Cabazitaxel

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Prostate cancer is the most common cancer in men and the second most common cause of cancer-related death in men (Jemal, Siegel, Xu, & Ward, 2010). Patients with advanced prostate cancer often derive significant benefit from androgen deprivation (chemical castration) in terms of survival and clinical symptoms, but hormone resistance invariably develops over time, necessitating alternative treatments (Moreau, Delavault, & Blumberg, 2006). Docetaxel, in combination with prednisone, was the first anticancer agent to show a survival benefit in patients with castration-resistant prostate cancer (CRPC) (Berthold et al., 2008). Until recently, no agent has shown a survival benefit in patients that have progressive disease after first-line docetaxel therapy.

Pharmacology

Cabazitaxel (Jevtana) is a taxane antitumor agent with a spectrum of activity similar to docetaxel. The mechanism of action of cabazitaxel is via tubulin binding. Cabazitaxel is able to promote microtubule formation and prevent disassembly, leading to a frozen microtubule state. As a result, the necessary cellular step of mitosis is suppressed. In vitro studies show cabazitaxel to be as potent as docetaxel in stabilizing microtubules (Mita et al., 2009). One advantage of cabazitaxel over docetaxel and paclitaxel is through resistance mechanisms. Cabazitaxel has a poor binding potential to the multidrug-resistant protein known as P-glycoprotein (Cisternino et al., 2003). P-glycoprotein is an efflux transporter implicated in constitutive and acquired resistance to many antineoplastics, including taxanes. Additionally, P-glycoprotein is involved in active drug transport across the blood-brain barrier (BBB). For these reasons, cabazitaxel may be a superior taxane with the potential for activity in paclitaxel- and docetaxel-resistant tumors, with added penetration across the BBB.

Clinical Studies

Two phase I and pharmacokinetic studies of cabazitaxel were performed in patients with advanced solid tumors (Mita et al., 2009; Goetz et al., 2001). In the first study a total of 25 patients were treated, 8 of whom had metastatic prostate cancer. No patients were administered prophylactic antinausea drugs and medications to prevent infusion reactions with the first cycle. Additionally, prophylactic use of colony-stimulating factors was prohibited. Dose levels started at 10 mg/m^2 at a frequency of every 3 weeks. Partial responses were seen in 2 of the 8

patients with prostate cancer. No patients experienced a dose-limiting toxicity (DLT) at 20 mg/m^2, but 3 of 7 patients experienced a DLT at 25 mg/m^2. The three dose-limiting toxicities were neutropenia related, with one incidence of febrile neutropenia. No patients reported hypersensitivity reactions without premedication. Unlike docetaxel, fluid retention was not observed. Clinically significant diarrhea was reported, but appeared to be controlled well with expectant use of antidiarrhea medication. A second phase I study reported early results of 14 patients treated with cabazitaxel every 3 weeks. Similar to the previous study, neutropenia was the primary hematologic toxicity and diarrhea was the predominant nonhematologic toxicity. There were no reports of infusion reactions or fluid retention. Unlike the first study, the maximum tolerated dose was 25 mg/m^2 when administered every 3 weeks.

A phase II single-arm study of 71 metastatic breast cancer patients assessed potential efficacy in a taxane-resistant group of patients (Pivot et al., 2008). Dosing was 20 mg/m^2 every 3 weeks as a 1-hour infusion, and increased to 25 mg/m^2 if there were no toxicities greater than grade 2 in cycle 1. In this study H_1 blockers were given, but no premedication for nausea including corticosteroids was allowed with the first cycle. Complete blood counts (CBCs) were checked weekly in all patients. Grade III/IV neutropenia occurred in 73% of patients and 43% of cycles, but febrile neutropenia was rare at 3%. Unlike the two phase I studies, hypersensitivity reactions did occur in 4% of patients. Other nonhematologic toxicities were similar to the phase I studies with diarrhea and fatigue being most common. The overall response rate was 14% with 2 complete responses seen. Median overall survival in this small study was 12.3 months.

An open-label randomized phase III study of cabazitaxel for metastatic CRPC was initiated to determine the effectiveness among patients that progressed after treatment with docetaxel (de Bono et al., 2010a). Patients were treated with 12 mg/m^2 of mitoxantrone or 25 mg/m^2 of cabazitaxel intravenously every 3 weeks with oral prednisone 10 mg daily. A total of 755 patients were randomized in a 1:1 ratio. The median age of the patients on cabazitaxel was 68 years old and only 18% were older than 75. Ninety-three percent of patients on cabazitaxel had a performance status of 0 or 1. The median docetaxel dose received prior to study was 576.6 mg/m^2 among patients treated with cabazitaxel. All patients treated with cabazitaxel were premedicated with a corticosteroid and an H_1 and H_2 antagonist. Additional antiemetic coverage was not required due to the infrequent incidence of nausea and vomiting observed in the phase I and II studies. Weekly complete blood counts were required with each treatment cycle and use of granulocyte colony-stimulating factor was not allowed with the first cycle. The dose chosen for the phase III study was 25 mg/m^2 despite conflicting phase I and II study dosing. All patients received a maximum of 10 cycles of therapy on the study.

Results of the study showed an overall survival benefit of 2.4 months for cabazitaxel vs. mitoxantrone (15.1 vs. 12.7 months), which was statistically significant. There was also a statistically significant improvement in progression-free survival (2.8 vs. 1.4 months). A median of 6 cycles of treatment were given to patients treated with cabazitaxel vs. 4 cycles among those treated with mitoxantrone. There was a consistent improvement in survival observed across subgroups. Most patients treated with cabazitaxel did not require dose reductions (12%), but the frequency of growth factor use on trial was not reported. Treatment delays were required in 28% of patients treated with cabazitaxel vs. 15% of patients treated with mitoxantrone.

Adverse Effects

The most frequent toxicities observed among patients treated with cabazitaxel were hematologic, primarily neutropenia (de Bono et al., 2010a). In the phase III study 82% of patients had grade III or worse neutropenia. This resulted in a febrile neutropenia rate of 8% among patients treated with cabazitaxel. Two percent of patients on cabazitaxel died as a direct result of neutropenia. When looking at subgroups, neutropenia was more common among men ≥ 65 vs. men < 65 years of age. Additional hematologic toxicities were leukopenia and anemia (grade ≥ 3, 68% and 11%, respectively). The most common nonhematologic toxicities included diarrhea (47%), fatigue (37%), nausea (34%), vomiting (23%), constipation (20%), asthenia (20%), and hematuria (17%). Peripheral neuropathy was only reported in 14%

of patients. Peripheral edema occurred in 9% of patients. In the study 6% of patients reported severe (grade ≥ 3) diarrhea, indicating a high frequency of stools (> 7/day) and/or severe cramping or incontinence.

Role in Therapy for Prostate Cancer

Cabazitaxel is the first agent to be approved for patients with metastatic prostate cancer after failure or progression on docetaxel. An overall survival benefit of approximately 2.4 months over mitoxantrone was observed, which was statistically significant. While the approval of cabazitaxel provides a much needed option for the treatment of metastatic prostate cancer, questions remain. In patients that fail docetaxel first line, should treatment with cabazitaxel be initiated due to a rising PSA or progressively symptomatic disease? Second, is the benefit of cabazitaxel clinically significant, especially in the elderly where toxicity was more common?

New preliminary data on a novel androgen synthesis inhibitor in patients who have also progressed after chemotherapy with docetaxel may soon provide an alternative to treatment with cabazitaxel. A phase III study comparing abiraterone acetate vs. placebo was recently presented at the 35th European Society for Medical Oncology (ESMO) Congress (de Bono et al., 2010b). Abiraterone is a selective inhibitor of androgen synthesis, which can potentiate growth in patients with CRPC. In this study abiraterone was compared to placebo, yielding an overall survival of 14.8 vs. 10.9 months with placebo. Adverse effects were not severe, mainly consisting of fluid retention, hypokalemia, and hypertension. While the results are preliminary and the drug has not yet been approved by the FDA, abiraterone could be an alternative to treatment with cabazitaxel.

In the phase III study of cabazitaxel more than 2% of patients died as a direct result of neutropenia or neutropenic sepsis, dehydration, and renal failure. The overall incidence of diarrhea was nearly 50% and 6% of patients experienced grade 3 or greater diarrhea. Additionally, there was a very high rate of grade 3/4 neutropenia and neutropenic fever in this palliative setting. As a result of the high neutropenia rate among subgroups, the package insert recommends evaluation of high-risk features to determine if primary prophylaxis should be used. These include poor performance status, a prior history of neutropenic fever, age > 65, significant radiation ports, malnutrition, and serious comorbidities (Sanofi-Aventis, 2010). General widespread use of growth factor support and/or dose reductions and dose delays will be common. Weekly CBCs are recommended in the first cycle and may be required thereafter. As a result of the multiple deaths related to neutropenia, cabazitaxel should only be administered if the absolute neutrophil count is > 1,500 cells/μL. Future study should compare every-3-week dosing of 25 mg/m^2 vs. 20 mg/m^2 to determine if efficacy can be maintained while reducing hematologic toxicity.

Implications for the Advanced Practitioner

Cabazitaxel is the first agent to demonstrate a survival benefit among patients with metastatic prostate cancer after progression following treatment with docetaxel. The approval of cabazitaxel now provides a sequencing option that has been able to prolong survival in patients with metastatic prostate cancer. It will be imperative for advanced practitioners to be able to predict and prevent expected toxicities of cabazitaxel. Even with careful monitoring, toxicities may require dose reductions or treatment delays. The predominant toxicities noted in the phase III study were neutropenia and diarrhea. Advanced practitioners should become comfortable with identifying risk factors that support the use of primary growth factor prophylaxis.

All patients should be educated on nonpharmacologic and pharmacologic intervention for the prevention and management of diarrhea. Dietary education on acceptable foods including diets such as the BRAT diet (bananas, rice, applesauce, toast), in addition to foods to avoid, should be presented. Fluid replacement with electrolyte-containing beverages should also be discussed. Patients should also be educated on pharmacologic intervention with over-the-counter medications such as loperamide. It will be important to discuss not just the high cost of cabazitaxel, but also the costs and potential costs of growth factor (filgrastim, pegfilgrastim), red blood cell and platelet support, and potential hospital admission for neutropenic fever.

See Table 1 for dosage and administration guidelines for cabazitaxel.

Table 1. Dosage and Administration of Cabazitaxel

Dose	25 mg/m^2 IV
Schedule	Infusion over 1 h every 3 weeks Prednisone 10 mg po daily throughout treatment with cabazitaxel
Premedication	All recommended IV 30 min prior to infusion Antihistamine: Diphenhydramine 25 mg or equivalent Corticosteroid: Dexamethasone 8 mg or equivalent H_2 antagonist: Ranitidine 50 mg or equivalent
Reconstitution and administration	Two-step dilution required: 1. Supplied vial 60 mg/1.5 mL reconstituted with 5.7 mL diluent to achieve a concentration of 10 mg/mL 2. Final dose withdrawn and added to a non-PVC 0.9% NaCl or 5% dextrose 250 mL solution Final concentration should be between 0.1 and 0.26 mg/mL A 0.22-µ in-line filter should be used for administration

Note. From the Jevtana Package Insert (Sanofi-Aventis, 2010)

Summary

Cabazitaxel is the first antineoplastic agent approved for CRPC after progression with docetaxel. Overall survival was significantly improved over mitoxantrone, but hematologic toxicity was severe and early deaths were reported. Application of this agent into community oncology settings will require plans for toxicity prevention in addition to careful and frequent monitoring.

DISCLOSURES

The authors have no conflicts of interest to disclose.

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