Cancer Chemotherapy Update

Procarbazine, Lomustine, and Vincristine (PCV) Regimen for Central Nervous System Tumors

Dominic A. Solimando, Jr, MA, FAPhA, FASHP, BCOP, and J. Aubrey Waddell, PharmD, FAPhA, BCOP

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: PCV

Origin of name: PCV is an acronym for the drugs, procarbazine, lomustine (CCNU), and vincristine, in the regimen.

COMMENTS

Two versions, a standard dose¹⁻²⁰ and an enhanced dose,²¹⁻²⁵ of the PCV regimen have been widely studied. This review will focus on the standard dose regimen (Table 1).

INDICATIONS

The PCV regimen has been studied for treatment of primary brain tumors, particularly gliomas and astrocytomas.¹⁻³² Current guidelines recommend PCV as adjuvant therapy or treatment for recurrent low-grade astrocytoma, oligodendroglioma, anaplastic gliomas, and glioblastoma.³³

DRUG PREPARATION

Follow institutional policies for the preparation of hazardous medications when preparing vincristine and dispensing procarbazine and lomustine.

A. Procarbazine

1. Procarbazine is available as 50 mg capsules.
2. Store at controlled room temperature (15°C to 30°C [59°F to 86°F]).

B. Lomustine

1. Use 10 mg, 40 mg, or 100 mg capsules.
2. Store at controlled room temperature (15°C to 30°C [59°F to 86°F]).
3. Lomustine is given as a single dose.
4. All the capsules may be dispensed in a single container to reduce patient confusion.
5. The container should be clearly labeled to take all the capsules at one time.

C. Vincristine

1. Use vincristine sulfate injection 1 mg/mL.
2. Vincristine should be diluted in 25 mL or 50 mL of 0.9% sodium chloride injection in polyvinyl chloride bags.
3. Dispensing diluted vincristine in minibags, rather than undiluted in syringes, has been recommended to prevent inadvertent intrathecal injection.
4. Brief (less than 24 hours) exposure to temperatures up to 30°C (86°F) is acceptable.

Table 1. PCV regimen¹⁻²⁰

Drug	Dose	Route of administration	Administered on day(s)	Total dose/cycle
Procarbazine	60 mg/m ²	PO	8 through 21	840 mg/m ²
Lomustine	110 mg/m ²	PO	1	110 mg/m ²
Vincristine ^a	1.4 mg/m ²	IV	8 & 29	2.8 mg/m ²
<i>Cycle repeats: every 6-8 weeks</i>				
^a 2 mg fixed dose of vincristine ¹⁷				

Variations

1. Procarbazine 75 mg/m² PO days 8 through 21, lomustine 130 mg/m² PO day 1, vincristine 1.4 mg/m² IV days 8 & 29 every 6-8 weeks^{10,11,21-25}
2. Procarbazine 60 mg/m² PO days 8 through 29, lomustine 110 mg/m² PO day 1, vincristine 1.4 mg/m² IV days 8 & 29 every 8 weeks²³
3. Procarbazine 100 mg/m² PO days 1 through 14, lomustine 75 mg/m² PO day 1, vincristine 1.4 mg/m² IV days 1 & 8 every 29 days²⁶
4. Procarbazine 60 mg/m² PO days 8 through 22, lomustine 110 mg/m² PO day 1, vincristine 1.5 mg/m² IV days 8 & 22 every 6 weeks²⁷
5. Procarbazine 75 mg/m² PO days 1 through 28, lomustine 50 mg/m² PO days 1 & 15, vincristine 1 mg/m² IV days 1 & 15 every 8 weeks²⁸
6. Procarbazine 100 mg/m² PO days 1 through 10, lomustine 100 mg/m² PO day 1, vincristine 1.5 mg/m² IV day 1 every 6 weeks^{29,30}
7. Procarbazine 60 mg/m² PO days 2 through 15, lomustine 110 mg/m² PO day 1, vincristine 1.4 mg/m² IV days 1 & 22 every 6 weeks³¹
8. Procarbazine 150 mg/m² PO days 1 through 7, lomustine 130 mg/m² PO day 0, vincristine 1.5 mg/m² IV day 0 every 28 days³²

Note: IV = intravenous; PO = oral.

DRUG ADMINISTRATION

A. Procarbazine is given orally as a single daily dose or in 3 or 4 divided doses.

B. Lomustine

1. Lomustine is given orally as a single dose.
2. The drug should be taken on an empty stomach (1 hour before or 2 hours after eating).
3. Take at bedtime 30 to 60 minutes after taking an antiemetic.
4. Although not well documented in the literature, some clinicians believe taking lomustine at bedtime reduces the incidence and/or severity of nausea.

C. Vincristine is administered as a short (10 to 15 minute) intravenous (IV) infusion.

SUPPORTIVE CARE

A. Acute and Delayed Emesis Prophylaxis: The PCV regimen is predicted to cause acute emesis

in 30% to more than 90% of patients.³⁴⁻³⁸ The studies reviewed reported nausea or vomiting in 5% to 80% of patients.^{3-5,13,15,20} Prophylactic antiemetic therapy with a serotonin antagonist is recommended.³⁵⁻³⁸ 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 lomustine on day 1.
2. Granisetron 1 mg to 2 mg PO, ±dexamethasone 12 mg PO, given 30 minutes before lomustine on day 1.
3. Dolasetron 100 mg PO, ±dexamethasone 12 mg PO, given 30 minutes before lomustine on day 1.
4. Palonosetron 0.25 mg IV and dexamethasone 12 mg PO, given 30 minutes before lomustine on day 1 only.

The antiemetic therapy should continue for at least 3 days, then resume on days 8 through 21 when

procarbazine is given. 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 with the procarbazine.³⁹ One of the following regimens is recommended:

1. Metoclopramide 0.5 to 2 mg/kg PO every 4 to 6 hours, $\pm$ dexamethasone 4 mg PO twice a day for 3 days, $\pm$ diphenhydramine 25 to 50 mg PO every 6 hours if needed, starting on day 2 of PCV.
2. Prochlorperazine 10 mg PO every 4 to 6 hours, $\pm$ dexamethasone 4 mg PO twice a day for three days, $\pm$ diphenhydramine 25 to 50 mg PO every 6 hours if needed, starting on day 2 of PCV.
3. Promethazine 25 to 50 mg PO every 4 to 6 hours, $\pm$ dexamethasone 4 mg PO twice a day for 3 days, $\pm$ diphenhydramine 25 to 50 mg PO every 6 hours if needed, starting on day 2 of PCV.

Patients who experience significant nausea or vomiting with one of these regimens should receive an agent from a different pharmacologic category.³⁴⁻³⁸ 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.⁴⁰⁻⁴⁴

B. Breakthrough Nausea and Vomiting³⁴⁻³⁸: 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, $\pm$ diphenhydramine 25 to 50 mg PO every 6 hours if needed.
2. Prochlorperazine 10 mg PO every 4 to 6 hours if needed, $\pm$ diphenhydramine 25 to 50 mg PO every 6 hours if needed.
3. Prochlorperazine 25 mg rectally every 4 to 6 hours if needed, $\pm$ 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, $\pm$ diphenhydramine 25 to 50 mg PO every 4 to 6 hours if needed.

C. 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.^{45,46} The incidence of febrile neutropenia reported in the PCV trials reviewed was only 1%²⁰; prophylactic use of CSFs is not recommended.^{45,46} CSFs should be considered if a patient experiences febrile neutropenia or grade 4 neutropenia in a prior cycle of PCV.

D. Extravasation: Vincristine is a moderate vesicant; extravasation should be avoided. If extravasation occurs, stop the infusion immediately and aspirate as much of the extravasated solution as possible before withdrawing the needle. The limb should be elevated and cooled intermittently (ice packs for 15-20 minutes 4 times a day for 3 days)^{46,47} Although Larson reported applying ice to all extravasations,^{47,48} most other groups suggest dry heat for 30 minutes 4 times a day for 3 days.⁴⁹ Hyaluronidase 150 units/1 mL injected intradermally at the extravasation site also has been recommended for treatment of vinca alkaloid extravasations.⁴⁹

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:** Stroke 4%,¹² thromboembolic events 1%.¹⁷
- B. Constitutional:** Fatigue (grade 1) 37%,²⁰ (grade 2) 20%,²⁰ (grade 3) 8%,²⁰ (grade 4) 1%²⁰; weight loss (grade 1) 11%,²⁰ (grade 2) 8%,²⁰ (grade 3) 3%.²⁰
- C. Dermatologic:** Rash 15% to 17%,^{4,9} urticaria 10%,⁵ unspecified skin toxicity (grade 3) 10%.¹³
- D. Gastrointestinal:** Anorexia (grade 1) 18%,²⁰ (grade 2) 6%,²⁰ (grade 3) 1%²⁰; constipation 33%,⁴

(grade 1) 13%,²⁰ (grade 2) 9%²⁰; nausea “severe” 33%⁴; nausea (grade 1) 21% to 37%,^{3,20} (grade 2) 23%,²⁰ (grade 3) 3% to 6%^{15,20}; nausea/vomiting 80%,⁵ (grade 2) 15%,³ (grade 3) 5% to 11%,^{3,13} (grade 4) 1%¹³; vomiting (grade 1) 18%,²⁰ (grade 2) 12%,²⁰ (grade 3) 3%,²⁰ (grade 3) 6%.¹⁵

E. Hematologic: Anemia (grade 1) 26%,²⁰ (grade 2) 9%,²⁰ (grade 3) 5% to 6%,^{15,20} (grade 3 or 4) 19%,¹⁰ (grade 4) 1%^{15,20}; febrile neutropenia (grade 4) 1%²⁰; leukopenia 36%,⁶ (grade 1) 14% to 17%,^{3,6,9} (grade 2) 11% to 43%,^{3,6,9} (grade 3) 1% to 27%,^{3,6,9,15} (grade 3 or 4) 81%,¹⁰ (grade 4) 3% to 8%^{3,15}; lymphopenia (grade 2) 2%,²⁰ (grade 3) 1%²⁰; “myelosuppression” 66%,⁴ (grade 2) 37%,¹² (grade 3) 63%¹²; neutropenia (grade 1) 6%,²⁰ (grade 2) 9%,²⁰ (grade 3) 30% to 35%,^{13,20} (grade 4) 9% to 15%^{13,20}; thrombocytopenia (grade 1) 7% to 16%,^{3,6,9,20} (grade 2) 3% to 17%,^{3,6,9,20} (grade 3) 1% to 24%,^{3,6,9,13,15,20} (grade 3 or 4) 44%,¹⁰ (grade 4) 1% to 11%,^{3,6,13,15} unspecified hematologic toxicity (grade 2 or 3) 10%.¹⁷

F. Hepatic: Increased alanine aminotransferase (ALT) (grade 1) 9%,²⁰ (grade 2) 1%,²⁰ (grade 3) 1%,²⁰ (grade 4) 1%²⁰; increased aspartate aminotransferase (AST) (grade 1) 9%,²⁰ (grade 2) 1%,²⁰ (grade 4) 1%²⁰; increased liver enzymes (grade 2) 5%,⁶ (grade 2 or 3) 10%.¹⁷

G. Hypersensitivity: Allergic reactions (grade 2 or 3) 10%,¹⁷ allergic skin reactions (grade 3) 1%,¹⁵ generalized erythema 4%.¹²

H. Infection: Herpes zoster (grade 2 or 3) 1%¹⁷; pneumonia 4%,¹² (grade 2 or 3) 1%,¹⁷ unspecified (grade 1) 9%,²⁰ (grade 2) 12%,²⁰ (grade 3) 10%.²⁰

I. Neurologic: Motor paresthesias 11%¹²; neuropathy, unspecified 8%,⁹ (grade 1) 15%,³ (grade 2) 15%,³ (grade 3) 8%³; paresthesias 17% to 24%^{4,6}; polyneuropathy (grade 3) 2%,¹⁵ (grade 2 or 3) 7%¹⁷; reduced/loss of tendon reflexes/reduced vibration sense 100%¹²; sensory loss 22%.¹²

J. Pain: Abdominal 33%.⁴

PRETREATMENT LABORATORY STUDIES NEEDED

A. Baseline

1. AST/ALT
2. Total bilirubin
3. Serum creatinine
4. Complete blood count (CBC) with differential

B. Prior to Each Treatment

1. AST/ALT
2. Total bilirubin

3. Serum creatinine

4. Complete blood count (CBC) with differential

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. White blood cell count (WBC):

- a. Within normal limits¹
- b. Greater than or equal to 3,000 cells/mcL.^{6,9,15}
- c. Greater than or equal to 2,000 cells/mcL.⁸

2. Absolute neutrophil count (ANC):

- a. Within normal limits.¹
- b. Greater than or equal to 1500 cells/mcL.¹³
- c. Greater than 500 cells/mcL.²⁰

3. Platelet count:

- a. Within normal limits.¹
- b. Greater than or equal to 100,000 cells/mcL.^{6,9,15}
- c. Greater than or equal to 125,000 cells/mcL.^{8,13}
- d. Greater than 50,000 cells/mcL.²⁰

4. Hemoglobin:

- a. Within normal limits.¹
- b. Greater than or equal to 10 g/dL.^{6,9}

5. Serum creatinine:

- a. Within normal limits.¹
- b. Less than or equal to 1.5 mg/dL.¹³
- c. Less than 120 mmol/L (~1.36 mg/dL).¹⁵

6. Serum bilirubin:

- a. Within normal limits.¹
- b. Less than 25 mmol/L (~1.47 mg/dL).¹⁵
- c. Less than or equal to 1.5 times the ULN.^{8,13}

7. AST/ALT:

- a. Within normal limits.¹
- b. Less than or equal to 2 times the upper limit of normal (ULN).¹³

8. ALT: Less than or equal to 2 times the ULN.⁸

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

DOSAGE MODIFICATIONS

A. Renal Function

1. Procarbazine: Dose reduction may be required; no formal guidelines available.⁵⁰
2. Lomustine – creatinine clearance:
 - a. No information available.⁵¹
 - b. Less than 60 mL/min, reduce dose 25%.⁵²
 - c. Less than 45 mL/min, reduce dose 30%.⁵²

- d. Less than 30 mL/min, do not give the drug.⁵²
- e. Greater than 50 mL/min, no adjustment required.⁵³
- f. Less than or equal to 50 mL/min and greater than or equal to 10 mL/min, reduce dose 25%.⁵³
- g. Less than 10 mL/min, reduce dose 50% to 75%.⁵³
- 3. Vincristine:
 - a. No adjustment required.⁵³
 - b. No information available.⁵⁴

B. Liver Function

- 1. ALT or AST greater than 3 times the ULN²⁰:
 - a. Hold all drugs until ALT and AST are less than or equal to 2 times the ULN, and
 - b. Then reduce all drug doses 25%.
- 2. Procarbazine:
 - a. Dose reduction may be required; no formal guidelines available.⁵⁰
 - b. Bilirubin greater than 5 mg/dL or ALT/AST greater than 180 international units, do not give the drug.⁵⁵
 - c. Bilirubin greater than 5 mg/dL or ALT/AST greater than 3 times the ULN, do not give the drug.⁵⁶
 - d. ALT/AST 1.6 to greater than 6 times the ULN, reduce dose 25%.⁵⁶
 - e. ALT/AST greater than 6 times the ULN, use clinical judgement.⁵⁶
- 3. Lomustine: No information available.⁵¹
- 4. Vincristine:
 - a. Bilirubin greater than 3 times the ULN, reduce dose 50%.⁵⁴
 - b. Bilirubin greater than or equal to 1.5 mg/dL and less than or equal to 3 mg/dL or ALT/AST 2 to 3 times the ULN, reduce dose 50%.^{55,56}

C. Myelosuppression

- 1. WBC:
 - a. Greater than or equal to 3,000 cells/mcL and less than or equal to 3,900 cells/mcL, reduce lomustine and procarbazine dose 25%.⁶
 - b. Less than 3,000 cells/mcL⁶:
 - (1) Do not give lomustine or procarbazine.
 - (2) When toxicity resolves, reduce lomustine and procarbazine dose 25%.
 - c. Less than 1,000 cells/mcL, reduce procarbazine dose 67%.¹²
- 2. ANC: Less than or equal to 500 cells/mcL, reduce lomustine and procarbazine dose 25%.²⁰

3. Platelet count:

- a. Greater than or equal to 75,000 cells/mcL and less than or equal to 120,000 cells/mcL, reduce lomustine and procarbazine dose 25%.⁶
- b. Less than 75,000 cells/mcL⁶:
 - (1) Do not give lomustine or procarbazine.
 - (2) When toxicity resolves, reduce lomustine and procarbazine dose 25%.
- c. Less than 50,000 cells/mcL, reduce procarbazine dose 67%.¹²
- d. Less than or equal to 50,000 cells/mcL, reduce lomustine and procarbazine dose 25%.²⁰

4. Hemoglobin:

- a. Greater than or equal to 10 g/dL and less than or equal to 11.9 g/dL, reduce lomustine and procarbazine dose 25%.⁶
- b. Less than 10 g/dL⁶:
 - (1) Do not give lomustine or procarbazine.
 - (2) When toxicity resolves, reduce lomustine and procarbazine dose 25%.

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