Cancer Chemotherapy Update

Pentostatin, Cyclophosphamide and Rituximab (PCR) 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, email: 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: PCR

Origin of name: PCR is an acronym for the 3 drugs in the regimen pentostatin, cyclophosphamide, and rituximab.

INDICATIONS

The PCR regimen (Table 1) has been studied as initial therapy for chronic lymphocytic leukemia (CLL),¹⁻⁶ small lymphocytic lymphoma,² Waldenstrom's macroglobulinemia/lymphoplasmacytic lymphoma,^{7,8} and low-grade B-cell lymphomas.⁹

Current guidelines do not list the PCR regimen as one of the regimens for treatment of Waldenstrom's macroglobulinemia/lymphoplasmacytic lymphoma.¹⁰ It is listed as one of the recommended regimens for first-line treatment of CLL in patients who are less than 65 years old without comorbidities.¹¹

DRUG PREPARATION

Follow institutional policies for preparation of hazardous medications when preparing pentostatin, cyclophosphamide, and rituximab.

A. Pentostatin

1. Use pentostatin for injection.
2. Reconstitute with sterile water for injection (SWFI), 0.9% sodium chloride (NS), or 5%

dextrose in water (D5W) to a concentration of 2 mg/mL.

3. Dilute in 25 to 50 ml NS or D5W.

B. Cyclophosphamide

1. Use cyclophosphamide powder for injection.
2. Reconstitute cyclophosphamide to a concentration of 20 mg/mL with SWFI or NS.
3. Dilute with 100 to 1,000 mL of NS, D5W, or a saline/dextrose solution.

C. Rituximab

1. Use rituximab injection, 10 mg/mL.
2. Dilute to a final concentration of 1 to 4 mg/mL with NS or D5W.

DRUG ADMINISTRATION

A. Pentostatin

1. Pentostatin is administered as a short (20 to 30 minute) intravenous infusion.
2. Patient should be hydrated with 500 to 1,000 mL NS, D5W, or a saline-dextrose solution prior to infusion and 500 mL after infusion.

B. Cyclophosphamide

1. Cyclophosphamide should be administered by IV infusion over 10 to 30 minutes.
2. Some institutions give doses less than 1,000 mg as a slow (1 to 10 minutes) IV push injection.

Table 1. Pentostatin, cyclophosphamide and rituximab (PCR) regimen^{1,5,7-9}

Drug	Dose	Route of administration	Administered on day(s)	Total dose/cycle
Pentostatin	4 mg/m ²	IV	1 (2) ⁸	4 mg/m ²
Cyclophosphamide	600 mg/m ²	IV	1 (2) ⁸	600 mg/m ²
Rituximab	375 mg/m ²	IV	1 ^a	375 mg/m ²

Cycle repeats: every 3 weeks

Variations

1. Rituximab cycle 1: 100 mg IV day 1, 375 mg/m² days 2 & 3; cycle 2-6: 375 mg/m² IV day 1 every 3 weeks.²
2. Pentostatin 2 mg/m² IV day 1, cyclophosphamide 600 mg/m² IV day 1, rituximab 375 mg/m² IV day 1 every 3 weeks.^{3,4}
3. Pentostatin 2 mg/m² IV; cyclophosphamide 600 mg/m² IV; rituximab cycle 1: 100 mg IV day 1, 375 mg/m² days 2 & 3; cycle 2-6: 375 mg/m² IV day 1, every 3 weeks.⁶

^a Reynolds et al gave rituximab 100 mg on day 1, and the remainder of the dose on day 9 in the first cycle.⁵

Note: IV = intravenous; PO = oral.

C. Rituximab

1. The manufacturer recommends that rituximab be given over several hours.¹²
 - a. First infusion: Rituximab should be administered at an initial rate of 50 mg/h.
 - (1) 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.
 - (2) 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
 - (1) 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.
 - (2) If the patient did not tolerate the first infusion well, follow the guidelines for first infusions.
2. If the patient did not experience a reaction with the first cycle of therapy, rituximab can be safely administered as a rapid (90 minute) infusion in subsequent cycles.¹³⁻¹⁵

reported mild (grade 1 or 2) nausea in 25% to 31% of patients⁷; moderate to severe (grade 3 or 4) nausea or vomiting was reported in 2% to 3% of patients, respectively.^{1,5,9} Prophylactic antiemetic therapy with a serotonin antagonist is recommended¹⁶⁻¹⁹ but may not be required in all patients. One group suggests addition of a neurokinin (NK₁) antagonist may be appropriate in some patients.¹⁶ One of the following regimens given 30 minutes prior to therapy is recommended:

1. Ondansetron 8 mg to 16 mg orally (PO), ±dexamethasone 12 mg PO, given 30 minutes before PCR.
2. Granisetron 1 mg to 2 mg PO, ±dexamethasone 12 mg PO, given 30 minutes before PCR.
3. Dolasetron 100 mg orally, ±dexamethasone 12 mg PO, given 30 minutes before PCR.
4. Palonosetron 0.25 mg IV and dexamethasone 12 mg PO, given 30 minutes before PCR on day 1 only.

The antiemetic therapy should continue for at least 3 days. A meta-analysis of several trials of serotonin antagonists recommends against prolonged (greater than 24 hours) use of these agents, making a steroid or steroid and dopamine antagonist combination most appropriate for follow-up therapy.²⁰ One of the following regimens is recommended:

1. Dexamethasone 4 mg PO twice a day for 3 days, ±metoclopramide 0.5 to 2 mg/kg PO every 4 to 6 hours, ±diphenhydramine 25 to 50 mg PO every 6 hours if needed, starting on day 2 of PCR.
2. Dexamethasone 4 mg PO twice a day for 3 days, ±prochlorperazine 10 mg PO every 4 to 6 hours,

SUPPORTIVE CARE

A. Acute and Delayed Emesis Prophylaxis: The PCR regimen is predicted to cause acute emesis in 30% to 90% of patients.¹⁶⁻¹⁹ The studies reviewed

±diphenhydramine 25 to 50 mg PO every 6 hours if needed, starting on day 2 of PCR.

3. Dexamethasone 4 mg PO twice a day for 3 days, ±promethazine 25 to 50 mg PO every 4 to 6 hours, ±diphenhydramine 25 to 50 mg PO every 6 hours if needed, starting on day 2 of PCR.

If a neurokinin antagonist is used, one of the following regimens is recommended:

1. Netupitant 300 mg/palonosetron 0.5 mg PO, given 30 minutes before chemotherapy.
2. Aprepitant 125 mg PO, given 30 minutes before chemotherapy, then 80 mg PO on days 2 and 3.
3. Fosaprepitant 150 mg IV, given 30 minutes before chemotherapy.
4. Rolapitant 180 mg PO (increase dexamethasone to 20 mg), given 1 to 2 hours before chemotherapy.

The onset of cyclophosphamide-induced emesis is often delayed for up to 12 hours after drug administration and may persist for up to 120 hours.^{21,22} Although not well documented in the literature, some clinicians divide the daily antiemetic dose into 2 doses on days when cyclophosphamide is administered.

Patients who experience significant nausea or vomiting with one of these regimens should receive an agent from a different pharmacologic category.¹⁶⁻¹⁹ There is no evidence that substituting granisetron for ondansetron in subsequent treatment cycles, or increasing the dose, even to very high doses, is effective. This approach is not recommended.²³⁻²⁷

B. Breakthrough Nausea and Vomiting¹⁶⁻¹⁹: Patients should receive a prescription for an antiemetic to treat breakthrough nausea. One of the following regimens is recommended:

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 4 to 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 4 to 6 hours if needed.

C. Hydration: Patients receiving cyclophosphamide must be adequately hydrated to reduce the risk of hemorrhagic cystitis secondary to

cyclophosphamide. Patients should be encouraged to empty their bladder frequently. This can be accomplished by encouraging liberal fluid consumption (3 to 4 L/day) during each day of treatment with cyclophosphamide, and for at least 24 hours after the last cyclophosphamide dose. No hemorrhagic cystitis was reported in the studies reviewed; however, Stillwell reports it may occur following a single intravenous dose.²⁸ The risk of hemorrhagic cystitis increases with higher total doses of cyclophosphamide and may be further increased by radiation therapy.²⁸

The risk of hemorrhagic cystitis still exists with oral administration, especially since hydration cannot be monitored as closely as with IV administration. Patients taking oral cyclophosphamide should be instructed to take the medication early in the day to prevent the toxic metabolite from accumulating in the bladder overnight.²⁹

D. Hypersensitivity Precautions: Severe, potentially fatal, infusion-related reactions to rituximab have been reported.^{12,30,31} Symptoms include urticaria, hypotension, angioedema, hypoxia, bronchospasm, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, and/or non-immunoglobulin E (IgE)-mediated reactions.³⁰ Immediate hypersensitivity, potentially IgE-mediated, are estimated to account for 5% to 10% of the reported reactions.^{30,31} Severe reactions usually occur within the first 30 to 120 minutes of the first infusion. Approximately 80% of fatal reactions occur with the first infusion.¹²

The incidence of reactions decreases, with subsequent decrease with each subsequent exposure. The rate of occurrence of infusion reactions on first exposure also varies depending on the treatment indication (12% for Waldenström's macroglobulinemia, 27% for rheumatoid arthritis, and 77% for non-Hodgkin lymphoma) for reasons that are unknown.¹²

Premedication and treatment of these reactions with acetaminophen and diphenhydramine is recommended. Use of bronchodilators, IV saline, glucocorticoids, or epinephrine may be indicated in some patients.¹²

Rapid desensitization for hypersensitivity reactions to rituximab was described by Castells et al in a series of 413 desensitizations to various antineoplastic agents in 98 patients.³¹ Castells' group described the efficacy of a 3-solution, 12-step,

rapid desensitization protocol for cancer patients who experienced hypersensitivity reactions to their first-line chemotherapy agent.³²

- E. Hematopoietic Growth Factors:** Accepted practice guidelines and pharmacoeconomic analysis suggest that an antineoplastic regimen 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.^{33,34}

Since febrile neutropenia was reported in 6% of patients in the trials of PCR⁵, prophylactic use of CSFs is not recommended. Grade 3 or 4 neutropenia was reported in 20% to 53% of patients.^{1,5,7} CSFs should be considered if a patient experiences febrile neutropenia or grade 4 neutropenia in a prior cycle of PCR.

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://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14/QuickReference_8.5x11.pdf). 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%.

- A. Cardiovascular:** Dehydration (grade 3) 6%.⁵
- B. Central Nervous System:** Disturbances of consciousness (grade 3 or 4) 8%,⁸ dizziness (grade 3) 0.4%.⁹
- C. Constitutional:** Asthenia (grade 3) 6%⁵; chills (grade 1 or 2) 18%⁵; fatigue (grade 3) 7%,⁹ (grade 4) 1%⁹; fever (grade 1 or 2) 29%,⁵ (grade 3 or 4) 6%.⁵
- D. Dermatologic:** Alopecia (grade 3) 2%.⁵
- E. Gastrointestinal:** Constipation (grade 3) 1%⁹; diarrhea (grade 3) 0.2%⁹; nausea (grade 1 or 2) 50%,⁷ (grade 3) 2% to 3%^{1,5}; nausea or vomiting (grade 3) 3%⁹; vomiting (grade 1 or 2) 25%,⁷ (grade 3) 2%.⁵
- F. Hematologic:** Anemia (grade 1 or 2) 31%,⁷ (grade 3) 3%,⁵ (grade 3 or 4) 9% to 25%,^{1,7,8} (grade 4) 1%⁵;

febrile neutropenia (grade 3 or 4) 6%⁵; leukopenia (grade 1 or 2) 56%,⁷ (grade 3) 13%,⁵ (grade 3 or 4), 25% to 38%,^{7,8} (grade 4) 3%⁵; neutropenia (grade 1 or 2) 29%,⁵ (grade 3 or 4) 33% to 53%,^{1,5,7} (grade 4) 37%⁵; thrombocytopenia (grade 3) 4%,⁵ (grade 3 or 4) 16% to 19%,^{1,7} (grade 4) 1%.⁵

- G. Hypersensitivity:** (grade 3) 4%.⁵
- H. Infections:** Catheter-related (grade 1 or 2) 6%⁷; pneumonia (grade 1 or 2) 3%,⁵ (grade 3) 1%,⁵ (grade 3 or 4) 1% to 25%^{1,5,7}; septicemia (grade 3 or 4) 6%⁷; unknown origin (grade 3 or 4) 4%¹; upper airway (grade 1 or 2) 13%⁷; sepsis (grade 3) 1%,⁵ (grade 4) 1%⁵; unspecified (grade 3) 2%,⁹ (grade 1 or 2) 3%,⁵ (grade 3 or 4) 3% to 29%^{5,8}; urinary tract (grade 1 or 2) 2%.⁵
- I. Neurologic:** Myasthenia (grade 3) 2%.⁵
- J. Ophthalmic:** Blurred vision (grade 3) 0.2%.⁹
- K. Pain:** Muscle pain (grade 3) 4%,⁹ (grade 4) 1%⁹; unspecified (grade 3) 4%,⁵ (grade 3 or 4) 4%,⁸ (grade 4) 1%.⁵
- L. Pulmonary:** Dyspnea (grade 3) 1% to 4%,^{5,9} (grade 4) 2%⁵; unspecified (grade 3 or 4) 4%.⁸
- M. Renal:** Renal failure (grade 3) 2%,⁵ (grade 4) 1%⁵; unspecified (grade 1 or 2) 13%,⁷ (grade 3) 8%,² (grade 3 or 4) 4%,⁸ (grade 4) 8%.²

PRETREATMENT LABORATORY STUDIES NEEDED

- A. Baseline**
 1. Adequate bone marrow function.⁵
 2. Adequate hepatic function.⁵
 3. Aspartate aminotransferase (AST) less than 5 times the upper limit of normal (ULN).^{5,9}
 3. Serum creatinine:
 - (a) Less than or equal to 2 mg/dL.^{1,8}
 - (b) Less than 132.6 μ mol/L (~1.47 mg/dL).⁹
 - (c) Less than 41 mL/min with serum creatinine greater than or equal to 1.5 mg/dL.⁵
 - (d) Less than or equal to 1.2 times baseline.¹
 4. Creatinine clearance: Greater than or equal to 50 mL/min.¹
- B. Prior to Each Treatment**
 1. CBC with differential
 2. Serum creatinine
 3. AST level
- C. Recommended Pretreatment Values:** The minimally acceptable pretreatment CBC values required to begin a cycle with full-dose therapy in the protocols reviewed were:
 1. Absolute neutrophil count (ANC): Greater than or equal to 1,000 cells/mcL.⁹

2. Platelet count: Greater than or equal to 75,000 cells/mcL.⁹
3. Serum creatinine
 - (a) Less than or equal to 2 mg/dL.^{1,8}
 - (b) Less than or equal to 20% above the patient's baseline.¹
 - (c) Greater than or equal to 132.6 μ mol/L (~1.47 mg/dL).⁹

In clinical practice, a pretreatment absolute neutrophil count (ANC) of 1,000 cells/mcL and platelets of 75,000 cells/mcL are usually considered acceptable.

DOSAGE MODIFICATIONS

A. Renal Function

1. Pentostatin – creatinine clearance:
 - (a) Greater than 60 mL/minute, no adjustment needed.³⁵
 - (b) Less than or equal to 60 mL/min and greater than 40 mL/min, reduce dose 25%.³⁵
 - (c) Less than 40 mL/min and greater than or equal to 21 mL/min, reduce dose 50%.³⁵
 - (d) Less than 60 mL/min, no information available.³⁶
2. Cyclophosphamide – creatinine clearance:
 - (a) Less than 24 mL/min, monitor for toxicity.³⁷
 - (b) Greater than or equal to 10 mL/min, no adjustment needed.³⁸
 - (c) Less than 10 mL/min, reduce dose 50%.³⁸
3. Rituximab: No information available.³⁹

B. Liver Function

1. Pentostatin: No information available.³⁶
2. Cyclophosphamide:
 - (a) No adjustment required.⁴⁰
 - (b) Severe hepatic dysfunction, monitor closely.⁴¹
 - (c) Bilirubin greater than or equal to 3.1 mg/dL and less than or equal to 5 mg/dL or ALT/AST greater than 3 times the ULN, reduce dose 25%.⁴²
 - (d) Bilirubin greater than 5 mg/dL, do not give the drug.⁴²
3. Rituximab: No information available.³⁹

C. Myelosuppression

1. ANC greater than or equal to 500 cells/mcL and less than 1,000 cells/mcL **or** platelet count greater than or equal to 50,000 cells/mcL and less than 75,000 cells/mcL, reduce pentostatin and cyclophosphamide dose 25%.⁹
2. ANC less than 500 cells/mcL **or** platelet count less than 50,000 cells/mcL, reduce pentostatin and cyclophosphamide dose 50%.⁹

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