Cabazitaxel (Jevtana®)

National Drug Monograph

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VA Pharmacy Benefits Management Services,
Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

Executive Summary:

Cabazitaxel is a novel taxane that shows anticancer activity against docetaxel sensitive and resistant cells in vitro. It is thought to be a weak substrate for p-glycoprotein, the main mechanism for taxane resistance.

It was approved by the FDA, in combination with prednisone, for the treatment of patients with castrate-resistant prostate cancer who progressed during or following therapy with a docetaxel containing regimen.

Efficacy
In a phase III trial comparing cabazitaxel (25mg/m^2) plus prednisone to mitoxantrone (12 mg/m^2) plus prednisone in patients with castrate-resistant prostate cancer who progressed during or following therapy with at least 225 mg/m^2 of docetaxel (suggesting a minimum of 12 weeks of treatment), cabazitaxel met its primary endpoint of increasing overall survival. The median overall survival of 15.1 months for cabazitaxel versus 12.7 months for mitoxantrone represents a 30% decrease in the relative risk of death (Hazard Ratio 0.70 95%CI 0.59-0.83).

Safety
There was a higher incidence of treatment related deaths in the cabazitaxel arm. The most common fatal adverse event was infection in 5 patients, 4 of whom had neutropenia and 1 with neutropenic fever. Four of the five fatal infections occurred after one dose. The fatal adverse event in 4 patients was renal failure.

Serious adverse events included: neutropenia, leukopenia, anemia, febrile neutropenia, diarrhea, fatigue, and asthenia.

Boxed warnings exist for neutropenic deaths and hypersensitivity reactions. Cabazitaxel is contraindicated in patients with a previous history of hypersensitivity reactions to drugs formulated with polysorbate 80.

Introduction

The purposes of this monograph are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating cabazitaxel for possible addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

Pharmacology/Pharmacokinetics

Cabazitaxel is new generation taxane. It binds to microtubules promoting tubulin assembly, stabilizes microtubules resulting in cell cycle arrest, and inhibits cell proliferation. In pre-clinical trials, cabazitaxel had activity in docetaxel sensitive and docetaxel resistant cell lines and was shown to cross the blood brain barrier. The most widely studied mechanism of inherited and acquired multidrug resistance to taxanes is over expression of p-glycoprotein. Sensitivity of docetaxel-resistant cell lines to cabazitaxel suggests it is a weak substrate for p-glycoprotein.

Table #1 Cabazitaxel Pharmacokinetics

Parameter	Drug
Metabolism	Extensively in liver, primarily CYP3A4/5 and to a lesser extent CYP2C8. 3 active metabolites and 17 others identified; all are excreted in urine and feces. Cabazitaxel is not a CYP inducer and has a low potential to inhibit drugs that are substrates for CYP isoenzymes
Elimination	80% of IV dose eliminated within 2 weeks, mainly excreted in feces as metabolites; 3.7% of an IV dose is eliminated renally
Half-life	Three compartment model with α half-life=4 minutes, β half-life=2 hours, and γ half-live=95 hours.

FDA Approved Indication(s)

Indicated in combination with prednisone for the treatment of patients with hormone-refractory prostate cancer previously treated with docetaxel-containing treatment regimen.

Potential Off-label Uses

This section is not intended to promote any off-label uses. Off-label use should be evidence-based. See VA PBM-MAP and Center for Medication Safety's Guidance on "Off-label" Prescribing (available on the VA PBM Intranet site only).

First-line therapy of hormone-refractory (castrate-resistant) prostate cancer in place of docetaxel.

Current Alternatives

Cabazitaxel is the only drug with an FDA indication for castrate-resistant prostate cancer in patients who progressed during or following therapy with a docetaxel containing regimen. Multiple regimens have been studied in patients with taxane resistant disease, but none have provided a survival benefit. The best alternative to cabazitaxel therapy is participation in a clinical trial.

Dosage and Administration

Pre-medications (at least 30 minutes prior to cabazitaxel to reduce the risk/severity of hypersensitivity reactions):

- Antihistamine IV (e.g. diphenhydramine 25mg or equivalent)
- Corticosteroid IV (dexamethasone 8mg or equivalent)
- H_2 antagonist IV (ranitidine 50mg or equivalent)

Preparation

- First Dilution- Mix the vial of cabazitaxel 60mg/1.5ml with the entire contents of the supplied diluents. Limit foaming during dilution; do not shake. **Final concentration of cabazitaxel is 10mg/mL.**
- Second Dilution- Withdraw the recommended dose from First Dilution and further dilute in 250mL PVC-free container with either 0.9% sodium chloride solution or 5% dextrose solution. If a dose needed is greater than 65 mg, use a larger volume of infusion solution so that the concentration of cabazitaxel does not exceed 0.26 mg/mL. The final concentration of cabazitaxel should be between 0.1 mg/mL and 0.26 mg/mL. Use this final solution within 8 hours stored at room temperature or within a total of 24 hours if refrigerated (included infusion time).

Dose

- Initial dose of 25 mg/m^2 over 1 hour as an intravenous infusion every three weeks in combination with prednisone 10 mg orally daily throughout treatment
- Dose Modifications- reduce dose to 20 mg/m^2 if patient experiences any of the following toxicities:

Toxicity	**Dosage Modification**
Prolonged Grade ≥Grade 3 neutropenia (greater than 1 week) despite appropriate medication including G-CSF	Delay treatment until neutrophil count is >1,500 cells/mm^3, then reduce dose to 20 mg/m^2. Use G-CSF secondary prophylaxis
Febrile neutropenia	Delay treatment until improvement or resolution, and until neutrophil count is >1,500 cells/mm^3, then reduce dose to 20 mg/m^2. Use G-CSF secondary prophylaxis
Grade ≥ 3 diarrhea or persisting diarrhea despite appropriate medications, fluids, and electrolyte replacement	Delay treatment until improvement or resolution, then reduce dose to 20 mg/m^2.

Use in Special Populations

- Renal Impairment- No formal trials have been conducted in patients with renal impairment. Population pharmacokinetic trials included patients with mild to moderate renal impairment; no meaningful effects were seen on the pharmacokinetics of cabazitaxel. No data are available on the use in patients with severe renal impairment or end-stage renal disease.
- Hepatic Impairment- No formal trials have been conducted in patients with hepatic impairment. Cabazitaxel is extensively metabolized by the liver; hepatic impairment is likely to increase cabazitaxel concentrations.

Efficacy

Efficacy Measures

Primary
- Overall Survival (Date of randomization to death)

Secondary
- Progression Free Survival (a composite endpoint of time from randomization to the first date of progression [PSA progression, tumor progression, pain progression] or death.
- PSA Response (reduction in PSA serum concentration of ≥50% if baseline PSA is ≥ 20 mcg/L)
- PSA progression (increase of ≥25% over nadir PSA if the increase in the absolute value is ≥5 mcg/L in men with no PSA response or ≥50% over nadir for patients showing a PSA response)
- Objective Tumor Response (in patients with measurable disease)
- Pain Response (for patients with a present pain intensity [PPI] score of ≥2 or a mean analgesic score of ≥10 points at baseline or both) defined as a reduction of 2 points or more from baseline median PPI score without increasing analgesic score or decrease of more than 50% in analgesic use without an increase in pain, maintained for 3 weeks or more.
- Pain Progression (increase in median PPI score of ≥1 point from reference value or an increase of ≥25% in the mean analgesic score or requiring palliative radiotherapy.
- Time to Tumor Progression (number of months from randomization until evidence of progressive disease by RECIST criteria).

Summary of efficacy findings

Phase III TROPIC trial: Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment.[1]

Study Design
- International (26 countries)
- Centrally randomized
- Open-label to patients and treating physicians
- Study team blinded to data analysis

Inclusion Criteria
- Pathologically proven prostate cancer
- Documented disease progression during or after completion of docetaxel therapy
    - Measurable disease- required documented disease progression by Response Evaluation Criteria in Solid Tumors (RECIST) with at least one visceral or soft tissue metastatic lesion
    - Non-measurable disease- rising serum PSA (at least 2 consecutive increases relative to a reference value at least 1 week apart) or the appearance of at least one new radiographic lesion
- ECOG Performance Status 0-2
- Prior and on-going castration by orchiectomy or LHRH agonist or both
- Antiandrogen withdrawal followed by progression at least 4 weeks (6 weeks in the case of bicalutamide) prior to enrollment

- Adequate hematological, hepatic, renal and cardiac function
- LVEF more than 50% assessed by MUGA or Echocardiogram
- Concomitant use of bisphosphonates if the dose was stable for 12 weeks before enrollment
- LHRH therapy mandated to be continued throughout trial

Exclusion Criteria

- Previous mitoxantrone therapy,
- Radiotherapy to 40% or more of bone marrow
- Cancer therapy (other than LHRH analogues) within 4 weeks of enrollment
- Grade 2 or higher peripheral neuropathy or stomatitis
- Other serious illness (including secondary cancers)
- History of hypersensitivity to polysorbate 80-containing drugs or prednisone
- Amendment after first 59 patients: Patients receiving a cumulative dose of docetaxel lower than 225 mg/m^2 (equivalent to 12 weeks of treatment)

Treatment

- All patients received prednisone 10mg daily (or equivalent dose of prednisolone)
- Randomized to either cabazitaxel 25 mg/m^2 IV over 1 hour or mitoxantrone 12 mg/m^2 IV over 15-30 minutes
- Cabazitaxel patients were pre-treated with a single dose of IV antihistamine, corticosteroids (8 mg dexamethasone or equivalent) and H_2 antagonist (except cimetidine) 30 minutes before cabazitaxel.
- Treatment was repeated every 21 days for a maximum of 10 cycles
- Crossover to cabazitaxel was not allowed for the mitoxantrone group
- Prophylactic G-CSF was not allowed for the 1st cycle but was allowed after the first occurrence of either neutropenia lasting more than 7 days or neutropenia complicated by fever or infection.

Baseline Patient Characteristics

Table #2 Baseline Characteristics

Characteristic	Mitoxantrone N=377	Cabazitaxel N=378
Age, median	67 (61-72)	68 (62-73)
≥75 years old	19%	18%
White	83%	84%
Asian	8%	7%
Black	5%	5%
ECOG 0 or 1	91%	93%
Metastatic Disease	94%	96%
Bone metastases	87%	80%
Visceral metastases	25%	25%
Pain at baseline	45%	46%
Previous therapy		
Hormonal	99%	99%
Number of chemotherapies		
1	71%	69^
2	21%	25%
>2	8%	6%
Radiation	59%	61%
Surgery	54%	52%
Total dose docetaxel (mg/m^2) median	529.2	576.6
Progression relative to docetaxel		

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