

Prolonged Therapy With Cabazitaxel in an Octogenarian With Metastatic Castration-Resistant Prostate Cancer

Sumanta K. Pal, Cy A. Stein

Clinical Practice Points

- In the phase III TROPIC trial, cabazitaxel in combination with prednisone was compared with mitoxantrone and prednisone in patients with metastatic castration-resistant disease (mCRPC) who had received previous therapy with docetaxel.
- Cabazitaxel therapy was associated with an improvement in overall survival (the primary endpoint of the study), leading to its approval by the US Food and Drug Administration for use in this setting.
- Although cabazitaxel was the first agent approved for use after docetaxel treatment, several other agents have entered (or are probably soon to enter) the therapeutic armamentarium, including abiraterone, MDV3100 and radium-223.
- The oncologist is faced with the issue of balancing the risks and benefits of diverse therapies in this setting in the absence of comparative data.
- Although the difficulties associated with cytotoxic therapy may cause both the patient and physician to delay the use of cabazitaxel after docetaxel, we present a case to illustrate that the agent can be well tolerated and efficacious even in the very elderly patient.
- Our patient, an octogenarian with mCRPC and evidence of progression after 10 cycles of docetaxel, has tolerated 24 cycles of cabazitaxel to date, with disease stabilization and minimal toxicity.
- Herein we discuss considerations in selecting appropriate therapies after docetaxel treatment in an increasingly complex therapeutic landscape.

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Case Report

A 73-year-old man with a past medical history of diabetes and gout was noted by his urologist to have an abnormal digital rectal examination in April 1997. Core biopsies of the prostate were performed, revealing Gleason 7 (4 + 3) disease comprising roughly 50% of 6 specimens. The patient was treated with brachytherapy, and the patient's prostatic-specific antigen (PSA) level declined to undetectable levels thereafter. However he experienced a biochemical recurrence in April 2002 and was treated by his urologist with the combination of leuprolide and flutamide. After 1 year, the patient's PSA level continued to rise and he was switched to leuprolide and bicalutamide. In June 2005, the patient was referred to the medical oncol-

ogy service with a PSA level of 0.28 ng/dL. By June 2006, his PSA level continued to rise, and therapy with bicalutamide withdrawal was attempted. This failed to reduce the patient's PSA level, and he was then treated with the combination of ketoconazole (titrated to 400 mg orally 3 times daily) and hydrocortisone. Notably, leuprolide was maintained while the patient was receiving this and all subsequent regimens.

His PSA level ultimately continued to rise while receiving ketoconazole/hydrocortisone, and by April 2008, it had reached a value of 32 ng/dL. Computerized tomography (CT) of the abdomen and pelvis performed at that time showed a prominent right external iliac node measuring 2.7 × 2.1 cm. Biopsy of the lesion confirmed a diagnosis of prostatic adenocarcinoma. No other evidence of metastasis was observed at that time. Ketoconazole/hydrocortisone therapy was discontinued, and when the patient's PSA level continued to rise in June 2009, docetaxel chemotherapy was initiated at the conventional dose of 75 mg/m² intravenously (IV) every 3 weeks (q3wk) with prednisone. Notably, the patient was asymptomatic at this time. After 1 cycle of docetaxel therapy, the patient experienced grade 3 fatigue, and the dose was reduced to 60 mg/m² IV q3wk. He con-

Department of Medical Oncology and Experimental Therapeutics, City of Hope Comprehensive Cancer Center, Duarte, CA

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Address for correspondence: Sumanta K. Pal, MD, Department of Medical Oncology and Experimental Therapeutics, City of Hope Comprehensive Cancer Center, Duarte, CA 91010

Fax: 626-301-8233; e-mail contact: spal@coh.org

continued receiving docetaxel therapy for a total of 10 cycles, with stabilization of his PSA level during the course of treatment. However repeated CT of the abdomen and pelvis showed an increase in the extent of pelvic adenopathy. The patient remained asymptomatic, and he was observed with intermittent clinical examination and PSA evaluation.

By August 2010, approximately 4 months after his last dose of docetaxel therapy, the patient's PSA level had risen to a value of 300 ng/dL. He remained asymptomatic but elected to receive therapy with cabazitaxel and prednisone. Therapy was initiated at the recommended starting dose of 25 mg/m² IV q3wk with growth factor support (pegfilgrastim). The patient reported no toxicity in association with cabazitaxel therapy, and after 12 cycles of therapy at the starting dose, a reduction in his PSA level from 300 to 110 ng/dL was reported. CT of the abdomen and pelvis revealed a reduction in the size of a right external iliac node (the previously noted index lesion) from 2.7 to 2.0 cm in lesser cross-sectional dimension. The patient remained asymptomatic and was therefore maintained on cabazitaxel therapy for a total of 24 cycles at most recent follow-up. His radiographic evaluations continue to demonstrate stable disease, and he reports no toxicity in association with therapy.

Discussion

The therapeutic landscape of metastatic castration-resistant prostate cancer (mCRPC) has evolved markedly over the past several years. Until recently, cytotoxic chemotherapy was the mainstay of treatment for patients whose disease had progressed after hormonal manipulation. Mitoxantrone in combination with prednisone was compared with prednisone alone in a randomized study published by Tannock et al in 1996.¹ Treatment with mitoxantrone and prednisone (compared with prednisone alone) led to improved disease palliation, but no benefit in survival was identified. Nearly a decade later, 2 randomized phase III studies were published, demonstrating an overall survival (OS) benefit with docetaxel-based therapy compared with mitoxantrone/prednisone.^{2,3} These studies firmly established improvement in OS as a threshold for approval of subsequent therapies for mCRPC.

Several agents have met this rigorous threshold over the past 3 years. The agents differ widely in mechanism and were examined in varying settings within the spectrum of metastatic castration-resistant disease. For instance, the autologous dendritic cell vaccine sipuleucel-T was examined in patients with asymptomatic or minimally symptomatic metastatic disease who were primarily chemotherapy-naïve.⁴ In this setting, treatment with sipuleucel-T was associated with a median OS of 25.8 months, compared with 21.7 months with placebo ($P = .03$). In contrast, pivotal studies leading to the approval of the CYP17 lyase/hydroxylase inhibitor abiraterone were conducted in patients who had previously received docetaxel-based therapy.⁵ Abiraterone (compared with placebo) improved median OS from 10.9 to 14.8 months ($P < .001$). Recently presented phase III data for MDV3100 (a novel antiandrogen that blocks nuclear translocation of androgen receptor) also suggest an improvement in OS in this setting (18.4 vs. 13.6 months; $P < .0001$).⁶ Radioisotopes may also play a role in docetaxel-refractory disease—the phase III ALSYMPCA study assessed radium-223 vs. placebo in patients with bone metastases whose disease was either refractory to docetaxel or

who were ineligible for docetaxel therapy; a survival benefit of 2.8 months was demonstrated.⁷

Nevertheless cytotoxic chemotherapy still plays a critical role in therapy after docetaxel treatment. Cabazitaxel is a novel taxane that differs structurally from docetaxel by the presence of 2 methoxy side moieties substituting for hydroxyl groups, which leads to improved cellular retention compared with docetaxel.⁸ Cabazitaxel has been shown to have activity in preclinical models of docetaxel resistance.⁹ The phase III TROPIC trial randomized 755 patients with docetaxel-refractory mCRPC to either cabazitaxel/prednisone or mitoxantrone/prednisone.¹⁰ Cabazitaxel was shown to improve OS (15.4 vs. 12.7 months; $P < .001$), satisfying the primary endpoint of the study. Relevant to the current case, both older and younger patients appeared to benefit from cabazitaxel—the hazard ratio (HR) for benefit was 0.81 (95% confidence interval [CI], 0.61-1.08) in patients younger than 65 years, compared with 0.62 (95% CI, 0.50-0.78) in patients 65 year of age or older.

Although no studies to date directly compare abiraterone and cabazitaxel in docetaxel-refractory disease, editorial comments have suggested favoring the former option because of toxicity considerations.¹¹ The patient cited herein, who received cabazitaxel therapy at the age of 80 years with minimal toxicity, underscores the potential therapeutic potential of cabazitaxel, even in at-risk groups.

Several findings from the TROPIC study may inform the use of cabazitaxel after docetaxel treatment. First, the study identified a high rate of grade ≥ 3 neutropenia (82%), with 8% of patients having febrile neutropenia. In interpreting these statistics however it is critical to recall that the study did not allow for the use of prophylactic growth factors in the first cycle of therapy. Recommendations accompanying the publication of TROPIC now suggest the use of growth factors in high-risk populations, including older adults. With the use of pegfilgrastim with every cabazitaxel infusion, the patient described in the previous scenario was able to receive in excess of 20 cycles of therapy without complications from myelosuppression. The TROPIC study also noted a 6.6% higher rate of diarrhea in patients older than 65 years of age, suggesting the value of vigilant monitoring of patients receiving these therapies and institution of fluid resuscitation and supportive care measures when warranted. Interestingly, with the caveats of cross-trial comparisons in mind, toxicities such as alopecia and neuropathy appeared to be less prominent in patients receiving cabazitaxel compared with those receiving docetaxel.

In addition to safety considerations, therapeutic decision making after docetaxel treatment also hinges on efficacy. Here, cross-trial comparisons become especially problematic. Numerically, the phase III study leading to the approval of cabazitaxel showed an improvement in OS of 2.7 months compared with the control population. In contrast, abiraterone showed a 3.9-month improvement in OS compared with the control population. The nature of controls is a key consideration—cabazitaxel was compared with mitoxantrone, whereas abiraterone was compared with placebo. Again, acknowledging the caveats of cross-trial comparisons, the metaphorical bar was likely higher in TROPIC, as active cytotoxic therapy was used as a comparator.

Previous therapies may also compromise the efficacy of postdocetaxel therapies. Ryan et al reported a phase II experience assessing abiraterone in 33 patients with mCRPC, 19 of whom had received previous therapy with abiraterone.¹² Declines in PSA levels $\geq 50\%$ were observed less frequently in patients who had previous ketoconazole

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zole therapy compared with patients who were ketoconazole-naive (47% vs. 64%, respectively). Notably, since previous ketoconazole therapy was an exclusion criterion for both the pre- and postdocetaxel phase III evaluations of abiraterone for mCRPC, the benefit of abiraterone in the postketoconazole setting (ie, the aforementioned patient) is difficult to infer.

In summary, the current case demonstrates the potential to render extended therapy with docetaxel in older adults with substantial efficacy and reasonable safety. With abundant therapies emerging for castration-resistant prostate cancer, it is important to remember that cytotoxic therapy remains a cornerstone of treatment of this disease.

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