Cancer Chemotherapy Update

Idelalisib and Rituximab Regimen

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The complexity of cancer chemotherapy requires pharmacists be familiar with the complicated regimens and highly toxic agents used. This column reviews various issues related to preparation, dispensing, and administration of antineoplastic therapy, and the agents, both commercially available and investigational, used to treat malignant diseases. Questions or suggestions for topics should be addressed to Dominic A. Solimando, Jr, President, Oncology Pharmacy Services, Inc., 4201 Wilson Blvd #110-545, Arlington, VA 22203, e-mail: OncRxSvc@comcast.net; or J. Aubrey Waddell, Professor, University of Tennessee College of Pharmacy; Oncology Pharmacist, Pharmacy Department, Blount Memorial Hospital, 907 E. Lamar Alexander Parkway, Maryville, TN 37804, e-mail: waddfour@charter.net. The information presented in this review is based on published data and clinical expertise and includes information not included in the product labeling. Incorporation of such published data provides a more robust assessment of the drugs and assists pharmacists in evaluation of orders for off-label use of these agents.

Regimen Name: Idelalisib plus rituximab
Origin of Name: The regimen is named for the 2 drugs, idelalisib and rituximab, in the regimen.

INDICATION(S)

The idelalisib plus rituximab regimen (Table 1) has been studied as initial therapy of chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) in older patients¹ and as salvage therapy of chronic lymphocytic leukemia (CLL) in patients unable to receive cytotoxic agents.² Current guidelines list the idelalisib plus rituximab regimen as first-line therapy for relapsed/refractory CLL/SLL without del(17p)/TP53 mutation in patients who received at least one previous therapy and as second-line therapy in patients with relapsed/refractory CLL/SLL with del(17p)/TP53 mutation who have failed first-line therapy.³

DRUG PREPARATION

Follow institutional policies for preparation of hazardous medications when preparing rituximab and when dispensing idelalisib.

Table 1. Idelalisib plus rituximab regimen

Drug	Dose	Route of administration	Administration
Idelalisib ¹	150 mg	PO	bid x 48 weeks
Rituximab	375 mg/m ²	IV	Weekly x 8 weeks
<i>Or</i>			
Idelalisib ²	150 mg	PO	bid
Rituximab	375 mg/m ²	IV	Once
	500 mg/m ²	IV	Every 2 weeks x 4 doses, then every 4 weeks x 3 doses

Note: bid = twice a day; IV = intravenous; PO = oral.

A. Idelalisib

1. Idelalisib is available as 100 and 150 mg tablets.

B. Rituximab

1. Use rituximab injection, 10 mg/mL.
2. Dilute to a final concentration of 1 to 4 mg/mL with 0.9% sodium chloride injection (NS) or 5% dextrose in water (D5W).

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DRUG ADMINISTRATION**A. Idelalisib**

1. Take idelalisib by mouth twice daily.
2. The drug may be taken on a full or empty stomach.
3. Missed doses may be taken within 6 hours of the scheduled time.

B. Rituximab

1. The manufacturer recommends rituximab be given over several hours.⁴
 - a. First infusion: Rituximab should be administered at an initial rate of 50 mg/h. If hypersensitivity or infusion reactions do not occur, escalate the infusion rate in 50 mg/h increments every 30 minutes, to a maximum of 400 mg/h. If a reaction develops, the infusion should be temporarily slowed or interrupted. The infusion can continue at one-half the previous rate upon improvement of patient symptoms.
 - b. Subsequent infusions: If the patient tolerated the first infusion well, subsequent rituximab infusions may be administered at an initial rate of 100 mg/h and increased by 100 mg/h increments at 30-minute intervals to a maximum of 400 mg/h as tolerated. If the patient did not tolerate the first infusion well, follow the guidelines for first infusions.
2. Rituximab can be safely administered as a rapid (90 minute) infusion.^{5,6}

SUPPORTIVE CARE

A. Acute Emesis Prophylaxis: The idelalisib plus rituximab regimen is predicted to cause acute emesis in less than 30% of patients.^{7,8} The studies reviewed reported any grade vomiting in 12% to 22% of patients^{1,2} and grade 3 or 4 vomiting in 3% of patients.¹ The studies reviewed reported any grade nausea in 24% to 38% of patients^{1,2} and grade 3 or 4 nausea in 2% of patients.¹ According to current guidelines, routine antiemetic prophylaxis may be considered.⁷⁻⁹

One of the following regimens is suggested:

1. Dexamethasone 8 to 12 mg orally (PO)
2. Metoclopramide 10 to 20 mg PO
3. Prochlorperazine 10 mg PO
4. Promethazine 25 to 50 mg PO
5. Granisetron 1 to 2 mg PO
6. Ondansetron 8 to 16 mg PO

Patients who experience significant nausea or vomiting with one of these regimens should have an agent from a different pharmacologic category added to the regimen.⁷⁻⁹

B. Breakthrough Nausea and Vomiting⁷⁻⁹: Patients should receive an antiemetic prescription to treat breakthrough nausea and vomiting. A meta-analysis of several trials of serotonin antagonists recommends against prolonged (>24 hours) use of these agents, making a steroid, or steroid and dopamine antagonist combination, most appropriate.¹⁰

One of the following regimens is suggested:

1. Metoclopramide 0.5 to 2 mg/kg PO every 4 to 6 hours if needed, ± diphenhydramine 25 to 50 mg PO every 6 hours if needed.
2. Prochlorperazine 10 mg PO every 4 to 6 hours if needed, ± diphenhydramine 25 to 50 mg PO every 6 hours if needed.
3. Prochlorperazine 25 mg rectally every 4 to 6 hours if needed, ± diphenhydramine 25 to 50 mg PO every 6 hours if needed.
4. Promethazine 25 to 50 mg PO every 4 to 6 hours if needed, ± diphenhydramine 25 to 50 mg PO every 6 hours if needed.

C. Hematopoietic Growth Factors: Accepted practice guidelines and pharmacoeconomic analysis suggest that an antineoplastic regimen must have a greater than 20% incidence of febrile neutropenia before prophylactic use of colony stimulating factors (CSFs) is warranted. For regimens with an incidence of febrile neutropenia between 10% and 20%, use of CSFs should be considered. For regimens with an incidence of febrile neutropenia less than 10%, routine prophylactic use of CSFs is not recommended.¹¹ The studies reviewed reported febrile neutropenia in 5% of patients.^{1,2} Prophylactic use of CSFs is not recommended with this regimen. CSFs may also be considered if a patient experiences febrile neutropenia or grade 4 neutropenia in a prior cycle of idelalisib plus rituximab.

MAJOR TOXICITIES

Most of the toxicities listed below are presented according to their degree of severity. Higher grades represent more severe toxicities. Although there are several grading systems for cancer chemotherapy toxicities, all are similar. One of the frequently used systems is the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events

(<http://ctep.info.nih.gov>). Oncologists generally do not adjust doses or change therapy for grade 1 or 2 toxicities but make, or consider, dosage reductions or therapy changes for grade 3 or 4 toxicities. Incidence values are rounded to the nearest whole percent unless incidence was less than or equal to 0.5%. The toxicities listed in the protocols reviewed were:

- A. **Cardiovascular:** Dehydration (grade 3 or 4) 3%.¹
- B. **Constitutional:** Chills (any grade) 22% to 36%,^{1,2} (grade 3 or 4) 2%²; fatigue (any grade) 24% to 31%,^{1,2} (grade 3 or 4) 3%²; night sweats (any grade) 10% to 16%^{1,2}; pyrexia (any grade) 29% to 42%,^{1,2} (grade 3 or 4) 3%.^{1,2}
- C. **CNS:** Headache (any grade) 23%,¹ insomnia (any grade) 20%.¹
- D. **Dermatologic:** Pruritus (any grade) 17%,¹ (grade 3 or 4) 2%¹; rash (any grade) 10% to 58%,^{1,2} (grade 3 or 4) 2% to 13%.^{1,2}
- E. **Endocrine/Metabolic:** Hypokalemia (any grade) 16%,¹ (grade 3 or 4) 2%¹; hyponatremia (any grade) 30%,¹ (grade 3 or 4) 3%.¹
- F. **Gastrointestinal:** Constipation (any grade) 12% to 17%^{1,2}; decreased appetite (any grade) 12%²; diarrhea and/or colitis (any grade) 19% to 64%,^{1,2} (grade 3 or 4) 4% to 43%^{1,2}; nausea (any grade) 24% to 38%,^{1,2} (grade 3 or 4) 2%¹; vomiting (any grade) 12% to 22%.^{1,2}
- G. **Hematologic:** Anemia (any grade) 23% to 25%,^{1,2} (grade 3 or 4) 3% to 5%^{1,2}; leukopenia (any grade) 31%,¹ (grade 3 or 4) 6%¹; lymphocytopenia (any grade) 21%,¹ (grade 3 or 4) 5%¹; neutropenia (any grade) 53% to 55%,^{1,2} (grade 3 or 4) 28% to 34%^{1,2}; febrile neutropenia (any grade) 5%,² (grade 3 or 4) 5%¹; neutropenic sepsis (any grade) 3%²; thrombocytopenia (any grade) 14% to 17%,^{1,2} (grade 3 or 4) 2% to 10%.^{1,2}
- H. **Hepatic:** Aspartate aminotransferase/alanine aminotransferase (AST/ALT) elevation (any grade) 35% to 67%,^{1,2} (grade 3 or 4) 5% to 23%^{1,2}; alkaline phosphatase elevation (any grade) 34%¹; hyperbilirubinemia (any grade) 25%.¹
- I. **Hypersensitivity:** Infusion-related reaction (any grade) 15%.²
- J. **Infections:** Cellulitis (any grade) 1%,² (grade 3 or 4) 3%¹; pneumonia (any grade) 6% to 28%,^{1,2} (grade 3 or 4) 19%¹; *Pneumocystis jirovecii* pneumonia (any grade) 3%²; sepsis (any grade) 4%²; urinary tract

infection (any grade) 16%,¹ (grade 3 or 4) 6%.¹

- K. **Musculoskeletal:** Arthralgia (any grade) 17%,¹ (grade 3 or 4) 2%¹; back pain (any grade) 16%,¹ (grade 3 or 4) 2%.¹
- L. **Respiratory:** Cough (any grade) 15% to 33%,^{1,2} (grade 3 or 4) 2%¹; dyspnea (any grade) 11% to 25%,^{1,2} (grade 3 or 4) 2% to 6%^{1,2}; hypoxia (grade 3 or 4) 3%¹; pneumonitis (any grade) 4%,² (grade 3 or 4) 3%¹; pulmonary fibrosis (grade 3 or 4) 3%¹; respiratory failure (grade 3 or 4) 3%.¹
- M. **Renal:** Increased serum creatine (any grade) 17%,¹ (grade 3 or 4) 2%.¹
- N. **Treatment-Related Death:** Metastatic malignant melanoma 2%,¹ pneumonitis 3%,¹ sepsis 2%.¹

PRETREATMENT LABORATORY STUDIES NEEDED

- A. **Baseline**
 1. AST/ALT
 2. Total bilirubin
 3. Serum creatinine
 4. Complete blood count (CBC) with differential
- B. **Monitoring**
 1. CBC with differential
 - a. Every 2 weeks for first 3 months.
 - b. Weekly in patients with greater than or equal to grade 3 neutropenia.¹²
 2. AST/ALT
 - a. Every 2 weeks for first 3 months, every 4 weeks for the next 3 months, and every 1 to 3 months thereafter.^{12,13}
 - b. Weekly for ALT or AST greater than 5 times the upper limit of normal, until resolved.¹²

DOSAGE MODIFICATIONS

- A. **Renal Function**
 1. Idelalisib: No dose reduction recommended. Idelalisib has not been studied in patients with creatine clearance less than 15 mL/min.¹⁴
 2. Rituximab: No dose reduction recommended.
- B. **Liver Function**
 1. Idelalisib:
 - a. One study showed that a single dose of idelalisib in patients with moderate to severe liver impairment (Child Pugh classes B and C) was well tolerated, although a 1.7-fold increase in area under the curve (AUC) was observed.¹³ Exercise caution when giving

idelalisib to such patients.

b. ALT/AST greater than 5 to 20 times the upper limit or bilirubin greater than 3 to 10 times the upper limit, hold idelalisib, monitor weekly until less than or equal to 1 times the upper limit, then resume at a dose of 100 mg twice daily (bid).¹²

c. ALT/AST greater than 20 times the upper limit or bilirubin greater than 10 times the upper limit, discontinue idelalisib permanently.¹²

2. Rituximab: No dose reduction recommended.

C. Hematology

1. ANC less than 500, hold idelalisib, monitor weekly until ANC is greater than 500, then resume at a dose of 100 mg bid.¹²

2. Platelets less than 25,000, hold idelalisib, monitor weekly until platelets are greater than 25,000, then resume at a dose of 100 mg bid.¹²

D. Diarrhea

1. Severe diarrhea (≥ 7 stools per day over baseline) or hospitalization due to diarrhea, hold idelalisib until resolved, then resume at a dose of 100 mg bid.¹²

2. Life-threatening diarrhea, discontinue idelalisib permanently.¹²

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