you cannot expect. Making the time to learn the current practice and workflow will allow you to integrate yourself more successfully into a clinic. It is important to establish boundaries and be honest with your supervisor, your colleagues, and, most important, yourself about what you need to be successful. ●●

Actionable Mutations in Solid Tumors

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It has long been understood that cancer develops due to an accumulation of genomic mutations in healthy cells. Alterations in oncogenes and tumor suppressor proteins, like p53, lead to dysregulation of cell cycle control resulting in transformation of normal cells to a cancer phenotype. The identification of mutations that drive the onset of cancer has led not only to a better understanding of cancer physiology but also to significant advancements in the development of drugs that target specific mutations in a tumor. *Precision oncology* is the term used to describe personalized cancer treatment based on the genetic changes in an individual patient's tumor. The utility of precision oncology in clinical practice has been made possible by advances in technology such as next-generation sequencing (NGS), along with intensive research efforts made possible by funding from programs like the $200 million Precision Medicine Initiative announced by President Barack Obama in 2015.[1] This article summarizes the principles of precision oncology and provides guidance to pharmacists on using genomic information in clinical practice.

"Because genomic-based decision making has become a routine part of oncology clinical practice, it is important for pharmacists to know where to find up-to-date information on the clinical actionability of a genomic variant."

Types of Mutations and Clinical Significance

It is important to understand the type and function of a mutation and its biological significance when using genomic analyses to design a patient treatment plan. Tumor cells have both inherited and somatic variants in their genome. Hereditary mutations, referred to as germline mutations, are gene changes in the germ cells (sperm or oocyte) that are passed to every cell in the offspring.[2] Many germline mutations in cancer are known, such as *BRCA1/2*, *TP53*, *ATM,* and *PALB2*, and they are most often associated with increased cancer susceptibility and more aggressive cancer phenotypes.[3]

Alternatively, somatic mutations are not present in germ cells and develop spontaneously in an individual's DNA over time. These acquired changes in human oncogenes are known to play a role in the development of cancer. Moreover, the number of somatic mutations in the tumor can change over time, potentially leading to treatment resistance and disease progression.

Understanding common terms used to describe the clinical significance of cancer mutations is also essential. An *actionable mutation* is defined as a genetic aberration in a patient's tumor that is targetable with an available anticancer treatment or is the target of novel therapeutics in development. A *driver mutation* is a mutation that may not be targetable with a specific treatment but is known to play a role in cancer development, resistance, or progression. *Passenger mutations* are nonpathogenic and are thought to have little or no biological significance to cancer biology but are linked to driver mutations on the same gene.[2-4] Thus, given the diversity of genetic aberrations in cancer, it is essential to understand the clinical relevance of each type of mutation in solid tumors.

Further, some genomic aberrations are predictive of treatment response, prognostic of outcomes, or both, depending on the tumor type. For example, mutations in the *RAS* genes *KRAS* and *NRAS* predict a poor response to epidermal growth factor receptor (EGFR) therapies, like cetuximab and panitumumab, in colorectal cancer. In non-small-cell lung cancer (NSCLC) tumors, the presence of a *KRAS* mutation predicts a poor response to EGFR tyrosine kinase inhibitors, like erlotinib. Prognostically, NSCLC tumors with mutant *KRAS* demonstrate poor survival compared with tumors having wild-type *KRAS*.[5] To date, no therapies specifically targeting Ras proteins have been approved by the U.S. Food and Drug Administration (FDA), so the clinical significance of *KRAS* in solid tumors remains as a predictor of treatment responses and a prognostic marker of clinical outcomes.

The presence of a germline *BRCA1/2* mutation is known to increase the risk of developing breast and ovarian cancer. More so, it is well known that breast cancer patients with *BRCA1/2* mutations have an overall worse prognosis compared to patients with sporadic breast cancer, and the presence of a *BRCA1* mutation is associated with triple negative breast cancer, which has a worse prognosis than hormone receptor or human epidermal growth factor receptor 2 (HER2)–positive disease.[3] Likewise, the pivotal study by Antoniou and colleagues analyzed more than 8,000 cases of breast and ovarian cancer and showed that the cumulative risk of ovarian cancer development was 39% in patients with *BRCA1* and 11% in patients with and *BRCA2*.[6] Interestingly, the presence of *BRCA1/2* mutations in ovarian cancer has been shown to prolong survival and confer sensitivity to platinum chemotherapy.[7]

Next-Generation Sequencing

The use of precision oncology to guide treatment decisions has increased because of recent advancements in NGS. NGS is a genomic profiling technology based on high-throughput DNA and RNA sequencing platforms that analyze specific gene panels for molecular changes and actionable driver mutations.[8] NGS technology can be used to analyze DNA or RNA from tumor tissue or circulating

tumor DNA (ctDNA) from the blood, also called a liquid biopsy. ctDNA is composed of small fragments of tumor DNA shed by the tumor into the blood when cells undergo apoptosis.[9] Studies have shown that genomic changes detected using NGS from liquid biopsy have a strong correlation to NGS testing from tumor tissue. A liquid biopsy can be used in cases where tumor tissue is not available, cannot be obtained, or is of poor quality. Two FDA-approved liquid biopsy assays are available, Guardant360 and FoundationACT, which currently analyze more than 70 genes that are relevant in solid tumors.[10,11] For FDA-approved targeted therapies, companion NGS tests, both tissue- and liquid-based, are used to detect the presence of the associated mutation.

Taking Action on an Actionable Mutation

Essential questions need to be addressed when one is analyzing NGS reports to guide treatment decisions in solid tumors. Is a mutation benign or pathogenic (i.e., is it a driver mutation)? Is it prognostic of outcomes or predictive of response to certain therapies? Is the mutation a variant of known significance? Is there an approved targeted therapy?

Moreover, it is as important to identify mutations that do not convey response to targeted agents as it is to identify ones that correlate with efficacy. For example, fusions in neurotrophic-tropomyosin receptor kinase (*NTRK*) genes are known drivers of oncogenesis, and various solid tumors harboring

Table 1. Selected Clinically Actionable Mutations and Associated Targeted Therapies [19-27]

Gene	Alteration	Tumor Type	Drugs
ALK	Fusion	NSCLC	alectinib, brigatinib, ceritinib, crizotinib, lorlatinib
BRAF	V600E	Melanoma	dabrafenib, vemurafenib
		NSCLC	dabrafenib + trametinib
		Colorectal	dabrafenib + trametinib + (cetuximab or panitumumab) encorafenib + (cetuximab or panitumumab) +/- binimetinib
	V600E, V600K	Melanoma	dabrafenib + trametinib; cobimetinib + vemurafenib; binimetinib + encorafenib
BRCA1/2	Mutations	Ovarian	olaparib, rucaparib, niraparib
		Breast	olaparib, talazoparib
		Pancreatic	olaparib
EGFR	Mutation	NSCLC	erlotinib, gefitinib, afatinib, osimertinib, dacomitinib
EGFR T790M			osimertinib
FGFR2/3	Fusion	Bladder	erdafitinib
KIT	Mutation	GIST	imatinib
		Melanoma	imatinib
MET–Exon 14	Mutation	NSCLC	crizotinib
NTRK	Fusions	Solid Tumors	entrectinib, larotrectinib
dMMR/MSI-H		Solid Tumors	pembrolizumab
		Colorectal	pembrolizumab; nivolumab; nivolumab + ipilimumab
PDGFRA	Mutation	GIST	imatinib
PDGFRA D842V			dasatinib, avapritinib
PIK3CA	Mutation	Breast	alpelisib + fulvestrant
ROS1	Fusion	NSCLC	crizotinib, entrectinib, ceritinib, lorlatinib

Note. dMMR = deficient DNA mismatch repair; GIST = gastrointestinal stromal tumor ; MSI-H = microsatellite instability-high; NSCLC = non-small-cell lung cancer.

NTRK fusions have been shown to have response rates of up to 79% to *NTRK* inhibitors, like larotrectinib. On the other hand, point mutations in *NTRK* are associated with a lack of response to *NTRK* inhibitors. Therefore, an *NTKR* inhibitor should be used only in a patient with an *NTRK* fusion-positive tumor.[12]

For FDA-approved targeted therapies, the relevance of a specific mutation and the efficacy of the associated treatment have been validated in clinical trials. **Table 1** summarizes known actionable mutations and their matched anticancer therapies. Although most targeted agents are approved for a specific tumor type harboring a mutation, clinical guidelines may recommend that these agents be used off-label in a different tumor type with the same mutation. Further, when a mutation of known significance is identified but no approved therapy exists, a clinical trial should be considered.

Last, it is important to consider the appropriate time to reevaluate NGS throughout the course of treatment in patients with advanced disease. The frequency of existing somatic mutations can fluctuate with a treatment response, and new somatic mutations may develop with disease progression; therefore, NGS may be most beneficial at the time of treatment failure or progression.

Microsatellite Instability and Deficient DNA Mismatch Repair

Microsatellite instability and deficient DNA mismatch repair (dMMR) can be conceptually hard to understand. Microsatellites are known short sequences of DNA with repeated nucleotides (e.g., CTGTGTGTGTGCA) that are inherited in all cells throughout the body. When a tumor cell contains a microsatellite with a different sequence compared to the same microsatellite in a normal cell, this is called *microsatellite instability*, or MSI. The frequency of abnormal microsatellites in a tumor determines whether it is characterized by an MSI-Low or MSI-High phenotype.

Tumors with dMMR are not able to repair DNA damage because of germline mutations in mismatch repair genes, allowing cancer cells to proliferate with aberrant DNA. Microsatellites are susceptible to errors during DNA replication because of the repetitive nucleotides, but without a functional DNA repair system, these errors are not repaired in proliferating tumor cells. MSI status is therefore a surrogate marker for dMMR in solid tumors.[13]

MSI-H/dMMR status may be a useful biomarker for identifying a patient's response to anti-programmed-death 1 (PD-1) and anti-programmed-death-ligand 1 (PD-L1) immunotherapies. Cancers that are considered MSI-H/dMMR harbor thousands of mutations that code for neoantigens that potentially increase the immunogenicity of the tumor and upregulate immune checkpoint blockade proteins. Hence, pembrolizumab is approved for tumors with MSI-H or dMMR regardless of the tumor's origin.[14]

Likewise, in tumors with *BRCA1/2* mutations, the intrinsic DNA repair processes are often dysregulated. Poly (ADP-ribose) polymerase (PARP) is an enzyme that plays a critical role in DNA repair in *BRCA1/2* deficient solid tumors. Currently, four PARP inhibitors have been approved for use in ovarian and breast cancers with *BRCA1/2* mutations, and recent clinical trials have demonstrated efficacy of these agents in treating prostate and pancreatic cancers with *BRCA1/2* deficiency.[15,16]

The Role of the Pharmacist in Precision Oncology

Because genomic-based decision making has become a routine part of oncology clinical practice, it is important for pharmacists to know where to find up-to-date information on the clinical significance and actionability of a genomic variant. OncoKB and the Catalogue of Somatic Mutations in Cancer (COSMIC) are comprehensive and curated databases that provide evidence-based information about the clinical significance of somatic mutations in cancer. **Table 2** provides a list of resources for interpreting genomic

Table 2. Online Resources for Assessing the Clinical Significance of Genomic Variants in Cancer [28-29]

Online Database	Web Address	Utility
Cancer Driver Log (CanDL)	https://candl.osu.edu	Provides molecular pathologists and laboratory specialists with a curated database of actionable mutations
Catalogue of Somatic Mutations in Cancer (COSMIC)	https://cancer.sanger.ac.uk/cosmic	Provides an in-depth description of somatic gene variants in cancer and links to primary literature
ClinVar	https://www.ncbi.nlm.nih.gov/clinvar	Provides guidance on the clinical significance of variations in the human genome using standardized terms; is not cancer specific
My Cancer Genome	https://www.mycancergenome.org	Provides information on gene alterations involved in cancer growth and resistance and matches mutations to targeted therapies and clinical trials
OncoKB	https://www.oncokb.org	Determines actionability of somatic mutations and provides information on treatment options and clinical trial options
Personalized Cancer Therapy: Knowledge Base for Precision Oncology	https://pct.mdanderson.org	Provides a tool for clinicians and patients to access treatment options for known genomic alterations

variants in cancer. It is recommended that each patient's genomic report undergo a comprehensive review under the guidance of a molecular tumor board (MTB) if one exists at the institution. If an MTB does not exist, it is recommended that all NGS findings be presented at an interdisciplinary tumor board when determining the best treatment approach for the patient.[17]

Walko and colleagues published a report in 2016 detailing three pharmacist-led precision oncology models at different institutions.[18] Their report showed the different roles an oncology pharmacist can play in the implementation of precision medicine in clinical practice, including but not limited to participation in an MTB, selection of therapy, and procurement of off-label medications. Their report also recommends the development of continuing education programs for oncology pharmacists and the incorporation of precision oncology modules into residency programs and school of pharmacy curricula. As the genomic-guided approach to cancer care expands in practice, it will be imperative that practicing pharmacists have a strong understanding of precision oncology principles and access to appropriate tools and educational resources for confident decision making. ●●

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When the Continuum of Cancer Care Hits Close to Home

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A young adult male presents with sudden-onset symptoms of constipation, abdominal pain, cramping, abdominal distention, and decreased appetite. What is the diagnosis? Gastroesophageal reflux disease, severe constipation, infectious colitis, and idiopathic gastroparesis. These were all diagnoses my 30-year-old husband, Tom, received over the span of a few months while we visited three emergency departments. He received more tests than I can count, and the final diagnosis was a mild, early case of Crohn's disease. After that, we spent much of our time researching this new diagnosis and meeting with physicians to discuss management options. We had an overwhelming amount of information to process, but we were thankful to finally have an explanation for his symptoms. We were also thankful that the diagnosis didn't include one word—*cancer*, the word we were most afraid of.

Four months later, Tom's symptoms began to return. We attributed this to a change in his medications and what we thought was just life with Crohn's disease. How could it be anything else? He was young and healthy, he had no family medical history that caused us concern, and we had seen so many doctors and run so many tests. His symptoms progressively worsened to the point that he was febrile with a pain so intense he was unable to stand up straight. He was a teacher, so he had probably just caught the stomach bug that was going around school, and it was nothing to worry about, we thought. We made our fourth visit to the emergency room that night. A new CT scan showed an 18-by 22-centimeter mass in his abdomen. Where did this come from? How long had it been there? How was that possible? *We had done everything right*.

Tom was admitted to the surgical service, and we gave an extensive history from the onset of his symptoms and including the diagnosis of Crohn's disease. We were told that the mass could also represent an infection stemming from his recent colonoscopies and might be just an abscess. We were thinking about only one word, though—*cancer*—but that word was still not being discussed, at least not with us. The team started antibiotics for a possible abscess while we waited for the scheduling of a biopsy. As a postgraduate year-1 pharmacy resident interested in becoming an oncology pharmacist, I knew that biopsy was the gold standard for diagnosis of the word that we feared.

We waited…and waited…and waited, until about 5 days later, when Tom was finally taken to interventional radiology for a biopsy. When he came out of the procedure, he told us that the radiologist had asked what had happened because the appearance of the mass had changed significantly. The next few minutes of that day are very much a blur. I remember being excited—maybe it was just an abscess! That excitement was quickly stifled when the surgeon rushed in to say that my husband's intestines had perforated during the wait for the biopsy, which explained why the imaging looked different. The excitement turned to panic, which amplified as we rushed to the operating room. Tom underwent an exploratory laparotomy, leaving him with an ileostomy, a surgical drain, and a ticket to the intensive care unit. We got the biopsy but not in the way it was originally planned.

About a week after surgery, we started hearing the dreaded C-word. Tom was finally diagnosed with cancer, what we had feared all along. Because this is not an article about treatment decisions, I will refrain from using details related to his specific diagnosis. However, I will say that his diagnosis was not straightforward. He received his chemotherapy treatment as an inpatient, and despite being very disheartened at the thought of spending so much time in the hospital, he tolerated the treatment with minimal issues. We even started to attempt to go back to our normal lives, what we craved the most.

> **"Sometimes you do everything right: you seek medical care for symptoms, you receive the appropriate tests, you are being closely followed by physicians you trust—and *it is not enough*."**

Tom's scans throughout treatment looked great and showed significant disease response. However, about 1 week before the appointment to review his final scan, he started showing clinical signs of disease progression. After yet another trip to the emergency room and a long discussion between the surgeon and the oncologist to determine whether the scan resembled postsurgical changes or disease burden, it was confirmed that Tom had progressive disease. His next-best treatment option was to participate in a clinical trial.

I do not know the behind-the-scenes proceedings of finding a clinical trial for Tom, but I do know about this process from my own clinical experience. It is not clearly established who owns the role of finding a clinical trial. The patient? The physician? An advocacy organization? A friend's friend who heard that this place has a new drug they are studying? If the patient is lucky enough to find a clinical trial, getting the trial institution the correct information and managing a smooth transition is an entirely separate issue. Although significant travel was required, we were so thankful when we learned that there was an available trial for Tom. We showed up to our appointments, signed the consent forms, and did all the things we were instructed to do, but it still wasn't enough.

On our second day of trial appointments, we received word in a phone call that Tom's exact pathology did not match the inclusion criteria, and he could no longer be enrolled. After going to multiple trial appointments and traveling all this way, he was no longer a

candidate. The difficulty of clinical trials goes far beyond the issue of finding the trial. It includes strict inclusion and exclusion criteria and protocol requirements, and unless you are lucky enough to have a local trial available, participation requires extensive patient travel and the need for sharing of records between institutions. This highlights an important issue for oncology patients: effective communication and record sharing. Cancer patients and their loved ones are already struggling to process the information they are receiving about their diagnosis and prognosis and to manage their day-to-day lives. Unfortunately, they also serve as their own medical record for disease-related information. Lack of communication and issues related to transferring medical records between institutions should not be a barrier to receiving timely cancer care, but they unfortunately are things that patients, including Tom, deal with routinely.

Because of his ineligibility for the clinical trial, we were now stuck—in a new city, with no promise of hope from a trial, but still with a rapidly progressing disease. We stayed and got a second opinion that did not differ much from the first. We tried a few more rounds of chemotherapy and attempted to get access to off-label medications without success. In my eyes, there were not many things left to try. In the physician's eyes, Tom was young and had plenty of options; this was a perspective I came to see as a common barrier to care.

Sometimes in the healthcare setting we avoid difficult conversations, which ultimately can prevent patients from receiving the necessary information to make end-of-life decisions. Seeing my husband told that he had plenty of options when I knew that he didn't was more than I could handle, because I knew that this burden would now fall on me, his wife. Just as the conversations about the initial diagnosis and treatment are important, so are the conversations about treatment goals and end-of-life wishes. Although I do not think it is within my scope as a pharmacist to have these conversations, I can serve as a reminder of their importance to the physicians I work with each day. I will carry this lesson with me as an oncology pharmacist forever.

Shortly after returning home and following an appropriate discussion about his goals, Tom transitioned to hospice care. He passed away about 6 weeks later, only 9 months after his initial diagnosis. Those 9 months spent as a caregiver, along with my experience as an oncology pharmacist, have illustrated a few of the barriers and roadblocks that cancer patients may encounter at the time of their diagnosis and throughout their treatment.

The first barrier is related to common frustrations with the healthcare system and the difficulty of scheduling appointments with specialists. For us this meant being told about an 18-by-22-centimeter mass while we were standing in the middle of the emergency room because there was not a room available. It meant our having to repeat Tom's medical history, including all his tests and emergency room visits, to multiple teams of physicians and hoping we remembered the important details. It meant Tom's waiting in the hospital for a biopsy and subsequently developing a perforation that resulted in emergency surgery. All of these are examples from my own experience, but we see similar situations so frequently in our healthcare systems. For patients and loved ones dealing with the thought of the C-word, nothing will ever happen in a timely enough manner—but sometimes delays can lead to more than just worsening anxiety.

The second barrier is the common assumption that because a patient is young or healthy, the diagnosis isn't cancer. Looking back, I can see the avoidance of the word and the diagnosis. From the medical perspective, the diagnosis may not have been deemed worth discussing until it had been confirmed, but it was always crossing our minds.

The third barrier, though uncontrollable, is related to cancer itself. Sometimes you do everything right: you seek medical care for symptoms, you receive the appropriate tests, you are being closely followed by physicians you trust—and *it is not enough*. The cancer is too smart, too sneaky. That was the case with Tom.

In Tom's story we had many things to be thankful for: we lived in close proximity to a cancer center, he had a family member with oncology knowledge, he had insurance coverage, we speak English as our first language, and the list could go on. However, we also ran into some of the most common and formidable barriers that arise in cancer care.

The purpose of this article is not to complain about Tom's care or our circumstances, but to provide—from the viewpoint of both a caregiver and an oncology pharmacist—even the smallest insight into the issues that so many patients diagnosed with cancer encounter. It is my hope that, by sharing Tom's story, I can raise awareness, spark empathy, and increase understanding of the day-to-day challenges that many cancer patients and their loved ones face. ●●

Disclaimer: The account in this article is based on my memory of events as they occurred. It is meant in no way to criticize or discount the wonderful care my husband received from his healthcare team but to highlight the general need for improvement in areas surrounding cancer care.

Changes in Chemotherapy Treatment Plans Made as a Result of the Etoposide Shortage

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Drug shortages have been unrelenting during the past 10 years, with 1,950 new drug shortages occurring from 2008 to 2018. Chemotherapy is consistently among the top five most common drug classes on shortage.[1] Chemotherapy drug shortages are of particular concern because the number of comparable therapeutic alternatives are limited. Specific chemotherapy drugs that have had shortages in the past 10 years include fluorouracil, cytarabine, and liposomal doxorubicin.[2,3]

In 2018, a national shortage of etoposide injection occurred, requiring conservation strategies to be employed at Pennsylvania Hospital in Philadelphia, PA. Management of this drug shortage required a coordinated effort among prescribers, pharmacists, and drug suppliers. Because of the severity of the shortage, mitigation plans were also discussed across the health system, and a local strategy was approved through the hospital's Ethics Committee and Pharmacy and Therapeutics Committee. The decision was made to prioritize etoposide supply for patients receiving treatment with curative intent. However, treatment was not withheld from other patients if supply was available.

Difficult decisions like these in response to drug shortages have the potential to affect patient care. Most of the literature on oncology drug shortages consists of provider surveys that report increased medication errors, increased costs, and the need for modification of therapy as a result of drug shortages.[2,3] Unfortunately, empirical data on the consequences of oncology drug shortages are sparse.

"Chemotherapy drug shortages are of particular concern because the number of comparable therapeutic alternatives are limited."

A 2018 study aimed to describe the clinical impact of the etoposide injection shortage. This single-center retrospective study consisted of chart review for patients treated between January and August 2018.[4] Patients were included if they had been prescribed an etoposide-containing chemotherapy regimen. The study timeframe was selected because the etoposide shortage at the institution was the most critical during this time. The primary aim of the study was to determine the percentage of patients who required a change in therapy during the shortage. Change in therapy was defined as (1) use of an alternative therapy other than etoposide injection, which included switching the patient to oral etoposide or Etopophos injection, or (2) omission of therapy, where the patient did not receive any formulation of etoposide in at least one treatment cycle. Secondary endpoints were assessed between two subgroups: patients who received etoposide injection and patients who received alternative etoposide formulations (oral etoposide or Etopophos injection). Secondary endpoints included incidence of adverse drug events, medication errors, delays of 3 days or more for scheduled chemotherapy, progression of disease, and associated drug costs.

A total of 22 patients were included in the study. The mean age was 60 years, and the most common types of cancer were lung cancer (n = 10), sarcoma (n = 6), and non-Hodgkin lymphoma (n = 4). For the primary endpoint, seven (32%) patients required a change in treatment during the etoposide injection shortage. Six (27%) patients received an alternative formulation of etoposide, and etoposide was withheld for one patient.

No significant difference was seen in secondary endpoints between patients who received etoposide and those who received alternative etoposide formulations. This included no difference in incidence of side effects (100% vs. 100%, p = 1.00), medication errors (0% vs. 0%, p = 1.00), treatment delays (7% vs. 0%, p = 1.00), or disease progression (53% vs. 33%, p = 0.64). The average wholesale acquisition cost for etoposide per cycle per patient was considerably higher for patients who received alternative formulations of etoposide ($58 USD for standard etoposide vs. $806 USD for alternative formulations).

To our knowledge, this was the first study to characterize the clinical impact of the etoposide injection shortage. At this institution, etoposide supply was prioritized and allocated on a cycle-by-cycle basis for patients. Other strategies include allocating the drug on a dose-by-dose basis or reserving the amount required to complete a full treatment course. In this study, approximately one-third of patients required a change in their chemotherapy treatment plan because of the shortage.

In an earlier study Becker and colleagues reported that 9.8% of patients required alternative therapy because of an oncology drug shortage. They also reported decreased use of drugs on shortage compared to historical use, which may indicate that a higher percentage of patients were actually affected.[5] In this study, one patient had treatment with etoposide omitted because of a delay in insurance approval for oral etoposide, and another patient had a delay in treatment. This second patient was scheduled to receive an autologous stem cell transplant with an etoposide-based conditioning regimen, but the transplant was delayed because of an inadequate supply of etoposide. Both scenarios reveal the possibility that consequences of oncology drug shortages are underreported. This earlier study by Becker and colleagues had notable limitations, including the small sample size from a single institution. Furthermore, the study was unable to capture patients who had never been prescribed etoposide and instead were initiated on alternative regimens because the prescriber had knowledge of the etoposide shortage.[5]

It seems that no end to chemotherapy drug shortages is in sight. As part of an attempt to design a plan to eradicate drug shortages, the U.S. Food and Drug Administration Drug Shortages Task Force urges "quantification of the harms of drug shortages, particularly those that lead to worsened health outcomes for patients and increased cost for health care providers."[6] Further research to characterize the impact that oncology drug shortages have on patients is needed as an impetus for change. ●●

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Updates in HER2-Targeted Therapy for the Treatment of Metastatic Breast Cancer

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Breast cancer is the most commonly diagnosed malignancy and the second leading cause of cancer-related mortality in women.[1] Approximately 15%–20% of breast cancers overexpress the human epidermal growth factor receptor 2 (HER2) protein.[2] Compared with other subtypes of breast cancer, hormone receptor–negative, HER2-positive disease has a greater likelihood of metastasizing to the brain.[3-5] In the absence of systemic HER2-targeted therapy, HER2-positive breast cancer (HER2BC) has historically been associated with more aggressive disease and a worse prognosis. For patients with unresectable or metastatic HER2BC, the combination of docetaxel, pertuzumab, and trastuzumab has been established as the preferred initial therapy on the basis of progression-free survival (PFS) and overall survival (OS) benefits demonstrated in the phase 3 CLEOPATRA study.[6,7] In the phase 3 EMILIA trial, ado-trastuzumab emtansine showed an improvement in PFS and OS in the second-line setting following receipt of trastuzumab and a taxane.[8] Although these therapies have significantly extended survival outcomes for patients with metastatic HER-2BC, disease progression continues to remain inevitable in most cases. Subsequent treatment options have primarily included trastuzumab plus chemotherapy, or capecitabine plus lapatinib or trastuzumab, with no previously established standard of care in the third-line setting. This article summarizes recent therapy updates and emerging treatments for metastatic HER2BC.

"The recent advances in the treatment of HER2-positive metastatic breast cancer provide promising options for many patients who have exhausted first- and second-line therapies for this breast cancer subtype."

New Approvals

Fam-trastuzumab deruxtecan-nxki (Enhertu) is a new addition to the armamentarium for the treatment of metastatic HER2BC. The U.S. Food and Drug Administration (FDA) granted the drug accelerated approval on December 20, 2019, for patients with HER2-positive unresectable and/or metastatic breast cancer after at least two prior anti-HER2-based regimens in the metastatic setting. This antibody-drug conjugate (ADC), similar to ado-trastuzumab emtansine, consists of an HER2-directed antibody and cytotoxic drug joined by a cleavable linker. Fam-trastuzumab deruxtecan differs in several important ways from other currently available ADCs: notably, the inclusion of a potent topoisomerase I inhibitor as the cytotoxic drug, a higher drug-to-antibody ratio, and the ability of the cytotoxic portion to easily cross the cell membrane, which potentially allows for a more potent effect on nearby tumor cells regardless of target expression.[9]

The FDA approval of fam-trastuzumab deruxtecan was based on the results of the DESTINY-Breast01 trial.[9] This was an open-label multicenter single-arm phase 2 study of fam-trastuzumab deruxtecan in females with HER2-positive unresectable or metastatic breast cancer who had received previous treatment with trastuzumab and ado-trastuzumab emtansine. The efficacy analysis was based on 184 patients who received the recommended dose of 5.4 mg/kg. The majority of patients were heavily pretreated, receiving a median of six prior lines of therapy (range 2–27). Thirteen percent of patients enrolled had stable, treated brain metastases. The primary endpoint of overall response rate was 60.9% by independent central review, primarily driven by partial responses (54.9%). The median PFS was 16.4 months, and median duration of response was 14.8 months. This benefit was observed across all subgroups, including patients with brain metastases. The most common adverse effects that occurred in 20% or more of the study population were nausea, fatigue, vomiting, alopecia, constipation, decreased appetite, anemia, neutropenia, diarrhea, leukopenia, cough, and thrombocytopenia. Interstitial lung disease (ILD) developed in 13.6% of patients, of which the majority of cases were grade 1–2; however, four ILD-related deaths occurred during the study. The median time to onset was 4.1 months (range 1.2–8.3).[10]

The recommended dose of fam-trastuzumab deruxtecan is 5.4 mg/kg administered by intravenous infusion every 3 weeks until disease progression occurred or an unacceptable level of toxicity was reached. Dose interruption or reduction recommendations exist for neutropenia, febrile neutropenia, left ventricular dysfunction, and ILD/pneumonitis. Black-box warnings exist for embryo-fetal toxicity and ILD/pneumonitis; patients should therefore be closely monitored for signs and symptoms, including cough, dyspnea, fever, and other new or worsening respiratory symptoms. Prompt investigation with radiographic imaging, consultation with a pulmonologist, interruption of the drug, and possibly initiation of corticosteroids (based on grade) are recommended for suspected ILD. Similar to other HER2-targeting drugs, fam-trastuzumab deruxtecan may increase the risk of developing left ventricular dysfunction; however, only three cases of asymptomatic left ventricular ejection fraction (LVEF) decrease were reported in

DESTINY-Breast01.[9] LVEF should be assessed prior to initiation of fam-trastuzumab deruxtecan and at regular intervals during treatment as clinically indicated.[10]

The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology recommend fam-trastuzumab deruxtecan for metastatic HER2BC in accordance with FDA labeling.[11] Ongoing trials are focused on initiation of fam-trastuzumab deruxtecan earlier in the disease course (DESTINY-Breast02[12] and DESTINY-Breast03[13]) and on the potential role of this agent in patients with HER2 low-expressing breast cancer.[14]

Neratinib (Nerlynx) is an oral tyrosine kinase inhibitor (TKI) initially approved by the FDA for extended adjuvant treatment of early-stage HER2BC.[15] In the phase 3 NALA study, the combination of neratinib and capecitabine was compared to lapatinib and capecitabine in patients with HER2-positive metastatic breast cancer who had received at least two prior lines of therapy in the metastatic setting.[16] Patients were randomized 1:1 to 21-day cycles of either neratinib 240 mg orally daily continuously plus capecitabine 750 mg/m^2 orally twice daily on days 1 through 14 or lapatinib 1,250 mg orally daily continuously plus capecitabine 1,000 mg/m^2 twice daily on days 1 through 14. Though PFS was significantly improved in the neratinib arm (hazard ratio [HR], 0.76; 95% confidence interval [CI], 0.63–0.93; p = .006), OS benefit with neratinib did not reach statistical significance (HR, 0.88; 95% CI, 0.72–1.07; p = .2086). PFS and OS rates at 12 months with neratinib versus lapatinib were 28.8% versus 14.8% and 72.5% versus 66.7%, respectively.[16] Furthermore, the neratinib plus capecitabine combination delayed the time to intervention for symptomatic central nervous system disease (overall incidence, 22.8% vs. 29.2%; p = .043).

Although grade 3 diarrhea was more prevalent with neratinib than with lapatinib (24.4% vs. 12.5%), adverse events leading to treatment discontinuation were less common with neratinib (10.9% vs. 14.5%). On the basis of the NALA trial, the FDA approved the combination of neratinib plus capecitabine on February 24, 2020, for treatment of advanced or metastatic HER2BC after two or more prior anti-HER2-based regimens in the metastatic setting.[15] The combination was also added to the NCCN guidelines as an option among the other recommended regimens for HER2-positive metastatic breast cancer.[11]

Another exciting HER2-directed therapy to emerge recently is tucatinib, an oral TKI that selectively inhibits HER2.[18] This high specificity for the HER2 domain with negligible inhibition of the epidermal growth factor receptor distinguishes tucatinib from other currently approved HER2-targeted small-molecule TKIs and affects the toxicity profile.[17,18] Tucatinib was evaluated in combination with capecitabine and trastuzumab in the phase 3 HER2CLIMB study.[18] Patients with HER2-positive advanced breast cancer were included if they had previously received trastuzumab, pertuzumab, and ado-trastuzumab emtansine. Patients with brain metastases were included; those with leptomeningeal disease were not. A total of 612 patients were randomized 2:1 to receive either tucatinib 300 mg or placebo orally twice daily continuously, in combination with trastuzumab and capecitabine. Patients were heavily pretreated, with a median of three prior lines of therapy for metastatic disease (range 1–14). Approximately half (47.5%) had brain metastases. With regard to the primary endpoint of PFS in the first 480 randomized patients, the median PFS was 7.8 months with tucatinib versus 5.6 months with placebo (HR, 0.54, 95% CI, 0.42–0.71; p < .001) at 1 year. For patients with brain metastases, the median PFS was extended with the addition of tucatinib to 7.6 versus 5.4 months (HR, 0.48, 95% CI, 0.34–0.69; p < .001). Regarding safety, the most common adverse events of any grade that occurred more frequently with tucatinib included diarrhea, palmar-plantar erythrodysesthesia syndrome, nausea, vomiting, and stomatitis.[18]

On the basis of the results of the HER2CLIMB study, tucatinib (Tukysa) was approved by the FDA on April 17, 2020, in combination with trastuzumab and capecitabine for patients with advanced unresectable or metastatic HER2BC following receipt of at least one prior anti-HER2-based regimen in the metastatic setting.[19,20] Notably, the labeled indication specifically includes patients with brain metastases, and tucatinib is a welcome addition to the treatment options for this particular patient population.[20] Tucatinib is approved at a dose of 300 mg orally with or without food twice daily continuously, in combination with capecitabine 1,000 mg/m^2 orally twice daily on days 1 through 14 and trastuzumab at standard dose every 21 days.[20] Dose interruption or reduction recommendations exist for diarrhea and hepatotoxicity. Patients should be counseled on the potential for severe diarrhea and appropriate management. Hepatic function should be monitored every 3 weeks or as clinically indicated. Empiric dose reductions of tucatinib are indicated in the setting of severe hepatic impairment and concurrent use with a strong CYP2C8 inhibitor. Tucatinib is associated with other clinically relevant drug-drug interactions, and a thorough drug interaction screen is recommended prior to initiation.[20]

Emerging Therapies

Margetuximab is a monoclonal antibody derived from the parent compound of trastuzumab. Though both margetuximab and trastuzumab bind to the same epitope of HER2 and demonstrate similar affinity and antiproliferative activity, margetuximab's Fc region is engineered to increase affinity for the activating Fc receptor (FcR) CD16A while decreasing affinity for the inhibitory FcR CD32B.[21-23] The randomized phase 3 open-label SOPHIA trial evaluated margetuximab in patients with metastatic HER2BC who had received one to three prior lines of therapy, including pertuzumab, in the metastatic setting. Patients were randomized 1:1 to margetuximab 15 mg/kg or trastuzumab intravenously every 3 weeks, in addition to capecitabine, eribulin, gemcitabine, or vinorelbine. Initial results were presented at the 2019 American Society of Clinical Oncology annual meeting.[22] In the intention-to-treat (ITT) analysis of 536 patients, margetuximab showed an improved PFS versus trastuzumab, with a median of 5.8 months versus 4.9 months (HR, 0.76; 95% CI, 0.59–0.98; p = .033). The subset of patients with CD16A genotypes containing a 158F allele (a population that has been found to be less responsive to trastuzumab) saw an even greater PFS benefit with margetuximab, with a median of 6.9 months versus 5.1 months (HR, 0.68; 95% CI, 0.52–0.90; p = .005). Data

from the second interim OS analysis were presented at the 2019 San Antonio Breast Cancer Symposium. After a median follow-up of 15.6 months, the median OS in the ITT population was 21.6 months with margetuximab versus 19.8 months with trastuzumab plus chemotherapy (HR, 0.89; 95% CI, 0.69–1.13; p = .326).[23] Again, the outcomes were more pronounced in the patients with CD16A 158F allele, with a median OS of 23.7 months with margetuximab versus 19.4 months with trastuzumab (HR, 0.79; 95% CI, 0.61–1.04; p = .087). Though the OS data on margetuximab are not yet mature, preliminary outcomes are promising, and it is hoped that they will lead to another option for HER2-directed therapy.

Conclusion

The recent advances in the treatment of HER2-positive metastatic breast cancer provide promising options for many patients who have exhausted first- and second-line therapies for this breast cancer subtype. Fam-trastuzumab deruxtecan, as well as the combinations of neratinib and capecitabine and of tucatinib, capecitabine, and trastuzumab, have gained recent FDA approvals for treating metastatic HER2BC. Margetuximab may add to future treatment paradigms. Further discussions and ongoing studies will seek to define the optimal sequencing of these recent approvals, as well as the use of fam-trastuzumab deruxtecan for patients with HER2-low-expressing breast cancer. ●●

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INDICATION AND USAGE

Venofer® (iron sucrose) injection, USP is indicated for the treatment of iron deficiency anemia in patients with chronic kidney disease (CKD).

IMPORTANT SAFETY INFORMATION

DOSAGE AND ADMINISTRATION

Pediatric Patients (2 Years of Age and Older)

The dosing for iron replacement treatment in pediatric patients with Peritoneal-Dialysis- or Hemodialysis-Dependent CKD or Non-Dialysis-Dependent CKD have not been established.

CONTRAINDICATIONS

Known hypersensitivity to Venofer.

WARNINGS AND PRECAUTIONS

Serious hypersensitivity reactions, including anaphylactic-type reactions, some of which have been life-threatening and fatal, have been reported in patients receiving Venofer. Patients may present with shock, clinically significant hypotension, loss of consciousness and/or collapse. If hypersensitivity reactions or signs of intolerance occur during administration, stop Venofer immediately. Monitor patients for signs and symptoms of hypersensitivity during and after Venofer administration for at least 30 minutes and until clinically stable following completion of the infusion. Only administer Venofer when personnel and therapies are immediately available for the treatment of serious hypersensitivity reactions. Most reactions associated with intravenous iron preparations occur within 30 minutes of the completion of the infusion.

Venofer may cause clinically significant hypotension. Monitor for signs and symptoms of hypotension following each administration of Venofer. Hypotension following administration of Venofer may be related to rate of administration and/or total dose delivered.

Excessive therapy with parenteral iron can lead to excess storage of iron with the possibility of iatrogenic hemosiderosis. All adult and pediatric patients receiving Venofer require periodic monitoring of hematologic and iron parameters (hemoglobin, hematocrit, serum ferritin and transferrin saturation). Do not administer Venofer to patients with evidence of iron overload. Transferrin saturation (TSAT) values increase rapidly after intravenous administration of iron sucrose; do not perform serum iron measurements for at least 48 hours after intravenous dosing.

ADVERSE REACTIONS

Adult Patients: The most common adverse reactions (≥2%) include diarrhea, nausea, vomiting, headache, dizziness, hypotension, pruritus, pain in extremity, arthralgia, back pain, muscle cramp, injection site reactions, chest pain and peripheral edema.

Pediatric Patients: The most common adverse reactions (≥2%) are headache, respiratory tract viral infection, peritonitis, vomiting, pyrexia, dizziness, cough, nausea, arteriovenous fistula thrombosis, hypotension and hypertension.

Post-Marketing Experience

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. In post-marketing safety studies of Venofer in 1,051 patients with HDD-CKD, adverse reactions reported by >1% were cardiac failure congestive, sepsis and dysgeusia.

- *Immune system disorders:* anaphylactic-type reactions, angioedema
- *Psychiatric disorders:* confusion
- *Nervous system disorders:* convulsions, collapse, light-headedness, loss-of-consciousness
- *Cardiac disorders:* bradycardia
- *Vascular disorders:* shock
- *Respiratory, thoracic and mediastinal disorders:* bronchospasm, dyspnea
- *Musculoskeletal and connective tissue disorders:* back pain, swelling of the joints
- *Renal and urinary disorders:* chromaturia
- *General disorders and administration site conditions:* hyperhidrosis

Symptoms associated with Venofer total dosage or infusing too rapidly included hypotension, dyspnea, headache, vomiting, nausea, dizziness, joint aches, paresthesia, abdominal and muscle pain, edema and cardiovascular collapse. These adverse reactions have occurred up to 30 minutes after the administration of Venofer injection. Reactions have occurred following the first dose or subsequent doses of Venofer. Slowing the infusion rate may alleviate symptoms.

Injection site discoloration has been reported following extravasation. Assure stable intravenous access to avoid extravasation.

DRUG INTERACTIONS

Venofer may reduce the absorption of concomitantly administered oral iron preparations.

Geriatric Use

Dose administration to an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

OVERDOSAGE

No data are available regarding overdosage of Venofer in humans. Excessive dosages of Venofer may lead to accumulation of iron in storage sites potentially leading to hemosiderosis. Do not administer Venofer to patients with iron overload.

For additional Safety Information, please see Full Prescribing Information on Venofer.com.

You are encouraged to report Adverse Drug Events to American Regent, Inc. at 1-800-734-9236 or to the FDA by visiting www.fda.gov/medwatch or calling 1-800-FDA-1088.

Please see Brief Summary of Full Prescribing Information on following page.

REFERENCES: 1. IQVIA [NSP Audit from MAT November 2013 to November 2018]. **2.** Data on file. Iron Sucrose Periodic Safety Update Report, 2018. Shirley, NY: American Regent, Inc.

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PP-VE-US-0061 2/2020

Venofer®
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This is a Brief Summary of Important Information about Venofer® (iron sucrose) injection. Please see the Full Prescribing Information for additional information.

Venofer is an iron replacement product indicated for the treatment of iron deficiency anemia in patients with chronic kidney disease (CKD).

Venofer has not been studied in patients younger than 2 years of age.

CONTRAINDICATIONS: Known hypersensitivity to Venofer.

WARNINGS AND PRECAUTIONS: Hypersensitivity Reactions: Observe for signs and symptoms of hypersensitivity during and after Venofer administration for at least 30 minutes and until clinically stable following completion of each administration. Only administer Venofer when personnel and therapies are immediately available for the treatment of serious hypersensitivity reactions. Hypotension: May cause hypotension. Monitor for signs and symptoms of hypotension during and following each administration. Iron Overload: Regularly monitor hematologic and iron parameters. Do not administer to patients with iron overload.

ADVERSE REACTIONS: Adult patients: The most common adverse reactions (≥2%) are diarrhea, nausea, vomiting, headache, dizziness, hypotension, pruritus, pain in extremity, arthralgia, back pain, muscle cramp, injection site reactions, chest pain, and peripheral edema. Pediatric patients: The most common adverse reactions (≥2%) are headache, respiratory tract viral infection, peritonitis, vomiting, pyrexia, dizziness, cough, nausea, arteriovenous fistula thrombosis, hypotension, and hypertension.
Adverse Reactions from Post-Marketing Experience: The following adverse reactions have been identified during post-approval use of Venofer. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. In the post-marketing safety studies in 1,051 treated patients with HDD-CKD, the adverse reactions reported by > 1% were: cardiac failure congestive, sepsis and dysgeusia.
Immune system disorders: anaphylactic-type reactions, angioedema; *Psychiatric disorders:* confusion; *Nervous system disorders:* convulsions, collapse, light-headedness, loss-of-consciousness; *Cardiac disorders:* bradycardia; *Vascular disorders:* shock; *Respiratory, thoracic and mediastinal disorders:* bronchospasm, dyspnea; *Musculoskeletal and connective tissue disorders:* back pain, swelling of the joints; *Renal and urinary disorders:* chromaturia; *General disorders and administration site conditions:* hyperhidrosis.

Symptoms associated with Venofer total dosage or infusing too rapidly included hypotension, dyspnea, headache, vomiting, nausea, dizziness, joint aches, paresthesia, abdominal and muscle pain, edema, and cardiovascular collapse. These adverse reactions have occurred up to 30 minutes after the administration of Venofer injection. Reactions have occurred following the first dose or subsequent doses of Venofer. Symptoms may respond to intravenous fluids, hydrocortisone, and/or antihistamines. Slowing the infusion rate may alleviate symptoms.

Injection site discoloration has been reported following extravasation. Assure stable intravenous access to avoid extravasation.

PATIENT COUNSELING INFORMATION: Prior History of Reactions to Parenteral Iron Products - Question patients regarding any prior history of reactions to parenteral iron products. Serious Hypersensitivity Reactions - Advise patients to report any symptoms of hypersensitivity that may develop during and following Venofer administration, such as rash, itching, dizziness, light-headedness, swelling, and breathing problems.

To report SUSPECTED ADVERSE REACTIONS, contact American Regent, Inc. at 1-800-734-9236 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Full prescribing information can be obtained by contacting American Regent at 1-800-734-9236 or at www.americanregent.com

REF-1154 5/2019 [HOPA]

HOPA
Hematology/Oncology Pharmacy Association

HOPA's Public Policy Committee Prioritizes Patient Care Support During COVID-19

For updates on HOPA's most current advocacy work, visit

hoparx.org/resources/corona-virus-covid-19

Board Update

The Common Denominator

David DeRemer, PharmD BCOP FCCP FHOPA
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As an unprecedented spring comes to an end, I know I speak for many as we face uncertainty about our immediate future, the strain of daily social distancing, and mental fatigue. The shift from normalcy to the present circumstances has led me to an even deeper appreciation of the dedication of elementary school teachers. My wife and I are now in charge of our children's education because of school closures, so Google classroom, class Zoom meetings, and the occasional Khan Academy video have been incorporated into our daily routine. Despite these technological advances, many will agree with me that keeping a child focused on an educational task remains a challenge!

I am happy to report that, after sustained focus and practice, my daughter has mastered the mathematical concept of the least common denominator. The term *common denominator* can also be used to describe a feature shared by members of a group. HOPA continues to expand, with more than 3,600 members and a contingent of 300 volunteers serving on committees and task forces. Our organization has an important common denominator: to support pharmacy practitioners and promote and advance hematology/oncology pharmacy to optimize the care of individuals affected by cancer. And despite the challenges we now face, the board is focused on advancing our integrated strategic plan for 2020–2023. This effort is highly dependent on the tireless efforts of our volunteers. The board is cognizant of the constraining bandwidth of our members, and we are seeking to optimize the volunteer experience.

HOPA's board and other leaders began to revitalize our strategic plan in 2019, following the completion of our 5-year plan at year 3. This remarkable achievement is a testament to the activity and energy of our membership and external partners. Our new 3-year strategic plan is aspirational, but flexible, particularly in view of the challenges that COVID-19 has imposed on our committee activities. Our vision (the common denominator mentioned above) has not changed: that all individuals affected by cancer have a hematology/oncology pharmacist as an integral member of their care team. I have provided progress notes on each strategic pillar below.

Goal 1: Professional Development

HOPA is expanding its educational activities in order to meet the evolving needs of pharmacists. This summer we will launch two large initiatives in this area. You asked for it, and now you have it: HOPA's Board Certified Oncology Pharmacist (BCOP) Preparatory and Recertification Course! Our course will offer 25 content outlines, 14 webinars, 32 podcasts, 28 BCOP continuing education (CE) hours, and 33.5 Accreditation Council for Pharmacy Education CE hours. In addition, we are excited about "the Big Idea," formally known as the Core Competency Certification Program, which consists of 12 modules designed to enhance the fundamental knowledge of practitioners.

Goal 2: Tools and Resources

HOPA is using new and diverse methods for delivering tools and resources to our members. By now, I hope you have become acquainted with our HOPA Now podcast series and all the learning opportunities it offers. We will continue to invite industry experts to discuss topics that have an impact on your practice and daily life. Integrating podcast learning into our BCOP education will help us meet the needs of an emerging younger demographic in our organization. Also, the *Journal of Hematology Oncology Pharmacy* has been named the official publication of HOPA. This journal will be an excellent place for HOPA members to publish their original research and exchange practice innovations relevant to the field of hematology/oncology pharmacy.

Goal 3: Research

The efforts of our Practice Outcomes and Professional Benchmarking Committee were recently published in a *Journal of Oncology Pharmacy Practice* article titled "Trends in the Delivery of Care to Oncology Patients in the United States: Emphasis on the Role of Pharmacists on the Healthcare Team." This committee, along with our Basic and Translational Sciences Committee, continues to identify opportunities to support pharmacist researchers with funding for both early-stage and seasoned investigators.

Goal 4: Advocacy

Expanding HOPA's footprint in the areas of safety, quality, and access to care is part of our advocacy initiative. In September 2019, HOPA's Quality Oversight Committee organized a 1-day workshop as an introduction to the American Society of Clinical Oncology Quality Training Program. This workshop, attended by 26 HOPA members, was highly successful, and similar opportunities are planned for the near future. Another goal in this area is to expand successful partnerships with the Leukemia and Lymphoma Society, the Pancreatic Cancer Action Network, and the Society for Immunotherapy of Cancer.

I am honored to serve as the 17th president in our young organization's history. I feel immensely blessed to lead this team. Despite the immediate challenges we face, HOPA's board, committees, and task forces will elevate HOPA to continued successes in the coming year. Given the number and range of activities that will be offered in 2020–2021, I hope that this summer presents you and your family the opportunity to relax and perhaps even *travel!* Take care. ●●

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