Cancer Chemotherapy Update

Cabazitaxel and Prednisone Regimen for Prostate Cancer

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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.

<i>Regimen Name:</i>	Cabazitaxel and Prednisone
<i>Synonym:</i>	None
<i>Origin of Name:</i>	The regimen is named for the 2 medications in the regimen.

INDICATION(S)

The cabazitaxel and prednisone regimen (Table 1) has been studied and is recommended for metastatic, castration-resistant prostate cancer progressing after docetaxel treatment.¹⁻⁶

DRUG PREPARATION

Follow institutional policies for preparation of hazardous medications when preparing cabazitaxel.

A. Cabazitaxel^{7,8}

1. Use cabazitaxel 60 mg/1.5 mL for reconstitution.
2. Dilute cabazitaxel with the provided 13% (w/w) ethanol in water to a final concentration of 10 mg/mL.
3. Both the cabazitaxel vial and the diluent vial contain overfill to make up for liquid loss in preparation.
4. Dilution of the cabazitaxel vial with the entire contents of the diluent vial produces a solution of 10 mg/mL of cabazitaxel.

5. Dilute in 250 to 500 mL of 0.9% sodium chloride or 5% dextrose in water to a final concentration of 0.1 to 0.26 mg/mL.
6. Cabazitaxel solutions should be dispensed in non-polyvinylchloride (non-PVC) containers.
7. Vials of cabazitaxel should be used within 30 minutes of reconstitution.
8. Solutions for infusion are stable for 8 hours at room temperature (20°C to 25°C [68°F to 77°F]), or up to 24 hours if refrigerated (2°C to 8°C [36°F to 46°F]).

B. Prednisone

1. Prednisone is available in 1 mg, 2.5 mg, 5 mg, 10 mg, 20 mg, and 50 mg tablets; oral solution 1 mg/mL and 5 mg/mL.
2. Store at controlled room temperature (15°C to 30°C [59°F to 86°F]).

DRUG ADMINISTRATION

A. Cabazitaxel^{7,8}

1. Infuse through a non-PVC (low-sorbing) infusion set and 0.22 micron filter.
2. Cabazitaxel should be infused intravenously over 1 hour.

B. Prednisone

1. Usually given as a single daily dose.
2. To avoid gastric irritation, the drug should be taken with food or after a meal.

Table 1. Cabazitaxel and prednisone regimen¹⁻³

Drug	Dose	Route of administration	Administered on day(s)	Total dose/cycle
Cabazitaxel	25 mg/m ²	IV	1	25 mg/m ²
Prednisone	10 mg ^{1,3} or 5 mg twice daily ²	PO	1-21	210 mg
Cycle repeats every 21 days				

Variations:

1. Cabazitaxel 10 mg/m² IV weekly and prednisone 5 mg twice daily.⁴

2. Cabazitaxel 16 mg/m² IV days 1 and 15 and prednisone 10 mg PO daily, cycle repeats every 4 weeks.⁵

An equivalent dose of prednisolone was allowed if prednisone was not available.¹⁻³

Note: IV = intravenous; PO = oral.

SUPPORTIVE CARE

A. Acute Emesis Prophylaxis: The cabazitaxel and prednisone regimen is predicted to cause vomiting in 10% to 30% of patients.⁹ The studies reviewed reported nausea in 22% to 34%^{1,3} and vomiting in 15% to 23% of patients.^{1,3} Appropriate acute emesis prophylaxis includes a serotonin antagonist or corticosteroid or dopamine antagonist.^{9,10} One of the following regimens is suggested^{9,10}:

1. Ondansetron 16 to 24 mg orally (PO), or granisetron 2 mg PO, or dolasetron 100 mg PO, or palonosetron 0.25 mg IV 30 minutes before cabazitaxel, or
2. Dexamethasone 12 to 20 mg PO 30 minutes before cabazitaxel, or
3. Metoclopramide 10 to 40 mg PO or prochlorperazine 10 mg PO 30 minutes before cabazitaxel.

B. Breakthrough Nausea and Vomiting: Patients should receive a prescription for an antiemetic to treat breakthrough nausea. One of the following regimens is suggested^{9,10}:

1. Metoclopramide 10 to 40 mg 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 12.5 to 25 mg PO every 4 to 6 hours if needed, ± 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 antineoplastic regimens 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

In the trials reviewed, neutropenia was reported in 20% to 94%^{1,3} of patients and grade 3 to 4 neutropenia in 7% to 82%¹⁻³ of patients. Febrile neutropenia was reported in 2% to 8% of patients.¹⁻³ Prophylactic use of CSFs is not recommended with this regimen. CSFs should be considered if a patient experiences febrile neutropenia or grade 4 neutropenia in a prior cycle of cabazitaxel and prednisone.

D. Hypersensitivity Reactions: Cabazitaxel contains polysorbate 80, a solubilizing agent known to cause severe non-immunologic anaphylactoid reactions.¹² The studies reviewed did not report hypersensitivity reactions with cabazitaxel,¹⁻⁵ possibly due to the small amount of polysorbate 80 contained in the US Food and Drug Administration (FDA)-approved dose of cabazitaxel.^{1,7,8,13} The manufacturer of cabazitaxel warns that severe hypersensitivity may occur and may include generalized rash/erythema, hypotension, and bronchospasm.⁸ The following premedication regimen is recommended, all given intravenously 30 minutes before cabazitaxel^{1,7,8,13}:

1. Dexchlorpheniramine 5 mg, diphenhydramine 25 mg, or equivalent antihistamine, and
2. Dexamethasone 8 mg or equivalent corticosteroid, and
3. Ranitidine 50 mg, or equivalent H₂ antagonist.

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 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 they make, or consider making, 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:** Myocardial infarction (grade 3 or 4) 1%,² peripheral edema (all grades) 3% to 9%,^{1,3} pulmonary embolism (grade 3 or 4) 1%.²
- B. **Constitutional:** Asthenia (all grades) 17% to 20%,^{1,3} (grade 3 or 4) 3% to 5%^{1,3}; fatigue (all grades) 25% to 37%,^{1,3} (grade 3 or 4) 4% to 5%^{1,3}; pyrexia (all grades) 12%,¹ (grade 3 or 4) 1%.¹
- C. **Dermatologic:** Alopecia (all grades) 3%,³ (grade 3 or 4) 0.1%³; nail disorders (all grades) 1%.³
- E. **Gastrointestinal:** Constipation (all grades) 13% to 20%,^{1,3} (grade 3 or 4) 0.1% to 1%^{1,3}; decreased appetite (all grades) 14%,³ (grade 3 or 4) 1%³; diarrhea (all grades) 35% to 47%,^{1,3} (grade 3 or 4) 1% to 6%^{1,3}; dysgeusia (all grades) 6%,³ (grade 3 or 4) 0.1%³; enterocolitis (grade 3 or 4) 1%²; nausea (all grades) 22% to 34%,^{1,3} (grade 3 or 4) 1% to 2%^{1,3}; vomiting (all grades) 15% to 23%,^{1,3} (grade 3 or 4) 1% to 2%.^{1,3}
- F. **Genitourinary:** Hematuria (all grades) 8% to 17%,^{1,3} (grade 3 or 4) 1% to 2%^{1,3}; urinary tract infection (all grades) 7% to 8%,^{1,3} (grade 3 or 4) 1% to 2%.^{1,3}
- G. **Hematologic:** Anemia (all grades) 22% to 97%,^{1,3} (grade 3 or 4) 5% to 11%^{1,3}; febrile neutropenia (all grades) 6%,³ (grade 3 or 4) 2% to 8%^{1,3}; leukopenia (all grades) 11% to 96%,^{1,3} (grade 3 or 4) 7% to 68%^{1,3}; neutropenia (all grades) 20% to 94%,^{1,3} (grade 3 or 4)

7% to 82%^{1,3}; thrombocytopenia (all grades) 5% to 47%,^{1,3} (grade 3 or 4) 1% to 4%.^{1,3}

- G. **Infection:** Any (grade 3 or 4) 3%.²
- H. **Musculoskeletal:** Arthralgia (all grades) 11%,¹ (grade 3 or 4) 1% to 2%.^{1,2}
- I. **Neurologic:** Pain (all grades) 5%,¹ (grade 3 or 4) 1%¹; peripheral neuropathy (all grades) 4% to 14%,^{1,3} (grade 3 or 4) 0.1% to 1%.^{1,3}
- J. **Pain:** Abdominal pain (all grades) 12%,¹ (grade 3 or 4) 2%^{1,2}; back pain (all grades) 8% to 16%,^{1,3} (grade 3 or 4) 1% to 4%^{1,3}; bone pain (all grades) 5% to 7%,^{1,3} (grade 3 or 4) 1%^{1,3}; flank pain (grade 3 or 4) 1%²; pain in extremity (all grades) 8%,¹ (grade 3 or 4) 2%.¹
- K. **Pulmonary:** Dyspnea (all grades) 5% to 12%,^{1,3} (grade 3 or 4) 1%.^{1,3}
- L. **Treatment-related deaths:** Cardiac-related 1%,¹ cerebral hemorrhage 0.4%,¹ dehydration/electrolyte imbalance 0.4%,¹ non-neutropenic infection 1%,³ neutropenia and sepsis 1% to 4%,^{1,3} renal failure 1%.¹

PRETREATMENT LABORATORY STUDIES NEEDED

- A. **Baseline**
 1. Complete blood count (CBC) with differential
 2. Serum creatinine
 3. Aspartate aminotransferase (AST)/alanine aminotransferase (ALT)
 4. Total bilirubin
 5. Conjugated bilirubin
- B. **Prior to Each Treatment:** CBC with differential.
- C. **Recommended Pretreatment Values:** The minimally acceptable pretreatment values required to begin a cycle with full-dose therapy were absolute neutrophil count (ANC) of 1,500 cells/mcL,^{3,8} platelet count of 100,000 cells/mcL,³ hemoglobin of 10 g/dL,³ serum bilirubin less than upper limit of normal (ULN),^{3,8} AST and ALT less than 1.5 times ULN,^{3,8} creatinine clearance greater than 30 mL/min,^{8,14} and serum creatinine less than 1.5 times ULN or creatinine clearance greater than 60 mL/min if serum creatinine was ULN to 1.5 times ULN.³

DOSAGE MODIFICATIONS

- A. **Renal Function**
 1. Cabazitaxel: Use with caution in patients with creatinine clearance less than 30 mL/min.^{8,14}
 2. Prednisone: No adjustment required.

B. Hepatic Function

1. Cabazitaxel:
 - a. Bilirubin greater than ULN, do not give cabazitaxel.⁸
 - b. AST or ALT greater than 1.5 times ULN, do not give cabazitaxel.⁸
2. Prednisone: No adjustment required.

C. Myelosuppression

1. Cabazitaxel:
 - a. ANC less than 1,000 cells/mcL for greater than 1 week despite use of CSFs, delay treatment until ANC greater than 1,500 cells/mcL and reduce dosage to 20 mg/m² for next treatment.⁸
 - b. Febrile neutropenia, delay treatment until improvement or resolution and ANC greater than 1,500 cells/mcL and reduce dosage to 20 mg/m² for next treatment.⁸

D. Diarrhea

1. Cabazitaxel: Delay treatment until improvement or resolution, then reduce dosage to 20 mg/m² for grade greater than or equal to 3 diarrhea.⁸

E. Peripheral Neuropathy

1. Cabazitaxel:
 - a. Grade 2, delay treatment until improvement or resolution, then reduce dosage to 20 mg/m² for next treatment.⁸
 - b. Grade greater than or equal to 3, discontinue cabazitaxel.⁸

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