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Indication Withdrawals of Small Molecule Inhibitors from the Accelerated Approval Program

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Indication Withdrawals of Small Molecule Inhibitors from the Accelerated Approval Program

Jiyeon Joy Park, PharmD, BCOP
Pharmacy Clinical Coordinator
PGY1 Pharmacy Residency Program Director
Englewood Health

David Awad, PharmD, BCOP
Clinical Pharmacy Specialist, Hematology/Oncology
Robert Wood Johnson University Hospital

Introduction

The United States Food and Drug Administration's (FDA) Accelerated Approval Program, which expedites approval of drugs and biologics that treat serious conditions such as cancer, has drawn criticism for allowing products to reach the market only to see their failure to confirm clinical benefit months to years later.[1,2] Recent withdrawals of indications under the accelerated approval program include those of small molecule inhibitors.[3]

The Program, which began in 1992, allows for faster initial approval of drugs and biologics that treat serious conditions such as cancer. The Program approves products based on a surrogate endpoint, which helps shorten the approval process. Once the drug or biologic is approved through the Program, the manufacturer must conduct a subsequent confirmatory trial to obtain traditional approval of the drug.[4] If the confirmatory trial does not verify clinical benefit, the manufacturer may voluntarily withdraw the product, or the FDA may withdraw it after a public hearing.[5] Although the Program has been running for more than three decades, the majority of oncology indication withdrawals have occurred in the last 3 years. In 2021, many of the immune checkpoint inhibitor indications were withdrawn. Recently, small molecule inhibitors such as ibrutinib, umbralisib, idelalisib, duvelisib, and panobinostat have accounted for the majority of the indication withdrawals.[3]

In response to criticism, the FDA issued guidance in March 2023 that recommends manufacturers conduct randomized controlled trials rather than single-arm trials to support accelerated approval. The guidance also recommends that manufacturers perform blinded independent central review of the response assessment to minimize bias and variance in the assessment of tumor response.[6,7] This article seeks to summarize the recent indication withdrawals of small molecule inhibitors and how pharmacists and healthcare professionals can help manage patients who may be affected by these withdrawals. Table 1 provides a list of recently withdrawn indications of small molecule inhibitors.

"With the FDA's recent guidance provided to manufacturers to improve the transparency of accelerated approvals, costly withdrawals of drugs and biologics may be prevented in the future."

Withdrawal of Ibrutinib for Relapsed or Refractory Mantle Cell Lymphoma

In 2013, the FDA granted accelerated approval to ibrutinib for patients with mantle cell lymphoma (MCL) who have received at least one prior therapy. The accelerated approval was based on a non-randomized, open-label phase 2 study (NCT01236391) in patients with relapsed/refractory (R/R) MCL who received ibrutinib.[8] The study reported an overall response rate (ORR) of 68% (47% partial response [PR] and 21% complete response [CR]) with an estimated median follow-up of 15.3 months.[8] The phase 3 confirmatory trial (SHINE study, NCT01776840) analyzed previously untreated stage II to IV MCL patients receiving either ibrutinib in combination with bendamustine and rituximab (BR) or placebo in combination with BR.[9] Although the median progression-free survival (PFS) was longer in the ibrutinib group vs the placebo group (80.6 vs 52.9 months; HR 0.75; 95% CI 0.59-0.96; p=0.01), the overall survival (OS) at 7 years was similar between the two groups (55.0% vs 56.8%; HR 1.07; 95% CI 0.81-1.40). The ibrutinib group also had a higher rate of grade 3 or 4 adverse events (81.5 vs 77.3%) and a higher rate of death from adverse effects (10.7 vs 6.1%) compared to the placebo group.[9] As a result of the SHINE study, on April 6, 2023, AbbVie and Janssen, the manufacturers of ibrutinib, announced a voluntary withdraw of ibrutinib for R/R MCL. Ibrutinib was officially withdrawn on May 18, 2023 for this indication.[10,11]

Alternative Bruton's tyrosine kinase (BTK) inhibitors such as acalabrutinib and zanubrutinib are available as second-line treatment options for MCL, and pirtobrutinib is available as a third-line option.[12–14] Acalabrutinib and zanubrutinib are known to be more selective than ibrutinib for BTK with less off-target effects.[15,16] In patients with brain metastases, although rare in MCL, data concerning the efficacy of BTK inhibitors other than ibrutinib are scarce.[17,18] The withdrawal of ibrutinib for the MCL indication may pose challenges in treating MCL with central nervous system involvement. Clinicians should determine whether to continue treating these patients with ibrutinib off-label, which may or may not be covered under insurance policies. Of note, the National Comprehensive Cancer Network (NCCN) guidelines still have a category 2A recommendation for ibrutinib for R/R MCL as of June 2, 2023, although it is no longer listed under preferred regimens.[19] The guideline recommendation may help mitigate insurance issues. Clinicians should also note that acalabrutinib, zanubrutinib, and pirtobrutinib were all approved under the accelerated approval process, with confirmatory trials projected for completion in 2024, 2027, and 2026 respectively.[21] Clinicians should select appropriate

Table 1: List of Withdrawn Indications of Small Molecule Inhibitors from December 2021 to June 2023[3]

Drug Name (Brand)	Indication	Original Accelerated Approval Date	Withdrawal Date	Time from Accelerated Approval to Withdrawal	Original Trial Name(s) and Results	Confirmatory Trial Name(s) and Results
Ibrutinib (Imbruvica®)	Adult patients with MCL who have received at least one prior therapy	11/13/2013	5/18/2023	9.5 years	NCT01236391 • ORR: 68%	SHINE (NCT01776840) • Median PFS: Ibrutinib+BR 80.6 vs Placebo+BR 52.9 months (HR 0.75; 95% CI 0.59-0.96; p=0.01) • 7-year OS: Ibrutinib+BR 55.0% vs Placebo+BR 56.8%
	Adult patients with MZL who require systemic therapy and have received at least one prior anti-CD20-based therapy	1/18/2017	5/18/2023	6.3 years	PCYC-1121 (NCT01980628) • ORR: 48% • Median PFS: 14.2 months	SELENE (NCT01974440) • Median PFS: Ibrutinib+CI not reached vs Placebo+CI 91.6 months, (HR 0.73; 95% CI 0.31-1.68; p=0.4505) • Publication pending
Umbralisib (Ukoniq®)	Adult patients with R/R MZL who have received at least one prior anti-CD20- based regimen	2/5/2021	5/31/2022	1.2 years	UNITY-NHL (NCT02793583) • ORR: 49.3%	Not performed for MZL/FL; product withdrawn after safety concerns in Unity-CLL (NCT02612311)
	Adult patients with R/R FL who have received at least three prior lines of systemic therapy	2/5/2021	5/31/2022	1.2 years	UNITY-NHL (NCT02793583) • ORR: 45.3%	
Idelalisib (Zydelig®)	For the treatment of relapsed FL in patients who have received at least 2 prior systemic therapies and relapsed SLL in patients who have received at least 2 prior systemic therapies	7/23/2014	2/18/2022	7.6 years	DELTA (NCT01282424) • ORR: 54% in FL, 58% in SLL	Not performed
Duvelisib (Copiktra®)	Treatment of adult patients with R/R FL after at least 2 prior systemic therapies	9/24/2018	12/17/2021	3.2 years	NCT02204982 • ORR: 42%	Not performed
Panobinostat (Farydak®)	In combination with BTZ and DEX for the treatment of patients with MM who have received at least 2 prior regimens, including BTZ and an immunomodulatory agent	2/23/2015	3/24/2022	7.1 years	PANORAMA1 (NCT01023308) • PFS: 11.99 months	Not performed

BTZ: bortezomib; BR: bendamustine and rituximab; CI: chemoimmunotherapy; CR: complete response; DEX: dexamethasone; FL: follicular lymphoma; MCL: mantle cell lymphoma; MM: multiple myeloma; MZL: marginal zone lymphoma; NE: not evaluable; ORR: overall response rate; OS: overall survival; PR: partial response; PFS: progression free survival; R/R: relapsed or refractory; SLL: small lymphocytic lymphoma

alternative treatment options based on indication (second vs third line), patient/prescriber preference, side effect profile, patient tolerance, and cost. Also, there are no head-to-head prospective trials comparing the efficacy and safety of the various BTK inhibitors in this population. While ibrutinib has been withdrawn for R/R MCL, it has been studied as a first-line option in younger patients with MCL with promising results. The full manuscript is pending publication.[22]

Withdrawal of Ibrutinib for Relapsed or Refractory Marginal Zone Lymphoma

Ibrutinib was initially granted accelerated approval for previously treated marginal zone lymphoma (MZL) in 2017 based on a phase 2 study (NCT01980628). Patients who received at least one prior therapy, including at least one CD20-directed regimen, received ibrutinib 560 mg orally once daily until disease progression or unacceptable toxicity for a maximum of 3 years. The surrogate marker, ORR, was 48% (95% CI 35-62) and the median PFS was 14.2 months with a median follow up of 19.4 months.[23] The confirmatory SELENE trial (NCT01974440) failed to meet its primary endpoint of PFS in patients with MZL and follicular lymphoma (FL). The median PFS was not reached (95% CI 49.25-not evaluable [NE]) in the ibrutinib plus chemoimmunotherapy group and 91.6 months in the placebo plus chemoimmunotherapy group (95% CI 9.23-NE) (HR 0.73; 95% CI 0.31-1.68; p=0.4505). The full results are pending formal presentation at a medical meeting.[10,11,24]

Other BTK inhibitors, such as zanubrutinib and acalabrutinib, are available as second-line treatment options for MZL. Zanubrutinib was granted accelerated approval in 2021 for the treatment of patients with MZL who have received at least one anti-CD20-based regimen, and its confirmatory trial is projected to be completed in 2028.[14,21] For acalabrutinib, while data are available for the treatment of R/R MZL, it is currently used off-label for the indication.[25]

Although ibrutinib was withdrawn for R/R MZL, its efficacy in treatment-naive MZL is being studied in an ongoing phase 3 trial (NCT04212013) comparing ibrutinib and rituximab to placebo and rituximab.[26] Similar to those for MCL, the NCCN guidelines for MZL still include ibrutinib under a category 2A recommendation for second-line and subsequent therapy, but it has been moved from preferred regimens to other recommended regimens.[19]

Withdrawal of Umbralisib for Marginal Zone Lymphoma and Follicular Lymphoma

Umbralisib is the most recently approved phosphatidylinositol-3-kinase (PI3K) inhibitor through accelerated approval. It possesses a distinct mechanism of action from the others in this class, namely, dual inhibition of PI3Kδ and casein kinase-1ε.[27] Umbralisib was granted accelerated approval in 2021 for the treatment of R/R MZL after at least one prior anti-CD20-based regimen and R/R FL after at least three prior lines of systemic therapy.[28] The approval was based on the results of the Unity-NHL trial (NCT02793583), a phase IIb, open-label, multicohort study of umbralisib in patients with MZL, FL, small lymphocytic lymphoma (SLL), MCL, or diffuse large B-cell lymphoma.[29] The trial consisted of 69 patients with MZL and 117 patients with FL. Patients received umbralisib until disease progression or unacceptable toxicity. The primary endpoint was ORR, defined as patients achieving CR or PR. For patients with MZL and FL, respectively, ORRs were 49.3% and 45.3%. CR was seen in 11 (15.9%) and 6 (5.1%) patients with MZL and FL, respectively.[29]

Umbralisib was withdrawn for both MZL and FL indications following the results of the Unity-CLL trial (NCT02612311), which studied umbralisib in combination with ublituximab in chronic lymphocytic leukemia (CLL) patients. The Unity-CLL trial was a multicenter, phase 3 study of 421 patients with treatment-naive or R/R CLL. Patients were randomized to receive obinutuzumab plus chlorambucil (O+Chl), umbralisib plus ublituximab (U2), umbralisib monotherapy, or ublituximab monotherapy. At a median follow-up of 36.2 months, U2 significantly prolonged PFS compared to O+Chl (median 31.9 vs 17.9 months; HR 0.546, 95% CI 0.413-0.720, p<0.0001). OS data, however, were similar and not statistically significant. Updated findings from UNITY-CLL showed a possible increased risk of death in patients receiving umbralisib. Subsequently, umbralisib was withdrawn voluntarily by TG Therapeutics for both MZL and FL indications based on safety concerns from Unity-CLL.[30]

TG Therapeutics plans to make umbralisib available through expanded access.[30] Patients who were previously receiving treatment with umbralisib can be switched to copanlisib, the only PI3K inhibitor with an indication in MZL and FL.[31] Chimeric antigen receptor (CAR) T-cell therapy is also indicated in both diseases. For patients with R/R FL, clinicians may also consider alternatives such as chemoimmunotherapy (e.g., bendamustine with obinutuzumab or rituximab), lenalidomide-based therapy, or other CD20-based therapy such as mosunetuzumab, a CD20-directed bispecific T-cell engager which was granted accelerated approval in 2022 based on a study that reported 80% ORR and 60% CR (NCT02500407).[20,32] Additionally, there are open clinical trials studying umbralisib in MZL and FL (NCT03919175 and NCT03269669).[33,34]

Withdrawal of Idelalisib for Follicular Lymphoma and Small Lymphocytic Lymphoma and Duvelisib for Follicular Lymphoma

Idelalisib and duvelisib are both PI3K inhibitors approved for FL. Idelalisib received accelerated approval in 2014 for relapsed FL and relapsed SLL. The approval was based on a phase 2 study (DELTA, NCT01282424) which reported a 54% and 56% ORR in FL and SLL, respectively.[35] However, the manufacturer of idelalisib, Gilead, was not able to enroll enough patients in the confirmatory trial (NCT02536300) and decided to voluntarily withdraw the product from the market.[36,37]

Duvelisib received accelerated approval in 2018 for R/R FL after at least two prior systemic therapies based on a single-arm study (NCT02204982) in patients who were refractory to rituximab and chemotherapy or radioimmunotherapy. The ORR, as determined by an independent review committee, was 42% (95% CI 31-54), with 41% PR and 1.2% CR.[38] In 2022, duvelisib was withdrawn from the market due to the manufacturer's inability to conduct a confirmatory trial.[39]

For R/R FL and SLL, there are no currently available expanded access options for idelalisib or duvelisib. For SLL, clinicians should consider alternative options such as BTK inhibitors (e.g., ibrutinib, acalabrutinib, or zanubrutinib),[12,14,40] or venetoclax with or without an anti-CD20 monoclonal antibody. Clinical trials should be considered whenever appropriate.[41]

Withdrawal of Panobinostat for Multiple Myeloma

Panobinostat is an oral, pan-deacetylase inhibitor that was granted accelerated approval in February 2015 for the treatment of R/R multiple myeloma. Accelerated approval was based on the results of the PANORAMA1 trial (NCT01023308), a multi-center, randomized, placebo-controlled, double-blind phase 3 trial.[42] Patients with R/R multiple myeloma (n=768) after one to three prior treatments were randomized to receive panobinostat or placebo, in combination with bortezomib and dexamethasone. The median PFS was longer in patients who received panobinostat (11.99 vs 8.08 months; HR 0.63, 95% CI 0.52-0.76; p<0.0001). The OS data was not mature at the time of publication. In November 2021, the manufacturer of panobinostat, Secura Bio, Inc., submitted a letter to the FDA asking to withdraw the approval of panobinostat, stating it was not feasible to complete the required confirmatory trial to retain FDA approval.[43] Based on this request, the FDA withdrew the approval of panobinostat in March 2022.[3]

There are currently no clinical trials studying panobinostat in multiple myeloma. Since the removal of panobinostat, multiple therapies have been approved for relapsed multiple myeloma, including B-cell maturation antigen-targeting bispecific antibodies and CAR T-cell therapy.[44]

Impact of Accelerated Approval Withdrawals on Patient Care

Withdrawal of FDA indications can create an unsettling situation for patients, caregivers, and healthcare teams. Once an indication is withdrawn from the market, many questions arise regarding the

next steps. Clinicians and patients need to promptly establish a plan to address the barriers to treatment continuation and access. Patients can encounter difficulties obtaining refills or receiving authorization for treatment due to payor rejections.[2] From 2017 to 2019, Medicare Parts B and D spent at least $569 million on cancer drugs with accelerated approval indications that ultimately failed to prove OS benefit in confirmatory trials.[45] Distributors may also cease fulfilling medication orders if the medication has been removed from the market. Despite negative trial results, patients and providers may report positive clinical outcomes with their treatment, which can create hesitation in discontinuing treatment.[46] Ultimately, open and honest communication should be held between patients and the healthcare team as soon as any indication or product withdrawals are announced to ensure that the patients can benefit from an appropriate alternative therapy as soon as possible.[46] Treatment options such as expanded access or compassionate use programs, clinical trials, or alternative therapies approved in that disease state should be considered.

Useful Resources for Healthcare Professionals

Pharmacists and other healthcare professionals need to stay current with the status of accelerated approvals and withdrawals. The FDA has useful websites that summarize withdrawn cancer accelerated approvals, accelerated approvals that have obtained traditional approvals, and ongoing cancer accelerated approvals.[3,21,47] Healthcare professionals can also stay current with the FDA's drug safety communications, which provide guidance when a drug is withdrawn due to increased safety concerns.[48] In addition, the FDA's Project Confirm is an initiative by the FDA Oncology Center of Excellence to increase the transparency of the accelerated approval program for oncology indications. The Project Confirm website lists commonly asked questions and answers regarding the accelerated approval process.[5]

Conclusion

Small molecule inhibitors account for many of the withdrawals of indications initially approved through the FDA Accelerated Approval Program. With the FDA's recent guidance provided to manufacturers to improve the transparency of accelerated approvals, costly withdrawals of drugs and biologics may be prevented in the future. Healthcare professionals including pharmacists should promptly communicate with patients of any changes in their therapy due to these withdrawals and individualize alternative therapy options based on the patients' clinical status, side effect profile, adherence, previous therapy, financial and payor situation, and availability of compassionate use or clinical trials. ●●

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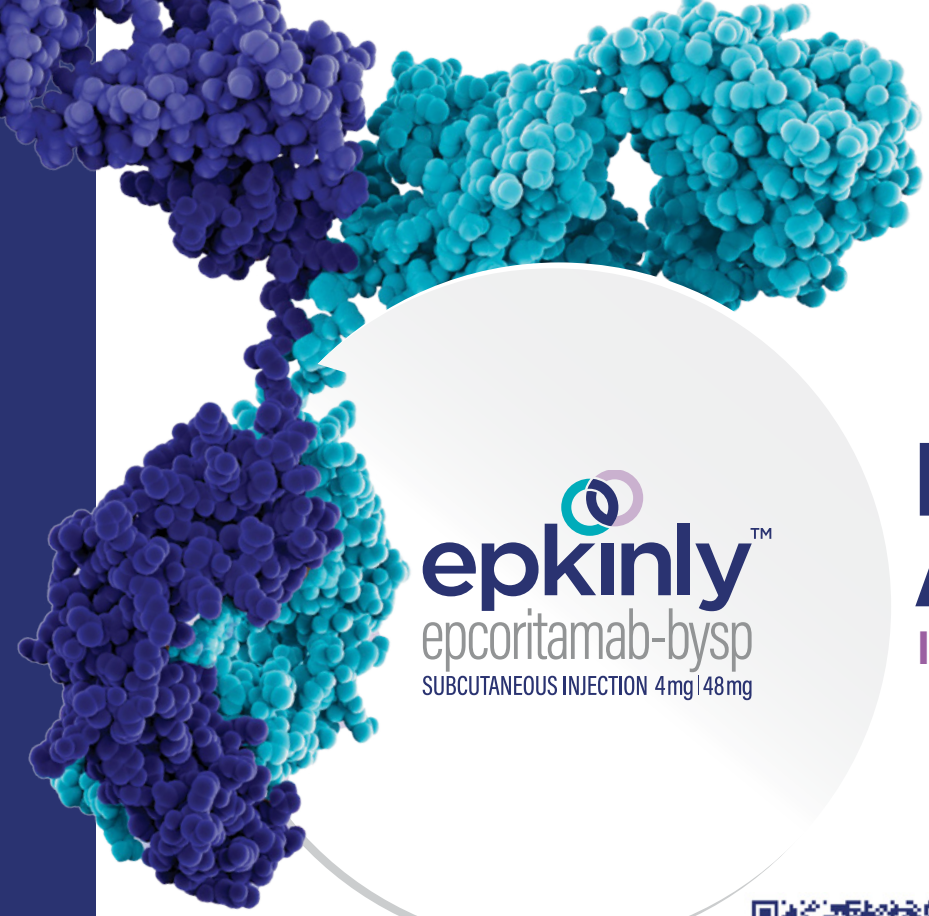

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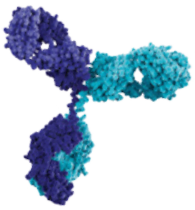

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INDICATION

EPKINLY is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified (NOS), including DLBCL arising from indolent lymphoma, and high-grade B-cell lymphoma (HGBL) after 2 or more lines of systemic therapy.

This indication is approved under accelerated approval based on response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

IMPORTANT SAFETY INFORMATION

BOXED WARNINGS

- **Cytokine release syndrome (CRS), including serious or life-threatening reactions, can occur in patients receiving EPKINLY. Initiate treatment with the EPKINLY step-up dosing schedule to reduce the incidence and severity of CRS. Withhold EPKINLY until CRS resolves or permanently discontinue based on severity.**
- **Immune effector cell–associated neurotoxicity syndrome (ICANS), including life-threatening and fatal reactions, can occur with EPKINLY. Monitor patients for neurological signs or symptoms of ICANS during treatment. Withhold EPKINLY until ICANS resolves or permanently discontinue based on severity.**

Cytokine Release Syndrome (CRS)

- EPKINLY can cause CRS, including serious or life-threatening reactions. CRS occurred in 51% of patients at the recommended dose in the clinical trial (37% grade 1, 17% grade 2, and 2.5% grade 3). Recurrent CRS occurred in 16% of patients. Of all the CRS events, most (92%) occurred during cycle 1. In cycle 1, 9% of CRS events occurred after the 0.16 mg dose (cycle 1, day 1), 16% after the 0.8 mg dose (cycle 1, day 8), 61% after the 48 mg dose (cycle 1, day 15), and 6% after the 48 mg dose (cycle 1, day 22). The median time to onset of CRS from the most recently administered EPKINLY dose across all doses was 24 hours (range, 0-10 days). The median time to onset after the first full 48 mg dose was 21 hours (range, 0-7 days). CRS resolved in 98% of patients; the median duration of CRS events was 2 days (range, 1-27 days).
- Signs and symptoms of CRS can include pyrexia, hypotension, hypoxia, dyspnea, chills, and tachycardia. Concurrent neurological adverse reactions associated with CRS occurred in 2.5% of patients and included headache, confusional state, tremors, dizziness, and ataxia.

- Initiate EPKINLY according to the step-up dosing schedule. Administer pretreatment medications to reduce the risk of CRS and monitor patients for potential CRS. Following administration of the first 48 mg dose, patients should be hospitalized for 24 hours. At the first signs or symptoms of CRS, immediately evaluate patients for hospitalization, manage per current practice guidelines, and administer supportive care as appropriate. Withhold or discontinue EPKINLY based on the severity of CRS.
- Patients who experience CRS (or other adverse reactions that impair consciousness) should be evaluated and advised not to drive and to refrain from operating heavy or potentially dangerous machinery until resolution.

Immune Effector Cell–Associated Neurotoxicity Syndrome (ICANS)

- EPKINLY can cause life-threatening and fatal ICANS. ICANS occurred in 6% (10/157) of patients in the clinical trial (4.5% grade 1, 1.3% grade 2, 0.6% fatal: 1 event). Of the 10 ICANS events, 9 occurred in cycle 1 of treatment. The median time to onset was 16.5 days (range, 8-141 days) from the start of treatment. Relative to the most recent administration, the median time to onset was 3 days (range, 1-13 days). The median duration of ICANS was 4 days (range, 0-8 days), with ICANS resolving in 90% of patients with supportive care.
- Signs and symptoms of ICANS can include confusional state, lethargy, tremors, dysgraphia, aphasia, and nonconvulsive status epilepticus. The onset of ICANS can be concurrent with CRS, following resolution of CRS, or in the absence of CRS.
- Monitor for potential ICANS. At the first signs or symptoms of ICANS, immediately evaluate patient and provide supportive therapy based on severity. Withhold or discontinue EPKINLY per recommendations and consider further management per current practice guidelines.
- Patients who experience signs or symptoms of ICANS or any other adverse reactions that impair cognition or consciousness should be evaluated, including potential neurology evaluation, and patients at increased risk should be advised not to drive and to refrain from operating heavy or potentially dangerous machinery until resolution.

Infections

- EPKINLY can cause serious and fatal infections. In the clinical trial, serious infections, including opportunistic infections, were reported in 15% of patients treated with EPKINLY at the recommended dose (14% grade 3 or 4, 1.3% fatal). The most common grade 3 or greater infections were sepsis, COVID-19, urinary tract infection, pneumonia, and upper respiratory tract infection.
- Monitor patients for signs and symptoms of infection prior to and during treatment with EPKINLY and treat appropriately. Avoid administration of EPKINLY in patients with active infections.
- Prior to starting EPKINLY, provide *Pneumocystis jirovecii* pneumonia (PJP) prophylaxis and consider prophylaxis against herpes virus.
- Withhold or consider permanent discontinuation of EPKINLY based on severity.

Cytopenias

- EPKINLY can cause serious or severe cytopenias, including neutropenia, anemia, and thrombocytopenia. Among patients who received the recommended dose in the clinical trial, grade 3 or 4 events occurred in 32% (decreased neutrophils), 12% (decreased hemoglobin), and 12% (decreased platelets). Febrile neutropenia occurred in 2.5%.
- Monitor complete blood counts throughout treatment. Based on severity of cytopenias, temporarily withhold or permanently discontinue EPKINLY. Consider prophylactic granulocyte colony-stimulating factor administration as applicable.

Embryo-Fetal Toxicity

- EPKINLY may cause fetal harm. Advise pregnant women of the potential risk to the fetus. Verify pregnancy status in females of reproductive potential prior to initiating EPKINLY. Advise females of reproductive potential to use effective contraception during treatment with EPKINLY and for 4 months after the last dose.

Adverse Reactions

- The most common (≥20%) adverse reactions were CRS, fatigue, musculoskeletal pain, injection site reactions, pyrexia, abdominal pain, nausea, and diarrhea. The most common grade 3 to 4 laboratory abnormalities (≥10%) were decreased lymphocyte count, decreased neutrophil count, decreased white blood cell count, decreased hemoglobin, and decreased platelets.

Lactation

- Advise women not to breastfeed during treatment and for 4 months after the last dose of EPKINLY.

Please see accompanying Brief Summary of full Prescribing Information, including Boxed Warnings, on the following pages.

3L=third line.

Reference: 1. EPKINLY [package insert]. Plainsboro, NJ: Genmab US, Inc. and North Chicago, IL: AbbVie Inc.

Distributed and marketed by Genmab US Inc.
777 Scudders Mill Road, Plainsboro, NJ 08536.
Distributed and marketed by AbbVie Inc.
1 North Waukegan Road, North Chicago, IL 60064.

05/2023 COM-US-EPK-0000128

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EPKINLY™ (epcoritamab-bysp) injection, for subcutaneous use. Rx Only.

PROFESSIONAL BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

WARNING: CYTOKINE RELEASE SYNDROME and IMMUNE EFFECTOR CELL-ASSOCIATED NEUROTOXICITY SYNDROME

Cytokine release syndrome (CRS), including serious or life-threatening reactions, can occur in patients receiving EPKINLY. Initiate treatment with the EPKINLY step-up dosing schedule to reduce the incidence and severity of CRS. Withhold EPKINLY until CRS resolves or permanently discontinue based on severity.

Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS), including life-threatening and fatal reactions, can occur with EPKINLY. Monitor patients for neurological signs or symptoms of ICANS during treatment. Withhold EPKINLY until ICANS resolves or permanently discontinue based on severity.

INDICATIONS AND USAGE: EPKINLY is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, including DLBCL arising from indolent lymphoma, and high-grade B-cell lymphoma after two or more lines of systemic therapy. This indication is approved under accelerated approval based on response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

IMPORTANT DOSING INFORMATION: Administer EPKINLY to well-hydrated patients. Premedicate before each dose in Cycle 1. EPKINLY should only be administered by a qualified healthcare professional with appropriate medical support to manage severe reactions such as cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS).

Administer EPKINLY subcutaneously according to the dosage schedule in Table 1 to reduce the incidence and severity of CRS. Due to the risk of CRS and ICANS, patients should be hospitalized for 24 hours after administration of the Cycle 1 Day 15 dosage of 48 mg.

RECOMMENDED DOSAGE: EPKINLY is for subcutaneous injection only. Administer EPKINLY in 28-day cycles until disease progression or unacceptable toxicity. EPKINLY Dosage Schedule—cycle 1, day 1: EPKINLY 0.16 mg (step-up dose 1); day 8: EPKINLY 0.8 mg (step-up dose 2); day 15: EPKINLY 48 mg (first full dose); day 22: EPKINLY 48 mg; cycles 2 and 3, days 1, 8, 15, and 22: EPKINLY 48 mg; cycles 4 to 9, days 1 and 15: EPKINLY 48 mg; cycles 10 and beyond, day 1: EPKINLY 48 mg.

CONTRAINDICATIONS: None.

WARNINGS AND PRECAUTIONS

Cytokine Release Syndrome: EPKINLY can cause CRS, including serious or life-threatening reactions. Cytokine release syndrome occurred in 51% of patients receiving EPKINLY at the recommended dose in the clinical trial, with Grade 1 CRS occurring in 37%, Grade 2 in 17%, and Grade 3 in 2.5% of patients. Recurrent CRS occurred in 16% of patients. Of all the CRS events, most (92%) occurred during Cycle 1. In Cycle 1, 9% of CRS events occurred after the 0.16 mg dose on Cycle 1 Day 1, 16% after the 0.8 mg dose on Cycle 1 Day 8, 61% after the 48 mg dose on Cycle 1 Day 15, and 6% after the 48 mg dose on Cycle 1 Day 22.

The median time to onset of CRS from the most recent administered EPKINLY dose across all doses was 24 hours (range: 0 to 10 days). The median time to onset after the first full 48 mg dose was 21 hours (range: 0 to 7 days). CRS resolved in 98% of patients and the median duration of CRS events was 2 days (range: 1 to 27 days).

In patients who experienced CRS, the signs and symptoms included pyrexia, hypotension, hypoxia, dyspnea, chills, and tachycardia. Concurrent neurological adverse reactions associated with CRS occurred in 2.5% of patients and included headache, confusional state, tremors, dizziness, and ataxia.

Initiate therapy according to EPKINLY step-up dosing schedule. Administer pretreatment medications to reduce the risk of CRS and monitor patients for potential CRS following EPKINLY accordingly. Following administration of the first 48 mg dose, patients should be hospitalized for 24 hours. At the first signs or symptoms of CRS, immediately evaluate patients for hospitalization, manage per current practice guidelines, and administer supportive care as appropriate. Withhold or discontinue EPKINLY based on the severity of CRS.

Patients who experience CRS (or other adverse reactions that impair consciousness) should be evaluated and advised not to drive and to refrain from operating heavy or potentially dangerous machinery until resolution.

Immune Effector Cell-Associated Neurotoxicity Syndrome: EPKINLY can cause life-threatening and fatal immune effector cell-associated neurotoxicity syndrome (ICANS). Immune Effector Cell-Associated Neurotoxicity Syndrome occurred in 6% (10/157) of patients receiving EPKINLY at the recommended dose in the clinical trial, with Grade 1 ICANS in 4.5% and Grade 2 ICANS in 1.3% of patients. There was one (0.6%) fatal ICANS occurrence. Of the 10 ICANS events, 9 occurred within Cycle 1 of EPKINLY treatment, with a median time to onset of ICANS of 16.5 days (range: 8 to 141 days) from the start of treatment. Relative to the most recent administration of EPKINLY, the median time to onset of ICANS was 3 days (range: 1 to 13 days). The median duration of ICANS was 4 days (range: 0 to 8 days) with ICANS resolving in 90% of patients with supportive care. Clinical manifestations of ICANS included, but were not limited to, confusional state, lethargy, tremor, dysgraphia, aphasia, and non-convulsive status epilepticus. The onset of ICANS can be concurrent with CRS, following resolution of CRS, or in the absence of CRS.

Monitor patients for potential ICANS following EPKINLY. At the first signs or symptoms of ICANS, immediately evaluate patient and provide supportive therapy based on severity. Withhold or discontinue EPKINLY per recommendations and consider further management per current practice guidelines.

Patients who experience signs or symptoms of ICANS or any other adverse reactions that impair cognition or consciousness should be evaluated, including potential neurology evaluation, and patients at increased risk should be advised not to drive and to refrain from operating heavy or potentially dangerous machinery until resolution.

Infections: EPKINLY can cause serious and fatal infections. In the clinical trial, serious infections, including opportunistic infections were reported in 15% of patients treated with EPKINLY at the recommended dose with Grade 3 or 4 infections in 14% and fatal infections in 1.3%. The most common Grade 3 or greater infections were sepsis, COVID-19, urinary tract infection, pneumonia, and upper respiratory tract infection.

Monitor patients for signs and symptoms of infection prior to and during treatment with EPKINLY and treat appropriately. Avoid administration of EPKINLY in patients with active infections. Provide PJP prophylaxis prior to initiating treatment with EPKINLY; consider initiating prophylaxis against herpes virus prior to starting EPKINLY.

Withhold or consider permanent discontinuation of EPKINLY based on severity.

Cytopenias: EPKINLY can cause serious or severe cytopenias, including neutropenia, anemia, and thrombocytopenia. Among patients who received the recommended dosage in the clinical trial, Grade 3 or 4 decreased neutrophils occurred in 32%, decreased hemoglobin in 12%, and decreased platelets in 12% of patients. Febrile neutropenia occurred in 2.5%.

Monitor complete blood counts throughout treatment. Based on the severity of cytopenias, temporarily withhold or permanently discontinue EPKINLY. Consider prophylactic granulocyte colony-stimulating factor administration as applicable.

Embryo-Fetal Toxicity: Based on its mechanism of action, EPKINLY may cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment with EPKINLY and for 4 months after the last dose.

ADVERSE REACTIONS, Clinical Trials Experience

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

The safety of EPKINLY was evaluated in EPCORE NHL-1, a single-arm study of patients with relapsed or refractory LBCL after two or more lines of systemic therapy, including DLBCL not otherwise specified, DLBCL arising from indolent lymphoma, high grade B-cell lymphoma, and other B-cell lymphomas. A total of 157 patients received EPKINLY via subcutaneous injection until disease progression or unacceptable toxicities according to the following 28-day cycle schedule: Cycle 1: EPKINLY 0.16 mg on Day 1, 0.8 mg on Day 8, 48 mg on Days 15 and 22; Cycles 2-3: EPKINLY 48 mg on Days 1, 8, 15, and 22; Cycles 4-9: EPKINLY 48 mg on Days 1 and 15; Cycles 10 and beyond: EPKINLY 48 mg on Day 1

Of the 157 patients treated, the median age was 64 years (range: 20 to 83), 60% male, and 97% had an ECOG performance status of 0 or 1. Race was reported in 133 (85%) patients; of these patients, 61% were White, 19% were Asian, and 0.6% were Native Hawaiian or Other Pacific Islander. There were no Black or African American or Hispanic or Latino patients treated in the clinical trial as reported. The median number of prior therapies was 3 (range: 2 to 11). The study excluded patients with CNS involvement of lymphoma, allogeneic HSCT or solid organ transplant, an ongoing active infection, and any patients with known impaired T-cell immunity. The median duration of exposure for patients receiving EPKINLY was 5 cycles (range: 1 to 20 cycles).

Serious adverse reactions occurred in 54% of patients who received EPKINLY. Serious adverse reactions in ≥ 2% of patients included CRS, infections (including sepsis, COVID-19, pneumonia, and upper respiratory tract infections), pleural effusion, febrile neutropenia, fever, and ICANS. Fatal adverse reactions occurred in 3.8% of patients who received EPKINLY, including COVID-19 (1.3%), hepatotoxicity (0.6%), ICANS (0.6%), myocardial infarction (0.6%), and pulmonary embolism (0.6%).

Permanent discontinuation of EPKINLY due to an adverse reaction occurred in 3.8% of patients. Adverse reactions which resulted in permanent discontinuation of EPKINLY included COVID-19, CRS, ICANS, pleural effusion, and fatigue.

Dosage interruptions of EPKINLY due to an adverse reaction occurred in 34% of patients who received EPKINLY. Adverse reactions which required dosage interruption in ≥ 3% of patients included CRS, neutropenia, sepsis, and thrombocytopenia.

The most common (≥ 20%) adverse reactions were CRS, fatigue, musculoskeletal pain, injection site reactions, pyrexia, abdominal pain, nausea, and diarrhea. The most common Grade 3 to 4 laboratory abnormalities (≥ 10%) were decreased lymphocyte count, decreased neutrophil count, decreased white blood cell count, decreased hemoglobin, and decreased platelets.

Adverse Reactions[§] ≥ 10% in patients treated with EPKINLY were as follows (all grades, grade 3 or 4[#]): cytokine release syndrome* (51%, 2.5%), fatigue[a] (29%, 2.5%), injection site reactions[b] (27%, 0%), pyrexia (24%, 0%), edema[c] (14%, 1.9%), [#]musculoskeletal pain (28%, 1.3%), abdominal pain[e] (23%, 1.9%), diarrhea (20%, 0%), nausea (20%, 1.3%), vomiting (12%, 0.6%), rash[f] (15%, 0.6%), headache (13%, 0.6%), decreased appetite (12%, 0.6%), cardiac arrhythmias[g] (10%, 0.6%). [§]Adverse reactions were graded based on CTCAE Version 5.0; [#]Only grade 3 adverse reactions occurred; *CRS was graded using ASTCT consensus criteria (Lee et al., 2019); [a]Fatigue includes asthenia, fatigue, lethargy; [b]Injection site reactions includes injection site erythema, injection site hypertrophy, injection site inflammation, injection site mass, injection site pain, injection site pruritus, injection site rash, injection site reaction, injection site swelling, injection site urticaria; [c]Edema includes edema, edema peripheral, face edema, generalized edema, peripheral swelling; [d]Musculoskeletal pain includes back pain, bone pain, flank pain, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain, non-cardiac chest pain, pain, pain in extremity, spinal pain; [e]Abdominal pain includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness; [f]Rash includes dermatitis bullous, erythema, palmar erythema, penile erythema, rash, rash erythematous, rash maculo-papular, rash pustular, recall phenomenon, seborrheic dermatitis, skin exfoliation; [g]Cardiac arrhythmias includes bradycardia, sinus bradycardia, sinus tachycardia, supraventricular extrasystoles, supraventricular tachycardia, tachycardia.

Clinically relevant adverse reactions in < 10% of patients who received EPKINLY included ICANS, sepsis, pleural effusion, COVID-19, pneumonia (including pneumonia and COVID-19 pneumonia), tumor flare, febrile neutropenia, upper respiratory tract infections, and tumor lysis syndrome.

Select laboratory abnormalities* ≥ 20% that worsened from baseline in patients treated with EPKINLY[†] were as follows (all grades, grade 3 or 4): lymphocyte count decreased (87%, 77%), hemoglobin decreased (62%, 12%), white blood cells decreased (53%, 22%), neutrophils decreased (50%, 32%), platelets decreased (48%, 12%), sodium decreased (56%, 2.6%), phosphate decreased[‡] (56%, N/A), aspartate aminotransferase increased (48%, 4.6%), alanine aminotransferase increased (45%, 5.3%), potassium decreased (34%, 5.3%), magnesium decreased (31%, 0%), creatinine increased (24%, 3.3%), potassium increased (21%, 1.3%). *Laboratory abnormalities were graded based on CTCAE Version 5.0; [†]The denominator used to calculate the rate varied from 146 to 153 based on the number of patients with a baseline value and at least one post-treatment value. [‡]CTCAE Version 5.0 does not include numeric thresholds for grading of hypophosphatemia; all grades represent patients with lab value < Lower Limit of Normal (LLN).

DRUG INTERACTIONS: For certain CYP substrates, minimal changes in the concentration may lead to serious adverse reactions. Monitor for toxicity or drug concentrations of such CYP substrates when co-administered with EPKINLY.

Epcoritamab-bysp causes release of cytokines that may suppress activity of CYP enzymes, resulting in increased exposure of CYP substrates. Increased exposure of CYP substrates is more likely to occur after the first dose of EPKINLY on Cycle 1 Day 1 and up to 14 days after the first 48 mg dose on Cycle 1 Day 15, and during and after CRS.

USE IN SPECIFIC POPULATIONS

Pregnancy—Risk Summary: Based on the mechanism of action, EPKINLY may cause fetal harm when administered to a pregnant woman. There are no available data on the use of EPKINLY in pregnant women to evaluate for a drug-associated risk. No animal reproductive or developmental toxicity studies have been conducted with epcoritamab-bysp.

Epcoritamab-bysp causes T-cell activation and cytokine release; immune activation may compromise pregnancy maintenance. In addition, based on expression of CD20 on B-cells and the finding of B-cell depletion in non-pregnant animals, epcoritamab-bysp can cause B-cell lymphocytopenia in infants exposed to epcoritamab-bysp in-utero. Human immunoglobulin G (IgG) is known to cross the placenta; therefore, EPKINLY has the potential to be transmitted from the mother to the developing fetus. Advise women of the potential risk to the fetus.

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

Lactation—Risk Summary

There is no information regarding the presence of epcoritamab-bysp in human milk, the effect on the breastfed child, or milk production. Because maternal IgG is present in human milk, and there is potential for epcoritamab-bysp absorption leading to serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with EPKINLY and for 4 months after the last dose.

Females and Males of Reproductive Potential: EPKINLY may cause fetal harm when administered to a pregnant woman.

Pregnancy Testing: Verify pregnancy status in females of reproductive potential prior to initiating EPKINLY.

Contraception—Females: Advise females of reproductive potential to use effective contraception during treatment with EPKINLY and for 4 months after the last dose.

Pediatric Use: The safety and efficacy of EPKINLY in pediatric patients have not been established.

Geriatric Use: In patients with relapsed or refractory LBCL who received EPKINLY in the clinical trial, 49% were 65 years of age or older, and 19% were 75 years of age or older. No clinically meaningful differences in safety or efficacy were observed between patients 65 years of age or older compared with younger adult patients.

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REF-01422 May 2023

LAB-9358 **MASTER**

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Stepping Out of Your Comfort Zone: Lessons from a First-time BCOP Presenter

Jordan Hill, PharmD, BCOP
Clinical Pharmacy Specialist
WVU Medicine Cancer Institute

Presenting a board-certified oncology pharmacist presentation at the Hematology/Oncology Pharmacy Association (HOPA) Annual Conference for the first time was an immensely rewarding experience, both on a personal and professional level. Presenting in front of a large audience of oncology experts definitely pushed me out of my comfort zone. Additionally, the varying level of participation in the care of patients living with breast cancer among attendees made engaging the entire audience a challenge. Having the opportunity to present to such a diverse group of oncology pharmacists certainly allowed me to improve my ability to articulate information in a manner that provided value to attendees that practice in breast cancer every day as well as those who don't. While it provided many challenges for me personally, it also helped fuel my passion for not only the essential role oncology pharmacists play in the management of early-stage breast cancer, but also my passion for teaching and sharing experiences with fellow oncology pharmacists.

"As with preparation for any presentation, it further deepened my knowledge of the literature and the impact we as oncology pharmacists can have on patient care."

On a more professional level, presenting at a national conference provided immense professional growth opportunities. As with preparation for any presentation, it further deepened my knowledge of the literature and the impact we as oncology pharmacists can have on patient care. Additionally, the question-and-answer session following the presentation allowed for further discussion and exchange of current practices and ongoing struggles among attendees which can be of great value in improving the care of our patients. This part of the session also allowed me to network with other breast cancer pharmacists as well as industry professionals and learners providing future opportunities for collaboration. Additionally, through the recognition of presenting at HOPA's Annual Conference, I have since had the opportunity to present in other forums outside of HOPA that I otherwise may not have been offered including live webinars on the role of the oncology pharmacist in early-stage breast cancer and an in-person session on therapies utilized in the metastatic setting at a national breast cancer meeting. These opportunities have also been invaluable learning experiences.

For oncology pharmacists considering presenting at HOPA's Annual Conference, it was a very challenging but also very rewarding experience. These are a few things I learned throughout the process.

- Waiting for the right time to present in an area I was really passionate about instead of pushing myself to present sooner was very beneficial for me. I had considered applying to present for a couple years, and I am especially glad I decided to wait for there to be a need to present on updates in early-stage breast cancer. It was easier for me to dedicate the extensive amount of time required since it was a topic I was very passionate about. I also think it makes the presentation more engaging when it's evident the speaker is highly invested.
- Following the timeline provided by HOPA can help to prevent procrastination. The first deadline was as early as September with the final deadlines not until March. If I were to do it again, I would still try to better space out the time I spent working on the different components of the presentation and assessment questions, but overall, having a structured set of timelines for myself and the blinded reviewers was very helpful.
- Working with an oncology pharmacist practicing in that area but at a different center and/or a different geographic location helps provide insight into varying clinical practices.
- Having a more seasoned mentor can assist in honing presentation skills (and calming nerves); HOPA offers to assign mentors to those interested in having one, and I definitely appreciated this option. This is even something I now could see myself doing in the future. Additionally, if there is someone you know personally, this would allow you to reach out earlier in the development process to seek guidance and advice.
- Seeking feedback from a variety of colleagues helps identify areas to refine such as improving visual aids (charts, graphs, diagrams), recognizing confusing language on slides, simplifying assessment questions, and enhancing audience engagement and participation.
- Incorporating patient stories and personal anecdotes throughout the presentation can make the presentation more relatable and impactful.

Reflection on Personal Impact and Growth

Presenting at HOPA's Annual Conference facilitated tremendous personal and professional growth by pushing me outside my comfort zone, refueling my passion for the essential role of an oncology pharmacist, enhancing my communication skills, fostering valuable connections, and creating further professional opportunities. I would highly encourage other oncology pharmacists to embrace the opportunity to present topics they are passionate about at national conferences.

A Primer on Revenue Cycle Basics for The Practicing Hematology/Oncology Pharmacist

Durga Zally, PharmD
Director Pharmacy Services, Hematology/Oncology
Geisinger

Arielle Malatesta, MBA
Senior Pharmacy Channel Consultant
Geisinger

Introduction

Robust revenue cycle management is critical now more than ever for the financial sustainability of health systems. Yet, ensuring optimal revenue integrity can be complex and daunting even for the most seasoned of executives. This is particularly true in the setting of the outpatient infusion center, which is often a core service in the provision of cancer and specialty infusions.

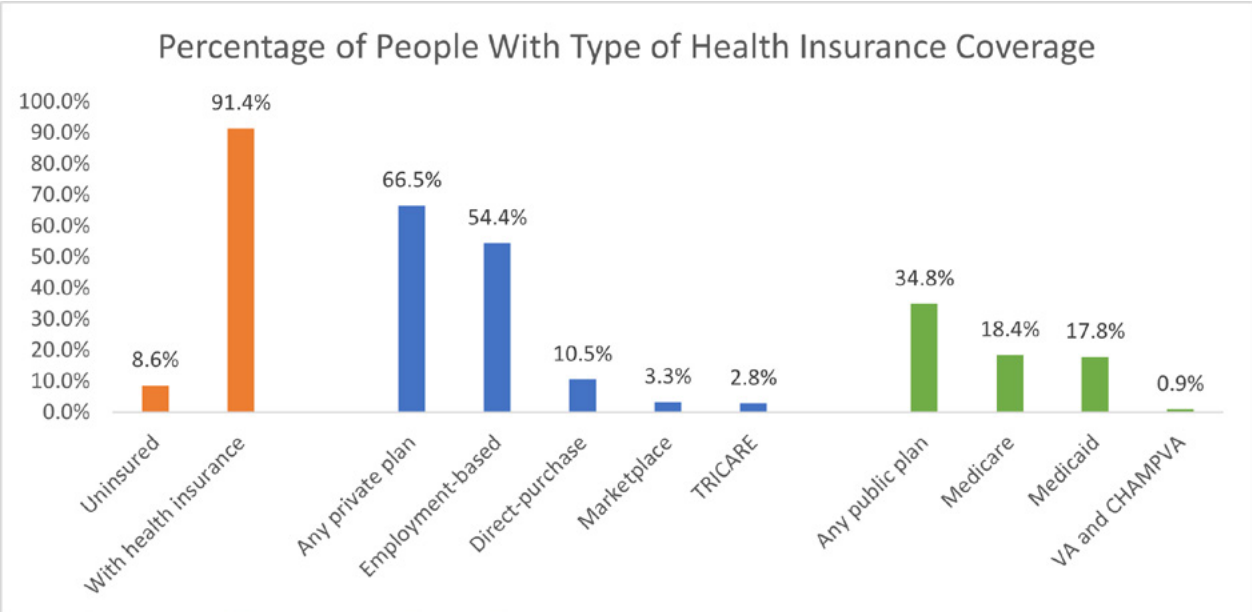
The increasing cost of medications, recurrence of drug shortages, ever-changing biosimilar preferences and payer mandates, and the increasing complexity in deciphering government and private payer polices, have made revenue cycle management challenging. The risk of payment denials and write-offs resulting from any gaps in the revenue cycle process have a substantial impact on the overall financial performance of organizations. Hematology and oncology pharmacists are in a unique position to not only positively impact the medication management process, but also in optimizing the revenue capture. Pharmacists' intervention at the front end of a claim cycle is critical to ensuring appropriate therapy selection and documentation that meets payer guidelines, thus further enhancing long-term departmental and organizational financial strength. Therefore, it is vital for such pharmacists to improve their understanding of the revenue cycle process.

Payer Landscape

Understanding health insurance coverage is a critical component of pharmacy reimbursement. Pharmaceutical medications are covered through either patient's pharmacy coverage/benefits (self-administered medications [i.e., orals and self-injectables]), or medical benefit coverage (facility administered medications). Such prescription or medical benefits are paid for and provided by the patient's insurer. Patients may be insured through a private or non-governmental organization, or through state or federal governmental programs like Medicaid or Medicare. Health insurers (i.e., insurance company/health plan) may have one or several lines of business, each with its own unique nuances of coverage. For example, a private insurer could offer commercial coverage through employer groups or the Marketplace, and government funded coverage through Managed Medicaid and Medicare Advantage Plans. Furthermore, each plan can offer various benefit types ranging from Health Maintenance Organization (HMOs) to Preferred Provider Organizations (PPOs).

Per the United States Census Bureau 2020 statistics on health insurance coverage, private insurance continues to dominate, with 66.5% of the population privately insured and 34.8% insured through various public coverage programs.[1] Figure 1 represents an approximate coverage spread throughout the year 2020.

Figure 1: Distribution of payer coverage for the United States in 2020*



*These numbers may not add up to 100% as some members may be enrolled for only part of the year and others may have switched from one type of coverage to another, or may have had dual coverage within the year 2020.[1]

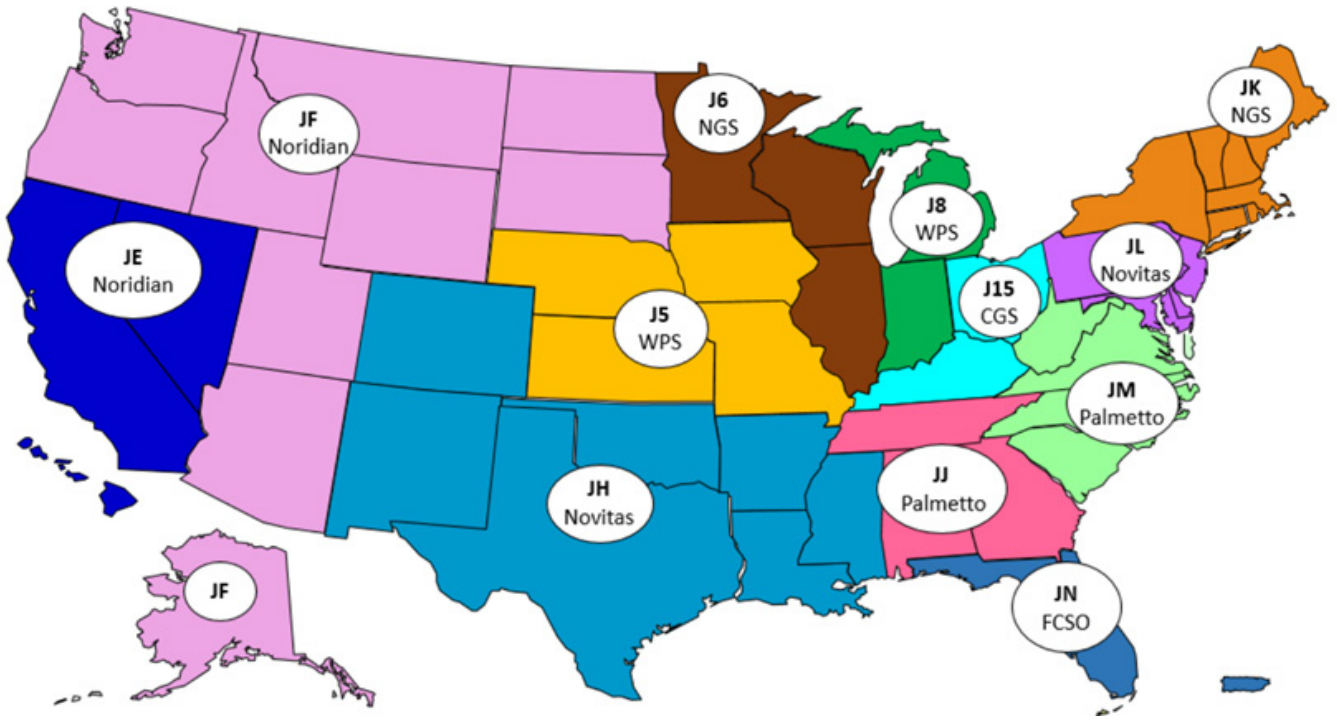
In addition to private coverage, patients may have health insurance coverage through federal or state governmental programs. Patients may be insured solely through a private insurer or a government program, or a combination of private and government funded programs. The Center for Medicare and Medicaid Services (CMS), within Department of Health and Human Services, administers the federal Medicare program and partners with state governments to administer Medicaid programs.[2] Medicare provides coverage for those citizens over 65 years old and some who are under 65 with certain disabilities.[3] Medicaid provides coverage for those with limited income and resources, and is administered by individual states. While Medicare coverage is generally standard across the United States, Medicaid coverage can have variations from state to state.

"As medication-related revenue plays a significant role in health system financials, pharmacists' knowledge and expertise can be a vital enhancement to the revenue integrity of the system."

Medicare coverage is provided for patients either through a Fee for Service (FFS) program or Medicare Advantage program. Fee for Service Medicare is administered by Medicare Administrative Contractors (MAC) with geographical jurisdiction.[4] Whereas, Medicare Advantage programs are administered by private payers, who may also provide commercial coverage. Both programs are governed by, and follow policies developed by CMS. However, Medicare Advantage plans may have additional plan-specific rules and guidelines which determine the coverage of outpatient medications in the infusion center. Many outpatient infusion medications administered in a medical facility are covered under Medicare Part B (outpatient medical benefit portion of Medicare). Generally, prior authorization is rarely required by Medicare; however, certain classes like immunoglobulins and erythrocyte stimulating agents may have specific policies guiding their utilization, and meeting the policy guidelines is imperative for receiving payment.[5] Guidelines developed by CMS outlining coverage are collectively known as National Coverage Determinations (NCDs). While MACs are required to follow NCDs, MACs may make additional coverage decisions by way of Local Coverage Determinations (LCDs) for items or services excluded or not mentioned in an NCD or Medicare manual.[6] The Medicare Part A and B jurisdiction map for MACs is provided in Figure 2.[7]

Medicaid programs are governed by individual states in which they are administered and may be either Fee for Service or administered by Managed Care Organizations (MCO). Medicaid program guidelines and policies are outlined by the State, and administrators follow these guidelines for claim adjudication. Often states list their covered and preferred medications on the Preferred Drug Lists (PDL). This is one-way that states manage medication benefits, and the PDLs vary by state, and may further vary based on whether members are enrolled via MCO or FFS.[8]

Figure 2: Medicare A & B Jurisdiction Map for Medicare Administrative Contractors[7]



Pre-certification

Due to the high cost of facility-administered medications, pre-certification (precert) is a critical part of the reimbursement life cycle. It is the requirement of the clinical provider, or appointed team(s) of delegates to obtain pre-certification before medication administration. Table 1 outlines the difference in pre-certification functions between the provider and health plan.

Ultimately, the outcome of the payer's pre-certification processing is either an approval or a denial. An approval indicates the provider is approved by the payer to proceed with the prescribed course of treatment. On the other hand, an authorization denial requires the completion of an appeal, peer-to-peer review, or a change in therapy. It is important to identify and remedy authorization denials before any treatment has been administered, as the payer may not reimburse the costs of the medication, putting the financial burden of payment on the health system or potentially patients.

Reimbursement Landscape

In traditional outpatient pharmacy settings, prescriptions are adjudicated in real time, meaning pharmacies know the outcome of the claim (i.e., approved or denied) prior to dispensing the medication to the patient. If the adjudication outcome is accepted, the payer accepts their responsibility to provide payment and the prescription moves forward through the dispensing workflow. If the adjudication outcome is declined, the pharmacist must resolve the rejections before proceeding with dispensing.

On the contrary, within infusion centers, several pieces of the revenue cycle function do not occur until after the administration of a medication. While pre-certification occurs proactively, this is not a guarantee of payment, and many processes/steps exist between therapy initiation and payment processing (see Figure 3).

Once treatment is administered, the billing process initiates and results in a processed claim to the patient's insurer. Comparable to the payer's pre-certification review process, the insurer will again review the claim to ensure the treatment was appropriate. One of the many challenges occurring in many large insurance companies is the team completing this review post-treatment may be different from the pre-certification team that provided the initial approval. This creates the possibility of a denial post-medication administration, even when the treatment was approved under the original pre-certification process.

Denials Management

A denial is a payer's refusal to provide payment for services rendered (i.e., medication administered). Denials can be appealed and over-turned, appealed and withheld (resulting in a write off), or written off without appealing. Some of the more common medication denials that infusion centers may encounter include:

- *Submission Errors* – Select payers have specific claims processing requirements and may issue a denial in the absence of an NDC, appropriate billing unit conversion, or billing modifiers.
- *Medical Necessity Not Met* - Typically this indicates the billed diagnosis is not considered covered, or that it does not align with what was pre-approved.
- *Lack of Authorization* – This does not necessarily mean an authorization is not on record, as it may be a payer processing error, or lack of an appropriate authorization. For instance, number of approved visits exceeded, site of care not covered, or medication is required to be supplied through pharmacy benefit are all examples of instances that can trigger such denial.
- *Provider Out of Network* – Insurer does not participate with provider's site of service.

One of the major challenges to denials management is determining how to best aggregate the denials data in a meaningful way. In a sea of outpatient hospital denials data including multiple specialties, treatment departments, and payers, it is difficult to efficiently analyze denial trends. Further compounding the complexity, the utilization of denial reasons or Claim Adjustment Reason Codes (CARC) is not standard across all payers. For instance, two payers may use the same denial code, however the root cause of each denial may be completely different. Lastly, the back-end revenue cycle teams supporting denials are typically more focused on resolving individual accounts, and many lack the time or expertise to positively impact future state denials through root cause analysis. To mitigate the financial damage of denied claims, the best defense is to prevent them from happening in the first place, and the most effective approach to this is bringing pharmacy and revenue cycle together.[9]

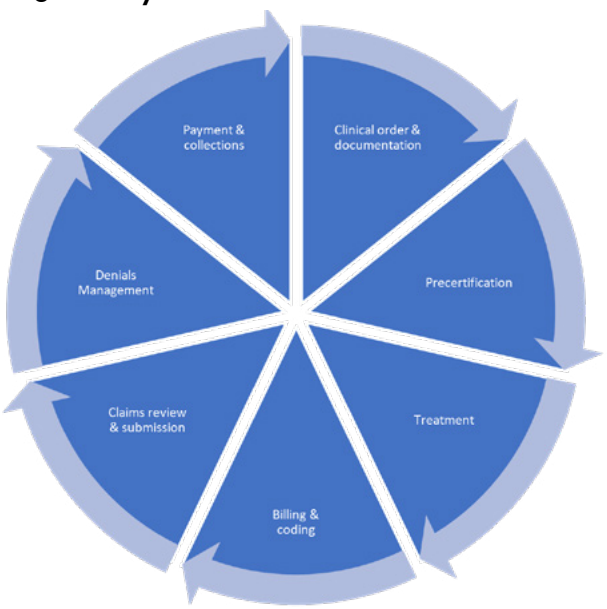
Pharmacist Value-added Interventions

Pharmacists can use their clinical acumen to decipher payer policy changes and support medical necessity reviews with appropriate diagnosis association. Further, they can support completing root

Table 1: Pre-certification Functions

Function	Provider/Delegates	Health Plan
Benefits investigation	Verify patient's insurance in Electronic Medical Record to confirm coverage is active	Verify patient's insurance in health plan's system to confirm coverage is active
Medical necessity review	Review medical policies to ensure clinical guidelines are met and ordered diagnosis is covered	Completes clinical review to confirm treatment meets payer's medical policy, typically derived from FDA approvals, clinical guidelines (covered diagnosis, site of care) and formulary alternatives (tiered or preferred biosimilar products)
Prior authorization	Submit request to insurance to pre-approve coverage	Administrative review is completed in addition (sometimes in parallel) to the clinical review

Figure 3: Life Cycle of a Claim



cause analysis for denials investigations and facilitate biosimilar interchanges based on payer preferences.

FDA approved indications and NCCN guidelines are regularly relied upon as part of a medical necessity review during the pre-certification process. Payers may have additional polices governing the utilization of certain therapies both in the oncology and non-oncology setting. Such policies may include clinical pathways, step-therapy protocols, restrictive formularies, and specialty tiers.[10] Understanding such policies, and ensuring a patient's therapy meets the appropriate criteria is essential prior to the start of treatment.

Investigating the root cause of the denial is labor intensive due to the complex life cycle of a medical claim. This requires a combination of clinical and revenue cycle expertise. Pharmacists can add value to this workflow by understanding the nuances of payer's medical policies and providing oversight to the clinical practices.

Biosimilar adoption is another area largely impacted by payer policies and is an ideal space for pharmacist intervention.[11] Ensuring the selection of the appropriate biosimilar on the front end can minimize treatment delays and avoid denials downstream. Payers may elect to have either the reference product or one or more biosimilars as their preferred agent. Medicaid manages the biosimilar preference by way of PDLs or prior authorization requirements.[8] Pharmacists can play an active role in ensuring the appropriate selection based on patient's coverage. Similarly, formulary restrictions and payer specific guidelines may also impact the selection of supportive care medications used within many oncology protocols.

Conclusion

Healthcare systems are being challenged with the rising costs of medications and complex revenue cycle processes for reimbursement. As medication-related revenue plays a significant role in health system financials, pharmacists' knowledge and expertise can be a vital enhancement to the revenue integrity of the system. Pharmacists can support this function on the front end by developing appropriate clinical guidelines and understanding and supporting the pre-certification process. They can further optimize revenue capture by providing clinical expertise needed for appeals and denial mitigation. Pharmacists' direct involvement in the provision of medication services for cancer patients makes them a valuable asset to not only ensure the wholesome care of the patient, but also the financial sustainability of the organization. ●●

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The Quality Oversight Committee of the Hematology/Oncology Pharmacy Association (HOPA) would like to congratulate the recipients of the Certificate of Recognition for Exemplary Research on Quality of Care in Oncology. The committee created a workgroup to review the completed research and trainee abstracts that were predetermined to be quality related. Each submission was evaluated and scored based on criteria that included quality of research, value metrics in the care of patients with cancer, and the potential impact on the current practice of oncology. Five certificates were awarded for abstracts presented at the HOPA 2023 Annual Conference in Phoenix, AZ. The following is a summary of these abstracts which showcased how oncology pharmacists are in a unique position to contribute to improving healthcare quality and value, while ultimately having a significant impact on patient care. Full versions of the completed research abstracts are published in the March 2023 JHOP Volume 13, Special Feature which can be found at jhoponline.com. All posters are available to attendees of the HOPA 2023 Annual Meeting through HOPA Learn (learn.hoparx.org).

Strategies for Implementing an Oral Medication Adherence Intervention[1]

Presenters: James B. Collins IV, PharmD & Benyam Muluneh, PharmD, BCOP, CPP

Drs. James Collins and Benyam Muluneh presented their research focused on identifying strategies to overcome barriers to an oral anticancer (OAC) medication adherence program. The study objective was to design pragmatic and stakeholder-informed strategies for the oral medication adherence program's adoption, implementation, and maintenance. An advisory panel of 9 physicians, 7 administrators, and 2 patients from an academic and a community cancer center was assembled. The advisory panel used a systematic approach called implementation mapping to select the best intervention strategies for the program. Likert-surveys and focus groups were used to evaluate the objectives, implementation strategies, and program evaluation outcomes. Ten performance outcomes and 18 performance objectives were identified from a series of qualitative consensus-based discussions and quantitative surveys. Next, 21 program strategies were proposed. After a series of focus group discussions and surveys, the list was narrowed to 7 proposed strategies for implementation: 1) formal program commitment documents, 2) key performance indicators, 3) a presentation justifying the program to leadership, 4) standard operating procedures outlining roles and responsibilities, 5) a workshop on motivational interviewing and adherence, 6) standardized adherence assessment integrated into the electronic medical record, and 7) establishing measurable performance indicators and metrics. The authors concluded that future research is warranted to ensure the appropriateness of the 7 strategies, followed by a pilot implementation study to gauge the effectiveness of the strategies proposed.

"The authors concluded that health system specialty pharmacists can play an important role in decreasing discontinuation rates of OAC agents through a 14-day treatment check-in."

Comparison of Discontinuation Rates in Patients Receiving an Oral Anticancer Agent Before and After Implementation of a 14-day Pharmacist Check-in Protocol[2]

Presenter: Kristin Hutchinson, PharmD, BCOP, CSP

Dr. Kristin Hutchinson evaluated the impact that health system specialty pharmacists can have on improving discontinuation rates of OAC agents. The primary objective of this study was to compare discontinuation rates in patients receiving OAC medication before and after a pharmacist-led check-in protocol is put in place to contact patients within 14 days of starting therapy. Baseline patient discontinuation rates and reasons were collected through a retrospective analysis from Trellis Rx network before initiating the protocol. At the 14-day pharmacist-led check-in, mitigation strategies, adverse effect management, and patient counseling were provided by the pharmacist. Furthermore, the pharmacist addressed all patient questions. If the patient required additional supportive care

medications, the provider was contacted. The system evaluated over 9000 OAC therapy regimens pre- and post-protocol. Before establishing the protocol, the discontinuation rate was 40.4% (n=4060), including 6.8% discontinuing due to intolerance. After establishing the 14-day follow up, discontinuation rates decreased to 29% (n=5354), and the discontinuation rate due to intolerance decreased to 2.8%. Overall, there was approximately an 11% decrease in discontinuation rates from the pre- and post-protocol initiative. The authors concluded that health system specialty pharmacists can play an important role in decreasing discontinuation rates of OAC agents through a 14-day treatment check-in.

Optimizing the Management of Oral Prostate Cancer Treatment Related Hypertension in an Ambulatory Hematology/Oncology Clinic[3]

Presenter: Sita K. Bhatt, PharmD

Dr. Sita Bhatt presented an ongoing quality improvement project evaluating the impact of a pharmacist on hypertension in patients receiving oral prostate cancer therapies. The objective of the project is to optimize blood pressure management in patients on OAC therapy and reduce the total time patients are off therapy due to uncontrolled hypertension by 50%. Blood pressure readings and adherence are recorded at each routine provider visit. Patients diagnosed with new or worsening hypertension without access to a primary care provider within the past 6 months are referred to a pharmacist-led antihypertensive program. Within this program, clinical pharmacy specialists manage hypertension using a treatment algorithm based on the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for hypertension. After meeting with the patient, interventions made by the clinical pharmacist are documented within the electronic medical record. The main outcome metric is the number of days patients are off OAC agents. Additional process metrics include number of dose reductions, number of antihypertensive agents added, and prostate-specific antigen levels. Balance metrics include number of patient visits and incidence of hypotension. Results of the project are pending, but the authors anticipate the conclusions will address changes in clinical practice and provide future opportunities of protocol expansion if the intervention proves to be successful.

Streamlining Scheduled Chemotherapy Admissions Within a Multihospital, Multistate, Integrated Health System[4]

Presenter: Alyssa Marquis, PharmD

Dr. Alyssa Marquis presented a project focused on the complex and time-consuming process of inpatient chemotherapy administration. The primary objective of this project was to implement an electronic health record report to recommend guidance on workflow adjustments and promote a well-ordered, efficient, and safe process for scheduled inpatient chemotherapy admission and administration. A report was developed within the electronic medical record to help identify 'failure points' within the current scheduled inpatient administration process. Through creation of an interdisciplinary chemotherapy admission workgroup, milestones for inpatient chemotherapy administration across the health system were identified. The group created a value stream map that identified failure points within their previous process that had the potential to delay patient care. These failure points were validated by the workgroup, and this led to the creation of a report within the electronic health record. The report calculated turnaround time data for various workflows, including the following: admission to order signature, lab result to order signature, order signature to release, admission to first drug administration, order release to first administration, and length of stay. Use of this report allows the health system to determine where workflow adjustments are needed to decrease healthcare costs, resource utilization, and length of stay while improving patient satisfaction and safety. Since implementation of this report, the oncology pharmacy department has been able to efficiently collect, sort, and evaluate data related to chemotherapy admission workflow. The authors concluded that the report allows for ongoing process improvement using targeted interventions for inpatient chemotherapy admission and administration.

Chemotherapy Education: A Prospective Comparison of Educational Modalities[5]

Presenter: Neha Betrabet, PharmD

Dr. Neha Betrabet presented an ongoing, prospective study evaluating different modalities of providing educational materials to patients receiving chemotherapy. The primary objective of the survey-based study is to compare patient knowledge retention after pharmacist-led education supplemented with either electronic or printed materials. The secondary objective is to compare overall patient satisfaction and to assess self-identification of toxicity. Patients with a new diagnosis of cancer who are planning to initiate 1 of 7 pre-specified chemotherapy regimens are eligible. Patients are randomized in a 1:1 ratio to receive pharmacist-led education with supplemental materials that are either electronic or printed. Immediately after education is complete, patients take a post-education survey and then repeat the survey 4 to 8 weeks later. The survey gathers patient demographic information and includes both general survey questions and regimen specific questions. The survey is also used to assess the level of satisfaction with the education experience provided by the pharmacist. Based on preliminary results, the authors concluded that the majority of patients were very satisfied with the pharmacist-led education and the educational materials added value. Average scores on the initial knowledge survey were 6.0 out of 8.0 (75%) for the online resource group and 6.4 out of 8.0 (80%) for the printed handout group. Knowledge of the chemotherapy regimen did not differ between groups, showing that the pharmacist was able to provide valuable information regardless of the supplemental material format. Patient enrollment and survey completion are ongoing. ●●

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All febRILED up About Antibiotics: Updates in Febrile Neutropenia

Jessica Freydman, PharmD
Clinical Pharmacist, Leukemia
Massachusetts General Hospital

Jack Malespini, PharmD
Clinical Pharmacist, Medical Oncology
Massachusetts General Hospital

Samantha O. Luk, PharmD, BCOP
Clinical Pharmacist Specialist – Oncology/Hematology: Immune Effector Cell Therapies/Cellular Therapy
Clinical Trials Pharmacist – Cellular Therapy
Massachusetts General Hospital

Febrile neutropenia (FN) is a common and potentially life-threatening complication seen in oncology patients. Optimal management of FN is a delicate balance between the appropriate use of empiric antimicrobial therapy (EAT) and prudent antimicrobial stewardship. This clinical pearl focuses on guideline-based recommendations, new literature, and a pharmacist's crucial role in antimicrobial stewardship programs and ensuring rational antimicrobial decisions.

The optimal duration of antibiotics remains unknown and discrepancies between guideline recommendations and clinical practice exist. Guideline recommendations can be broadly categorized into those with fever of unknown origin (FUO), clinically documented infection (CDI), and microbiologically documented infection (MDI).

The Infectious Diseases Society of America (IDSA) recommends that patients with FUO continue EAT until absolute neutrophil count (ANC) reaches or exceeds $0.5x10^9$/L. For patients with CDI/MDI, the duration of therapy is determined by the nature of the infection and EAT should be continued for at least the duration of neutropenia (until ANC $\geq 0.5x10^9$/L) or longer if clinically necessary. However, if a patient's treatment course has been completed and there are no signs or symptoms of the infection, neutropenic patients may transition to oral fluoroquinolone prophylaxis.[1]

The IDSA guidelines in 2011 set the precedent and subsequent guidelines have endorsed specific stewardship in cases of hemodynamic stability irrespective of neutrophil count. Although the 2022 National Comprehensive Cancer Network (NCCN) guidelines echo IDSA recommendations that EAT may be discontinued once ANC $\geq 0.5x10^9$/L in stable patients with FUO, the guideline also provides options to discontinue therapy, de-escalate to prophylaxis, or continue the current regimen in patients who remain neutropenic. Recommendations for patients with CDI/MDI align with the IDSA guidelines as well, emphasizing targeted treatment for documented infections and allowing for individualized de-escalation or duration of antimicrobial therapy based on specific patient factors.[2]

The European Society for Medical Oncology (ESMO) 2016 recommendations state that if a patient's ANC is $\geq 0.5\times10^9$/L and the patient is asymptomatic and afebrile for 48 hours with negative blood cultures, antibacterials can be discontinued. However, they also recommend antibacterial discontinuation prior to neutrophil recovery if the patient has no complications and is afebrile for 5-7 days. While it clarifies an exception of high-risk cases (acute leukemia and following high-dose chemotherapy) in which EAT is continued for up to 10 days or until the ANC reaches $\geq 0.5x10^9$/L, it does not provide supportive literature for this exception.[3]

Lastly, the European Conference of Infections in Leukemia (ECIL) (2013) supports EAT de-escalation after ≥72 hours of intravenous EAT in patients that are hemodynamically stable since presentation and afebrile for ≥48 hours, irrespective of their ANC or expected duration of neutropenia. However, if the patient remains neutropenic, it's recommended to continue inpatient observation for an additional 24-48 hours.[4]

"Emerging data suggest that EAT de-escalation prior to resolution of neutropenia is safe, theoretically decreasing antimicrobial resistance."

The differences between the guidelines for FN de-escalation reflect the evolution of diagnostics, improved outcomes through shortened time to start EAT, increased awareness of the link between extended broad-spectrum antibiotics and antimicrobial resistance, and emerging data regarding antimicrobial de-escalation. Emerging data suggest that EAT de-escalation prior to resolution of neutropenia is safe, theoretically decreasing antimicrobial resistance.

As a whole, the recent studies of early EAT de-escalation in high-risk FN patients suggest that the established mantra of waiting to de-escalate EAT until resolution of FN may not provide additional safety measures and may increase antibiotic exposure unnecessarily, especially as FN episodes often do not result in documented infection (Table 1).[1] The landmark HOW LONG trial in high-risk patients with hematological malignancies and FN supports discontinuation of empiric antibiotic therapy after 72 hours of apyrexia and clinical recovery irrespective of ANC as safe practice that reduced unnecessary exposure to antimicrobials.[5] Across all 4 studies, there were no significant differences in death, ICU admissions, and other adverse effects between early EAT de-escalation versus those that followed a more traditional EAT de-escalation strategy, despite the high-risk populations studied.[5–8] This suggests that in the absence of CDI/MDI, FN patients may be safely de-escalated more quickly than guideline recommendations, even in high-risk cancer populations such as those with malignant hematological diseases or bone marrow transplant recipients. Across the studies, the most common range for early EAT de-escalation was between 48 to 72 hours.[5–8] In addition, the studies demonstrated a statistically significant decrease in antibiotic exposure with early EAT de-escalation.[5–8] In the era of multi-drug resistant organisms, decreasing antibiotic

exposure, especially the broad-spectrum antibiotics used in FN, is especially crucial for the care of our cancer patients.

While guidelines and trials are constantly being updated, there exists an important bridge between published data and every-day practice. Quality improvement (QI) initiatives in health care focus on building frameworks and standardizing system-based processes aimed to reduce variation and improve results. QI data can help show the dynamic impact and sustainability of interventions on outcomes. The importance of data to analyze practice was highlighted in the HOPA QI workshop by quoting John F. Kennedy, who stated "For the great enemy of truth is very often not the lie – deliberate, contrived and dishonest – but the myth – persistent, persuasive, and unrealistic." Pharmacists are uniquely positioned to bridge the gap between guidelines and practice and to improve the care of oncology patients. At several institutions, pharmacists have already carved out their role in improving antibiotic utilizations in patients with FN.

Table 1. Summary of FN and EAT de-escalation studies in cancer patients

Trial	Patient Population	Interventions	Results	Conclusions
Aguilar-Guisado et al. 2017, HOW LONG trial[5] **Randomized, phase 4, comparative study**	n=157 Adult patients with hematological malignancies and/or bone marrow transplant with FUO	Experimental (n=78): EAT until apyrexia, resolution of all signs and symptoms of infection, normal vital signs for 72 hours or more vs Control (n=79): EAT continued until ANC > 500/mcL and the above criteria met	***Mean EAT-free days*** Experimental arm: 16.1 Control arm: 13.6 p=0.026 ***Mean total days of fever*** Not significantly different between arms ***Adverse effects*** Experimental arm: 323 Control arm: 257 p=0.057 ***Deaths*** Experimental arm: 1 Control arm: 3	For high risk patients with hematological malignancies and FN, EAT can be safely discontinued after 72 hours of apyrexia and clinical recovery despite neutropenia.
Le Clech et al. 2018, ANTIBIOSTOP trial[6] **Prospective, single-arm observational, open, non-randomized study**	n=123 Adult patients with hematological malignancies	2 consecutive phases in FUO group: 1. EAT discontinued 48 hours after fever resolution (n=68) 2. EAT discontinued on day 5 for all patients (regardless of fever status), but could be stopped earlier if afebrile for at least 48 hours (n=70) EAT discontinued regardless of ANC or expected neutropenia duration	No significant differences in the following: ***"Unfavorable outcome"*** (p=0.11) ***Median time to apyrexia*** (p=0.099) ***Hospital mortality*** (p=0.8) ***ICU admission*** (p=0.48) ***Recurrent fever or CDI/MDI <48 hours after discontinuation of EAT*** (p=0.82) ***Median duration of EAT*** Significantly lower during phase 2 (5 days) than phase 1 (7 days), (p=0.002)	For afebrile neutropenic patients, early EAT discontinuation in FUO is safe.
Schauwvlieghe et al. 2021 **Retrospective, comparative cohort study**	n=575 Patients with AML or MDS undergoing remission induction chemotherapy	EAT discontinued after 3 days of FN if no identified infection regardless of fever resolution (n=305) vs EAT until ANC recovery (n=270)	***Serious medical complications (death or ICU admission within 30 days of chemotherapy start***) No significant difference between the two groups (12.5% vs 8.9%, p=0.17) ***Median duration of EAT*** Significantly lower with 3 day EAT (9 vs 19 days, p<0.001)	Safe to discontinue EAT after 3 days of FN if no identified infection during remission induction chemotherapy.
Niessen et al. 2020[8] **Retrospective, comparative cohort study**	n=362 (FN episodes in 201 patients) FN related to chemotherapy or bone marrow transplant for AML or MDS	EAT discontinued after 3 days regardless of fever if vitals stable, no pulmonary focus, blood cultures negative (n=200) vs EAT until afebrile for 5 days (n=162)	***Antibiotic use*** Decreased carbapenem (p=0.03), vancomycin (p=0.01), and overall antibiotic use. ***Deaths, ICU admissions, and positive blood cultures*** No significant difference	Early EAT discontinuation decreases antibiotic exposure and appears to be safe.

AML: acute myeloid leukemia; ANC: absolute neutrophil count; CDI: clinically documented infection; EAT: empiric antimicrobial therapy; FN: febrile neutropenia; FUO: fever of unknown origin; ICU: intensive care unit; MDI: microbiologically documented infection; MDS: myelodysplastic syndromes

A single-center, pre–post, quasi-experimental study conducted at Michigan Medicine assessing the impact of an antibiotic de-escalation algorithm in high-risk patients with acute myeloid leukemia (AML) and FN found that antibiotic de-escalation in clinically stable, afebrile patients did not affect the rate of bacterial infection after de-escalation, all cause-mortality, or hospital length of stay.[9] The updated guideline, including an evaluation for de-escalation at day five regardless of ANC, was promoted daily on patient care rounds by the inpatient hematology/oncology clinical pharmacist specialists.[9] The study had a 70% rate of compliance, which is higher than previously reported rates for guideline-based management of FN and was likely the result of a multidisciplinary intervention that provided daily reinforcement by pharmacist specialists.[9] Of note, the study also evaluated antibiotic de-escalation in patients with suspected or microbiologically confirmed bacterial infection, a group not previously addressed. After implementation of the guideline, total antipseudomonal β-lactam days of therapy were significantly less in the intervention group as compared to the historical arm (14 vs 25; p<0.001), the incidence of *Clostridioides difficile* was significantly lower (3 [5.7%] vs 11 [27.5%]; p=0.007), and patients were more likely to have their intravenous antipseudomonal antibiotics de-escalated during the episode of neutropenia (38 [71.7%] vs 3 [7.5%]; p<0.001).[9]

In a similar initiative at Boston Medical Center, a pharmacist-led stewardship initiative was implemented using a common QI framework based on Plan-Do-Study-Act cycles. In this model, an initiative is implemented, data is collected and analyzed to assess its impact, and then a new initiative is formed based on the results. Stepwise cycles based on outcomes included updating the institutional FN treatment guideline, incorporating daily antimicrobial steward pharmacist reviews, and providing education to oncology care team members.[10] Particular focus was paid to properly identify patients eligible for empiric methicillin-resistant *Staphylococcus aureus* coverage and to consider observation off antibiotics in patients hemodynamically stable and afebrile for 72 hours without evidence of infection.[10] Over the course of 6 months, optimized antibiotic prescribing increased from 27.9% to 75.9% (n=22/29), including optimized empiric therapy which increased from 47.8% to 89.7% (n=26/29), antibiotic de-escalation which increased from 22.0% to 80.0% (n=16/20), and optimized duration of therapy which increased from 59.5% to 89.3% (n=25/28) pre- and post-initiative, respectively.[10]

Lastly, a single site prospective study in Thailand showed that a pharmacist-driven antibiotic stewardship program had a favorable impact in a multivariable analysis on 30-day infectious diseases-related mortality in chemotherapy-induced FN patients (OR 0.058, 95% CI 0.005–0.655, p=0.021).[11] The intervention group included the development of a recommended antibiotic regimen by a multidisciplinary group, daily prospective audits and feedback to the primary physician led by a clinical pharmacist, and education via lectures and posters by the pharmacist during monthly ward conferences.[11] The most common pharmacist interventions in comparison to the control group were de-escalation (22.2% vs. 20%, p=0.796) and adding additional antimicrobials (17.8% vs. 8.9%, p=0.215).[11] Although the frequency of infectious disease consultation was similar in both groups, the pharmacist initiative improved overall antibiotic appropriateness (88.9% vs. 51.1%, p<0.001), including appropriate empiric therapy (97.8% vs. 77.8%, p=0.007), dosage regimen (97.8% vs. 88.7%, p=0.049) and antibiotic coverage (100% vs. 91.1%, p=0.041).[11]

The above examples support that incorporation of pharmacist-led stewardship review and the promotion of multidisciplinary collaboration in recommendations are effective strategies to optimize antibiotic utilization and improve outcomes in patients with FN through promotion of adherence to recent data and changing guidelines. ●●

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Great Expectations – Walking the Fine Line Between Preceptor, Mentor, Friend, and Colleague

Rob Wills, PharmD, MS, BCPS, DPLA
Oncology Pharmacy Manager
St. Luke's Cancer Institute

"Why can precepting be such a chore?"

A friend said this to me at the recent HOPA Annual Conference in Phoenix this past spring. She went on to clarify that, *"okay, maybe chore is too strong a word, but just when you feel you have it locked in, a new resident or student forces you to rethink everything."*

Her story starts with a resident that was a clear superstar. A resident that stood out at every level up until now. Top of pharmacy class while serving as hospital intern, and student lead for the state pharmacy society. Success continued through a strong PGY1 year with projects that were accepted for publication and representation at national conferences.

As the Residency Program Director of her east coast site, she thought all the hard work was behind her. The slow grind of recruiting, interviews, and the Match, all done and dusted.

It seemed clear that this resident would just keep rolling, checking off boxes. All she had to do was chill until she had to start it all over again with the next recruiting cycle.

So why then did this resident end up almost not graduating from the residency program, virtually steps away from leaving oncology pharmacy altogether in favor of a contract with a national chain?

Looking back on the experience she couldn't help feeling like they had failed the resident somehow. Reflecting on the year, she started to see some common themes that occurred from preceptor to preceptor. In many cases there was a tendency by preceptors to be more of a friend, and less a teacher, coach, or preceptor. This was especially noticeable in the newer preceptors, those that were not very far removed from their own residencies.

Finding balance in the preceptor/resident relationship is not easy. Former Wharton Professor, Rachel Pacheco, has some useful tips that translate well to navigating this balance, and it all centers around setting good expectations.[1]

Why Our Best Intentions Often Get in the Way

One thing that trips up so many preceptors is expectation setting. While we may have the best intentions, with plans of sitting down and covering everything from the syllabus to unit norms, we find ourselves skipping forward, jumping into more pressing issues of the day. Whether it be the latest shortage crisis, the tech sick call, the infusion reaction in chair seven, one of the first things that is left behind is providing a clear picture of what is expected by that resident throughout the rotation. The result is missed opportunities that end up being passed on to the next preceptor and next rotation, where the cycle repeats, in perpetual madness.

Why are we so bad at setting good expectations for our residents? Turns out that it might not be what you think. Pacheco highlights that there are two main reasons that prevent us from setting clear expectations for our residents.

1. The internal fear of being a micromanager
2. The dreaded Dunning-Kruger Effect

Fear of Being a Micromanager?

I know you are thinking, "*No way, that's not me!*" You would be surprised, though, how much this occurs, especially with those stellar PGY2 residents. Your instinct is to want to be liked by the new resident, maybe even thought of as the "cool preceptor." The one that allows for resident independence and makes work-life balance the priority. One thing is for sure you are not going to nitpick or micromanage her rotation. Instead, you welcome her to the team. Give her a place to work and essentially treat her as an equal team member and friend.

Flash forward six weeks later and there is little growth in the resident's ability or skills. Why would there be? In fact, there were quite a few errors or issues you had to "clean" up for her because she didn't take the right steps laid out in protocol or she cut corners and didn't communicate a proper handoff. Well, no worries, she will learn on the next rotation...

"Finding balance in the preceptor/resident relationship is not easy."

Overcoming the fear of being a micromanager is tough but necessary. Instead of letting the resident figure it out, it is essential that you provide clear direction that allows the resident to solve problems and learn, and thus, thrive in the rotation. In fact, it turns out residents, like most of us, appreciate clear direction and communication. Of course, we don't want someone hanging over our shoulders telling us what to do in every second but providing the specifics on the goals and tasks at hand, followed by some after action review and feedback, can set the resident up for success and growth.

Dunning-Kruger

The second barrier is the known cognitive bias that creeps up when we sometimes think a person either knows more than they do, or that the task is easier to complete than it actually is. This situation is famously defined by David Dunning and Justin Kruger, now known as the Dunning-Kruger effect.[2] Pacheco notes that newbies, in this case residents, are overly confident in what they are doing, say working up a patient and recommending a treatment plan. Additionally, the resident will underestimate the time it takes to complete it. Suddenly you find yourself trying to help play catch up in a queue full of orders while that stellar resident continues to review and workup an antiemetic plan for a dose dense AC.

The above example also sheds light on the other component of the Dunning-Kruger effect where the expert (this is you the board-certified preceptor) believes that the task is easy to do since

you have done it hundreds of times. You can't understand why the resident is taking so long and it only fuels your frustrations.

Both issues, the fear of micromanaging and the propensity to fall prey to the Dunning-Kruger effect, can be remedied by setting out clear expectations at the very beginning. Pacheco goes one step, or maybe a few steps, further saying it's not just clear expectations, but that you need to make clear what "good" looks like and what is the timing.

For example, your new resident arrives on day one to start the Med/Onc rotation at your infusion clinic. You state that one of your goals is for the resident to be able to staff the clinic pharmacy independently one day per week starting the third week of the six-week rotation.

Okay, now, you've stated the goal in a broad text. The next step, specifying what this looks like, is key. For example, what this should look like for our resident is that she is able to review the patient lists first thing in the morning, identifying any new patients/first time infusions, and prepare antiemetic recommendations and education for the patient. The resident will address any infusion reactions and be the primary person responsible for the med verification coming out of the IV room. Lastly the resident will attend the morning nursing huddle and provide any updates to the staff as well as a 5-minute pearl on a new agent just approved at Oncology P&T. Thus, you've included one goal for the rotation. You identified when the resident should be able to satisfy that goal. And you've mentally painted a picture of what "good" should look like.

One last key step is to provide examples of what this should look like. In most cases that might be the easy part. You might say, "as an example, follow Sarah who is the lead pharmacist this Friday. She has a good technique in working up patients and communicates well with both the pharmacy techs and nurses." For a nice, step-by-step guide, check out Pacheco's free Expectation-Setting Template which can be found at bringinguptheboss.com/tools.[3]

The Feedback Special Sauce

Hold on. There is one more key ingredient in this process that Pacheco emphasizes – The need for frequent feedback. Feedback that is actionable and objective.

She points out that feedback is going to be awkward and uncomfortable most of the time. This goes against our tendency to want to be liked by the resident or student, but you still need to do it.

Her "super simple" framework consists of these four steps:[3]

1. Explain the situation (e.g., "I observed…", "I noticed…")
2. Explain how it affected the situation (e.g., "The lack of handoff made others feel…")
3. Pause for clarification (i.e., listen and answer any questions)
4. Suggest a change in behavior or process – Actionable!

Of course, a discussion on effective feedback can fill up an entire article or book, for that matter. Suffice it to say, setting clear expectations and following them up with frequent, constructive, and structured feedback can change the trajectory of your residents, helping them succeed and allowing you to grow as well. ●●

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FEATURE

To B or not to B: Considerations for Implementing Blinatumomab and ECOG 1910 in Adult Ph(-) ALL

Lydia Benitez, PharmD, BCOP
Outpatient Leukemia Pharmacy Specialist & Clinical Assistant Professor
Michigan Medicine and University of Michigan College of Pharmacy

Bernard Marini, PharmD, BCOP
Inpatient Hematology Pharmacy Specialist & Clinical Associate Professor
Michigan Medicine and University of Michigan College of Pharmacy

Anthony Perissinotti, PharmD, BCOP
Inpatient Hematology Pharmacy Specialist & Team Lead
Michigan Medicine

Practitioners specializing in the treatment of adults with Philadelphia chromosome-negative Acute Lymphoblastic Leukemia (Ph(-) ALL) are intimately familiar with the challenges of adopting Berlin-Frankfurt-Munster (BFM) style and/or pediatric inspired regimens to their population. Initially, the BFM group developed and popularized intensive multi-agent chemotherapy regimens, designed specifically for children aged 1-18 years, due to the prevalence of ALL as the most common pediatric malignancy.[1] Over time, BFM regimens have been augmented with various modifications including an emphasis on multiple doses of asparaginase. These modifications have contributed to the excellent long-term survival rate of over 90% in the pediatric population.[2] Given the remarkable outcomes associated with pediatric regimens in treating ALL, there has been a movement towards employing pediatric-inspired regimens, some of which borrow from BFM principles without being true BFM regimens, in adolescent and young adult (AYA) patients. Multiple retrospective comparisons have demonstrated superior event-free survival (EFS) and overall survival (OS) rates in AYA patients receiving pediatric-inspired therapy; however, there have not been prospective randomized controlled trials comparing pediatric-inspired therapy to adult regimens in this setting.

Complications from asparaginase and steroid toxicities can impede the effective delivery of pediatric-inspired regimens to adults, particularly those over the age of 50, where the second ALL incidence spike occurs. Notably, older patients, owing to their higher incidence of comorbidities such as obesity, hypertension, and hyperglycemia, have a greater predisposition to adverse events. Maintaining the intensity of the regimen over a period of 2-3 years without causing organ damage can also pose challenges. It is important to note that while many pediatric-inspired regimens are built from a BFM backbone, not all BFM regimens are pediatric inspired. That is to say, many BFM regimens for adults do not contain the same intensity of therapy or number of asparaginase doses that have been incorporated over time in pediatric regimens, due to the lower tolerability of these interventions in adults.[3] Additionally, non-asparaginase regimens have been developed, namely HyperCVAD/Methotrexate and Cytarabine, and many institutions across the country have adopted this regimen in their adult populations due to a perception of increased safety compared to the BFM approach, though these regimens have never been compared head-to-head in prospective trials.[4]

The Eastern Cooperative Oncology Group (ECOG) recently presented the results of the incorporation of blinatumomab to a BFM regimen, for the treatment of adults with Ph(-) B-cell ALL.[5] In the interim of a full publication to better appraise the results of this study, centers are pondering if and how to incorporate this regimen into their current Ph(-)ALL treatment approach. Herein, we summarize key findings of ECOG1910, potential implications and limitations of the study design, and available data to provide some guidance on clinical considerations for implementing ECOG1910.

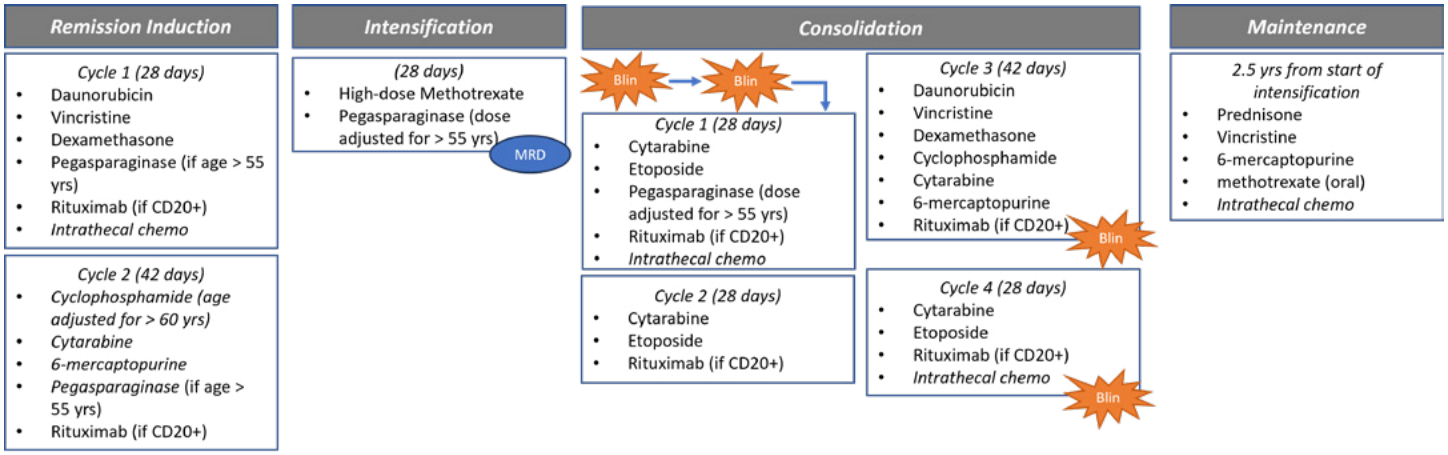
"Overall, an excellent question for clinicians to ask themselves when considering the application of these trial results is, 'Do we think the ECOG1910 BFM backbone regimen is the best regimen for this patient?' "

Trial Rationale and Methods

At this point the reader is likely itching to learn the pivotal findings of this study presented as a Late-Breaking abstract at the 2022 American Society of Hematology (ASH) conference in New Orleans, LA. However, to appraise these results, one must first dig into the intent of the study and its methods because this context is crucial for appropriate result appraisal. ECOG-ACRIN 1910 was a phase III trial that was originally intended to serve as one of two confirmatory trials for the BLAST trial, which led to the accelerated approval of blinatumomab for patients with B-cell ALL and measurable/minimal residual disease (MRD+) greater than 0.1%.[6] Post-marketing confirmatory trials are required when a drug is approved via the accelerated pathway to ensure that the intended clinical benefit is in fact seen when the treatment approved is compared to standard of care interventions.[7] ECOG 1910 randomized adult patients ages 30-70 years old with newly diagnosed B-cell Ph(-) ALL to a standard of care BFM regimen utilized in adult populations (based on the previously published ECOG 2993 regimen) to receive blinatumomab at various time points (Figure 1).[8] Readers are encouraged to review the protocol schema as well as the original ECOG2993 regimen closely to understand the randomizations and modifications.[9]

Patients who were in a morphologic complete remission (CR) at the end of induction (10 weeks from start of therapy) proceeded

Figure 1: Simplified Schema for ECOG 1910



MRD Denotes when the MRD assessment for randomization purposes occurred.

Blin Denotes a 28-day cycle of blinatumomab received in addition to the chemo if patients were randomized to this arm. Of note all MRD+ patients received blinatumomab after trial amendment.

to intensification (4 weeks of therapy) and were then randomized to receive an additional 4 cycles of consolidation chemotherapy or blinatumomab plus 4 cycles of consolidation with blinatumomab being incorporated at various time points for a total of 4 cycles (Figure 1). For the purposes of cohort development, MRD negativity (MRD(-)) was assessed at the end of intensification and was defined as less than 0.01% (1 in 10^{-4}) disease when assessed via multiparametric, 6-color flow cytometry. This definition is consistent with the definition used in the BLAST trial which led to the accelerated approval of blinatumomab in this setting. A full discussion about definitions of MRD (+) is beyond the scope of this article, and the authors refer the readers to several excellent reviews on this subject.[10-12] Nonetheless, it is important to note that in recent years the capabilities of MRD detection have improved significantly using more advanced techniques, including high-sensitivity 10-color flow cytometry as well as more sensitive modalities such as quantitative polymerase chain reaction (qPCR), allowing detection of much lower levels of MRD (e.g., $<10^{-4}$) and next-generation sequencing which can detect up to 10^{-6}. Thus, a proportion of patients considered MRD(-) in ECOG 1910, could be considered positive with current detection capabilities.

Originally, the primary objective of this trial was to confirm the clinical benefit of blinatumomab in patients with MRD(+) disease as previously discussed, thus these patients were randomized to receive blinatumomab. However, after the approval of blinatumomab in 2018 the trial protocol was amended to no longer randomize patients and instead assign all patients with MRD(+) disease after intensification to the blinatumomab-containing arm. Randomization for MRD(-) patients continued. With this shift in the protocol, the new primary objective was to assess the impact of blinatumomab on OS in patients who were MRD(-) at the end of intensification (i.e., after 14 weeks of therapy). Patients were allowed to proceed to allogeneic hematopoietic cell transplant (AlloHCT) per institutional guidance with a suggestion for it to occur after the first 2 cycles of blinatumomab if patients received this intervention, or at any time following intensification for those who were randomized to the standard chemotherapy arm. The late-breaking abstract at the 2022 ASH Annual Meeting summarized the findings of patients that were MRD(-) at the end of intensification.

Results

From 2013 through 2019, 488 patients from the United States, Canada, and Israel were enrolled of which 286 patients remained in a CR and were eligible for randomization at the end of intensification. Of these, 224 MRD(-) patients were randomized 1:1 to blinatumomab and chemotherapy versus standard chemotherapy (n=112 in both arms). The median age of the overall study population was 51 years (range 30-70 years). For the MRD(+) patients, 44 were randomized and the other 18 were assigned to the blinatumomab-containing arm after the protocol amendment was passed. With a median follow-up of 43 months, 56 patients who were MRD(-) died: 17 in the blinatumomab arm and 39 in the chemotherapy arm. Blinatumomab resulted in an improvement in OS with a median OS not reached versus 71.4 months (hazard ratio 0.42, 95% CI 0.24-0.75, p=0.0003).

The Applicability

So what is to be done with these findings? Overall, the survival rates in both arms are highly encouraging; however, it is important to note that randomization required patients to achieve MRD(-) CR without significant complications through 14 weeks of therapy, so there is some immortal time bias that limits cross-trial comparison to other studies and treatment strategies. While it is unfortunate

that randomization was stopped for MRD(+) patients, what conclusions can we draw from this study for Ph(-) ALL patients with MRD(-) disease? Should centers switch to the BFM regimen utilized in ECOG1910 with the addition of blinatumomab for all adults with Ph(-) ALL who are 30-70 years old? If centers utilize non-BFM regimens for adult patients, should blinatumomab be incorporated into those regimens? In the following sections, we break down our recommendations for Ph(-) ALL by specific age subgroups.

Adolescent Young Adult population (patients aged 15-39)

This study included AYAs between the ages of 30-39 years; however, the median age was 51, considerably older than the typical AYA patient. As mentioned previously, pediatric-inspired therapy is currently the standard of care for AYA patients with Ph(-) ALL. Two pediatric-inspired regimens, CALGB10403 and DFCI 00-01, are the NCCN guideline "preferred" regimens in this setting, based on retrospective comparisons to adult BFM regimens, whereas ECOG1910 with blinatumomab is considered an "other" recommended regimen.[13] It is important to note that while the chemotherapy arm of ECOG1910 does include some of the augmentations of a typical pediatric-inspired regimen, ECOG1910 was an adult BFM strategy, and patients in ECOG1910 received up to 4 pegasparaginase doses whereas typical pediatric-inspired regimens contain significantly more asparaginase courses (e.g., 7 doses of PEG-asparaginase in CALGB10403, 30 weeks of sustained depletion in DFCI 00-01). Another important note about ECOG1910 and how it compares to CALGB10403 is the addition of several courses of etoposide in consolidation which raises concerns from a survivorship perspective with regards to increased risk of infertility and development of secondary malignancies. It is unknown whether the addition of blinatumomab to an adult BFM regimen such as ECOG1910 is superior from an efficacy or toxicity standpoint to the current standard of care pediatric-inspired regimens in this population. It is also unknown whether blinatumomab would improve clinical outcomes when added to a pediatric-inspired therapy—particularly for those who are already MRD(-), a subgroup where approximately 80% achieve cure without the need for blinatumomab. Both questions require future randomized controlled trials, and there is no clear cut, correct approach.

Patients aged 40+ and fit to receive BFM regimen

For adult patients fit enough to receive BFM regimens, ECOG1910 has demonstrated that blinatumomab improves OS compared to standard BFM-based chemotherapy in MRD(-) patients. Thus, ECOG1910 + blinatumomab is now the NCCN preferred regimen for this population.[13] However, if centers utilize other BFM-based strategies (e.g., "Larson"/CALGB9511) with a similar chemotherapy backbone and asparaginase strategy to ECOG1910, it is likely reasonable to extrapolate results of ECOG1910 and incorporate blinatumomab to these regimens for MRD(-) patients, although a transition to ECOG1910 for such centers is more feasible and data-driven.[3,14-16] However, many centers currently utilize HyperCVAD, a much different chemotherapy backbone, for adult patients fit for chemotherapy. It is unknown whether blinatumomab improves outcomes in this setting, and future trials are required to assess the possible benefit of blinatumomab for MRD(-) patients in this setting and the optimal timing of such an approach.

Conclusion

Overall, an excellent question for clinicians to ask themselves when considering the application of these trial results is, "Do we think the ECOG1910 BFM backbone regimen is the best regimen for this patient?" If yes, then proceed, follow the protocol carefully noting when to omit, cap, and dose-adjust pegasparaginase, as well as when to dose adjust other agents; and add blinatumomab for patients who are MRD(-) at the end of 14 weeks on this regimen. A final important consideration is that patients who were deemed high-risk either due to disease features or MRD(+) at disease prognostic timepoints were encouraged to (and did) proceed to AlloHCT. As such, the incorporation of blinatumomab should not be seen at this time as a method to avoid AlloHCT in a high-risk patient, but rather as a method to achieve a deeper response prior to AlloHCT. ●●

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HOPA Annual Conference 2023 Sought to Empower Our Patients to Become Self-Advocates



Written by: Jameshia Below and Sara Leidy with additional edits by Oxana Megherea

This year's HOPA Annual Conference (AC) theme was "Reconnect. Rebuild. Reimagine." Members returned in person to reconnect with friends and colleagues during this week-long event. Those in attendance included members of the Patient Advisory Panel. A special Patient Advocacy Session was held that focused on the theme, "Empowering Our Patients to Become Self-Advocates: Improving Patient Care Together." This session was very engaging as patient panelists and members began to discuss a wide variety of topics. All those in attendance were engaged during this intriguing session that allowed for members and panelists to recount personal stories and share their experiences while undergoing treatment or while treating patients. The members of the Patient Advisory Panel help to provide patient perspectives for our committees, councils, and task forces and have become an integral part of HOPA.

"Hearing the patients' perspectives helped me to re-center on WHY I'm doing what I'm doing."

Q & A With the Patient Advisory Panel

Members who attended the Patient Advocacy Session were asked the following questions to help recount their experience during the HOPA AC 2023.

What is something you took away from attending the Patient Advisory Panel that you would like to share with readers?

Morgan Kelly – Panelist

I think that HOPA members understand how critical they are to healthcare teams, and the session not only reinforced that, but also provided new approaches for pharmacists to consider outside of their traditional strategies. I mean that in the sense of a hematology pharmacist getting feedback from a pancreatic patient – it's outside of their normal scope, but there are definitely aspects of the patient experience that cross over. Honestly, for me, my favorite part was that in speaking, and sharing my perspective, I actually learned about myself. One of the comments that I made at the session was that even though I am approaching 9 years post-treatment, I still take daily medications to deal with the effects of the chemotherapy that I received. I am a pharmacist, and while yes, I think "oh, I take X medication for Y condition" I'd never really thought about the fact that it was all a result of my chemotherapy and its side effects – it's humbling.

Karen Fancher – Panelist

An audience member asked the panelists what their worst experience was as a patient. Not a single one mentioned adverse effects, drug interactions, or essentially anything related to their drugs. However, they all discussed not feeling "heard," or feeling that their care team wasn't considering their unique situations thoroughly enough.

Erin Buss – Panelist

The ability to share my cancer journey and perspectives to (hopefully) create positive change for future patients. The opportunity to sit at the table and be invited into the conversations. Attending the conference is a good look into what is happening "behind the scenes" and to learn more about everything that goes into improving patient care and outcomes.

Emily Armgardt - Committee Member

Many of the panelists spoke about how isolated they felt during the initial diagnosis period and that they would get bombarded with information. This really struck a chord with me since pharmacists often see patients during this initial overwhelming period, so I think it highlighted that we need to ensure patients feel heard and feel like they can trust and communicate with every member of their health care team.

Sarah Wheeler - Committee Member

I took away that every encounter, especially those first ones, those first impressions, go a long way and that to earn a patient's trust, sometimes you only have one shot, so don't mess around, or ever discount the patient experience, their emotions, or that their world was just turned upside down. Thinking about that whirlwind period and how best to support and not overload patients with information as well.

Why do you believe that getting the patient perspective via the Patient Advisory Panel at HOPA is essential for practicing pharmacists?

Morgan Kelly – Panelist

My experience at HOPA AC is kind of unique, in that I am there as a patient advisor but also as a HOPA member. I work part time as an oncology infusion pharmacist, so HOPA AC is really a one stop shop for me: to advocate for patients and the patient experience, to see

and reconnect with colleagues, and to immerse myself in the learning opportunities available. I would tell other patients that HOPA AC is such a valuable experience because the people that you will meet at AC are hungry for the perspective and input of patients. At a conference like HOPA's, outside of the waiting areas and exam rooms and phones, there is really the opportunity to connect with each other and share stories and points of view.

Karen Fancher – Panelist
I think that just about everyone who enters the field of oncology pharmacy does so because they care about their patients. However, once we get to work, it's very easy to get caught up in the process and the "business" of our everyday routines. Hearing the patients' perspectives helped me to re-center on WHY I'm doing what I'm doing.

Emily Armgardt - Committee Member
The patient perspective is crucial to receive as an oncology pharmacist so that we can provide better care for all of our patients. Due to our background and education, it is very easy to take a more clinical view and forget the more personal aspects of our oncology patients and their care, so this helps us take a step back and reminds us why we choose this profession and how much pharmacists can have an impact.

Sarah Wheeler - Committee Member
I think that we all know WHY we are oncology pharmacists and beyond all of the mechanistically cool medications, it is to help the patients and caregivers understand and navigate through their cancer journey. I think the more we hear from patients the more educated we are on the best ways to help them and advocate for them as well as equip them with the knowledge and resources and advocate for themselves as well.

Where do you want to see these patient advocacy sessions go moving forward?

Morgan Kelly – Panelist
My one thought for the future, would be to maybe develop a framework around the financial side of patient advocacy versus the treatment decision support roles versus the overall social support systems? Each patient comes with such a unique combination of needs in those three areas. The financial toxicity piece pairs well with HOPA's work in oral parity. The treatment decision part pairs beautifully with HOPA's work to see a hematology/oncology pharmacist on each treatment team. And pharmacists as a whole are often well placed and suited to deal with other support systems, in addition to our partners like Stupid Cancer and Cancer Support Services.

Karen Fancher – Panelist
As someone who works with mainly geriatric patients, I was very intrigued by the young adult advocacy group that was present on the panel. Having more sessions with both patients and advocacy groups would benefit all HOPA members.

Emily Armgardt – Committee Member
Many of the panelists this year were early-stage cancer patients, so in the future it would be very interesting to hear from metastatic patients and their unique challenges throughout their journey.

Sarah Wheeler - Committee Member
There were a lot of cured or going to be cured patients, and maybe I am biased because my mother had stage IV colon cancer for 9.5 years, but a mix of early stage, late stage, and those like the pancreatic cancer patient that have beat the odds would be neat because perspectives are different. Set treatment cycle versus continue until toxicity, or progression is completely different and hearing the differences I think could be beneficial. ●●

HOPA2024

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WELCOME TO OUR 20TH ANNIVERSARY CELEBRATION!

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Planning is already underway! CE sessions are being developed and presenters are being secured. Poster abstracts are streaming in for completed research (trainee and late breaking calls open soon)* and, networking sessions are being planned.

Last but not least, HOPA is gearing up activities to celebrate our 20 years of optimizing cancer care!

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Hyperfractionated Cyclophosphamide and Dexamethasone Alone or in Combination with Daratumumab and/or Carfilzomib for the Treatment of Relapsed or Refractory Multiple Myeloma: A Single-Center Retrospective Analysis

Erin Yeung, PharmD, BCPS, BCOP
Clinical Pharmacy Specialist, Lymphoma/Myeloma
The University of Texas MD Anderson Cancer Center

Brian Primeaux, PharmD, BCOP
Clinical Pharmacy Specialist, Lymphoma/Myeloma
The University of Texas MD Anderson Cancer Center

Background

Despite major advancements in treatment options for both frontline and relapsed/refractory (RR) multiple myeloma (MM), it remains an incurable disease.[1] In the setting of high tumor burden, acute renal failure (ARF), plasma cell leukemia (PCL), and extramedullary disease (EMD), rapid disease control using aggressive cytoreductive chemotherapy regimens may be needed as a bridge to stem cell transplantation (SCT), chimeric antigen receptor T-cell (CAR-T) administration, or other less intensive therapies.[2] Historical regimens that have demonstrated response in RRMM include DT-PACE (dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide), DCEP (dexamethasone, cyclophosphamide, etoposide, and cisplatin), and VDT-PACE (bortezomib, dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide). [3-5]

"In this single-center retrospective analysis, we combine novel targeted agents with alkylator based chemotherapy and report the response and safety outcomes of HyperCd-based regimens, with and without carfilzomib and/or daratumumab, in patients with RRMM."

Hyperfractionated cyclophosphamide and dexamethasone (HyperCd)-based regimens such as hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone) and modified CBAD (mCBAD; a high-dose modified cyclophosphamide, bortezomib, doxorubicin, and dexamethasone regimen), can also achieve disease control to bridge patients to SCT.[2, 6-7] The addition of carfilzomib (K), a proteasome inhibitor, and daratumumab (D), an anti-CD38 monoclonal antibody, are thought to enhance the efficacy of anti-myeloma therapy while having distinct toxicity profiles from cytotoxic chemotherapy agents. Each has demonstrated efficacy in patients with heavily pre-treated myeloma, including those with high-risk cytogenetics.[8-9]

In this single-center retrospective analysis, we combine novel targeted agents with alkylator based chemotherapy and report the response and safety outcomes of HyperCd-based regimens, with and without carfilzomib and/or daratumumab, in patients with RRMM.

Methods

Adult patients with RRMM or PCL who received HyperCd alone or combined with D and/or K between May 1, 2016 and August 1, 2019 at The University of Texas MD Anderson Cancer Center (Houston, TX) were included in this retrospective analysis. Data was collected from patients' electronic medical records (EMRs). Toxicity data was collected for up to 28 days from the start of each cycle. Refer to Table 1 for dosing and supportive care details.

Results

A total of 97 patients received HyperCd (n=20), HyperCdK (n=31), D-HyperCd (n=19), and D-HyperCdK (n=27) for RRMM. Twelve patients had PCL. In total, 54 patients had EMD and four had leptomeningeal disease. The median number of prior therapies was five (range 1-17).

The median follow-up was 32.2 months (95% CI 24.1 months - not reached) across all groups. Best overall response rate (ORR), progression free survival (PFS), and overall survival (OS) results are located in Table 2. Treatment was stopped due to disease response and/or transition to SCT in 54% of patients. Nine patients underwent stem cell mobilization following treatment (HyperCd [n=1], HyperCdK [n=3], D-HyperCd [n=1], D-HyperCdK [n=4]). Twelve patients underwent autologous SCT (HyperCd [n=1], HyperCdK [n=4], D-HyperCd [n=1], D-HyperCdK [n=6]) and one patient underwent allogeneic SCT within 60 days following D-HyperCdK.

All but two patients received growth factor support. Following treatment, 85% of patients had grade 3/4 hematologic toxicities. Grade 3/4 neutropenia was seen in 65 patients (67%), febrile neutropenia in 44 patients (45%), grade 3/4 thrombocytopenia in 74 patients (76%), and grade 3/4 anemia in 70 patients (72%). Despite aggressive supportive care, 68% of patients were re-hospitalized. Twelve patients died within 60 days of treatment (11%), including four patients with PCL. The primary cause of death was disease (83%) followed by sepsis in the setting of pancytopenia (8%); cause of death was unknown for one patient.

Table 1. Details of the 28-Day Cycle Hyperfractionated Cyclophosphamide Plus Dexamethasone Combinations and Supportive Care

Chemotherapy Regimen	
Cyclophosphamide	300-350 mg/m2 IV every 12 hours days 1-4
Mesna	400 mg/m2 IV continuous infusion over 24 hours days 1-4
Daratumumab	16 mg/kg IV once weekly for 8 doses, then every 2 weeks for 8 doses
Carfilzomib	Cycle 1: 20 mg/m2 IV on days 1 and 2, then 27-36 mg/m2 on days 8, 9, 15, 16 Cycle 2 and beyond: 27-36 mg/m2 on days 1, 2, 8, 9, 15, 16
Dexamethasone[a]	20-40 mg PO/IV on days 1-4, 9-12, and 17-20
Supportive Care	
Antiviral Prophylaxis	Acyclovir or valacyclovir
Antibacterial	Fluoroquinolone (preferred), amoxicillin/clavulanate, or cefpodoxime
Antifungal	Fluconazole or nystatin
Peptic ulcer prophylaxis	Pantoprazole or famotidine
Granulocyte colony-stimulating factor	Filgrastim (or biosimilar) or pegfilgrastim (or biosimilar) were given after each cycle starting 24 hours after the end of the last cyclophosphamide dose

[a] Day of dexamethasone administration may be moved to give on days of daratumumab or carfilzomib

Discussion and Key Takeaways

Analyses of newer agents, such as K and D, in combination with traditional cytotoxic chemotherapy have demonstrated a high ORR and can facilitate bridging to SCT or CAR-T cell therapy in some patients.[6-10] Our cohort demonstrated an ORR of 72.7% and a median PFS of 4.3 months, which is comparable to results among RRMM patients reported by Narayan et al.[3] However, our study cohort was comprised of heavily pretreated patients with a median of five prior therapies, potentially contributing to the shorter median OS rate of 9 months seen in our study. Our cohort's lower rate of bridging to transplant or CAR-T (14%) is also likely influenced by a history of at least one autologous SCT in 71% of patients and the limited availability of CAR-T during the time analyzed.

Toxicities experienced were similar to those described with other cytotoxic chemotherapies.[2-5] The high rates of neutropenic fever, re-hospitalization, and treatment related mortality rate at 60 days are also likely influenced by the heavily pretreated nature of our patient population, which had pre-treatment grade 3/4 hematologic toxicities that persisted at completion of HyperCd-based treatment in 45% of patients.[6-7] Given the high percentage of toxicities related to this regimen, aggressive supportive care with growth factors, antimicrobials, transfusions, at least twice weekly lab monitoring, and careful patient selection are prudent.

This retrospective study is limited by cohort heterogeneity due to provider patient selection. Incomplete cytogenetic data may underestimate the impact of high-risk cytogenetics and R-ISS grade on efficacy and safety. This study is also limited by the inability to assess the influence of refractoriness to prior therapies or response to subsequent lines of therapy on PFS and OS. Direct comparisons of efficacy endpoints between the treatment groups could not be made due to the study's design and small, heterogeneous sample. Significant statistical differences were found between patient characteristics among the groups that could influence PFS and OS, including median time from diagnosis to start of treatment and median prior lines of therapy.

Ultimately, HyperCd-based regimens can be effective among patients with PCL, EMD, hepatic dysfunction, and those who have been heavily pre-treated with few remaining treatment options. In addition, the platinum-sparing regimens described in this report are advantageous in patients with renal impairment, which can be common in RRMM. Future studies examining the potential role of patient selection in optimizing outcomes with HyperCd-based regimens may be beneficial. ●●

The full manuscript for the research highlighted above can be found at: Clin Lymphoma Myeloma Leuk. 2023;23(4):279-290. doi: 10.1016/j.clml.2022.12.004

Table 2. Response and Survival Outcomes by Regimen

Characteristic	Total Cohort (n=97)	HyperCd (n=20)	HyperCdK (n=31)	D-HyperCd (n=19)	D-HyperCdK (n=27)
Best ORR, % (95% CI)	72.7% (62.2%, 81.7%)	75% (47.6%, 92.7%)	64.3% (44.1%, 81.4%)	73.3% (44.9%, 92.2%)	76.9% (56.4%, 91%)
Median PFS, months (95% CI)	4.3 (3.3, 5.6)	3.1 (2.5, 6.8)	4.5 (3.29, 7.3)	3.3 (2.5, 8.3)	6 (4.8, 13.2)
Median OS, months (95% CI)	9.0 (7.1, 13.9)	7.4 (6.5, NA)	9.0 (3.7, 16.0)	7.5 (4.8, 16)	15.2 (9.7, NR)

K: carfilzomib; HyperCd: hyperfractionated cyclophosphamide and dexamethasone; D: daratumumab; ORR: overall response rate; PFS: progression-free survival; OS: overall survival; NR: not reached; NA: not applicable

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Cannabis Use in Patients with Cancer: A-Okay or Let's Pause

Lisa Cordes, PharmD, BCACP, BCOP
Oncology Clinical Pharmacy Specialist
National Institutes of Health

Introduction

Navigating the clinical, societal, and regulatory aspects of cannabis use in patients with cancer has proven to be challenging for healthcare professionals. Clinical evidence to either support or refute its use in this population is scant. In a survey of medical oncologists, 70% reported not feeling equipped to provide recommendations to patients regarding cannabis.[1] However, cannabis use for medical purposes is on the rise. Surveys indicate that 24-40% of patients with cancer used cannabis within the last year.[2,3] Even in areas without legal cannabis access, reported use in patients with cancer is approximately 15%.[4] So ready or not, cannabis is here. Now the question remains: should we give patients the a-okay or politely recommend we take a pause?

Pharmacology & Regulatory Considerations

The terms cannabis and marijuana are often used interchangeably, but cannabis is a general term that describes organic products of the *Cannabis sativa* plant which include cannabinoids, marijuana, and hemp.[5] *Cannabis sativa* is one of the oldest cultivated plants and its medicinal use dates back thousands of years. The plant contains various natural compounds, including over 100 known cannabinoids. The most recognized and studied phytocannabinoids include delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), with THC harboring the most significant psychoactive effects.[6] Mechanisms and pathways for the potential therapeutic and adverse effects are not well understood, but 2 cannabinoid receptors are thought to be primarily responsible. Type-1 cannabinoid (CB1) receptors are largely found in the central nervous system (CNS) and other tissues including the uterus, prostate, and testis, whereas type-2 cannabinoid (CB2) receptors are predominantly located in the immune system.[6] Endogenous ligands that activate these receptors are known as endocannabinoids. The endocannabinoid system has been associated with various physiological processes including appetite stimulation, pain relief, and nausea/vomiting.[6]

The pharmacokinetics of cannabis are dependent on product formulation. Efficacy and adverse effects are determined, in part, by the route of administration (e.g., inhalation, oral, sublingual, topical). Smoking cannabis has the quickest onset of action, typically within 10 minutes, and the duration of effect is estimated to be between 2-4 hours. Conversely, oral cannabis typically has a peak of 1-2 hours and a duration of effect of 6-12 hours.[7] THC and CBD are metabolized in the liver by cytochrome P450 (CYP) and primarily excreted in the feces, and to a lesser extent, in the urine.[8,9] Notably, both CBD and THC are highly lipid soluble with a long terminal elimination half-life.[9]

Although 41 states and territories in the United States (US) have amended local laws to allow for the use of medical cannabis, the distribution and possession of cannabis with > 0.3% THC remains illegal according to the federal Controlled Substances Act.[10] A report by the Congressional Research Service acknowledges the policy gap between the US Federal Government and most states, and suggests the designation of cannabis as a Schedule I controlled substance, and the role of federal law enforcement in enforcing cannabis regulations, be considered by Congress.[10] Discrepancies in federal and state laws place prescribers in a difficult position. Even in states where medical cannabis is legal, prescribing by healthcare professionals is prohibited as federal laws pertaining to Schedule I substances are still in effect.[11] However, a physician may "recommend" that a patient is eligible for the use of cannabis, which ultimately requires healthcare providers to be gatekeepers.[11] Additionally, the federal status of cannabis makes it difficult to conduct clinical trials. According to the American Cancer Society, "the classification of marijuana as a Schedule I controlled substance by the US Drug Enforcement Administration imposes numerous conditions on researchers and deters scientific study on cannabinoids."[12]

> **"While there is some evidence suggestive of possible benefit for supportive care in oncology, the potential risks in this population must also be assessed. "**

Perspective: A-Okay

Advocates for the medicinal use of cannabis in patients with cancer tout its potential in oncology supportive care. Although large, randomized trials are virtually nonexistent for marijuana, the totality of evidence (including the synthetic cannabinoid products) suggests potential for select indications.

Chemotherapy-induced Nausea and Vomiting

Cannabis has antiemetic properties and is thought to work via emetic reflex pathways and possibly through 5-HT3 receptors.[13] Dronabinol, a synthetic THC, is a well-studied antiemetic that is FDA-approved for nausea and vomiting associated with chemotherapy in adult patients who failed conventional antiemetics.[14] However, data are limited for marijuana which is not recommended for this indication in national guidelines.[15]

A small, randomized, double-blind, placebo-controlled, phase II/III trial evaluated oral THC:CBD cannabis extract for the prevention of refractory chemotherapy-induced nausea and vomiting (CINV).[16] Eighty-one participants enrolled into the phase II portion of the study. The primary endpoint was complete response (CR) from 0-120 hours after chemotherapy. Cannabis extract improved the CR

rate from 14% to 25% (p=0.041). Although more patients experienced adverse effects, including sedation, dizziness, or disorientation, 83% preferred cannabis over placebo.

Multiple large, systematic reviews evaluated the safety and efficacy of THC-derived products compared to older available antiemetics.[17-19] Tramer and colleagues found that the cannabinoid products included in the trials (nabilone, dronabinol, and levonantradol) were overall more effective than their comparators (prochlorperazine, metoclopramide, chlorpromazine, thiethylperazine, haloperidol, domperidone, and alizapride) for patients receiving moderate emetic chemotherapy regimens; however, improvement was not seen with highly emetic chemotherapy.[17] Another review of 15 clinical trials reported that nabilone was superior to placebo or other antiemetics (prochlorperazine, domperidone, and alizapride).[18] The same review also assessed 14 studies using dronabinol, and reported dronabinol to have a greater antiemetic effect than chlorpromazine, and an equivalent antiemetic effect when compared to metoclopramide, thiethylperazine, and haloperidol. Whiting and colleagues found that cannabinoids were associated with a statistically significant improvement in nausea and vomiting when compared with placebo (CR 47% vs 20%, respectively).[19]

Cancer-related Anorexia

The premise of using cannabis for the treatment of cachexia is based on harnessing a well-documented effect of cannabis: hunger. Clinical trials are conflicting but have shown that for some patients, cannabinoids may be beneficial. Current guidelines recommend it as an option in this population.[20]

The data supporting cannabinoids for appetite stimulation are largely based in patients with acquired immunodeficiency syndrome (AIDS). Dronabinol is FDA-approved for anorexia associated with weight loss in adult patients with AIDS.[14] A randomized, double-blind, placebo-controlled trial evaluated the appetite stimulating effect of dronabinol for the treatment of AIDS-related anorexia. Mean appetite change from baseline was statistically improved in the dronabinol group when compared to placebo.

A large, randomized, double-blind, placebo-controlled trial by the Cannabis-In-Cachexia-Study-Group evaluated cannabis extract and THC in patients with cancer-related anorexia-cachexia syndrome.[21] Increased appetite was reported in 73%, 58%, and 69% of patients receiving cannabis extract, THC, and placebo, respectively; none of which were statistically significant. Another large, randomized, double-blind, placebo-controlled trial through the North Central Cancer Treatment Group evaluated the efficacy of dronabinol, megestrol, and the combination in patients with advanced cancer who reported at least a 5 pound weight loss and/or daily intake of 20 calories/kg or less.[22] Weight gain was reported in 75% and 49% of patients receiving megestrol and dronabinol, respectively. Similarly, appetite was improved in more patients receiving megestrol when compared to dronabinol (11% versus 3%). Interestingly, the combination of both dronabinol and megestrol did not result in improvements in either appetite or weight gain when compared to megestrol alone.

Cancer-associated Pain

Although the exact mechanism has yet to be elucidated, various pathways have been associated with the potential analgesic effect of cannabinoids.[13] CB1 receptors located in the nociceptive processing area of the CNS may play a role. Cannabinoid modulation of the inflammatory process has also been theorized. Small studies have suggested cannabis may improve chronic and neuropathic pain in patients with advanced cancer, but evidence is inconsistent.[23]

Whiting and colleagues conducted a large meta-analysis that assessed the effect of cannabis in chronic pain (both cancer-associated and noncancer pain).[19] The average number of patients reporting a 30% or higher pain reduction was greater with cannabinoids than placebo, although not statistically significant (OR, 1.41 [95% CI, 0.99-2.00]). Another trial by Abrams and colleagues evaluated inhaled THC for neuropathic pain. The randomized, placebo-controlled trial reported a statistically significant improvement in pain (OR, 3.43 [95% CI, 1.03-11.48]).[24] In this study, inhaled cannabis reduced sensory neuropathy pain by 34% versus 17% with placebo (p=0.03). A reduction in pain by greater than 30% was reported by 52% in the cannabis group compared to 24% in the placebo group (p=0.04). Pain reduction was seen as early as the first cannabis cigarette. However, it must be noted that the study population was patients with HIV-associated sensory neuropathy, making it difficult to apply these data to cancer patients.

Perspective: Let's Pause

While there is some evidence suggestive of possible benefit for supportive care in oncology, the potential risks in this population must also be assessed. Adverse effects, drug interactions, and product consistency and quality are among the many considerations.

Adverse Effects

Adverse effects are common in patients taking cannabis and may include the following: feeling "high," sedation, euphoria, dizziness, depression, hallucinations, paranoia, and hypotension.[17] A large meta-analysis concluded that high levels of cannabis are associated with an increased risk of psychotic outcomes.[25] However, data are conflicting. One theory for the discrepancy is based on inconsistent product supply and a wide range of cannabis potency.[26] Another toxicity reported with cannabis use is cannabis-induced hyperemesis syndrome.[27] Furthermore, a growing body of evidence suggests cannabis may be associated with adverse cardiovascular outcomes. A recent study using the All of Us cohort, associated increased risk of coronary artery disease with frequent cannabis use when compared to never-users.[28]

In addition to the above risks, smoking cannabis has been associated with route-specific concerns. Fungal or bacterial contamination of inhaled cannabis products is one concern, particularly for patients who are immunocompromised, as this can lead to an increased risk of pulmonary infection.[29,30] Cannabis smoke also includes some of the same carcinogens as tobacco smoke. In a study of active cannabis users, 70% reported using inhaled products, 70% used edibles, and 40% reported using both.[2] Another study suggested that patients with cancer smoked less frequently than non-cancer patients (80%

vs 91%, p=0.015) and an increased use of edibles was reported in this patient population (57% vs 44%, p=0.052).[31] Citing the known carcinogens contained in the inhaled products, the American Cancer Society opposes smoking or vaping marijuana.[12]

Drug Interactions

Multiple CYP450 enzymes have been implicated in potential drug-drug interactions with THC and CBD. After an analysis of the literature, Qian and colleagues concluded that in vitro findings were confirmed to be clinically relevant for cannabinoids and the following CYP450 enzymes: CYP2C19, CYP2C9, and CYP1A2.[32] Additionally, the pharmacokinetics for THC and CBD are anticipated to be altered by CYP3A4 inhibitors and inducers. Some data suggest UGT and CES1 may also be impacted by cannabis, but additional studies are required. In vitro studies suggest cannabis also inhibits CYP3A5 and CYP2D6, but a clinical correlation is needed. Furthermore, it is unclear whether the differences in product derivation (e.g., synthetic cannabinoids, marijuana) and formulation (e.g., inhaled, oral) influence the extent of the potential interactions.

Concurrent use of cannabis and immune checkpoint inhibitors has become increasingly common. One retrospective, observational study reported cannabis use in combination with nivolumab was associated with a reduced response rate compared to nivolumab alone (15.9% vs 37.5%, respectively, p=0.016).[33] No statistical difference in progression-free survival (PFS) or overall survival (OS) was reported. Another small study evaluated outcomes in patients concurrently using cannabis with immunotherapy.[34] Bar-Sela and colleagues concluded that in patients receiving immunotherapy, a lower response rate was reported in cannabis users. It has been theorized that the potential interaction may be related to the immunomodulatory properties of cannabis.[34]

Product Supply

As discussed above, the legal aspect of cannabis has historically been a challenge for healthcare providers. One untoward effect of the federal restriction is the lack of a safety reporting system.[11] As a result, it is difficult to fully evaluate the safety risks of cannabis. Additionally, the ambiguous regulations result in an unregulated manufacturing industry which is not required to abide by good manufacturing practices. Select states have contaminant requirements for cannabis growers but standardized guidance for reducing public health risk is lacking.[35] Multiple reports have highlighted quality control concerns in both consistency and contamination.[11,35-37] These reports have found that insecticides, fungicides, and heavy metals have been discovered in cannabis products.[35-37] Furthermore, the THC to CBD ratio varies significantly from product to product, which may result in unreliable efficacy or unanticipated adverse effects.[11] One report suggested a wide range of THC concentration from 0 to 85%.[26]

Conclusions

Despite its popularity, clinical evidence to support or refute the use of cannabis in patients with cancer is scant. Therefore, healthcare professionals are faced with navigating the regulatory and clinical aspects with minimal guidance. Should oncology providers embrace the perceived benefits and comfortably give patients with cancer the a-okay on cannabis use? Or should the lack of robust trials and potential risks be a reason for pause? Like all medical decisions, an individual provider-patient discussion of benefits and risks should occur early in the cancer diagnosis and regularly throughout treatment. ●●

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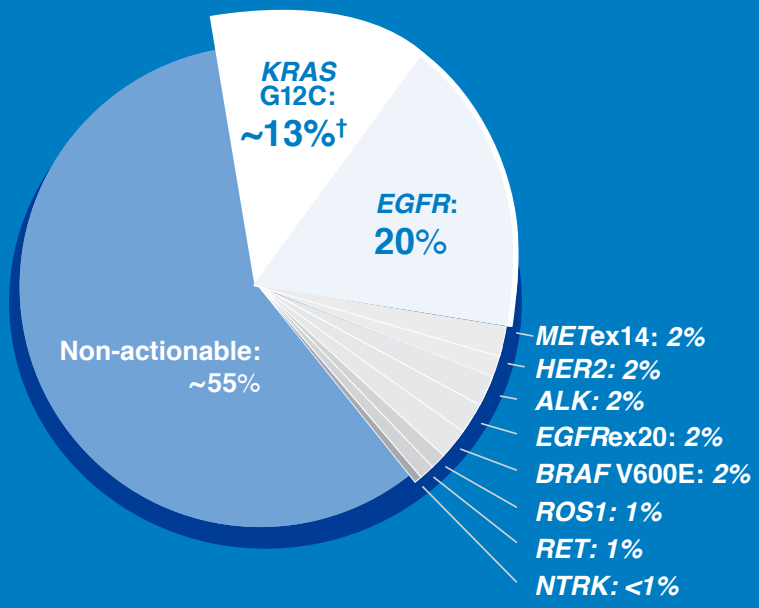
Test and Document for *KRAS* G12C in NSCLC

Prevalence of Oncogenic Drivers in Non-squamous NSCLC[1,*]



- ***KRAS* G12C and *EGFR* make up ~75% of all actionable driver mutations in non-squamous NSCLC[1]**
- ***KRAS* mutations generally occur early and persist as the disease progresses[2]**

Do you have a plan to keep track of test results for all actionable biomarkers for future reference?[3]

*Based on an analysis of NSCLC participants in the AACR genie version 12.0 dataset (n=19,777). Participating institutions include academic centers in western countries. This graph only includes alterations predictive of response to an FDA-approved drug in locally advanced or metastatic NSCLC.[1]

†With the addition of more NSCLC participants in the AACR genie version 12.0 dataset the prevalence of *KRAS* G12C was 12.4%.[1]

AACR, American Association for Cancer Research; *ALK*, anaplastic lymphoma kinase; *BRAF*, v-Raf murine sarcoma viral oncogene homolog B; *EGFR*, epidermal growth factor receptor; *HER2*, human epidermal growth factor receptor 2; *KRAS*, Kirsten rat sarcoma viral oncogene homolog; *MET*, mesenchymal epithelial transition; NSCLC, non-small cell lung cancer; *NTRK*, neurotrophic-tropomyosin receptor kinase; *RET*, rearranged during transfection; *ROS1*, rearrangement of the receptor tyrosine kinase 1.

For US Healthcare Professionals only.

Advocate for comprehensive biomarker testing during Lung Cancer Awareness Month

Learn more about testing and reporting *KRAS* G12C

References: 1. Data on file, Amgen; [Analysis of AACR Genie v12]. **2.** McGranahan N, et al. *Sci Transl Med.* 2015;7(283):283ra54. **3.** Li MM, et al. *J Mol Diagn.* 2017;19:4-23.

AMGEN® Oncology

Board Update

Committee-Driven Initiatives Keep HOPA Strong

LeAnne Kennedy, PharmD, BCOP, CPP, FHOPA
HOPA President (2023-2024)
Oncology Clinical Manager
Atrium Health Wake Forest Baptist
Winston-Salem, NC

Even as summer winds down, activity within HOPA is in full swing. I want to thank HOPA staff who reimagined our governance structure to create better alignment of committees, task forces – and now, advisory groups – with our strategic plan.

Each year, I feel so much gratitude to the hundreds of HOPA members who step forward to volunteer to serve the hematology/oncology pharmacy community. For additional opportunities, you will now find the Volunteer Activity Center open year round on our website.

The Governance Committee is also wrapping up a large initiative to review and revise the HOPA Bylaws and ensure language is clear, concise, and adherent. Following a 45-day comment period, members will be asked to vote on the revisions during the voting period of November 2-December 2, 2023.

Now, please join me in celebrating and promoting the following committee-driven initiatives.

Awards and Recognition. The Recognition Committee is accepting nominations for HOPA Member Awards, including two new categories: the Mentorship Award and Outstanding Clinician Award. Nominations are due by October 1 so please take a moment to nominate a colleague (or yourself!)

We are also looking for our next class of Fellows of HOPA and that application period closes on October 10. Best of luck to all of our candidates and thank you for your commitment to HOPA and the field of oncology pharmacy.

Board Elections. The Nominations Subcommittee recently closed its call for board member nominations. Though the slate was not yet decided at the time of this writing, we are confident members will have qualified candidates to choose from when Board Elections take place in November. This year, we are electing a President Elect, Secretary, and a Board Member at Large.

Practice Management 2023. PM23 has been expanded to two days and is set for November 9-10 in Austin, Texas. This year's theme, "Identifying Obstacles, Developing Strategies, and Moving Forward" acknowledges the personal and professional challenges within hematology/oncology pharmacy – and takes it a step further. PM23 content will focus on the importance of improving conditions and optimizing cancer care.

New this year: Informal roundtables to discuss hot topics and the addition of research posters. Registration is open – I hope to see you there!

Hill Day. HOPA returned to Capitol Hill for in-person conversations with the offices of elected officials on September 19. On the docket were oral chemo parity, drug shortages, and the importance of pharmacist recognition as a provider.

HOPA is now participating in Hill Day twice a year – in-person in the fall and virtually each spring. You do not need to have advocacy experience to participate and if you volunteer for an upcoming Hill Day you will get training and support along the way.

Drug Shortages Webinar. Over the summer, we partnered with the Association of Community Cancer Centers (ACCC) and the Association of VA Hematology/Oncology (AVAHO) for "Critical Conversations: Navigating Drug Shortages and Empowering Oncology Pharmacists." The virtual roundtable had more than 700 registered attendees and focused on the persistent shortages of cisplatin and carboplatin. Visit HOPA's YouTube channel for the full recording or download the Q&A from our website.

Core Competency 2023 Modules. The new Core Competency modules contain all the great science behind oncology pharmacy basics, plus the latest learning for oral anticancer agents and investigational drug principles. We are proud to have produced engaging and interactive content that is sought after by pharmacists and other providers who want to bridge the gap between their current and future oncology pharmacy skillsets.

HOPA Research Grant Fund. The grant period for the HOPA Research Fund Award recently closed but our dedication to pharmacist-led research continues. You can help by fueling our research grant fund with a donation of any size. If 25% of HOPA Members gave just $25, we would raise around $25,000 – all of which goes directly into sustaining the fund.

Thank you for your ongoing support and all you to do to help ensure everyone going through cancer treatment has an oncology pharmacists on their side. ●●

HOPA
Hematology/Oncology
Pharmacy Association

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HOPA 2023 PRACTICE MANAGEMENT

Identifying Obstacles • Developing Strategies • Moving Forward

Programming that reflects the current climate within hematology/oncology pharmacy.

- 11.0 CEs, including 2.25 BCOP credits
- Non-CE sessions, posters, and networking opportunities
- ***New this year!*** Informal roundtables for attendees to engage in discussions with a clinical focus or operational focus

Registration and programming available at hoparx.org

NOVEMBER 9-10
AT&T Conference Center
Austin, Texas