HOPA NEWS

Pharmacists Optimizing Cancer Care

VOLUME 15 | ISSUE 2

Updates on Chemotherapy-Induced Nausea and Vomiting: From Akynzeo to Zyprexa

page 3

HOPA
Hematology/Oncology Pharmacy Association

VOLUME 15 | ISSUE 2

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

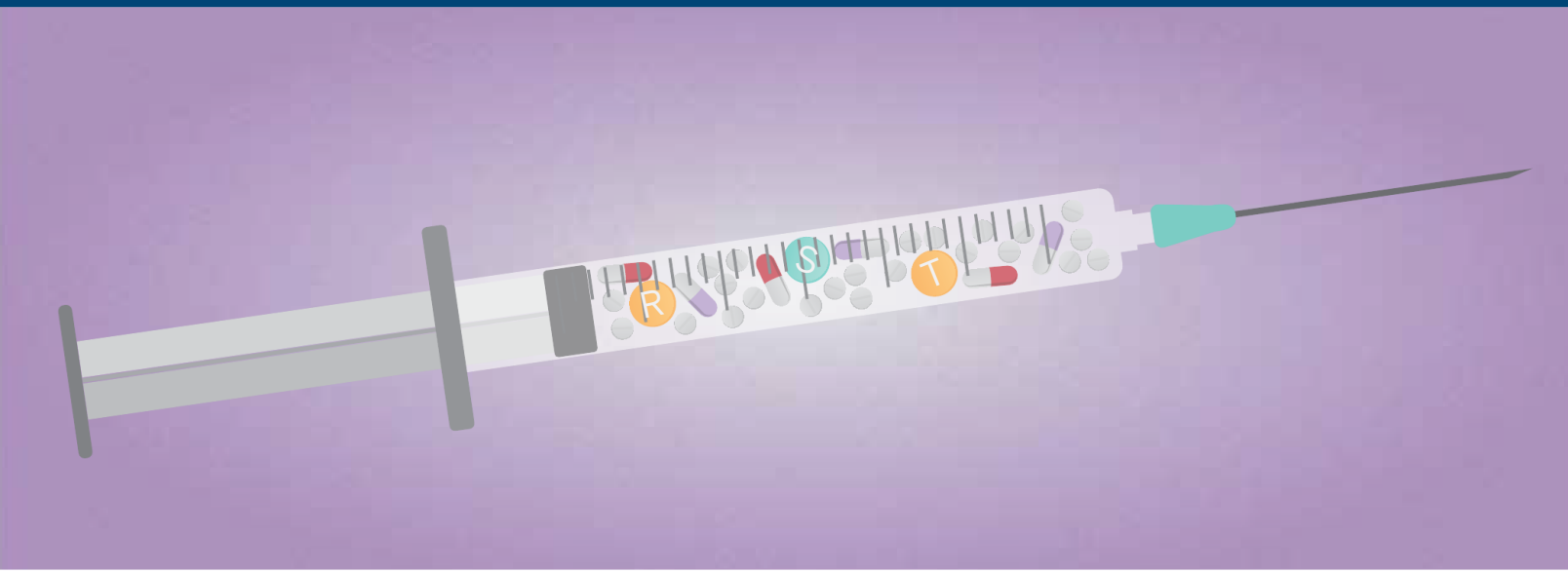
HOPA News is published by the Hematology/Oncology Pharmacy Association.

HOPA
Hematology/Oncology Pharmacy Association

Pharmacists Optimizing Cancer Care®

CONTENTS

FEATURE



Updates on Chemotherapy-Induced Nausea and Vomiting: From Akynzeo to Zyprexa

Maxwell A. Brown, PharmD
Clinical Pharmacy Manager, Bone Marrow Transplantation
New York-Presbyterian-Weill Cornell Medical Center
New York City, NY

Chemotherapy-induced nausea and vomiting (CINV) remains one of the most feared complications of cancer treatment and can have a significant impact on a patient's quality of life.[1–3] Furthermore, uncontrolled CINV can necessitate dose reductions or delays in a patient's treatment regimen, which may negatively affect patient outcomes.[4] Advances in the understanding of the pathophysiology of CINV, the development of increasingly effective antiemetic agents, and adherence to evidence-based consensus guidelines have resulted in improved control of CINV.[5] In 2017, the American Society of Clinical Oncology (ASCO) made significant updates to its clinical practice guideline on the use of antiemetics.[6] This article focuses on the literature supporting key guideline updates on the use of olanzapine, novel neurokinin-1 receptor antagonists (NK_1RAs), and extended-release (ER) injection of granisetron.

Olanzapine

The updated ASCO antiemetic guidelines recommend the addition of olanzapine (Zyprexa**)** to an NK_1RA, a 5-hydroxytryptamine-3 receptor antagonist ($5\text{-}HT_3$RA), and dexamethasone for prevention of CINV in adults receiving cisplatin and other highly emetogenic single agents as well as adults receiving an anthracycline combined with cyclophosphamide (AC).[6]

Olanzapine, a structural relative of clozapine, is a second-generation atypical antipsychotic in the class of thieno-benzodiazepine derivatives. Olanzapine binds with high affinity to a variety of neuronal receptors and displays antagonism of dopamine, serotonin, $alpha_1$-adrenergic, histamine H_1, and muscarinic receptors.[7] The oral formulation of olanzapine is currently approved by the U.S. Food and Drug Administration (FDA) for the treatment of schizophrenia, acute treatment of mixed and manic episodes of bipolar 1 disorder, and maintenance treatment of bipolar 1 disorder. However, olanzapine is also frequently used off-label for the treatment of delirium as well as for the prevention and treatment of CINV. Although the exact mechanism remains unknown, it has been suggested that the combined antagonism of olanzapine at the dopamine (D_2), $5\text{-}HT_{2C}$, and $5\text{-}HT_3$ receptors may be responsible for its antiemetic properties.[8]

The activity of olanzapine as an antiemetic agent was first published in a case report of a patient with leukemia who reported a significant improvement in chronic nausea with the use of olanzapine.[9] Additional publications describing the successful use of olanzapine as a treatment for nausea and vomiting[10] prompted a phase 1 study to investigate its utility for preventing CINV. Patients enrolled in the phase 1 study received granisetron and dexamethasone plus escalating doses of olanzapine. Thirteen of the 15 patients enrolled had complete control of delayed emesis, and the maximum tolerated dose (MTD) of olanzapine was identified as 5 mg orally once daily for 2 days prior to chemotherapy and 10 mg orally once daily on the day of chemotherapy and then continued for an additional 7 days.[13] These encouraging results led to a phase 2 investigation of olanzapine for prevention of CINV in chemotherapy-naive patients.

Using the MTD identified in the phase 1 study, olanzapine was added to granisetron (10 mcg/kg intravenous [IV] on day 1) and dexamethasone (20 mg orally on day 1, 8 mg orally twice daily on days 2 and 3, and 4 mg orally twice daily on day 4) in 30 patients receiving moderately emetogenic chemotherapy (MEC) and highly emetogenic chemotherapy (HEC). The rate of complete response (CR) for the overall period (0–120 hours postchemotherapy) was 85% for the 20 patients receiving MEC and 80% for the 10 patients receiving HEC, and no grade 3 or 4 toxicities were identified.[14] A subsequent phase 2 study in 40 chemotherapy-naive patients receiving

MEC or HEC investigated olanzapine (10 mg orally once daily on days 1–4) in addition to palonosetron (0.25 mg on day 1) and dexamethasone (8 mg on day 1 for MEC, 20 mg on day 1 for HEC). Despite the shorter duration of olanzapine and dexamethasone, the CR rate for the overall period (0–120 hours postchemotherapy) was 72% for the 32 patients receiving MEC and 75% for the 8 patients receiving HEC, with no grade 3 or 4 toxicities identified.[15]

Two phase 3 studies comparing olanzapine to aprepitant (both in combination with a 5-HT_3RA and dexamethasone) have been published. Both studies demonstrated that the effect of the two regimens on CINV is similar during the acute period (0–24 hours postchemotherapy) but that olanzapine is superior to aprepitant for control of nausea during the delayed period (0–120 hours postchemotherapy).[16,17] The recommendation to incorporate olanzapine into the previously standard three-drug antiemetic regimen for HEC was driven primarily by a phase 3 trial of 380 patients receiving either cisplatin-based or AC-based HEC. Patients were randomly assigned to receive either olanzapine 10 mg orally or placebo on days 1–4 plus a 5-HT_3RA (either palonosetron 0.25 mg IV, granisetron 1 mg IV or 2 mg orally, or ondansetron 8 mg orally or IV) on day 1, dexamethasone (12 mg orally on day 1 and 8 mg orally on days 2–4), and an NK_1RA (fosaprepitant 150 mg IV on day 1 or aprepitant 125 mg orally on day 1 and 80 mg orally on days 2 and 3). The proportion of patients who met the primary end point of no nausea (as defined by a response of 0 on the visual-analogue scale for nausea) was significantly greater in the olanzapine group than in the placebo group for all three assessment periods: early period (0–24 hours postchemotherapy), 74% vs. 45% (p = .002); later period (25–120 hours postchemotherapy), 42% vs. 25% (p = .002); and overall period (0–120 hours postchemotherapy), 37% vs. 22% (p = .002). Although sedation was significantly increased in the olanzapine group on day 2 when compared with baseline, the sedation resolved on days 2–4.[18]

One potential limitation of this phase 3 study, outlined in a correspondence article from Bossaer, is the dosing of dexamethasone on days 3 and 4, depending upon which NK_1RA was used. Bossaer asserts that although the recommended dosage of dexamethasone is the same for fosaprepitant and aprepitant on days 1 and 2, the dose of dexamethasone should have been 8 mg orally twice daily on days 3 and 4 for patients receiving fosaprepitant. Because fosaprepitant is given only on day 1, the drug interaction with dexamethasone is no longer present on days 3 and 4. Therefore, the subtherapeutic dexamethasone dosing on days 3 and 4 would create a substandard comparator for evaluation of CINV in the delayed period.[19] In response, the authors state that prior studies[20] as well as a subgroup analysis of olanzapine within their phase 3 trial showed no difference in results between aprepitant and fosaprepitant, despite higher dexamethasone dosing on days 3 and 4.

Another limitation of the phase 3 study identified by the authors was that only one dose of olanzapine was evaluated. A recently published phase 2 study compared olanzapine 10 mg to 5 mg orally on days 1–4 in combination with aprepitant, palonosetron, and dexamethasone.[21] No significant difference in the CR rates for nausea between groups for the acute, delayed, and overall periods was found. Additionally, the most significant adverse effect was somnolence, which was more frequently observed in the 10-mg group (53.3%) than in the 5-mg group (45.5%). The authors therefore recommended an olanzapine dose of 5 mg for future phase 3 investigations.

Netupitant/Palonosetron

Netupitant/palonosetron (Akynzeo) is a novel NK_1RA commercially available as a fixed-dose oral combination of netupitant 300 mg and palonosetron 0.5 mg (NEPA). NEPA was FDA-approved in 2014 for prevention of acute and delayed nausea and vomiting associated with repeat courses of cancer chemotherapy, including, but not limited to, HEC. In 2016, ASCO issued a focused update of its antiemetic guidelines to include NEPA as an antiemetic option for patients receiving HEC.[22]

Netupitant is a highly selective antagonist at the NK_1 receptor, maintaining greater than 75% receptor occupancy for up to 96 hours following a single dose.[23] Netupitant was combined with palonosetron because palonosetron has a greater binding affinity for the 5-HT_3 receptor and a longer half-life than other 5-HT_3RAs. In addition, palonosetron exhibits allosteric binding to the 5-HT_3 receptor with positive cooperativity and may inhibit cross-talk between the NK_1 and 5-HT_3 receptor–signaling pathways, further enhancing its antiemetic effect.[24]

Two phase 3 studies initially evaluated NEPA for prevention of CINV. The first evaluated NEPA plus dexamethasone versus palonosetron and dexamethasone in patients receiving their first cycle of AC-based chemotherapy. The CR rates during the delayed period were significantly higher in the NEPA group compared to the palonosetron group (76.9% vs. 69.5%; p = .001). NEPA also outperformed palonosetron alone during the acute and overall periods of CINV.[25] A second phase 3 study evaluated the safety and efficacy of NEPA over multiple cycles of MEC or HEC. Of note, patients in the control arm received aprepitant (in combination with palonosetron and dexamethasone), but comparisons between the NEPA and aprepitant group were made on the basis of safety alone. The most common adverse effects (AEs) noted in the NEPA group were constipation (3.6%) and headache (1%), and no increase in the incidence of AEs was observed over multiple treatment cycles. In addition, the CR rates during the overall period of cycle 1 were 81% and 76% for the NEPA and aprepitant groups, respectively, and continued antiemetic efficacy was demonstrated over multiple treatment cycles.[26]

An additional phase 3 study directly compared the efficacy of NEPA (plus dexamethasone) versus aprepitant (plus granisetron and dexamethasone) in patients receiving cisplatin-based HEC. This was the first clinical trial to directly compare the effectiveness of two NK_1RAs in a head-to-head fashion. For the primary efficacy end point, NEPA demonstrated noninferiority to aprepitant during the overall period of CINV (73.8% vs. 72.4%). The incidence of AEs was also similar between groups, with constipation (8% vs. 6.3%) and hiccups (2.7% vs. 1.4%) being the most common treatment-related AEs. Of note, the daily rates of patients with CINV events (defined as experiencing emesis or use of rescue medication or both) declined during the overall period of CINV and reached statistical significance on day 5 (8% vs. 13.9%; p = .0063).[27]

Rolapitant

Rolapitant (Varubi) is also a novel NK_1RA that was FDA-approved in 2015 for prevention of delayed CINV with MEC and HEC. Rolapitant is also quite selective for the NK_1 receptor, binding with high affinity and maintaining greater than 90% receptor occupancy in the brain for up to 5 days following a single 180-mg dose.[28] Furthermore, the drug interaction profile of rolapitant is unique when compared to the other NK_1RAs in that rolapitant does not inhibit the metabolic activity of cytochrome P450 (CYP) 3A4 but does have moderate inhibitory effects on CYP 2D6.[29] The updated ASCO antiemetic guidelines now recommend rolapitant as one of the NK_1RA options available for patients receiving HEC and for select patients receiving MEC.[6]

Two identical phase 3 studies (HEC-1 and HEC-2) of rolapitant for prevention of CINV after cisplatin-based chemotherapy formed the basis for its FDA approval in patients receiving HEC. In both studies independently, and in the pooled analysis of HEC-1 and HEC-2, use of rolapitant resulted in a significantly higher CR rate for control of nausea during the delayed period (25–120 hours postchemotherapy) when compared to placebo (pooled studies: 71% vs. 60%; $p = .0006$).[30] A third phase 3 study of rolapitant for prevention of CINV after MEC or AC-based chemotherapy gave it the FDA approval for patients receiving MEC. Again, rolapitant outperformed placebo for control of nausea in the delayed period (71% vs. 62%; $p = .002$).[31] Of note, this study was designed before the publication of the 2011 ACSO antiemetic guidelines[32] in which AC regimens were designated as HEC; prior to the publication of the 2011 ASCO guidelines, AC regimens were considered MEC.

In 2017, the FDA approved an IV formulation of rolapitant for prevention of delayed CINV after a study assessing exposure to rolapitant in healthy volunteers determined that the oral and IV formulations were bioequivalent.[33] A potential benefit of IV rolapitant compared with other NK_1RAs is that it is supplied in ready-to-use vials that do not require dilution, admixture, or refrigeration. However, the FDA recently released a safety alert stating that anaphylaxis, anaphylactic shock, and other serious hypersensitivity reactions have been reported in the postmarketing setting, in some cases requiring hospitalization. Therefore, healthcare professionals should be vigilant for signs of hypersensitivity or anaphylaxis in patients receiving IV rolapitant.[34]

Granisetron Extended-Release Subcutaneous Injection

In 2016, the FDA approved a subcutaneously (SQ) administered, ER formulation of granisetron (Sustol) for prevention of acute and delayed CINV following MEC or AC-based regimens. Granisetron ER injection uses an erosion-controlled drug-delivery system known as Biochronomer, which is designed to deliver therapeutic concentrations of granisetron for a period of 5 days.[35,36] The updated ASCO antiemetic guidelines now recommend granisetron ER injection as one of the 5-HT_3RA options available for patients receiving HEC and for select patients receiving MEC.[6]

In the phase 3 MAGIC trial, granisetron ER injection was compared with ondansetron (both in combination with an NK_1RA and dexamethasone) in patients receiving HEC, including patients receiving AC-based chemotherapy. For the primary end point of CR during the delayed period (25–120 hours postchemotherapy), granisetron ER injection was significantly better than ondansetron (64.7% vs. 56.6%; $p = .014$). However, no difference was seen between treatment arms during the acute and overall periods of CINV.[37] In addition, a post-hoc analysis of the MAGIC trial examined the rate of CR during the delayed period of CINV in the subgroup of patients receiving AC-based chemotherapy. Although a trend toward significance was noted, no statistically significant difference was seen between granisetron ER injection and ondansetron in this subgroup of patients (63.6% vs. 56.0%; $p = .062$).[38]

Another phase 3 trial compared granisetron ER injection with palonosetron (both in combination with dexamethasone) in patients receiving MEC and HEC. Granisetron ER injection demonstrated noninferiority to palonosetron in preventing both acute and delayed CINV after MEC and HEC.[39] This remained true in a subgroup analysis of breast cancer patients receiving MEC or HEC.[40] Of note, because evidence-based consensus guidelines on the use of antiemetics were updated after initiation of this study, patients receiving HEC did not receive an NK_1RA.

Granisetron ER injection was generally well tolerated in the phase 3 trials. The most common AEs observed were constipation, nausea, fatigue, headache, and injection-site reactions.[37,39] Injection-site reactions (primarily bruising, erythema, nodules, and pain, the majority of which were mild or moderate in severity) were seen in 61.8% of patients treated with granisetron ER injection.[37] However, healthcare providers should be aware of the risk of injection-site reactions, particularly in patients receiving anticoagulant or antiplatelet medications.

Conclusion

Nausea and vomiting due to chemotherapy can significantly affect a patient's quality of life, patient compliance, and the provider's ability to administer further treatment. Adherence to evidence-based consensus guidelines on the appropriate use of antiemetics has been shown to decrease the incidence of CINV.[5] With the development of increasingly effective medications for the prevention of CINV, it is imperative that healthcare providers maintain expertise in the proper use of antiemetic medications to reduce the burden of CINV and improve patient care. ●●

REFERENCES

1. Coates A, Abraham S, Kaye SB, et al. On the receiving end—patient perception of the side-effects of cancer chemotherapy. *Eur J Cancer Clin Oncol*. 1983;19:203-208.
2. Richardson JL, Marks G, Levine A. The influence of symptoms of disease and side effects of treatment on compliance with cancer therapy. *J Clin Oncol*. 1988;6:1746-1752.
3. Cohen L, De Moor CA, Eisenberg P, et al. Chemotherapy-induced nausea and vomiting: incidence and impact on patient quality of life at community oncology settings. *Support Care Cancer*. 2007;15(5):497-503.
4. Van Laar ES, Desai JM, Jatoi A. Professional educational needs for chemotherapy-induced nausea and vomiting (CINV): multinational survey results from 2,388 health care providers. *Support Care Cancer*. 2015;23(1):151-157.

5. Aapro M, Molassiotis A, Dicato M, et al. The effect of guideline-consistent antiemetic therapy on chemotherapy-induced nausea and vomiting (CINV): The Pan European Emesis Registry (PEER). *Ann Oncol.* 2012;23(8):1986-1992.
6. Hesketh PJ, Kris MG, Basch E, et al. Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol.* 2017;35(28):3240-3261.
7. Bymaster FP, Calligaro DO, Falcone JF, et al. Radioreceptor binding profile of the atypical antipsychotic olanzapine. *Neuropsychopharmacology.* 1996;14(2):87-96.
8. Bymaster FP, Falcone JF, Bauzon D, et al. Potent antagonism of 5-HT(3) and 5-HT(6) receptors by olanzapine. *Eur J Pharmacol.* 2001;430(2-3):341-349.
9. Pirl WF, Roth AJ. Remission of chemotherapy-induced emesis with concurrent olanzapine treatment: a case report. *Psychooncology.* 2000;9(1):84-87.
10. Passik SD, Lundberg J, Kirsh KL, et al. A pilot exploration of the antiemetic activity of olanzapine for the relief of nausea in patients with advanced cancer and pain. *J Pain Symptom Manage.* 2002;23(6):526-532.
11. Srivastava M, Brito-Dellan N, Davis MP, et al. Olanzapine as an antiemetic in refractory nausea and vomiting in advanced cancer. *J Pain Symptom Manage.* 2003;25(6):578-582.
12. Jackson WC, Tavernier L. Olanzapine for intractable nausea in palliative care patients. *J Palliat Med.* 2003;6(2):251-255.
13. Passik SD, Navari RM, Jung SH, et al. A phase I trial of olanzapine (Zyprexa) for the prevention of delayed emesis in cancer patients: a Hoosier Oncology Group study. *Cancer Invest.* 2004;22(3):383-388.
14. Navari RM, Einhorn LH, Passik SD, et al. A phase II trial of olanzapine for the prevention of chemotherapy-induced nausea and vomiting: a Hoosier Oncology Group study. *Support. Care Cancer.* 2005;13(7):529-534.
15. Navari RM, Einhorn LH, Loehrer PJ Sr, et al. A phase II trial of olanzapine, dexamethasone, and palonosetron for the prevention of chemotherapy-induced nausea and vomiting: a Hoosier Oncology Group study. *Support Care Cancer.* 2007;15(11):1285.
16. Tan L, Liu J, Liu X, et al. Clinical research of olanzapine for prevention of chemotherapy-induced nausea and vomiting. *J Exp Clin Cancer Res.* 2009;28(1):131.
17. Navari RM, Gray SE, Kerr AC. Olanzapine versus aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a randomized phase III trial. *J Support Oncol.* 2011;9(5):188-195.
18. Navari RM, Qin R, Ruddy KJ, et al. Olanzapine for the prevention of chemotherapy-induced nausea and vomiting. *N Engl J Med.* 2016;375:134-142.
19. Bossaer JB. Olanzapine for chemotherapy-induced nausea and vomiting. *N Engl J Med.* 2016;375:1395-1396.
20. Grunberg S, Chua D, Maru A, et al. Single-dose fosaprepitant for the prevention of chemotherapy-induced nausea and vomiting associated with cisplatin therapy: randomized, double-blind study protocol—EASE. *J Clin Oncol.* 2011;29(11):1495-1501.
21. Yanai T, Iwasa S, Hashimoto H, et al. A double-blind randomized phase II dose-finding study of olanzapine 10 mg or 5 mg for the prophylaxis of emesis induced by highly emetogenic cisplatin-based chemotherapy. *Int J Clin Oncol.* 2017. doi:10.1007/s10147-017-1200-4. Epub ahead of print.
22. Hesketh PJ, Bohlke K, Lyman GH, et al. Antiemetics: American Society of Clinical Oncology Focused Guideline Update. *J Clin Oncol.* 2016;34(4):381-386.
23. Spinelli T, Calcagnile S, Giuliano C, et al. Netupitant PET imaging and ADME studies in humans. *J Clin Pharmacol.* 2014;54(1):97-108.
24. Rojas C, Slusher BS. Pharmacological mechanisms of 5-HT_3 and tachykinin NK_1 receptor antagonism to prevent chemotherapy-induced nausea and vomiting. *Eur J Pharmacol.* 2012;684(1-3):1-7.
25. Aapro M, Rugo H, Rossi G, et al. A randomized phase III study evaluating the efficacy and safety of NEPA, a fixed-dose combination of netupitant and palonosetron, for prevention of chemotherapy-induced nausea and vomiting following moderately emetogenic chemotherapy. *Ann Oncol.* 2014;25(7):1328-1333.
26. Gralla RJ, Bosnjak SM, Hontsa A, et al. A phase III study evaluating the safety and efficacy of NEPA, a fixed-dose combination of netupitant and palonosetron, for prevention of chemotherapy-induced nausea and vomiting over repeated cycles of chemotherapy. *Ann Oncol.* 2014;25(7):1333-1339.
27. Zhang L, Lu S, Feng J, et al. A randomized phase III study evaluating the efficacy of single-dose NEPA, a fixed antiemetic combination of netupitant and palonosetron, versus an aprepitant regimen for prevention of chemotherapy-induced nausea and vomiting (CINV) in patients receiving highly emetogenic chemotherapy (HEC). *Ann Oncol.* 2018;29(2):452-458.
28. Jordan K, Jahn F, Aapro M. Recent developments in the prevention of chemotherapy-induced nausea and vomiting (CINV): a comprehensive review. *Ann Oncol.* 2015;26(6):1081-1090.
29. Rashad N, Abdel-Rahman O. Differential clinical pharmacology of rolapitant in delayed chemotherapy-induced nausea and vomiting (CINV). *Drug Des Devel Ther.* 2017;11:947-954.
30. Rapoport BL, Chasen MR, Gridelli C, et al. Safety and efficacy of rolapitant for prevention of chemotherapy-induced nausea and vomiting after administration of cisplatin-based highly emetogenic chemotherapy in patients with cancer: two randomised, active-controlled, double-blind, phase 3 trials. *Lancet Oncol.* 2015;16(9):1079-1089.
31. Schwartzberg LS, Modiano MR, Rapoport BL, et al. Safety and efficacy of rolapitant for prevention of chemotherapy-induced nausea and vomiting after administration of moderately emetogenic chemotherapy or anthracycline and cyclophosphamide regimens in patients with cancer: a randomised, active-controlled, double-blind, phase 3 trial. *Lancet Oncol.* 2015;16(9):1071-1078.
32. Basch E, Prestrud AA, Hesketh PJ, et al. Antiemetics: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol.* 2011;29(31):4189-4198.
33. Wang X, Zhang ZY, Powers D, et al. Bioequivalence of intravenous and oral rolapitant: results from a randomized, open-label pivotal study. *J Clin Pharmacol.* 2017;57(12):1600-1606.
34. Rolapitant injectable emulsion [package insert]. Waltham, MA: Tesaro, Inc.; 2017.
35. Gabrail N, Yanagihara R, Spaczy ski M, et al. Pharmacokinetics, safety, and efficacy of APF530 (extended-release granisetron) in patients receiving moderately or highly emetogenic chemotherapy: results of two phase II trials. *Cancer Manag Res.* 2015;7:83-92.
36. Deeks ED. Granisetron extended-release injection: a review in chemotherapy-induced nausea and vomiting. *Drugs.* 2016;76(18):1779-1786.
37. Schnadig ID, Agajanian R, Dakhil C, et al. APF530 (granisetron injection extended-release) in a three-drug regimen for delayed CINV in highly emetogenic chemotherapy. *Future Oncol.* 2016;12(12):1469-1481.
38. Schnadig ID, Agajanian R, Dakhil C, et al. APF530 versus ondansetron, each in a guideline-recommended three-drug regimen, for the prevention of chemotherapy-induced nausea and vomiting due to anthracycline plus cyclophosphamide–based highly emetogenic chemotherapy regimens: a post hoc subgroup analysis of the phase III randomized MAGIC trial. *Cancer Manag Res.* 2017;9:179–187.
39. Raftopoulos H, Cooper W, O'Boyle E, et al. Comparison of an extended-release formulation of granisetron (APF530) versus palonosetron for the prevention of chemotherapy-induced nausea and vomiting associated with moderately or highly emetogenic chemotherapy: results of a prospective, randomized, double-blind, noninferiority phase 3 trial. *Support Care Cancer.* 2015;23(3):723-732.
40. Boccia R, O'Boyle E, Cooper W. Randomized phase III trial of APF530 versus palonosetron in the prevention of chemotherapy-induced nausea and vomiting in a subset of patients with breast cancer receiving moderately or highly emetogenic chemotherapy. *BMC Cancer.* 2016;16:166.

TIME TO TALK CINV™

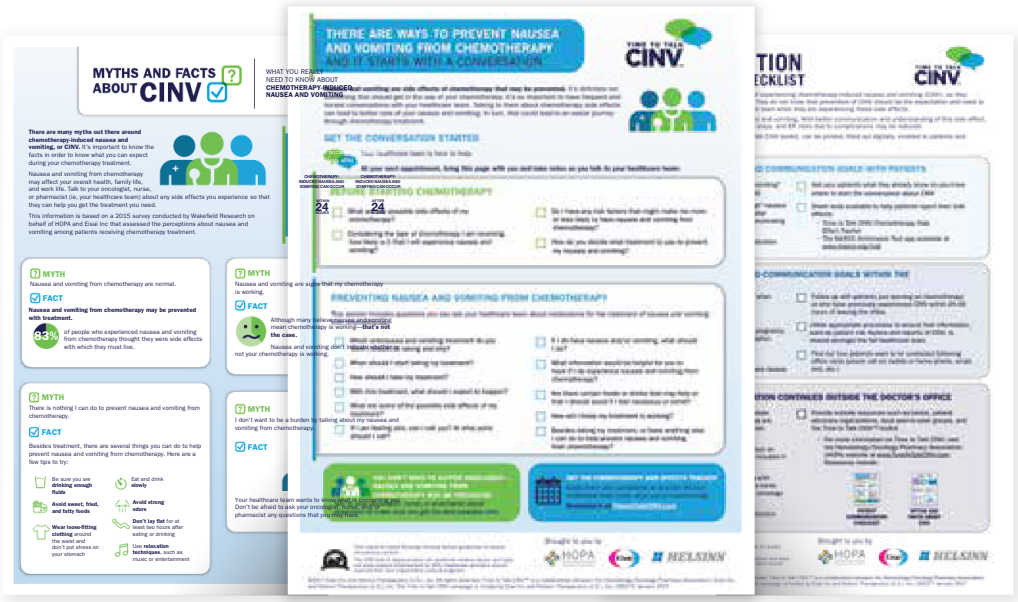
HOPA Hematology/Oncology Pharmacy Association

Eisai

HELSINN Building quality cancer care together

Visit www.timetotalkcinv.com for more resources.

Incorporate these tools into conversations with your patients.



Addressing the Risk of Financial Toxicity in an Ambulatory Oncology Practice: Results from an ASCO Quality Training Program

Gee Youn (Geeny) Kim, PharmD
PGY-2 Hematology/Oncology Resident
Hospital of University of Pennsylvania
Philadelphia, PA

Novel cancer therapies have undoubtedly exploded in the past few years. It has been an exciting journey for clinicians to witness the development and positive effects of oral antineoplastic agents and immunotherapy in patients' cancer treatments. Although these chemotherapeutics work through different and unique mechanisms to kill cancerous cells, unfortunately, the one toxicity profile common to all these new agents is financial toxicity. Concerns that their high price tags can cause disparities in cancer care and adversely affect patients' quality of life, symptom burden, adherence, and survival appear to be well-founded. As a result, a few ambitious members of the NorthShore University Health System initiated a project to reduce the risk of financial toxicity by improving patient education at the time of informed consent through the Quality Training Program (QTP) of the American Society of Clinical Oncology (ASCO).[1] Thomas A. Hensing, MD, the project leader, formed a multidisciplinary panel that included George Carro, RPh MS BCOP, director of oncology pharmacy services at NorthShore, and Anna Palafox, PharmD BCOP, a clinical pharmacy specialist at NorthShore.

The aim of their project was to increase the proportion of oncology patients receiving information about financial risks and support resources available for high-cost treatments at the time of informed consent. The first phase of the pilot project specifically targeted immune checkpoint inhibitors because of their frequent use and high cost. Disappointingly, at the beginning of the project it was determined that none of the patients receiving these medications routinely received information on the financial risks of high-cost cancer treatments or the financial support services that were available to them. This omission compromised their ability to make informed decisions and caused them financial distress. A cause-and-effect diagram revealed that the main reasons that clinicians did not address financial risk during the informed-consent process were the lack of educational tools and a poorly understood prior-authorization process. To address these problems, the first rapid-cycle plan-do-study-act (PDSA) initiative involved developing an educational tool to use with patients during the informed-consent process, which was approved by the institution's patient advisory board. The second PDSA initiative involved revising and optimizing the prior-authorization process. The third and final PDSA initiative focused on monitoring patient distress and financial toxicity through the National Comprehensive Cancer Network's distress and patient-reported-outcome tools, respectively.

The results of the initiatives were dramatic. The proportion of patients receiving information about the risk of financial toxicity during the informed-consent process increased from 0% (0/20) in the preintervention group to 53% (9/17) in the postintervention group. The percentage of patients who successfully secured prior authorization before starting therapy jumped from approximately 50% (10/20) to 94% (16/17) after the interventions. Furthermore, with the optimization of workflows and staff education on financial toxicity and the early involvement of the patients' financial advocates, the time required for successful prior authorization decreased significantly. Because of the success seen with these rapid-cycle PDSA initiatives, plans are now under way to expand the project to include all therapies, including oral chemotherapeutics. In addition, NorthShore University Health System was able to expand the number of financial advocates because this project's findings supported the need for additional assistance. This change will advance the project and, more important, help achieve improvements in patients' cancer care.

Overall, this project demonstrated that the involvement and empowerment of patients and providers in discussing the financial impact of high-cost chemotherapy is feasible at the time of informed consent. Optimization in the prior-authorization workflow led to immediate decreases in time to successful prior authorization and increases in the number of patients reached with educational tools. However, the long-term effects of this project, such as ability to gauge patient distress and financial toxicity, will need to be continually monitored.

In an interview with ASCO featuring pharmacy professionals and their multidisciplinary involvement in the QTP, George Carro emphasized his positive experiences in working with staff in other disciplines. All the stakeholders were supportive and encouraging during this collaboration, working toward the shared goal of improving patients' cancer care. The interdisciplinary work of George Carro and Anna Palafox exemplifies the importance of teamwork and collaboration in optimizing the efficacy and safety of patients' cancer care while minimizing financial toxicity. ●●

REFERENCE

1. Hensing T, Bauer T, Palafox A, Whalen M, Carro G. Addressing risk of financial toxicity in an ambulatory oncology practice: our institutional experience with the ASCO Quality Training Program. Poster presentation, ASCO Quality Care Symposium, Orlando, FL, March 3–4, 2017.

Using Goal Setting to Achieve More

Jill S. Bates, PharmD MS BCOP CPP
Clinical Pharmacist Practitioner
University of North Carolina Medical Center
Associate Professor of Clinical Education
University of North Carolina Eshelman School of Pharmacy
Chapel Hill, NC

My daughter Payton is 6 years old. Our family has dubbed her "Pistol Payton." She is a nurturing, caring, smart, and spunky little girl! She is my joy. But I had quite a bit of drama during my pregnancy with her, one of which included pregnancy-induced dysautonomia. The pregnancy-induced dysautonomia continued postpartum and caused me to randomly faint multiple times per day. Although my cardiologist said it was a benign condition, to me it was terrifying. My doctor instructed me, as part of my treatment, to "retrain my body." At the same time, my family was going through crisis, and I found myself under significant duress. I was not exactly sure what "retrain my body" meant, but I stuck to my treatment regimen anyway and just got started: first doing yoga, then walking, and finally running. Thus began my passion for distance running.

Running has completely transformed my life. When I first started to run, I could not even run a half-mile without stopping to rest. In 2017, I ran 529.43 miles! I started running during a time of significant stress, which led to personal growth. My journey as a runner began my journey toward becoming an authentic leader, which I am still in the midst of today. In the context of being a new mom (for the second time), I wanted to better define who I was. I needed to understand my values and create a new vision and purpose for my life. I realized that I lacked clarity of purpose. However, when I run, my mind is clear. During my runs, I have to pay attention to my breathing to keep pace. I notice nature, I have creative ideas, I can think without distraction.

After I had been running for about a year and was achieving runs of only 1–2 miles per course, my neighbor approached me to say that she wanted to start running. We mapped out a plan to level our running skills (this was not too difficult and happened immediately) and began to schedule runs together. I welcomed this. First, I really like spending time with my neighbor. Second, she was aware of my medical history, and I felt safe knowing that she would care for me if something happened. Consequently, with her by my side, I felt brave enough to push myself and go farther. We started by discussing what we would focus on in our running. We decided to concentrate only on distance, not on time. This relieved the pressure we placed on ourselves to perform. Focusing on distance was simple and measurable.

When we started to run together, we had many things to learn and discover about what we were capable of. How much running was too much for our bodies? What were the best courses to take? What shoes or equipment did we need? How long did each course take to run? How could we fit running into our busy schedules? How could we avoid injuries? Neither of us was a professional runner, and although both of us had been athletic "back in the day," we did not do distance running. We had no baseline experience, and so we talked about how we felt on our runs in order to work through questions and establish habits that supported our goals. Aesop's fable "The Tortoise and the Hare" helped frame our discussions as we reminded ourselves "slow and steady wins the race."

When it became clear what our bodies were capable of, my running partner and I began to set goals. We started by looking at our immediate circumstances. We could manage to hit 10 miles per week by running 2 miles 3 days during the week and 3 miles on each weekend day. That actually comes to 12 miles, not 10. My running partner and I always include a buffer when we map out our goals to account for unforeseen circumstances like bad weather. If we did actually run 10 miles per week, we needed to run 40 miles per month to hit our final goal of 500 miles for the

(continued on p. 19)

TAKE-AWAY POINTS

1. Identify and prioritize your values.
2. Create a vision and purpose for your life.
3. Using your imagination, reflect on who you are and what you are capable of.
4. Identify an accountability partner (I recommend choosing someone besides your significant other).
5. Create SMART goals (goals that are specific, measureable, achievable, and realistic and that have a timeline) in accordance with your values, vision, and purpose.
6. Regularly review your goals with your accountability partner.

Preparing for USP Chapter <800>: The Road to Remodeling

Corbin Bennett, PharmD MPH
Senior Director of Oncology and Outpatient Infusion Pharmacy Services
National Pharmacy Programs and Services
Kaiser Permanente
Fresno, CA

As the implementation date of U.S. Pharmacopeia General Chapter 800 (USP <800>), Hazardous Drugs—Handling in Healthcare Settings, quickly approaches, healthcare organizations are faced with challenges to ensure timely delivery of compliant clean rooms. USP <800> outlines facilities and engineering standards "to promote patient safety, worker safety, and environmental protection." Pharmacy leaders must balance potential regulatory risk with cost when determining how and when to remodel existing clean rooms in order to meet USP <800> facilities standards. At Kaiser Permanente (KP), Pharmacy Services is closely collaborating with internal architects, engineers, and the finance department to remodel more than 100 sterile compounding pharmacies in nine states.

The Cost of Compliance

The initial USP <800> implementation date of July 1, 2018, was moved to December 1, 2019, in September 2017 to ensure alignment with the expected revision of USP Chapter <797>.[1] Prior to the delay, the National Alliance of State Pharmacy Associations (NASPA) released a chart outlining USP <800> adoption by state boards of pharmacy.[2] Only 14 states had adopted or planned to adopt USP <800> by the original implementation date of July 1, 2018. In most states a decision had been made not to enforce USP <800>, or discussions were just beginning. Despite the current general lack of state enforcement, the Joint Commission has begun enforcing elements of USP <800> related to facilities, including air-pressure differentials and primary engineering controls requirements.[3]

Some states may be reluctant to adopt USP <800> because of the potential high cost of upgrading sterile compounding facilities. This is understandable because costs to remodel to USP standards may total in the millions.[4] The average remodeling cost at KP is roughly $2 million per project, with some projects exceeding $3 million. Why the excessive cost? Three primary cost drivers are at work: space, location, and mechanical components.

Space is at a premium in all organizations. Many pharmacies built before the release of USP <800> lack a negative-pressure buffer room or dedicated receiving area. In the Kaiser Permanente National Template, a minimum of 170 square feet is suggested to ensure adequate room for equipment (biological safety cabinet, refrigerator, carts, etc.) in a negative-pressure buffer room to support a small-volume hazardous drug operation. Fifty square feet is the suggested size for a dedicated receiving area. This is in addition to the required positive-pressure room for nonhazardous drugs (110 sq. ft.), anteroom (170 sq. ft.), and nonclassified work space (250 sq. ft.). Kaiser Permanente hospital pharmacies are generally more expensive per square foot to remodel when compared to ambulatory outpatient clinics. This is primarily because of the limited options available in hospital space.

Location of the pharmacy is a significant cost driver. In many of our projects, bathrooms, exam rooms, offices, and other premium spaces have been sacrificed to carve out room for pharmacy expansion. This has a domino effect, causing other departments to be relocated, which in turn requires additional capital outlay to ensure operational harmony. Another aspect of the domino effect is the need for temporary space during the remodeling period. Temporary clean rooms built in a separate location and mobile clean rooms add to the cost of a project.

In a majority of KP projects, the phenomenon of trying to "fit a square peg in a round hole" also occurs, requiring unique solutions to meet compliance in less-than-ideal spaces. Pharmacy leaders need to begin crucial conversations now with the executive staff and other primary decision makers for space allocation. Healthcare leaders need to understand space and adjacency requirements up front. Organizations with "regulatory muscle," such as those located in states or licensed spaces requiring compliance with USP <800>, may find it easier to procure adequate space. The delay in implementing USP <800> may have weakened this muscle in the short term, but pharmacy leaders understand that 18 months is a very tight timeline for procuring, designing, and constructing a new space.

Mechanical—or heating, ventilation, and air conditioning (HVAC)—design and construction is complex for even the simplest pharmacy remodel. But if your pharmacy is located in the basement of a multistory building, it becomes almost impossible. Mechanical upgrades in KP remodels are accounting for roughly 40 percent of the total cost. Discussions between pharmacy leadership and the design team are required to ensure clear understanding of the differences between the regulatory minimum and best practices. USP <800> requires the following: "Sterile and nonsterile HDs [hazardous drugs] must be compounded within a C-PEC [containment primary engineering control or hood] located in a C-SEC [containment secondary engineering control or buffer room]. The C-SEC used for sterile and nonsterile compounding must be externally vented, be physically separated (i.e., must be a room different from other preparation areas), have an appropriate air exchange (e.g., appropriate number of air changes per hour), and have a negative pressure between .01 and .03 inches of water column relative to all adjacent areas."[5] Organizations can meet these standards by using the biological safety cabinet (BSC) as the sole source of exhaust at a minimum. Although this is not stated in USP <800>, design consultants recommend a more elegant design using dedicated air-handling units with low exhausts built within the walls of the buffer room and also automated pressure controls with monitoring. The difference in capital outlay between the minimum and best-practice standard totals in the hundreds of thousands of dollars. However, in the long run the best practice

ensures a cleaner space and may reduce the chance of failure in the environmental sampling program.

BSC selection is another cost driver. USP <800> requires that sterile compounding be done in a Class II Type A2, B1, or B2 BSC. Type A2 BSCs provide a portion of air that is recycled through a high-efficiency particulate air (HEPA) filter while exhausting the remaining air. Type B2 BSCs exhaust 100% of the air from the buffer room to the external environment.[6] The difference in equipment cost of these two hoods is negligible. However, Type B2 BSCs require a complex design, making it difficult to maintain air balancing in the sterile compounding area. This leads to higher maintenance and energy costs for Type B2s. Type B2s are generally reserved for compounding volatile agents such as cyclophosphamide and fluoruracil.[5] KP recently completed an internal study showing equivalent employee protection with the Type A2 and B2 BSCs when a volatile agent was being compounded. The KP standard for BSCs was changed to a Type A2 on the basis of these results.

Mobile Solutions

Mobile compounding trailers have created a significant buzz over the past year as a potential option for both temporary and permanent sterile compounding solutions. These units are self-contained, including buffer room, anteroom, and work rooms with compounding equipment (Type A2 hoods), all within a trailer on wheels. The small footprint allows for positioning on hospital or clinic property similar to mobile imaging units. Using mobile trailers may be a better option than remodeling a temporary space on the medical campus. However, pharmacy leaders must consider volume, regulatory requirements, and cost when evaluating the benefits of mobile trailers.

Mobile trailers can snugly accommodate two 3-foot hoods in each of the hazardous and nonhazardous buffer rooms, potentially allowing four technicians to compound at the same time. However, because of storage constraints, it is more likely that each buffer room will comfortably accommodate only one technician. The work area is small, making its use for document storage difficult. High-volume compounding pharmacies may be challenged to transition all sterile preparations to the mobile unit.

Regulatory requirements for mobile trailers vary by state. Some states allow for a "plug-and-play" model; compounding may commence after the trailers are parked and electricity and water have been connected. Other states require licensure prior to operation. California, for example, requires that mobile trailers be licensed by three regulatory bodies (Board of Pharmacy, California Department of Public Health, and the Office of Statewide Health Planning and Development).[7] If the trailer is moved to a new location, even within the same medical campus, it must be relicensed. Licensure may take approximately 6 months from application submission to final inspection. This significantly limits the utility of mobile units as short-term solutions for pharmacies that require immediate support (i.e., pharmacies with positive environmental samples forced to cease compounding operations). The bottom line: it's important to research your state's regulatory requirements for licensing mobile trailers prior to purchase.

Cost must also be considered. Mobile compounding vendors offer both lease and purchase options. Lease options currently range from $25,000 to $30,000 per month with a 12-month minimum agreement. The cost to purchase may be nearly $1 million. If the mobile trailer will be used for more than 2 years, purchase may be the better option. In addition, some states may require registration with the Department of Motor Vehicles, which may add a significant cost.

KP has purchased one mobile trailer and leased two additional mobile trailers for temporary support of small- to medium-sized pharmacies. KP is still assessing the long-term potential for the purchased trailer at this time. The overall benefit of these mobile trailers remains to be seen.

Conclusion

The design and construction of clean rooms is a complex endeavor that requires thoughtful planning, significant capital, and careful timing. Pharmacy leaders are required to make a multitude of decisions during the process and must partner closely with facilities experts to ensure compliance while containing costs. Leaders must first assess the regulatory landscape and then engage organization leaders to identify space and capital. In addition, solutions for compounding during the construction period need to be identified; these may include mobile trailers and temporary compounding areas. ●●

REFERENCES

1. International Academy of Compounding Pharmacists. USP announces general chapter <800> implementation postponement to December 2019. September 29, 2017. http://www.iacprx.org/news/368148/USP-Announces-General-Chapter-800-Implementation-Postponement-to-December-2019.htm.
2. National Alliance of State Pharmacy Associations. USP 800 adoptions by state. August 17, 2017. https://naspa.us/2017/08/usp-800-adoptions-state/.
3. The Joint Commission. Prepublication Requirements. June 19, 2017. https://www.jointcommission.org/assets/1/18/PrePub_MC_OME_Final.pdf.
4. Beans BE. USP <800> adds significant safety standards. *P T*. 2017;42(5):336-339.
5. USP Compounding Compendium 2017. Rockville, MD: United States Pharmacopeial Convention; 2017. USP <800> Hazardous Drugs—Handling in Healthcare Settings, Section 5.3.
6. USP Compounding Compendium 2017. Rockville, MD: United States Pharmacopeial Convention; 2017. USP <800> Hazardous Drugs—Handling in Healthcare Settings, Appendix 3.
7. Office of Statewide Health Planning and Development Facilities Development Division. Advisory Guide for Sterile Compounding Pharmacies. December 2017. https://www.oshpd.ca.gov/FDD/Training_Education/AdvisoryGuideA2-Pharmacy12072017.pdf.

The Transition from Resident to Preceptor

Leah Edenfield, PharmD BCOP BCPS
Hematology/Oncology Clinical Pharmacy Specialist
Wake Forest Baptist Health
Winston-Salem, NC

Adapting to postresidency life brings several challenges, one of which is adjusting to a new role as preceptor. After spending years focusing on your own learning, being responsible now for the development of others into oncology pharmacists can seem daunting. A few obstacles you may encounter include managing time, working with people who have different levels of experience and ways of learning, keeping up with your own professional development, and learning to give effective feedback. You can continue to acquire the skills needed to address these issues while you are growing as a new practitioner.

The trajectory for your learning when you were a resident was generally set by your preceptors. As a preceptor, however, you have the task of setting the right course for learners by deciding what aspects of the ever growing body of pharmacy knowledge should have priority. In planning a learning experience, you must take into account your practice setting and specialty area as well as the experience and individual goals of the learners. You will also need to develop a strategy for your own lifelong learning so that you are teaching students and residents the most current and evidence-based information. Getting updates from journals and organizations in oncology can help you stay current. Your institution may also provide for continuing education. In addition, you can learn from your residents, who see with fresh eyes and bring their own inquisitiveness, especially as new guidelines are released and pharmacy practice changes. Precepting students and residents as they learn about novel therapies provides excellent motivation for your own learning.

Though having a plan is the first step, finding the time to execute it can be another hurdle. On a typical day of residency, you likely expect to stay at the office longer than your preceptor. Between tending to patient care responsibilities, projects, and topic discussions and locating drug information, you have honed your time management skills in order to fit so much learning into a single residency year. However, as a preceptor you may find yourself working long hours on the other side as you organize the learning experience, ensure that the patient care interventions of your preceptees are complete, address any questions, plan discussion sessions, and complete evaluations. In one survey of pharmacy residency preceptors, 60% reported that their greatest challenge was "effectively precepting while meeting employment responsibilities."[1] It is crucial to strive to maintain a healthy work-life balance after residency, so you will want to increase your efficiency as a preceptor, dedicating adequate time to your preceptees without experiencing burnout. With the first few learners, you can develop tools (syllabi, schedules, and other learning materials) that can be used in the future. When precepting residents in particular, giving them increasing autonomy over the course of a rotation will free up some of your time and encourage them to develop confidence and responsibility. You can provide oversight without micromanaging when both you and the learner are comfortable with an increased level of independence. Layered learning and resident-preceptor models encourage residents to take more ownership of the precepting process when multiple levels of learners are completing a rotation simultaneously, and this helps residents develop skills for precepting on their own in the future.[2,3] Additionally, you can involve students and residents in research projects, quality improvement initiatives, and teaching in your institution.

During residency, you became familiar with how you learn best and became accustomed to your own preceptor's expectations. Though residents are often involved in some teaching, the primary focus is on their own learning and professional development. Now you will be involved with more learners and will need to adapt your precepting to other learning styles, skill levels, and goals. You may encounter a variety of learners— from students who do not plan to think about oncology again after this rotation to PGY-2 residents eager to expand their oncology knowledge. Some learners will require more external motivation and direction, while others will be high performers who can still be challenged to advance their clinical judgment. Setting clear expectations and goals while seeking to understand those of the learner can help you tailor your approach to individual students and residents. For example, knowing the preceptee's career plans allows you to look for the most relevant learning opportunities and discussion points to keep the learner engaged. Depending on the learner's experience level and comfort, different levels of independence and coaching may be appropriate. You may find that some students and residents learn best from hands-on application, while others do well with reading or repetition. Giving and receiving feedback continually throughout a rotation will provide insight into how to personalize the experience.

Self-assessment is part of residency, but it should also continue throughout your career. Giving feedback helps your students and residents grow and helps you develop as a preceptor. Students and residents want to know how they are doing, and feedback is best received when given in a timely manner. Rather than just saving your thoughts and suggestions for a formal evaluation, you can give on-the-spot guidance on communication skills, projects, and presentations. Also, learners should be actively engaged in these conversations and encouraged to reflect on their own performance.[4] For more significant concerns, it may be necessary to bring in faculty members from the school of pharmacy or the residency program director for students and residents, respectively. Having specific examples and documentation in these situations is useful.

As you evaluate your preceptees, give constructive feedback and positive reinforcement that can help the person succeed in the future. Buck and colleagues offer a series of questions that prompt the preceptor to assess whether evaluation comments are effective. These questions address topics such as development of skills to

meet the resident's goals, areas for improvement, reinforcement of strengths, and plans for future learning experiences.[5] You can also seek feedback from other preceptors and providers with whom you work, because the learner will likely be spending time with others on the rotation too. This can help you identify issues and opportunities you may not have thought of and ensure that the learner is receiving consistent guidance regarding professionalism and communication. In addition to giving feedback to learners, seek their suggestions for improvement. Especially if they are beginning a new rotation, they can give insight into preferences for organization, experiences, and content. Although learners will likely have different opinions on some issues, you may see some themes emerge.

Fortunately, you do not have to embark on your journey of precepting alone. Remember to take advantage of support from your colleagues, mentors, and those who have gone before you in precepting. There is always room for improvement, but you do not have to reinvent the wheel if your fellow preceptors or residency program director have tools such as a syllabus and discussion topics that have been useful in previous rotations. The residency program director will be able to provide guidance on a resident's goals and overall progress in the course of the residency that can be helpful in designing a rotation or giving feedback. Meeting with your fellow preceptors at regular intervals can aid in identifying problems and inconsistencies, which can lead to smoother transitions for those working with multiple preceptors and provide more experiences for the learner than your specific practice area entails. You can sometimes share the work of arriving at discussion topics, for example, with other preceptors. In addition, pharmacy organizations such as the American Society of Health-System Pharmacists offer tools for preceptor development.[6] You can also turn to schools of pharmacy for preceptor development resources and assistance with difficult students. Staff members at those institutions also want your learners to succeed and have the ability to look at the bigger picture in the student's progress to address growth needed from rotation to rotation. They can also provide additional resources, which can be especially helpful for those at smaller practice sites.

As a new preceptor, you will have the opportunity to pass on what you have recently learned as a resident. You will face questions and obstacles specific to both your own learning experience and that of your individual students and residents, but these are just a few areas where you can adapt to a new perspective and grow in your oncology practice. Finally, be excited about the challenging but rewarding work of precepting ahead of you. ●●

REFERENCES

1. Hartzler ML, Ballentine JE, Kauflin MJ. Results of a survey to assess residency preceptor development methods and precepting challenges. *Am J Health-Syst Pharm*. 2015; 72:1305-1314.
2. Loy BM, Yang S, Moss JM, Kemp DW, Brown JN. Application of the layered learning practice model in an academic medical center. *Hosp Pharm*. 2017;52(4):266-272.
3. Anderegg SV, Christenson JC, Padgett CP. An accelerated, practice-based model for fostering precepting skills in pharmacy residents. *Hosp Pharm*. 2014;49(8):713-716.
4. Wilkinson ST, Couldry R, Phillips H, and Buck B. Preceptor development: providing effective feedback. *Hosp Pharm*. 2013;48(1):26-32.
5. Buck B, Wilkinson ST, Phillips H. Preceptor development: providing effective feedback, part 2. *Hosp Pharm*. 2014;49(6):521-529.
6. American Society of Health-System Pharmacists. Mentoring and Preceptor Development. https://www.ashp.org/New-Practitioner/New-Practitioners-Forum/Resources/Mentoring-and-Preceptor-Development. Accessed February 22, 2018.

The Emerging Role of Venetoclax for Hematologic Malignancies Beyond Chronic Lymphocytic Leukemia

Jeffrey Baron, PharmD BCOP
Clinical Pharmacy Specialist
Roswell Park Cancer Institute
Buffalo, NY

Eugene Przespolewski, PharmD BCOP
Clinical Pharmacy Specialist
Roswell Park Cancer Institute
Buffalo, NY

Venetoclax is currently approved by the U.S. Food and Drug Administration (FDA) for patients with relapsed or refractory (RR) chronic lymphocytic leukemia (CLL) who harbor a 17p deletion, with 71% of such patients responding to therapy and 20% achieving complete response (CR).[1,2] Venetoclax is a B-cell leukemia/lymphoma-2 (BCL-2) inhibitor that, when given, results in activation of pro-apoptotic pathways[2] to which CLL is exquisitely sensitive, leading to a high incidence of tumor lysis syndrome (TLS) in CLL. To mitigate this risk, the FDA approval information for CLL advises that venetoclax be dosed on a weekly ramp-up schedule with additional supportive care and possible inpatient admission, depending on the disease burden and preexisting hyperuricemia.[1] Overexpression of BCL-2 is not unique to CLL and is found in non-Hodgkin lymphoma (NHL), multiple myeloma (MM), and acute myeloid leukemia (AML), leading to trials exploring the use of venetoclax in treating these malignancies.

Non-Hodgkin Lymphoma and Multiple Myeloma

Overexpression of BCL-2 is observed in many subtypes of NHL. The phase 1 dose-escalation M12-175 trial led to the FDA approval of venetoclax for CLL, but it also included patients with NHL subtypes such as mantle cell lymphoma (MCL); follicular lymphoma (FL); diffuse large B-cell lymphoma (DLBCL), including those with Richter transformation; marginal zone lymphoma (MZL); and Waldenstrom macroglobulinemia (WM).[4] Venetoclax doses were escalated in a 3+3 design from 200 mg to 1,200 mg. The maximum tolerated dose (MTD) was not reached, and safety expansion proceeded with the 1,200-mg daily dose. Overall response rates (ORR) were 75% in MCL, 38% in FL, 18% in DLBCL, 43% in DLBCL with Richter transformation, 67% in MZL, and 100% in WM. The median progression-free survival (PFS) for the entire population was 6 months but varied among the histologies. These encouraging data led to further studies examining venetoclax in NHL.

Venetoclax in combination with ibrutinib in RR MCL has been studied in a phase 2 trial, given that ibrutinib can decrease MCL-1 levels and possibly prevent venetoclax resistance.[5] Twenty-four patients received ibrutinib 560 mg daily for 4 weeks followed by venetoclax ramp-up to a target of 400 mg daily (this was a lower dose than the single-agent dose because of potential overlapping toxicities and pharmacokinetic interactions). At 16 weeks, 63% achieved CR. The ongoing phase 3 trial of ibrutinib and venetoclax is based on these encouraging data.[6] Venetoclax has also been combined with bendamustine and rituximab (BR) in RR FL.[7,8] In a three-arm trial (venetoclax plus rituximab, venetoclax plus BR, and BR alone), the ORR for venetoclax and rituximab was 32% but was 64% in patients not refractory to prior therapy, with 50% achieving CR. Outcomes with venetoclax plus BR versus BR alone were similar, with both showing approximately 65% ORR but greater CRs with the addition of venetoclax (50% vs. 41%).

The efficacy of venetoclax in MM is most promising for patients with t(11;14).[9] In a phase 1 dose-escalation study, 66 RR MM patients received 21-day cycles of venetoclax at daily doses of 300–1,200 mg without reaching the MTD. Although the ORR was only 21%, 12 out of 14 responders harbored t(11;14), with a median duration of response (DOR) of 10 months. Very good partial responses (VGPRs) were noted in 10 out of 12 t(11;14) patients. Venetoclax has been combined with bortezomib in MM to mitigate venetoclax resistance.[10] In a phase 1b study of venetoclax, bortezomib, and dexamethasone, an ORR of 67% was observed, with greater than 50% of patients achieving at least a VGPR independent of the presence of t(11;14), with a median DOR of 10 months.

Clinical TLS was not observed in trials of venetoclax in MM and was rare in single-agent venetoclax trials in NHL.[9,10] Clinical TLS occurred only in 2 patients with MCL treated in the ibrutinib and venetoclax combination study.[5] Laboratory TLS occurred in both the single-agent phase 1 venetoclax NHL trial and in combination with BR.[4,7] The most common adverse event (AE) was gastrointestinal distress, and the most severe AE was myelosuppression. Risk of TLS correlates most closely with disease characteristics and patient-associated risk factors.

Acute Myeloid Leukemia

Older patients with AML who are unable to tolerate induction are commonly managed with low-intensity therapy such as hypomethylating agents (HMAs; azacitidine and decitabine) or low-dose cytarabine (LDAC), limited by low response rates and short overall survival (OS). However, the activity of HMAs, which act via epigenetic modification of p53 and the anti-apoptotic pathway, provides a compelling rationale for BCL-2 inhibition with venetoclax as a single agent and in combination with chemotherapy.

The safety and efficacy of venetoclax in high-risk RR AML or newly diagnosed (ND) patients deemed unfit for induction was established via a phase 2 single-arm study.[11] Thirty-two patients received single-agent venetoclax 800 mg daily, with a 19% ORR, enriched for patients with isocitrate dehydrogenase (IDH) mutations, which showed 33% CR or CR with incomplete count recovery (CRi) rate. Following these encouraging results, venetoclax was evaluated in combination with LDAC in a phase 1b/2 study for ND AML in patients 65 years and older who were considered unfit for induction.[12] Venetoclax was given as a 5-day dose escalation

starting at 50 mg daily up to a target dose of 600 mg daily with LDAC on days 1–10 of a 28-day cycle. Seventy percent achieved a CR or CRi, with 1 year OS estimated to be 75%. Notably, median time to response was 30 days, a shorter period than that of the 2–4 cycles often required for HMAs. A long-term update has been presented by 71 patients enrolled with a 62% CR or CRi and median DOR of 15 months. Venetoclax 600 mg daily plus LDAC is being evaluated.

Venetoclax has also been combined with HMAs in the treatment of elderly patients who have ND AML and intermediate- or poor-risk cytogenetics in a phase 1b study.[13] Patients were enrolled in one of three groups: (A) venetoclax plus decitabine 20 mg/m^2 on days 1–5, (B) venetoclax plus azacitidine 75 mg/m^2 on days 1–7, and (C) venetoclax plus decitabine (dosed as above) with posaconazole (to assess venetoclax pharmacokinetics). Venetoclax dose escalation followed a standard 3+3 design up to 1,200 mg daily. Fifty-seven patients were enrolled: 23 in group A, 22 in group B, and 12 in group C. Overall, 61% achieved CR or CRi. An updated report described results for 145 patients enrolled; 60 received venetoclax 400 mg, 74 received venetoclax 800 mg, and 11 received venetoclax 1,200 mg, with an ORR of 83%, including 66% CR or CRi and a median OS of 17.5 months. Venetoclax 400 mg daily was determined to be the optimal dose and is currently being evaluated in a phase 3 study with HMAs.

The efficacy of venetoclax in combination with LDAC or HMAs in AML is encouraging. It is important to note that no new safety signals were identified. The most common AEs were gastrointestinal distress and myelosuppression. One patient who received venetoclax plus LDAC developed tumor lysis. This low TLS incidence may be due to lesser tumor burden compared to CLL patients with leukocytosis and lymphadenopathy. However, in all the AML trials discussed above, the first cycle was administered on an inpatient basis with a dose-escalation phase, which may complicate interpretation of the true risk if the therapy had been given on an outpatient basis.

Conclusion

Venetoclax is the first FDA-approved BCL-2 inhibitor, and data are rapidly emerging on its use in treating numerous hematologic malignancies that are sensitive to BCL-2 inhibition, including NHL, MM, and AML. As oncology pharmacists, we are in an ideal position to assist in identifying patients who may benefit from this agent and to assist in toxicity management. Across the studies discussed above, laboratory TLS appears to be uncommon, and clinical TLS even less common. Risk for TLS appears to be tied to the disease and the patient; those with high tumor burden, aggressive disease characteristics, and patient-related risk factors seem to be at highest risk. For AML patients starting venetoclax at our institution, the first cycle is administered on an inpatient basis for TLS monitoring. Patients with NHL and MM are monitored in an observation status for the first few days of each early dose escalation.

We can also assist with drug acquisition and insurance coverage. NHL, MM, and AML are currently off-label indications, so insurance coverage is highly variable, but this situation may improve with the emergence of phase 3 data in these indications. We must also be prudent about screening for drug interactions. Concomitant use of strong (e.g., voriconazole, posaconazole) or moderate (e.g., isavuconazole, fluconazole) CYP3A4 inhibitors may be necessary in treating these hematologic malignancies. Venetoclax should be dose reduced 50% with a moderate CYP3A4 inhibitor and 75% with a strong CYP3A4 inhibitor.[1] Venetoclax is an exciting addition to the therapeutic armamentarium for several hematologic malignancies. ●●

REFERENCES

1. Venclexta (venetoclax) [prescribing information]. December 2017. North Chicago, IL: AbbVie Inc;.
2. Roberts AW, Davids MS, Pagel JM, et al. Targeting BCL2 with venetoclax in relapsed chronic lymphocytic leukemia. *N Engl J Med*. 2016;374(4):311-322.
3. Souers AJ, Leverson JD, Boghaert ER, et al. ABT-199, a potent and selective BCL-2 inhibitor, achieves antitumor activity while sparing platelets. *Nat Med*. 2013;19(2):202-208.
4. Davids MS, Roberts AW, Seymour JF, et al. Phase I first-in-human study of venetoclax in patients with relapsed or refractory non-Hodgkin lymphoma. *J Clin Oncol*. 2017;35(8):826-833.
5. Tam CSL, Roberts AW, Anderson MA, et al. Combination ibrutinib (Ibr) and venetoclax (Ven) for the treatment of mantle cell lymphoma (MCL): primary endpoint assessment of the phase 2 AIM study. *J Clin Oncol*. 2017;35(15_suppl):7520.
6. Tam CS, Rule S, Le Gouill S, et al. Phase 3 study of ibrutinib in combination with venetoclax in patients with relapsed/refractory mantle cell lymphoma (MCL). *Hem Oncol*. 2017;35:421-422.
7. Zinzani PL, Topp MS, Yuen SL, et al. Phase 2 study of venetoclax plus rituximab or randomized ven plus bendamustine+rituximab (BR) versus BR in patients with relapsed/refractory follicular lymphoma: interim data. *Blood*. 2016;128(22):617.
8. Salles GA, Boyd TE, Morschhauser F, et al. Updated safety and preliminary efficacy data from a phase 1b study combining venetoclax (GDC-0199, ABT-199) with bendamustine/rituximab in patients with relapsed/refractory or previously untreated chronic lymphocytic leukemia. *Blood*. 2015;126(23):829.
9. Kumar S, Kaufman JL, Gasparetto C, et al. Efficacy of venetoclax as targeted therapy for relapsed/refractory t(11;14) multiple myeloma. *Blood*. 2017;130(22):2401-2409.
10. Moreau P, Chanan-Khan A, Roberts AW, et al. Promising efficacy and acceptable safety of venetoclax plus bortezomib and dexamethasone in relapsed/refractory MM. *Blood*. 2017;130(22):2392-2400.
11. Konopleva M, Pollyea DA, Potluri J, et al. Efficacy and biological correlates of response in a phase ii study of venetoclax monotherapy in patients with acute myelogenous leukemia. *Cancer Discov*. 2016;6(10):1106-1117.
12. Wei A, Strickland SA, Roboz GJ, et al. Safety and efficacy of venetoclax plus low-dose cytarabine in treatment-naive patients aged ≥65 years with acute myeloid leukemia. *Blood*. 2016;128(22):102.
13. DiNardo CD, Pratz KW, Letai A, et al. Safety and preliminary efficacy of venetoclax with decitabine or azacitidine in elderly patients with previously untreated acute myeloid leukaemia: a non-randomised, open-label, phase 1b study. *Lancet Oncol*. 2018;19(2):216-228.

Update on HOPA's Health Policy Activities

Sarah Nichelson, JD
HOPA Health Policy and Advocacy Manager

Congressional Actions

Congress used the latter part of 2017 to pass Public Law No. 115-97, known as the Tax Cuts and Jobs Act. One provision of the signed law repealed the "individual mandate" of the Affordable Care Act—the requirement that most Americans obtain and maintain health insurance, or an exemption, each month or pay a tax penalty. The Congressional Budget Office estimated that by 2025, 13 million fewer people would have health insurance because of this repeal.

Congress also passed a bill that would fund the government through September 30, the end of the 2018 fiscal year (FY). As part of the spending bill signed on March 23, 2018, the Department of Health and Human Services was funded at $37 billion (an increase of $10 billion). The bill also increased funding to the National Institutes of Health by $3 billion. The National Cancer Institute received $5.66 billion, and the Cancer Moonshot initiative received $300 million. Congress also allocated an additional $3 billion in 2018 and an additional $3 billion in 2019 to help address the opioid crisis. HOPA will continue to partner with those working in oncology and those affected by cancer to ensure adequate funding levels for FY 2019 initiatives and research programs.

The Opioid Crisis

As noted above, both the President and Congress have begun to address the opioid crisis through funding and legislation. The funding will help the Department of Health and Human Services carry out its five-part strategy to

- improve access to prevention, treatment, and recovery services
- increase the availability and distribution of overdose-reversing drugs
- improve public health data and reporting
- increase research on pain and addiction
- improve pain management practices.

In addition, the House of Representatives' Ways and Means Committee recently requested input from stakeholders on efforts to address the opioid crisis. The committee sought to learn more about overprescribing, data tracking, treatment options, and ways to communicate with and educate both patients and providers about the adverse effects of opioid use. HOPA submitted comments that emphasized the need for oncology patients to have continued access to pain treatment options.

At the other end of the spectrum of concern about opioids, hospitals are reporting a shortage of injectable pain medications. This shortage has been caused by several factors, including third-party production issues and government-set restrictions on production. HOPA continues to monitor this issue.

Right-To-Try Legislation

The Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina Right to Try Act of 2018 (H.R. 5247), a bill that would allow patients with a terminal or life-threatening illness to have access to unapproved experimental drugs, was passed along party lines in the House of Representatives on March 21, 2018. This bill differs slightly from S. 204, sponsored by Senator Ron Johnson (R-WI). H.R. 5247 broadens the definitions of the terms *eligible patient* and *eligible investigational drug* and requires the sponsor or manufacturer to notify the Secretary of Health and Human Services of the use of the eligible investigational drug, requires reporting of adverse events, and allows the Food and Drug Administration (FDA) to consider the clinical outcomes of eligible investigational drugs in certain scenarios. The bill also waives liability for alleged actions or omissions in certain scenarios. Critics fear a lack of sufficient FDA oversight, although FDA Commissioner Scott Gottlieb has recently said he believes that the FDA is equipped to protect patients under the right-to-try laws.

Commissioner Gottlieb has also indicated that the FDA may soon be reviewing its expanded-access (or compassionate-use) program, which allows patients with terminal or life-threatening illnesses to have access to investigational drugs (i.e., those that have not been approved by the FDA). The goal would be to change the program to make investigational drugs easier for such patients to access.

Joint Commission Statement on Using Closed-System Transfer Devices to Extend Beyond-Use Dates of Single-Dose Containers

In the "Standards FAQ Details" section of its website, the Joint Commission recently posted a statement on using closed-system transfer devices to extend beyond-use dates of single-dose vials:

"The Joint Commission would evaluate compliance with the use of a closed system transfer device (CSTD) based on the FDA approved indications of a device. Based on feedback received directly from the FDA, the extension of a beyond use date beyond 6 hours for a single dose vial has not been approved as an indication."

"The Joint Commission is aware of published articles which [support] the use of these devices to extend beyond use dating longer than the 6 hours allowed for a single dose vial. However, this has not been approved by the FDA and is not supported as a standard of practice."

HOPA is investigating the implications of this interpretation for our members and developing a response. This information may be helpful to those whose institutions will soon be undergoing a Joint Commission survey. Please continue to monitor *HOPA News* and HOPA Member Updates for more information. ●●

HOPA 2018 PRACTICE MANAGEMENT

SAVE THE DATE

6th Annual

HOPA

Oncology Pharmacy Practice Management Program

This 2-day program is designed to guide oncology pharmacy providers in effective management of the expensive, high-risk care and oncology medications they provide, while allowing for the implementation of new technologies and also ensuring improved safety and patients' compliance with medication instructions. Attendees will have the opportunity to earn up to 13.5 Accreditation Council for Pharmacy Education credits.

Program Topics

- Investigational Drug Services
- Value-Based Care
- Information Technology
- Implementation of CAR-T Therapy
- Oral Chemotherapy
- Operations and Safety
- Reimbursement Updates
- Updates on the Medicare Access and CHIP Reauthorization Act

September 14–15, 2018

Loews Chicago O'Hare Hotel · Rosemont, IL

Learn more or get registered now at **hoparx.org**.

Specialty Pharmacy Models and the Oncology Pharmacist's Role

Ronni Miller, PharmD BCOP
Thoracic Oncology Clinical Pharmacist
University of Colorado Hospital, Anschutz Cancer Pavilion
Aurora, CO

Specialty pharmacy focuses on high-cost, high-touch medication therapy for patients with complex disease states—cancer, multiple sclerosis, and many others.[1] In 2017, the U.S. Food and Drug Administration (FDA) approved 48 oncology drugs, of which 24 were oral medications.[2] Every year, the number of oral oncolytics approved steadily increases. The cost of these medications has led not only to insurance restrictions but also to specialty pharmacy restrictions. Patients' access to these medications is further complicated by the need for financial assistance. If a patient is privately insured, then enrollment using a copay card can easily be completed online. However, if a patient is federally insured (e.g., through Medicare), the process becomes more complex: an application with the signatures of both patient and provider, as well as financial documents, must be included. With all these hoops to jump through, members of the clinic staff are often left frustrated and exhausted, while patients may experience delays in treatment initiation or potentially have to go without therapy.

Many drug companies offer hub forms for the provider and patient to fill out. The hub then coordinates benefits, routes the script to the appropriate pharmacy, and helps prepare financial assistance documents. The specialty pharmacy then contacts the provider to complete the prior authorization. This outsourcing model has many benefits, including offering services to many oncology offices that do not have the necessary resources to provide them on their own and giving the clinic staff more control over patient follow-up.[3] However, one of the challenges in the age of the electronic medical record is the potential duplication of prescriptions. The application contains an embedded prescription, and the provider must enter a prescription into the patient's chart. Also, the application process is labor intensive, particularly if the patient cannot provide a signature in person and does not live near the office. Clinic staff must coordinate the application process and follow up with patients in addition to their other responsibilities. Finally, the process can delay the beginning of the patient's therapy for 14 days or more. All these issues led University of Colorado Health (UCH) to develop the Medication Access and Renewal Center (MARC) program.

The MARC prior authorization program was developed in 2014. This team is composed of pharmacists and pharmacy technicians who complete prior authorizations, write appeal letters, determine and reroute prescriptions to the correct specialty pharmacy (depending on access and insurance restrictions), and helps with financial assistance documents. An automated drug list (ADL) was created to help with completion of these tasks. The list consists of high-cost medications that typically require a prior authorization in more than 90% of cases. When a provider prescribes a medication on this list, the prescription is automatically routed to a queue in the ambulatory pharmacy setting. The specialty pharmacy team then works exclusively on this queue, adjudicating claims and handling insurance issues. When possible, the specialty team offers pharmacy services, like adherence follow-up and toxicity assessments. All documentation is contained in the patient's chart, allowing for clear communication between the clinic and specialty staff. MARC's initial attempt to onboard services in the cancer center used an integrated model similar to that used by the University of Illinois and by Vanderbilt.[3,4] The existing clinic-based pharmacist reviewed patient profiles and provided education. In the event that a prior authorization was denied, the specialty pharmacy team notified the clinical pharmacist so that assistance in writing appeal letters could be given. Otherwise, the clinical pharmacist and specialty pharmacy teams operated separately. The benefits of this model included a decreased number of handoffs and improved communication between providers because documentation and staff were within the system. However, the major challenge of the model was that it required a pharmacist to be based in nearly every clinic. The University of Colorado Cancer Center is a National Cancer Institute–designated institution, a National Comprehensive Cancer Network member, and a Quality Oncology Practice Initiative–certified facility that encompasses 14 clinics in Aurora, CO.[5] However, only 4 of these clinics had clinical oncology pharmacists on staff at the time. Lack of funding for additional pharmacists limited expansion of the program. As a result, the program shifted to a hybrid model.

The hybrid model incorporating specialty pharmacy services into clinical practice was implemented at the University of Colorado Cancer Center in 2015. On the specialty side, a pharmacist completes the previously listed tasks, makes medication-adherence calls for all oncology patients who are filling oral oncolytics at our specialty pharmacy, and writes appeal letters for any clinic that does not have a clinical pharmacist. Adherence calls occur at therapy initiation, at 21 days, and then every 84 days while the patient is on therapy. This same pharmacist also has hours in the thoracic oncology clinic twice a week, giving him or her opportunities to see patients, provide counseling, and recommend supportive care measures. A major benefit of the hybrid position is being able to coordinate more easily between clinic staff and specialty pharmacy staff, providing this pharmacist the ability to identify and triage issues in real time and make adjustments on the specialty pharmacy side. An additional benefit is the ability to build mutual trust with patients up front, which may alleviate stress when insurance issues or copay issues are encountered. This model also allows the pharmacist to stay up-to-date on the latest treatment options and clinical reasoning, which can contribute to improved appeal writing and staff education on criteria for authorizations. The major challenge for pharmacists in this position is the need to balance both roles; however, revenue generated from an increase in internal prescription capture as a result of direct involvement

with the clinic and specialty pharmacy may be justification for additional clinical oncology pharmacist support.

With the development of expensive oral oncolytics, the role of specialty pharmacy will continue to grow. Each model described has challenges and benefits (see **Table 1**), so it is important to carefully consider the needs and resources of the oncology practice to determine which model is the best fit for an institution. ●●

Table 1. Overview of Specialty Pharmacy Models

	Outsourcing Model	Integrated Model	Hybrid Model
Description	The clinic uses the hub form provided by the drug manufacturer to assist with specialty and financial services.	An internal specialty pharmacy team provides services and works with a pharmacist based in the clinic.	A pharmacist provides services for both the specialty pharmacy team and the clinic.
Benefits	The model is easily used in smaller practices where resources are limited, and the clinic can control patient follow-up.	Documentation and communication are internal.	The pharmacist is able to serve as a liaison between clinical and specialty pharmacy services
Challenges	Paperwork is labor intensive, and prescriptions and communication are stored outside the electronic medical record.	A clinical pharmacist is required for each oncology clinic.	Balancing both roles can be overwhelming.

REFERENCES

1. American Pharmacists Association. Specialty Pharmacy. November 28, 2017. https://www.pharmacist.com/specialty-pharmacy. Accessed February 14, 2018.
2. U.S. Food and Drug Administration. Hematology/Oncology (Cancer) Approvals and Safety Notifications. February 8, 2018. https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm279174.htm. Accessed February 10, 2018.
3. Hanson RL, Habibi M, Khamo N, et al. Integrated clinical and specialty pharmacy practice model for management of patients with multiple sclerosis. *Am J Health-Syst Pharm*. 2014;71:463-469.
4. Bagwell A, Kelley T, Carver A, et al. Advancing patient care through specialty pharmacy services in an academic health system. *J Manag Care Spec Pharm*. 2017;23:815-820.
5. UCHealth University of Colorado Cancer Center–Anschutz Medical Campus. (2017). https://www.uchealth.org/locations/uchealth-university-of-colorado-cancer-center-anschutz/. Accessed February 12, 2018.

Using Goal Setting to Achieve More *(continued from p. 9)*

year (remember the buffer practice). We mapped out how we would incorporate this plan into our busy lives, considering our physiology (am I a night owl or an early riser?), work schedules, and family schedules. My running partner is a realtor full time, but she has more flexibility in her busy schedule than I do as a pharmacist. So each of us worked to set up habits to support our goals in a way that works for our own lifestyle. We do things differently, but both of us hit 10 miles per week consistently.

After our first year of running 500 miles, we celebrated the New Year together and discussed resolutions. This discussion continued for several weeks. We now hold this discussion annually and include setting goals in different areas of focus, such as spiritual growth, fitness, personal growth, finances, and family. The discussions are meaningful, candid, and humbling. You get to know someone pretty well when you run 500 miles together annually. You see each other's strengths and weaknesses. Consequently, we can check each other to ensure that our goals line up with our values, are achievable, and are realistic (i.e., they are SMART goals—see the sidebar on p. 9). My running partner and I live in different daily worlds and come to the table with different experiences and fears. However, many issues we face transcend our individual circumstances. For example, both of us love what we do for a living, get excited by a lot of things, and as a result have a tendency to overcommit. We work hard to help each other avoid this problem. So when new opportunities arise, we discuss ways to help each of us identify "the essential few from the trivial many." We are each other's accountability partner.

Running has completely transformed my life on all levels. I am physically fit with improved mental well-being. I eat better and sleep better. I have more clarity of purpose. I strive each day to be an authentic leader. Each year I grow in my personal and professional development, having set SMART goals and having worked hard to achieve them throughout the year. Key for me has been establishing a connection with my accountability partner. She has motivated me to push myself beyond the boundaries of my fears and set goals that were previously unimaginable. I challenge you to set SMART goals for yourself to achieve more! ●●

Incorporating Brentuximab Vedotin into First-Line Therapy for Advanced Hodgkin Lymphoma: The ECHELON-1 Trial

Karen M. Fancher, PharmD BCOP
Assistant Professor of Pharmacy Practice
Duquesne University School of Pharmacy
Clinical Pharmacy Specialist
University of Pittsburgh Medical Center Passavant
Pittsburgh, PA

Over the past four decades, significant progress has been made in the treatment of Hodgkin lymphoma. Five-year survival rates are unparalleled, and every newly diagnosed patient who receives appropriate treatment has an overwhelming likelihood of being cured.[1] For this reason, concerns about long-term toxicity should be considered when one is selecting therapy.

The most commonly used treatment regimen—doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD)—includes bleomycin, an antitumor antibiotic that has been associated with both acute and chronic pulmonary toxicity. Bleomycin-induced pulmonary toxicity (BPT) occurs in up to 46% of patients, with mortality as high as 27%.[2-4] Risk factors for the development of BPT may include age, renal insufficiency, receipt of radiation therapy, underlying lung disease, smoking, and the use of granulocyte colony–stimulating factor (G-CSF) support.[2] Minimizing or eliminating the risk of such toxicity in a potentially curable malignancy has been a topic of great interest.

Alternatively, brentuximab vedotin (BV) is an antibody-drug conjugate composed of an anti-CD30 monoclonal antibody conjugated to monomethyl auristatin E, a microtubule-disrupting agent. This agent has substantial activity as monotherapy and thus gained approval by the U.S. Food and Drug Administration (FDA) for the treatment of relapsed Hodgkin lymphoma after failure of autologous stem cell transplantation or two or more chemotherapy regimens. It is also approved for consolidation after stem cell transplantation in patients who are at risk for relapse or disease progression.[5]

A phase 1 dose-escalation study incorporated brentuximab vedotin into frontline therapy for advanced Hodgkin lymphoma with promising results.[6] On the basis of these findings, the phase 3 ECHELON-1 trial was conducted, which compared regimens containing brentuximab vedotin and bleomycin, and the results have recently been published.[7]

The ECHELON-1 Trial

ECHELON-1 was an open-label multicenter phase 3 trial in patients with previously untreated stage 3 or 4 classic Hodgkin lymphoma. Patients were randomly assigned in a 1:1 ratio to receive brentuximab vedotin, doxorubicin, vinblastine, and dacarbazine (A+AVD) or ABVD on days 1 and 15 for up to six cycles. Patients were stratified according to treatment region and International Prognostic Score (IPS) risk group (low, intermediate, and high). Patients with pre-existing peripheral or motor neuropathy, known cerebral or meningeal disease, clinically relevant cardiac conditions, or diagnosis of a previous cancer were not eligible to participate in the trial.[7]

The primary end point was *modified progression-free survival*, defined as time to disease progression, modified disease progression, or death. Modified progression was characterized as evidence of noncomplete response after completion of first-line therapy as assessed by independent reviewers via a Deauville score of 3–5 on *positron emission tomography* (PET), followed by subsequent anticancer therapy. The study investigators chose to use a modified end point because metabolically detectable residual disease is a reliable predictor of imminent disease progression, and it is accepted practice to initiate subsequent anticancer treatment on the basis of the results of imaging scans at the end of first-line chemotherapy. The key secondary end point was overall survival.[7] Patients were assessed with computed tomographic (CT) and PET scans after cycle 2 and after administration of the last dose of first-line therapy.[7]

Results

A total of 1,334 patients at 218 sites in 21 countries underwent randomization, and baseline characteristics were well balanced between the treatment groups. At a median follow-up of 24.6 months (range 0–49.3 months), the rate of modified progression-free survival as assessed by independent reviewers was 82.1% (95% confidence interval [CI], 78.8–85) in patients who received A+AVD compared to 77.2% (95% CI, 73.7–80.4) in patients who received ABVD. This corresponded to a 23% risk reduction in progression, modified progression, or death (hazard ratio [HR] .77, 95% CI, .6–.98, p = .04). Investigator assessment revealed similar findings, with a 91% concordance between independent review and investigator assessment of the primary end point. Complete response and overall response rates were similar between the two groups (73% vs. 70% and 86% vs. 83%, respectively).[7]

The benefits of A+AVD were noted in the majority of subgroups, with some subgroups showing greater benefit than others: men, patients from North America, those with stage 4 disease, and those under 65 years of age all had an HR less than 1 for modified progression-free survival.

The interim 2-year overall survival rate was 96.6% (95% CI, 94.8–97.7) in patients who received A+AVD compared to 94.2% (95% CI, 92–95.9) in patients who received ABVD. This end point was not statistically significant at the time of study publication, but investigators noted that the final overall survival analysis will be conducted after 112 deaths have occurred.[7]

Adverse Effects

Grade 3 or higher adverse events and serious adverse events were more common in the A+AVD group than in those who received ABVD (83% vs. 66% and 43% vs. 27%, respectively). Neutropenia was experienced by 58% of patients who received A+AVD and

by 45% of patients who received ABVD. Febrile neutropenia was reported in 19% and 8% of patients, respectively. After 75% of study enrollment was complete, the independent data and safety monitoring committee recommended the initiation of primary prophylaxis with G-CSF for patients who were yet to be enrolled and would receive A+AVD.[7]

Peripheral neuropathy occurred in 67% of patients who received A+AVD and in 43% of patients who received ABVD, resulting in the discontinuation of a study drug in 10% of patients in the A+AVD group compared to 4% in the ABVD group. Among patients in the A+AVD group who developed peripheral neuropathy, two-thirds had resolution or improvement by at least one grade at the time of the last follow-up visit.[7]

Pulmonary toxicity was reported in 2% of patients who received A+AVD and in 7% of patients who received ABVD. No deaths related to pulmonary toxicity occurred in the A+AVD group; 11 patient deaths were due to or related to pulmonary toxicity in the ABVD group.[7]

Summary and Implications

The phase 3 ECHELON-1 trial demonstrated that treatment with brentuximab vedotin in combination with AVD resulted in a statistically significant improvement in modified progression-free survival as compared to treatment with ABVD. The benefit of A+AVD was observed in the majority of patient subgroups, and the results of the interim overall survival analysis favored A+AVD as well. The surprisingly high incidence of febrile neutropenia with brentuximab vedotin resulted in a protocol modification to administer primary prophylaxis with G-CSF in patients who received A+AVD. Peripheral neuropathy was reported more frequently in the A+AVD group but was reversible in the majority of patients. Pulmonary toxicity was reported less frequently with A+AVD than with ABVD.[7] On the basis of these results, the incorporation of brentuximab vedotin into first-line therapy should be considered in patients with stage 3 or 4 Hodgkin lymphoma.[8]

However, other recently published studies suggest that a response-adapted approach may allow for bleomycin to be omitted from the ABVD regimen after negative findings on interim PET scans without compromising efficacy. Such findings may minimize the concerns about BPT.[9,10] Further, brentuximab vedotin has traditionally been used in the salvage setting; its subsequent use after incorporation into the first-line setting remains undefined. Finally, the use of a first-line monoclonal antibody conjugate will undoubtedly increase cost of treatment.

The ECHELON-1 trial represents an important and exciting possibility in the treatment of advanced Hodgkin lymphoma. Updates to treatment guidelines, revised position statements, and future trials are all eagerly awaited to further determine its ultimate place in therapy. ●●

REFERENCES

1. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology. Hodgkin Lymphoma v1.2018. Available at www.nccn.org. Accessed February 10, 2018.
2. Martin WG, Ristow KM, Habermann TM, et al. Bleomycin pulmonary toxicity has a negative impact on the outcome of patients with Hodgkin's lymphoma. *J Clin Oncol*. 2005;23:7614-7620.
3. Sleijfer S. Bleomycin-induced pneumonitis. *Chest*. 2001;120:617-624.
4. Lewis BM, Izbicki R. Routine pulmonary function tests during bleomycin therapy: tests may be ineffective and potentially misleading. *JAMA*. 1980;243:347-351.
5. Adcetris [package insert]. Bothell, WA: Seattle Genetics, Inc., 2017.
6. Younes A, Connors JM, Park SI, et al. Brentuximab vedotin combined with ABVD or AVD for patients with newly diagnosed Hodgkin's lymphoma: a phase 1, open-label, dose-escalation study. *Lancet Oncol*. 2013;14:1348-1356.
7. Connors JM, Jurczak W, Straus DJ, et al. Brentuximab vedotin with chemotherapy for stage III or IV Hodgkin's lymphoma. *N Engl J Med*. 2018;378:331-344.
8. Johnson P, Federico M, Kirkwood A, et al. Adapted treatment guided by interim PET-CT scan in advanced Hodgkin's lymphoma. *N Engl J Med*. 2016;374:2419-2429.
9. Longo DL, DeVita VT. Progress in the treatment of Hodgkin's lymphoma. *N Engl J Med*. 2018;378:392-394.
10. Behringer K, Goergen H, Hitz F, et al. Omission of dacarbazine or bleomycin, or both, from the ABVD regimen in treatment of early-stage favourable Hodgkin's lymphoma (GHSG HD13): an open-label, randomised, non-inferiority trial. *Lancet*. 2015;385;1418-1427.

Board Update

HOPA Strong

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

Ryan Bookout, PharmD BCOP BCPS
HOPA President (2018–2019)
Blood and Marrow Transplantation Pharmacy Supervisor
Moffitt Cancer Center
Tampa, FL

From Susannah Koontz, HOPA's Outgoing President

"Earn it." This was the motto of the 2017 Houston Astros baseball team. During my presidency I saw this motto everywhere: at baseball games at Minute Maid Park and all over Houston on T-shirts, banners, billboards, and bumper stickers. It was not merely a motivational slogan but a reminder of what a *team* culture of hard work and collaboration (along with determination and grit) can achieve—in this case, a World Series championship. Even when facing significant obstacles—like being displaced from their home park during Hurricane Harvey—the Astros, supported by their fans, remained "Houston Strong."

Although HOPA didn't hoist the Major League Baseball Commissioner's Trophy at the end of our "season," we too have a great deal to be proud of. I detailed many of our accomplishments in the March 15 HOPA Member Update e-blast (hoparx.org/2017accomplishments). Once again, thank you for your steadfast support and unwavering commitment in ensuring HOPA's vitality and growth this past year.

As I mentioned during my President's Welcome at the 2018 Annual Conference in Denver, I'm grateful to you for electing me to lead our association this past year—a role that has proved to be the professional opportunity of a lifetime. In my remarks, I also harked back to my election statement from 2015, where I made a commitment to you to strive to

- establish HOPA as a leader in oncology education and a model for other organizations
- advocate passionately for our members and profession
- build relationships with other organizations to both maximize our resources and ensure that pharmacists are key members of the healthcare team as new payment models evolve
- continue HOPA's commitment to promote and improve professional certification of oncology pharmacists
- responsibly expand and improve HOPA's educational activities, training programs, leadership development opportunities, practice standards, and professional tools
- increase the use of technology to serve all members
- expand HOPA's resources for supporting pharmacy research and mentoring young investigators
- ensure an open-door policy of accessibility and accountability to HOPA members.

I think you will agree that, by working collaboratively, we have met or are well on our way to meeting each of these objectives.

I now pass the presidential baton to Ryan Bookout, our 15th president. As I take up my new role as immediate past president, I'm eager to see how HOPA's next chapter unfolds. I leave the presidency having helped us make marked improvements in our operations, introduce innovative programs, strengthen our external stakeholder relationships, and solidify our finances. We are "HOPA Strong," and I hope I've earned your respect as I take my place among the illustrious past presidents who have come before me.

"Your volunteerism, your ideas, your energy, and your experience and expertise are the means by which HOPA will achieve our dreams and goals."

From Ryan Bookout, HOPA's Incoming President

Sitting back in Tampa, FL, 2 weeks after the 14th Annual HOPA Conference in Denver, CO, I am wondering how all of you are feeling about the year ahead. Many of you have probably fallen back into the usual routines: answering the hundreds of e-mails that arrived in your inbox while you were away, doing the accumulated piles of laundry, getting hellos and hugs from the people dearest in your life. As the normalcy of April begins to seep in, I want to take a moment to distill some of the energy and excitement from our time together at the conference.

Who are we? HOPA is an *inclusive* association embracing all pharmacists who participate in or support oncology patient care: community oncology pharmacists, inpatient pharmacists, decentralized pharmacists, clinical specialists, research pharmacists, oncology faculty members, pharmacy administrators, insurance providers, health outcomes pharmacists, specialty pharmacists, retail pharmacists, pharmacists in industry roles, pharmacy technicians, and more.

What is our future? HOPA's future is to be the association that is all these things: the *educator* of all oncology pharmacists, the *advocate* for all oncology pharmacists, the *research driver* for all oncology pharmacists, and the *professional home* for all oncology pharmacists.

How do we get there? Your volunteerism, your ideas, your energy, and your experience and expertise are the means by which HOPA will achieve our dreams and goals. Our members are the heart and soul of this organization. Without you, there is no HOPA. Without you, there is no future.

HOPA's mission is clear, and our goals are lofty, covering a wide range of areas:

Research

- Expansion of grant funding in basic science and translational research, workforce metrics and benchmarking, health economics, and the quality and value of oncology (and oncology pharmacists)
- Providing HOPA seed grants and building a strong support network for HOPA researchers

Advocacy

- The Pharmacy and Medically Underserved Areas Enhancement Act
- Oral chemotherapy parity
- 340B drug pricing
- Patient advocacy with outreach for collaboration and inclusion of our patients' voices
- The opioid crisis and protection of our oncology patients
- Efforts to strengthen external relations and build strong collaborative partnerships

Education

- Combinations of Board Certified Oncology Pharmacist programs with other Board of Pharmacy Specialties programs
- Combined educational offerings for practitioners: advanced practice professionals, nurses, case managers, and social workers
- Educational partnerships with Industry Relations Council participants
- Educational opportunities for residents, students, and technicians

Standards

- HOPA publications and statements: Scope of Hematology/Oncology Pharmacy Practice, Part 2; oral oncolytics
- Specialty pharmacy accreditation standards
- United States Pharmacopeia Chapter <800>: Hazardous Drugs—Handling in Healthcare Settings

HOPA is *your* association. Your drive, energy, ideas, and work are what make HOPA. Please seize the opportunities available through HOPA's Volunteer Activity Center. This vehicle is not just for committees and subcommittees that already exist. It is also used when volunteers are needed for newly developing task forces, member representatives on national committees and in national groups, reviewers of national guidelines and federal mandates, and other work that you have told us HOPA should be involved in. Be the change makers for your association and our profession. Engage in your area of oncology practice, your city, your state, and our nation. *You* are the drivers of HOPA's future, a bright future rich with opportunity, and I look forward to partnering with you in this important work!

HOPA
Hematology/Oncology
Pharmacy Association

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

Oral Chemotherapy Education

Your best resource for oral chemotherapy education for patients has arrived.

Oral Chemotherapy Education (OCE) is a concise, patient-friendly resource for healthcare professionals and patients alike. OCE provides information about oral chemotherapy drugs and their side effects to cancer patients and their caregivers.

Oral Chemotherapy Education is a collaboration between four organizations:

ACCC
Association of Community Cancer Centers

HOPA
Hematology/Oncology
Pharmacy Association

NCODA
National Community Oncology Dispensing Association, Inc.
PASSION FOR PATIENTS

ONS
Oncology Nursing Society

See the full library and more information at **OralChemoEdSheets.com.**