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Optimal Management of Adverse Events From Copanlisib in the Treatment of Patients With Non-Hodgkin Lymphomas

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Abstract

Copanlisib, an intravenously administered agent with inhibitory activity that predominantly targets the alpha and delta isoforms of phosphoinositol 3-kinase, was granted accelerated approval by the United States Food and Drug Administration on the basis of its activity in the third-line treatment of follicular non-Hodgkin lymphoma. Copanlisib is associated with several potentially serious adverse conditions, some of which are not shared with other phosphoinositol 3-kinase inhibitors

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Disclosure

B. Cheson reports a consulting relationship with AbbVie Inc, Acerta Pharma, Bayer HealthCare Pharmaceuticals, Celgene, Roche-Genentech, and TG Therapeutics. S. O'Brien reports a consulting relationship with Bayer HealthCare Pharmaceuticals. M. Ewer reports a consulting relationship with Bayer HealthCare Pharmaceuticals. M. Goncalves reports a consulting relationship with Bayer HealthCare Pharmaceuticals. G. Lenz reports a consulting relationship with Bayer HealthCare Pharmaceuticals, Gilead Sciences, Janssen Pharmaceuticals Inc, Celgene, Hoffmann-LaRoche, and Hexal AG. A. Yu reports a consulting relationship with Bayer HealthCare Pharmaceuticals. R. Fisher reports a consulting relationship with Pharmacyclics, Hoffman-LaRoche, Kite Pharma, Seattle Genetics, Sandoz, Celgene, Genentech, Bayer HealthCare Pharmaceuticals, AstraZeneca, Adaptive Bio-technologies, and Ion Solutions. P. Zinzani reports a consulting relationship with Bayer HealthCare Pharmaceuticals, Celgene, Hoffmann-LaRoche, Servier, Sandoz, Bristol-Myers Squibb, Merck & Company, Inc, Janssen Pharmaceuticals Inc, and Gilead Sciences. M. Dreyling reports a consulting relationship with Bayer HealthCare Pharmaceuticals, Celgene, Gilead Sciences, Janssen Pharmaceuticals Inc, Mundipharma, Hoffmann-LaRoche, and Sandoz. A. Farooki reports nothing to disclose.

(ie, infusion-related hyperglycemia and hypertension). Education and guidance are needed to help physicians manage adverse effects associated with copanlisib treatment. Therefore, this panel developed recommendations and guidance for the optimal management of adverse events associated with copanlisib treatment in patients with follicular lymphoma.

Introduction: Copanlisib is a phosphoinositol 3-kinase (PI3K) inhibitor approved for the third-line treatment of follicular non-Hodgkin lymphoma. Although the drug is generally well-tolerated, it can be associated with several unique and potentially serious adverse effects (AEs). Two of the most common toxicities not seen with other PI3K inhibitors include hyperglycemia and hypertension, which primarily occur during infusion and resolve shortly thereafter, and likely relate to targeting the PI3K alpha isoform. Other toxicities less commonly observed with copanlisib than with other approved drugs in this class include non-infectious pneumonitis, infections, diarrhea and colitis, and hep-atobiliary toxicity.

Materials and Methods: A panel composed of experts in lymphoma, diabetes, and hypertension convened to develop guidance pertaining to the administration of copanlisib and the management of the AEs associated with copanlisib treatment.

Results: Recommendations were formulated pertaining to the management of AEs associated with copanlisib treatment, particularly infusion-related hyperglycemia and hypertension, noninfectious pneumonitis, infections, diarrhea, and colitis. The recommendations herein reflect the consensus of the members of this panel, all of whom contributed to these suggested approaches to patient supportive care.

Conclusion: There are a number of challenges associated with the use of copanlisib. Infusion-related hypertension and hyperglycemia occur frequently, although they are transient, reversible, and rarely of clinical significance; this report provides guidance as to their management.

Keywords

Copanlisib; Follicular lymphoma; Hyperglycemia; Hypertension; PI3K

Introduction

Follicular non-Hodgkin lymphoma (FL) is the most common indolent non-Hodgkin lymphoma (NHL) subtype. Although it is very treatable with conventional chemoimmunotherapy regimens, it is not curable in most patients. Patients can be distinguished into 2 groups: those who do not experience an event (ie, progression of disease) within 2 years and those who do. The patients in the former group have a 90% likelihood of long-term survival, comparable with an age-matched population, whereas those who progress have less than a 50% likelihood of long-term survival.¹ Therapy for patients whose disease recurs is usually determined by the quality and durability of initial therapy and the regimen that was used. Treatments approved for second- or later-line therapy include rituximab, bendamustine,² bendamustine-obinutuzumab,³ ⁹⁰Y-ibrutumomab tiuxetan,⁴ idelalisib,⁵ and, most recently, copanlisib.^{6,7}

Over the past few years, a number of new, active agents have been developed that target various intracellular pathways involved in the longevity and proliferation of malignant

lymphoid cells. One class of therapeutic targets is the phosphatidylinositol 3-kinase (PI3K) family of kinases that regulate cell proliferation, metabolism, protein synthesis, and survival.⁸ The PI3K enzymes catalyze the phosphorylation of a hydroxyl group on position 3 of the inositol ring of phosphatidylinositol 4,5-bisphosphate, generating a tri-phosphorylated phosphoinositide (phosphatidylinositol 3,4,5-trisphosphate, PIP3) that mediates protein recruitment and progression of downstream signaling. There are 8 catalytic PI3K subunits, which are categorized in 3 classes based on structure and substrate specificity. Class I is subdivided into Class IA and IB based on modes of regulation. Class IA are heterodimers, containing 1 catalytic subunit (p110 α , p110 β , or p110 δ) that associates with any of the regulatory subunits (p85 α , p55 α , p50 α , p85 β , or p55 γ) that form PI3K α , PI3K β , and PI3K δ , respectively.^{9–11} Class IB is also a heterodimer, consisting of the catalytic subunit p110 γ and the regulatory subunit p101 or p84, forming PI3K γ . Although p110 α and p110 β are expressed ubiquitously, p110 γ and p110 δ are mainly expressed in leukocytes, making them attractive drug targets for lymphoid cell malignancies.^{12,13} PI3K activity in B cells is regulated in both a B-cell receptor-dependent and -independent fashion.¹⁴

Idelalisib, a delta isoform-specific PI3K, was the first to receive United States Food and Drug Administration (FDA) approval based on data in third-line treatment of FL and low-grade lymphoma.¹⁵ This oral agent achieved a response rate of 57%, including a 6% rate of complete remissions (CRs) with a median progression-free survival (PFS) of 11 months.⁵ Early enthusiasm for this agent has been dampened by the observation of a number of serious and life-threatening toxicities—including diarrhea and colitis, pneumonitis, hepatotoxicity, infections, and intestinal perforation—resulting in Black Box warnings from the FDA and a requirement for the concomitant use of prophylactic antimicrobial agents.¹⁵

Most recently, copanlisib, an agent with inhibitory activity pre-dominantly targeting the alpha and delta isoforms of PI3K, was granted accelerated approval by the FDA on the basis of its activity in the third-line treatment of FL,^{6,16} which needs to be validated in a confirmatory phase III trial.¹⁷

Nevertheless, copanlisib is associated with several troublesome and potentially serious adverse conditions, some of which are unique to this agent (see Table 1). In an effort to provide a rational basis for managing these events while continuing effective anti-cancer therapy, a multidisciplinary consensus meeting was held to develop opinions as to the optimal management of patients at risk for or experiencing these events. The recommendations that are included in this paper reflect the consensus of this panel of experts in lymphoma, diabetes, and hypertension, all members of which contributed to these suggested approaches for the supportive care of affected patients.

Materials and Methods

In October 2017, the adverse event (AE) profile of copanlisib was reviewed and discussed by the panel to devise approaches for the optimal management of AEs associated with copanlisib treatment in patients with FL. After this meeting, the panel drafted the following guidance, which was subsequently revised and refined by consensus of the entire panel.

Results

Clinical Experience With Copanlisib

The initial study of copanlisib in patients with lymphoma was a phase II trial published by Dreyling et al,¹⁶ including 33 patients with indolent and 51 with aggressive NHL. The overall response rate was 43.8% in patients with indolent histologies and 29.4% in those with an aggressive histology, which mostly comprised diffuse large B-cell and peripheral T-cell lymphomas. Toxicities were considered manageable. Nonetheless, more than one-half of the patients experienced hyperglycemia (57.1%; grade 3 in 25.0%) or hypertension (54.8%; grade 3 in 40.5%), followed by fatigue in 48.8% (grade 3 in 11.9%) and diarrhea in 40.5% of patients (grade 3 in 4.8%). Neutropenia was reported in 34.5% of patients, which was grade 4 in 11.9% of patients.

Copanlisib was approved by the FDA largely on the basis of data from the Copanlisib either as monotherapy or combination therapy in relapsed indolent NHL patients (CHRONOS)-1 trial.⁶ Patients with FL and low-grade NHL who had failed at least 2 prior lines of systemic treatment received copanlisib 60 mg intravenously on days 1, 8, and 15 of a 28-day cycle until disease progression or unacceptable toxicity was encountered. There were 142 patients at a median age of 63 years (range, 25–82 years) with a median of 3 prior lines of therapy, all failing prior rituximab and an alkylating agent. Sixty-one percent were refractory to their last regimen. FL was the most-common histology (73.2%), and 81% had advanced-stage disease at study entry. The overall response rate was 58%, and 14% of patients achieved a CR. The median PFS was 11.2 months in both the patient population as a whole and in the FL subset (data on file). The median overall survival had not been reached at the time of publication. The median duration of treatment was 22 weeks, with a median of 5.5 cycles. Of note, dose interruptions occurred in 74% of patients, and dose reductions to 45 mg occurred in 26% and to 30 mg in 6% of all patients. Of the dose interruptions or delays, 91% were because of AEs. Nonetheless, 55% of the dose interruptions lasted less than 1 week. Permanent discontinuations owing to treatment-related AEs occurred in 16% of patients.

Of the most widely studied of the current PI3K δ inhibitors, copanlisib is the only one that targets the alpha isoform, which may be, at least in part, responsible for its unique toxicity profile. The safety analysis showed that 98.6% of patients experienced at least 1 AE, with more than one-half of patients experiencing a grade 3 AE, and 28% experiencing a grade 4 AE. The most common AE was hyperglycemia (49.3% of patients) which was grade 3 or 4 in 40% of patients.⁷ Hypertension was documented in almost 30% of patients, being grade 3 in 23.2% of patients, with no grade 4 events. Both hyperglycemia and hypertension were infusion-related and transient in nature. Diarrhea was noted in one-third of patients, but was grade 3 in only 6.3% of patients; no grade 4 diarrhea was noted. Other toxicities occurring in more than 20% of patients included neutropenia, pyrexia, fatigue, and nausea. In contrast to the selective delta isoform inhibitor idelalisib, instances of pneumonitis and hepatotoxicity were rarely observed. Infections were uncommon and mostly grade 1 or 2. A single case of colitis was observed in a patient with prior diverticular disease.⁶

The toxicity profile of copanlisib was recently updated with no late-onset toxicities identified, and the label does not have any Black Box warnings.^{7,17} This agent appears to have a more favorable safety profile than either idelalisib (PI3K δ inhibitor) or duvelisib (PI3K δ , γ inhibitor) with respect to colitis, pneumonitis, hepatotoxicity, and infectious episodes, possibly owing to its intermittent and parenteral dose schedule,^{5,7,20,21} and it compares relatively well with umbralisib (PI3K δ inhibitor) in terms of these toxicities (Table 1).¹⁸ Nevertheless, copanlisib is associated with different toxicities, including hyperglycemia and hypertension.

Hyperglycemia

Hyperglycemia is defined by a laboratory test result that shows an elevation in blood sugar concentration, and is usually an indication of diabetes mellitus or glucose intolerance. Hyperglycemia is an expected on-target effect of PI3K α inhibition and thus is relatively specific to copanlisib among the PI3K δ inhibitors.⁶ PI3K α is responsible for the insulin-mediated production of PIP3 in all metabolic tissues and, therefore, is fundamental for most biological responses exerted by insulin. Acute, systemic inhibition of PI3K α transiently blocks skeletal muscle glucose uptake and enhances hepatic glucose production, creating a hyperglycemic state.

In a phase I pharmacodynamic study including 63 patients, the maximum change in plasma glucose from baseline was observed at 5 hours after infusion.²² Plasma glucose levels returned to baseline by 24 hours after infusion (data on file). Overall, hyperglycemia was transient, asymptomatic, and manageable, showing consistency in glucose values over 2 cycles.²²

In a phase I, first-in-human study, infusion-related hyperglycemia was observed in both diabetic as well as nondiabetic patients.²³ Peak plasma glucose values were observed 5 to 8 hours after the start of the infusion on cycle 1, day 1, but returned to baseline values by the time of the next infusion. For the entire group, the mean change in percent glycated hemoglobin (HbA1c) compared with the last value on treatment was 0.63 (n = 43).²³ During the study, diabetic patients were managed with short-acting insulin and/or oral glucose-lowering agents following copanlisib infusion. In these patients, the mean baseline HbA1c was 7.4%, which changed to 7.3% after treatment with copanlisib. In a pooled analysis, the mean glucose value at the end of treatment showed an increase of 6.5 mg/dL compared with baseline in the pooled patient population.²³

In some copanlisib clinical trials, glucose monitoring was performed pre-dose, and 1, 3, 4, 5, 6, 8, and 24 hours after infusion.^{6,16,22,23} On cycle 1, days 2 and 3, glucose monitoring was performed 3 times per day. In the phase I trial, patients fasted for 8 hours before and 3 hours after the start of the copanlisib infusion on cycle 1, day 1, after which they were allowed to eat. Hyperglycemia management was managed per investigator discretion, and may have included insulin. In the phase II study for patients with indolent and aggressive NHL (Part A), rapid, short-acting insulin was recommended per investigator discretion for hyperglycemia on cycle 1, day 1; in subsequent cycles, investigators could, at their discretion, recommend the use of an intermediate- or long-acting insulin or an oral hypoglycemic agent.¹⁶ Insulin was administered to 17 out of 84 patients to manage infusion-

related hyperglycemia.¹⁶ However, owing to hypoglycemic events following short-acting insulin use, further recommendations were to use only intravenous hydration in insulin-naive patients.⁶ In the phase II CHRONOS-1 study,^{6,24} a fasting plasma glucose level ≤ 125 mg/dL for nondiabetic patients, or ≤ 160 mg/dL for those with diabetes, was required prior to the first infusion. Patients with type I or II diabetes with HbA1c $> 8.5\%$ or a fasting glucose of > 160 mg/dL were excluded at screening. Hyperglycemia during treatment was managed by a rapid- or short-acting insulin at investigator's discretion; but a 3-hour close observation was required after the administration of insulin to monitor potential hypoglycemia. No patients developed diabetic ketoacidosis or a nonketotic hyperosmolar state.²³

Based on experience from these clinical trials, the current recommendations highlighted in the FDA-approved label for patients with a pre-infusion fasting plasma glucose of ≤ 160 mg/dL, or a random glucose of ≤ 200 mg/dL are that copanlisib should be withheld until the fasting glucose is ≤ 160 mg/dL or the random glucose is ≤ 200 mg/dL. For those patients with a post-dose blood glucose ≤ 500 mg/dL, on first occurrence, copanlisib should be withheld until the fasting glucose is ≤ 160 mg/dL, or the random blood glucose is ≤ 200 mg/dL. No dose reduction is warranted as the hyperglycemia is transient. However, in our opinion, close monitoring is imperative in subsequent cycles, and metformin or other oral drugs such as a sodium-glucose cotransporter-2 inhibitor could be considered. If the hyperglycemia becomes difficult to manage, copanlisib should be discontinued. Oral hydration should be encouraged, unless patients are unable to take them. For such patients with a post-dose blood glucose > 500 mg/dL, referral to an endocrinologist/diabetologist should be considered in order to help prevent such an increase in subsequent cycles.

To summarize the copanlisib monotherapy data across multiple studies (data on file), which included 317 patients with hematologic malignancies and solid tumors, grade 3 (> 250 to 500 mg/dL) or 4 (> 500 mg/dL) hyperglycemia occurred in 41% of patients, but with only 2.8% considered serious AEs.¹⁷ As indicated in the CHRONOS-1 study, patients were largely asymptomatic and were managed with oral or intravenous fluids.⁶ At 24 hours after infusion, hyperglycemia was noted in 17.7% of patients. Of 155 patients with baseline HbA1c of $< 5.7\%$, only 10% had an HbA1c of $> 6.5\%$ at the end of treatment, with no posttreatment follow-up of HbA1c levels. In 168 patients with an indolent NHL, hyperglycemia of any grade occurred in 54% of patients: occurrences of grade 3 and 4 were 33% and 6%, respectively.¹⁷ Hyperglycemia leading to dose reduction and drug discontinuation was observed in 7% and 2% of patients, respectively. Of the 20 patients in CHRONOS-1 with diabetes, 7 (35%) developed grade 4 hyperglycemia and 2 discontinued treatment.^{6,17}

Of note, it has been recommended by a National Cancer Institute task force that acute hyperglycemia developing in the setting of PI3K inhibition should not lead to immediate discontinuation of oncologic agent; rather "Dose modifications or discontinuation of PAM (PI3K/AKT/mTOR) pathway inhibitors should only be considered in situations of severe events or if progressive metabolic derangement persists after therapeutic interventions have been attempted for a sufficient duration."²⁵

Panel Recommendations

Nondiabetic Patients.

1. For nondiabetics, there is no need for postinfusion monitoring, although the glucose can be re-checked 24 hours after infusion.
2. The use of insulin for hyperglycemia control is discouraged in nondiabetic patients who are insulin-naive; it may put patients at risk for developing hypoglycemia, as the duration of hyperglycemia may be shorter than the time required for insulin to act.
3. Patients who develop an increase in HbA1c during copanlisib treatment should be re-tested in 3 months and again, after discontinuing treatment to determine whether HbA1c level has returned to baseline.

Prediabetic and Diabetic Patients.

1. In patients at risk for diabetes, including those with obesity and/or a family history of diabetes, HbA1c screening should occur prior to treatment to identify prediabetic or uncontrolled diabetic patients.
2. Diabetic or prediabetic patients may consider consulting with an endocrinologist prior to the start of copanlisib treatment. Special consideration should be given to the use of the sodium-glucose cotransporter-2 inhibitor class of medications, as these agents have shown efficacy in combination with PI3K α inhibitors in pre-clinical models (unpublished data). Other oral hypoglycemics that do not cause hypoglycemia may also be considered. Sulfonylureas or other oral insulin secretagogues, which have the potential to cause hypoglycemia, should not be used.
3. Diabetic patients should only be treated with copanlisib following adequate glucose control and should be monitored closely. Diabetic patients should be monitored post-infusion for several hours; however, there are no data to specify the optimal duration of observation.
4. Diabetic patients who eat within 8 hours postinfusion should consume an American Diabetes Association-approved or low carbohydrate diet.
5. Endocrinologists or primary care physicians will not be aware of copanlisib's mechanism of action or duration of hyperglycemic effect, so education and guidance initiatives are essential.
6. For insulin-naive diabetic patients, caution should be exercised before treatment with short-acting insulin owing to the risk of hypoglycemia.

Hypertension.—In clinical trials with copanlisib, on cycle 1, day 1, blood pressure was monitored prior to infusion, and then at 30 minutes, 1 hour, 1.5 hours, 2 hours, 3 hours, 4 hours, and 6 hours postinfusion. On subsequent infusions, blood pressure was monitored pre-infusion, at 30 minutes, and at the end of the infusion. In the phase I trial, elevations in blood pressure were managed at the discretion of the investigator.²³ In the phase II

CHRONOS-1 study, investigators were advised that antihypertensive drugs could be used to manage blood pressure if necessary.²⁴ Hypertension associated with copanlisib therapy usually occurs after cycle 1, day 1 and peaks at 2 hours after the infusion; it then starts decreasing 2 hours post-infusion.^{17,22} The increases typically resolve within 24 hours.^{22,23} The mean increases in systolic and diastolic blood pressure were 16.8 mm Hg and 7.8 mm Hg, respectively.¹⁷ Grade 3 hypertension (systolic blood pressure of \geq 160 mm Hg or diastolic blood pressure of \geq 100 mm Hg) occurred in 26% of 317 patients with hematologic malignancies or solid tumors treated with copanlisib monotherapy.¹⁷ Serious hypertensive events requiring hospitalization were rare, occurring in 0.9% of patients. No patient experienced grade 4 hypertension (life-threatening complications, hypertensive crisis), and there were no treatment discontinuations for hypertension.¹⁷ Similarly, in the CHRONOS-1 trial, 29.6% of patients developed hypertension, almost all grade 3 with no grade 4.⁶

Panel Recommendations

1. Pre-existing hypertension should be recognized and treated prior to initiation of copanlisib, with the goal of achieving a blood pressure less than 140/90 mm Hg.
2. For patients with a pre-dose blood pressure of \geq 150/90 mm Hg, hold treatment with copanlisib until 2 consecutive readings of $<$ 150/90 mm Hg are obtained, measured at least 15 minutes apart as recommend in the label.
3. For those patients with a post-dose blood pressure of $<$ 150/90 mm Hg: if antihypertensive therapy was not required, copanlisib should be continued at the previous dose.
4. The decision of whether to treat copanlisib-induced hypertension with antihypertensive therapy should be individualized based on several factors, including baseline blood pressure, severity of blood pressure elevation during treatment, and preexisting cardiovascular risk factors (eg, diabetes or chronic kidney disease) or cardiovascular disease (eg, ischemic heart disease, stroke or TIA, peripheral vascular disease, or heart failure).
5. Given the short anticipated duration of elevated blood pressure secondary to copanlisib treatment, short acting anti-hypertensives are preferred.
6. If blood pressure remains uncontrolled (\geq 150/90 mm Hg) despite up-titration or initiation of anti-hypertensive therapy, copanlisib should be reduced from 60 mg to 45 mg, or from 45 mg to 30 mg. If blood pressure remains uncontrolled despite dose reduction, copanlisib should be discontinued. Patients with life-threatening consequences should discontinue copanlisib.

Noninfectious Pneumonitis.—Signs and symptoms of noninfectious pneumonitis include cough, dyspnea, hypoxia, or interstitial infiltrates on radiologic exam. Noninfectious pneumonitis is an uncommon event with copanlisib, occurring in approximately 5% of 317 treated patients, with 1.9% of patients experiencing grade 3 events; there were no grade 4 events (data on file). Those patients were successfully managed by withholding the drug and administration of steroids.¹⁷ In the CHRONOS-1 study, patients were monitored for respiratory symptoms coinciding with the weekly intervals of copanlisib infusion and, in the

event of pneumonitis, therapy to manage pneumonitis was at the discretion of the treating physician. Of note is that none of 10 patients who had received prior lung involved-field radiation developed pneumonitis. However, 5 experienced other pulmonary-related events including *Pneumocystis jirovecii* pneumonia, fungal pneumonia, upper respiratory tract infection, and exertional dyspnea (data on file).

Panel Recommendations

1. In the event of grade 2 pneumonitis, withhold copanlisib and treat patients with steroids until their pneumonitis improves to grade 0 or 1. At that point, copanlisib can be restarted at a dose of 45 mg. Copanlisib should be discontinued in patients who experience pneumonitis of grade 3 or higher.

Infections.—Given the concerns with infections related to idelalisib, careful attention was paid to infections in trials of copanlisib. Of 142 patients in the CHRONOS-1 trial, there were 2 (1.4%) patients with a grade 3 upper respiratory infection; 9.9% of patients had grade 3 or 4 (1.4% grade 4) pneumonia, and there was a single (0.7% of patients) death from lung infection that was considered to be treatment-related.^{6,7} Prophylaxis was not routinely given to subjects receiving copanlisib as a monotherapy in CHRONOS-1, although 18 patients did receive it at the investigator's discretion.⁶ Among all patients treated with copanlisib monotherapy in clinical trials, which included 317 patients with hematologic and solid tumors, 19% of patients experienced serious infections, which included 7 (2.2%) deaths owing to infections.¹⁷ The most common serious infection was pneumonia. Serious *Pneumocystis jirovecii* pneumonia was diagnosed in 0.6% of all patients. Of 168 patients with NHL, 21% had lower respiratory tract infections, of which 12% were grade 3 and 2% were grade 4.¹⁷

Panel Recommendations

1. Before initiating treatment with copanlisib, treating physicians should consider *Pneumocystis jirovecii* pneumonia prophylaxis for high-risk patients.
2. Patients receiving copanlisib should be monitored carefully for signs and symptoms of infection; treatment should be interrupted for infections of grade 3 or worse until resolution.
3. Given the infrequency of this AE, the prophylaxis for pneumonia recommended with idelalisib therapy is not recommended.

Diarrhea and Colitis.—One of the most serious complications of idelalisib is colitis, which begins to appear around 8 months into therapy; this explains why it was not reported in the pivotal study by Gopal et al, which had a median follow-up of only 9.7 months.⁵ Copanlisib seems to be associated with a lower incidence of this complication, possibly owing to its intermittent and parenteral dose schedule.^{7,20} Grade 3 diarrhea was reported in 5% (n = 8) of 168 patients treated with copanlisib monotherapy, with no cases of grade 4 toxicity. There was a single case of infection-related colitis among 142 patients treated on the CHRONOS-1 study in a patient with a history of diverticulosis.^{6,7} This led to a transient

interruption of the drug and dose reduction in association with antibiotic therapy. The patient received 5 subsequent cycles of copanlisib with no recurrence of the colitis (data on file).

Panel Recommendations

1. Patients should monitor the frequency and consistency of their stools on a daily basis, and be instructed to call their physician if they experience diarrhea for more than 1 day.
2. Those who develop diarrhea should consider adequate hydration and eating several small meals a day and adhering to the BRAT diet (bananas, rice, applesauce, toast); they should also avoid dairy products, high-fat and high-fiber foods, spicy foods, caffeine, and alcohol.
3. In patients with grade 3 diarrhea, copanlisib should be withheld until diarrhea resolves to grade 1 or better; it then can be restarted at 45 mg. If diarrhea of grade 3 or worse recurs, copanlisib should be discontinued. Assessments are needed to ensure that unresolved diarrhea is managed accordingly.
4. If grade 3 or 4 diarrhea persists after treatment discontinuation, additional work-up should be pursued to determine other etiologies.

Hepatobiliary Toxicity.—The CHRONOS-1 study included only patients with normal or mildly impaired hepatic function (total bilirubin $< 1.5 \times$ upper limit of normal [ULN] (< 3 for those with Gilbert syndrome or those with cholestasis secondary to nodal compression), aspartate transaminase/alanine transaminase $< 2.5 \times$ ULN ($< 5 \times$ ULN for those with liver involvement by lymphoma). Treatment-emergent AEs were reported in 3 (2.1%) patients: 1 case each of cholangitis, cholecystitis, and acute pancreatitis. Aspartate transaminase and alanine transaminase increases were reported in 2 (1.4%) and 4 (2.8%) patients, respectively.⁶ Bilirubin increases of grade 1 and grade 2 treatment-emergent AEs were noted in 1 patient each (data on file). As there was no treatment-induced liver injury associated with copanlisib, there is no mandate for frequent liver enzyme monitoring, and routine standard monitoring of liver function tests is recommended per the direction provided in the label.¹⁷

Other Laboratory Abnormalities.—Other hematologic toxicities in patients treated with copanlisib (n = 168) include decreased hemoglobin in 78% of patients, which was grade 3 in 4% of patients; decreased platelet count in 65% of patients, which was grade 3 in 7% and grade 4 in 2% of patients.¹⁷ Serum chemistry abnormalities included hypertriglyceridemia (58%; 5% grade 3); hypo-phosphatemia (44%, 15% grade 3); hyperuricemia (25%, grade 3 in 24%, grade 4 in 1%) and increased serum lipase (21%, grade 3 in 7%, grade 4 in 1%).¹⁷ A complete blood count should be monitored at least weekly during treatment with copanlisib, with standard routine monitoring for laboratory toxicities as recommended in the label.¹⁷

Discussion

Novel targeted agents offer safe and effective alternatives to cytotoxic chemotherapy in patients with relapsed and refractory FL and low-grade NHL. Idelalisib, a delta isoform-

targeting PI3K inhibitor, was approved by the FDA based on a response rate of 57% and a median PFS of 11.0 months, demonstrating that PI3K is a promising therapeutic target. Despite early encouraging data on idelalisib, unexpected toxicities, including infections, pneumonitis, hepatotoxicity, and colitis, were observed with a longer follow-up and dampened enthusiasm for its use. Copanlisib, a pan-PI3K inhibitor with predominant activity against the alpha-delta isoforms, has demonstrated efficacy and tolerability in a variety of histologic types of lymphoma, including FL and other indolent subtypes, as well as diffuse large B-cell lymphoma.^{6,7,17} The available data, now with a longer median follow-up of 29 weeks (range, 1–140 weeks) with 29.6% of patients followed for safety for greater than 1 year, suggests an efficacy that is comparable with that of idelalisib, but with a lower risk of colitis, pneumonitis, and hepatotoxicity.⁷ Incidence of hypertension and hyperglycemia associated with copanlisib does occur, but no late, unexpected AEs have been observed. Nonetheless, there are a number of challenges in its use. Infusion-related hypertension and hyperglycemia occur frequently, although they are transient, reversible, and rarely of clinical significance; this report provides guidance as to their management.

A few issues remain unanswered. The rate of HbA1c decreases 3 months after treatment cessation in patients who develop elevated HbA1c while on copanlisib is unknown, as are the immediate and long-term clinical effects of the elevated HbA1c after therapy. The data available are primarily for the first cycle, and it is unknown whether there is any correlation between blood glucose in cycle 1 and subsequent cycles in “at-risk” patients, especially for those who experience hyperglycemia of grade 3 or 4. The incidence of hyperglycemia and hypertension are higher in cycle 1 than in subsequent cycles; however, it remains to be determined whether there is a subset of patients who continue to experience grade 3 hypertension in subsequent treatment cycles. No life-threatening cardiovascular events have yet resulted from the transient hypertension.⁷

Given copanlisib’s atypical AEs and the need to properly manage for safe drug administration, it is essential to educate physicians, nurses, and patients to ensure appropriate patient selection for treatment and adherence to the recommendations provided in this article.

Although drugs such as copanlisib offer effective therapy for patients who have failed multiple prior lines of therapy, the ultimate goal is to use them in combinations that will achieve even more clinical benefit, and to include them earlier in the course of the disease. Experience, however, has taught us that combining targeted agents whose individual safety profiles are tolerable may lead to serious and unexpected untoward events. Therefore, it is of critical importance that we best understand the toxicities of each individual component of a combination and develop multi-agent regimens with the utmost care. Such as chemotherapy-free approaches may improve the outcome of patients with lymphoma, increasing their likelihood of cure.

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Clinical Practice Points

- Copanlisib was granted accelerated approval by the FDA on the basis of its activity in the third-line treatment of follicular NHL.
- Copanlisib is an intravenously administered agent with inhibitory activity that predominantly targets the alpha and delta isoforms of PI3K.
- Copanlisib is associated with several potentially serious adverse conditions, some of which are not shared with other PI3K inhibitors (ie, infusion-related hyperglycemia and hypertension).
- Because copanlisib is a new treatment, physicians may be unfamiliar with the optimal management of the AEs that were observed in copanlisib-treated patients in clinical trials.
- The recommendations herein reflect the consensus of this panel of experts in lymphoma, diabetes, and hypertension, all of whom contributed to these suggested approaches to patient supportive care.

Warnings and Grade 3 AEs for Approved and Emerging PI3K Inhibitors for Indolent NHL^{6,15,17–19}

Table 1

MoA	Copanlisib PI3Ki (α, δ)	Idelalisib PI3Ki (δ)	Duvelisib PI3Ki (δ, γ)	Umbralisib PI3Ki (δ), cMyc
Black Box warning	None	Fatal and/or serious toxicities: <ul style="list-style-type: none"> • Hepatotoxicity (11%–18%) • Severe diarrhea or colitis (14%–19%) • Pneumonitis (4%) • Infections (21%–36%) • Intestinal perforation 	Fatal and/or serious toxicities: <ul style="list-style-type: none"> • Diarrhea or colitis (18%) • Cutaneous reactions (5%) • Infections (31%) • Pneumonitis (5%) 	N/A
Grade 3 AEs (in patients with FL unless otherwise noted) ^b				
Hypoglycemia	40% (infusion-related)	N/A	N/A	N/A
Hypertension	27% (infusion-related)	N/A	N/A	N/A
Pneumonitis	1%	16% ^d	5% ^f	< 1.5% ^a
Lung infection	16%		16% ^e	5% ^e
Diarrhea	5%	14%	18%	3%
Colitis	1% ^c			
ALT increased	1.4%	18%	18%	3%
AST increased	1.4%	12%	12%	3%

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; FL = follicular lymphoma; MoA = mechanism of action; N/A = not available; NHL = non-Hodgkin lymphoma.

Table is for comparison purposes only. There are no clinical data comparing any of these drugs.

^a All grades.

^b For copanlisib, AEs reported are for patients with FL and other hematologic malignancies.

^c Patient had medical history of diverticulosis.

^d Includes patients with pneumonia, other lung infections, or pneumonitis.

^e Pneumonia only.

^f Reported as severe events.