Case Report: Responses to Cabazitaxel in Metastatic Castration-Resistant Prostate Cancer After Extensive Docetaxel Treatment

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Clinical Practice Points

- Cabazitaxel is the first FDA-approved agent for second-line chemotherapy in metastatic castration-resistant prostate cancer (mCRPC) after treatment with docetaxel.
- Cabazitaxel can safely be administered to patients with mCRPC, including those with advanced visceral disease and tumor-related disseminated intravascular coagulation (DIC), who are heavily pretreated with docetaxel-containing chemotherapy regimens.
- Treatment with cabazitaxel can reverse mCRPC-related DIC and produce objective prostate-specific antigen responses and stabilization of visceral disease.

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Introduction

Cabazitaxel is a novel taxane that was approved by the US Food and Drug Administration in June 2010, in combination with prednisone, for metastatic castration-resistant prostate cancer (mCRPC) previously treated with docetaxel.[1] Approval of this agent was based on a randomized, open-label, phase III trial (XRP6258 Plus Prednisone Compared to Mitoxantrone Plus Prednisone in Hormone Refractory Metastatic Prostate Cancer [TROPIC]) of 755 men with mCRPC with progression of disease during or after treatment with docetaxel. Participants were randomized to cabazitaxel (25 mg/m^2 every 3 weeks) or mitoxantrone (12 mg/m^2 every 3 weeks), both in combination with prednisone 10 mg daily.[2] The cabazitaxel-treated patients demonstrated statistically significant improvements in overall survival (15.1 vs. 12.7 months) and progression-free survival (2.8 vs. 1.4 months). We describe 2 patients with extensive mCRPC, heavily pretreated who experienced dramatic responses with prostate-specific antigen (PSA) decline, improvement in tumor-related disseminated intravascular coagulation (DIC), and stabilization of visceral disease with cabazitaxel. These cases illustrate that meaningful responses with low toxicity can be achieved with cabazitaxel in aggressive mCRPC despite significant prior exposure to taxanes.

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Case Report 1

In July 1995, a 49-year-old man presented with a PSA of 18.4 and Gleason 7 (3 + 4) prostate adenocarcinoma. He underwent a radical prostatectomy and had extensive perineural invasion and extracapsular extension of tumor. His postoperative PSA nadir was 4.0, and he received salvage external beam radiation with a PSA nadir of 1.0. He began androgen deprivation therapy (ADT) in February 1996, and over the next 6 years received multiple hormonal agents, including flutamide and bicalutamide, for PSA recurrence. In 2002, he received fowlpox vaccination combined with interleukin-2. He was treated with ketoconazole for asymptomatic bone metastases and PSA declined from 180 to 42 over 6 months. From 2004 through 2010, he received a total of 5 separate docetaxel-containing chemotherapy regimens for progression of bone-only metastatic disease accompanied by decreases in PSA with intermittent breaks for fatigue: single-agent docetaxel (4 cycles), docetaxel and/or carboplatin (12 cycles), mitoxantrone and/or prednisone (14 cycles), docetaxel and/or carboplatin (2 cycles), docetaxel and/or oxaliplatin (3 cycles), and navelbine (3 cycles).

By March 2009, PSA was 2564, and he was started on a trial of a novel phosphatidylinositol 3 kinase (PI3K)/mammalian target of rapamycin (mTOR) inhibitor. After his first cycle of treatment, he developed a decrease in fibrinogen and platelets accompanied by a rise in prothrombin time (PT), partial thromboplastin time (PTT), and international normalized ratio (INR). He was diagnosed with DIC secondary to progression of metastatic prostate cancer and taken off study. He resumed ketoconazole and remained stable for 14 months during which time his thrombocytopenia and coagulation

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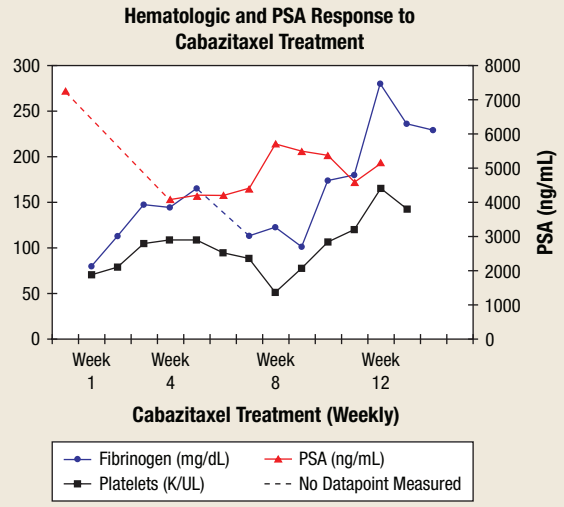
Figure 1 Hematologic and Prostate-Specific Antigen (PSA) Tumor Marker Response to Cabazitaxel Treatment for the Patient Presented in Case 1



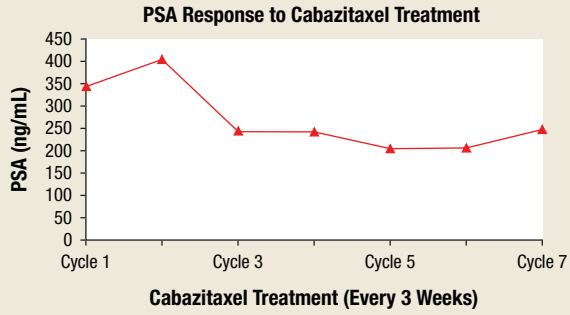
studies improved. In June 2010, he began weekly docetaxel for recurrent cancer-related DIC with apparent bruising and gum bleeding. After a total of 12 treatments of weekly docetaxel, his fibrinogen and platelets were no longer responsive to treatment, PSA had risen to 7258, and his performance status (PS) had declined 2.

In November 2010, he began cabazitaxel at 10 mg/m^2 every other week with improvement in his thrombocytopenia and fibrinogen and decline in PSA to 4500 (see Figure 1). By February 2011, he developed recurrent eccymoses, and his platelets fell to 50,000 with a slight decline in fibrinogen and rise in PSA to 5500. The cabazitaxel dose was increased to weekly (no growth factor support) with improvement in laboratory values. After 22 weeks, he had a hospital admission for syncope and he elected to stop cabazitaxel and begin treatment with abiraterone. Adverse effects of cabazitaxel included stable anemia and leucopenia without fever or infections.

Case Report 2

In 1989, a 64-year-old man presented with prostate adenocarcinoma metastatic to pelvic lymph nodes. He was treated with radiation therapy and ADT. In 2002, after 13 years of ADT, he was found to have isolated biopsy-proven prostate cancer in his mediastinal lymph nodes. He began chemotherapy with docetaxel/estramustine. He experienced a complete radiographic and PSA response after 3 cycles. Subsequent to this first course of chemotherapy, he began ketoconazole for a rising PSA. In July of 2004, he presented with dyspnea and chest pain and had recurrent disease in the mediastinum with a soft tissue mass surrounding the left upper lobe bronchus. He received 6 cycles of docetaxel/estramustine with a PSA response followed by palliative radiation to the mediastinum. Between September 2007 and August 2010, he received 4 more courses of docetaxel (docetaxel/estramustine [3 cycles], single-agent docetaxel [7 cycles], and docetaxel/carboplatin [12 cycles]) for progression of mediastinal lymphadenopathy and the development of pulmonary lymphangitic carcinomatosis and liver metastases. Each course of chemotherapy

Figure 2 Prostate-Specific Antigen (PSA) Tumor Marker Response to Cabazitaxel Treatment for the Patient Presented in Case 2



resulted in PSA and radiographic responses however subsequent courses were associated with a smaller PSA decline and shorter time to relapse. He received a second course of palliative radiation to the mediastinum for left upper lobe collapse secondary to compressive adenopathy and radiation to skull and C1 vertebrae.

In November 2010, he presented with worsening PS, weight loss, progression of visceral disease, and PSA of 345. He began treatment with cabazitaxel 20 mg/m^2 every 3 weeks with pegfilgrastim; after his first cycle, he experienced a PSA flare to over 400 with subsequent decline to 200 (Figure 2). He tolerated therapy well with improved PS and weight gain, despite mild fatigue and a slight anemia. He did not experience any fever or documented infections. He elected to stop cabazitaxel after 20 weeks of therapy after a hospital admission for dehydration, and he was treated with abiraterone.

Discussion

The average life expectancy for mCRPC ranges from 9 to 23 months.[3] DIC with subsequent end-organ failure secondary to thrombus formation in small blood vessels is a recognized complication of mCRPC,[4] though debate exists over the actual incidence.[5] As with other etiologies of DIC, hematologic abnormalities resolve after successful treatment of the underlying condition, and reports document improvements in DIC in mCRPC with multiple forms of hormonal manipulation.[6-8] Chemotherapy with docetaxel has also been reported to reverse mCRPC-related DIC.[9,10]

The TAX 327 trial established docetaxel with prednisone as the standard of care for men with chemotherapy-naive mCRPC.[11] After a median duration of follow-up of 21 months, patients treated with docetaxel (75 mg/m^2 every 3 weeks), had a median survival of 18.9 months compared with 16.5 and 17.4 months for the groups treated with mitoxantrone or weekly docetaxel, respectively. These survival differences persisted after 3.5 years of follow-up.[12,13] However, the majority of patients with mCRPC progress within 9 months of first-line chemotherapy,[11,14,15] and less than 50% receive any form of second-line therapy despite a good PS and the desire for additional treatment.[16] Cabazitaxel is the first FDA-approved agent for second-line chemotherapy in mCRPC after treatment with docetaxel.

As illustrated by the 2 cases presented, some patients with advanced disease, including DIC, visceral metastases, and extremely elevated PSA, will continue to respond to docetaxel well into their

5th and 6th courses of treatment with this agent. These patients demonstrate that neither significant prior docetaxel, nor aggressive, advanced disease preclude treatment responses to the cabazitaxel. This is supported by preclinical data which confirmed activity of cabazitaxel in cell lines resistant to docetaxel.[17,18] Review of the baseline characteristics and treatment histories of patients in the TROPIC study further highlights how the 2 patients described here represent extremes in clinical presentation and heavy prior treatment. The median serum PSA concentration of patients in TROPIC who received cabazitaxel was 143.9,[2] in contrast to 7258 and 403 in the patient presented in Case 1 and Case 2 respectively. Eighty-four percent of patients treated with cabazitaxel in TROPIC had received a single previous docetaxel-based regimen, and only 2% had received $\geq$ 2 regimens for a median total previous docetaxel dose of 576.6 mg/m^2. The patient in Case 1 received a cumulative dose of docetaxel in excess of 3800 mg/m^2; the patient in Case 2 received a cumulative dose in excess of 5400 mg/m^2. It is our clinical impression that the 2 patients reported here received improved quality of life and a survival benefit from cabazitaxel.

The recommended dose of cabazitaxel based on phase I studies was 25 mg/m^2 administered as a 1-hour infusion every 3 weeks.[19,20] Weekly doses up to 12 mg/m^2 were also evaluated in phase I and considered safe. The most common toxicities observed with cabazitaxel in the TROPIC trial were anemia (97%) and neutropenia (94%), febrile neutropenia (8%), and there were 7 deaths related to neutropenia and infection. Given this toxicity profile, we prescribed cabazitaxel with caution in our patients choosing 10 mg/m^2 every other week initially (increasing to 10 mg/m^2 weekly) in the patient in Case 1 and 20 mg/m^2 with pegfilgrastim in the patient in Case 2. Both patients received clinical and radiographic benefit from cabazitaxel for 20 to 22 weeks and both had an ECOG PS of 1 at the time cabazitaxel was stopped and abiraterone was started.

Conclusion

Second-line chemotherapy options for mCRPC were an unmet need in oncology until the recent approval of cabazitaxel. Even with significant prior treatment with docetaxel, responses to cabazitaxel are seen in the setting of aggressive, advanced mCRPC, and cabazitaxel can be administered safely in heavily pretreated patients. As experience with cabazitaxel grows, it will be important to identify patients and disease-specific factors predictive of response to cabazitaxel in order to treat patients who are most likely to benefit.

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