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Prolonged therapy with cabazitaxel in an octogenarian with metastatic castration-resistant prostate cancer

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Abstract

In the phase III TROPIC trial, cabazitaxel in combination with prednisone was compared to mitoxantrone with prednisone in patients with metastatic castration-resistant disease (mCRPC) that 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 FDA approval for use in this setting. Although cabazitaxel was the first agent approved in the post-docetaxel space, several other agents have entered (or are probably soon to enter) the therapeutic armamentarium, including abiraterone, MDV3100, and radium-223. As such, 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 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. 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 post-docetaxel therapies in an increasingly complex therapeutic landscape.

Keywords

Cabazitaxel; older adult

Case Description

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

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

His PSA ultimately continued to rise while on ketoconazole/hydrocortisone, and by April of 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 continued to rise in June of 2009, docetaxel chemotherapy was initiated at the conventional dose of 75 mg/m^2 intravenous (IV) every 3 weeks (q3wks) with prednisone. Notably, the patient was asymptomatic at this time. After one cycle of docetaxel therapy, the patient developed grade 3 fatigue, and the dose was reduced to 60 mg/m^2 IV q3wks. He continued on docetaxel therapy for a total of 10 cycles with stabilization of his PSA during the course of treatment. However, repeat 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 of 2010, approximately 4 months after his last dose of docetaxel therapy, the patient's PSA had risen to a value of 300 ng/dL. He remained asymptomatic, but elected to receive therapy with cabazitaxel and prednisone. The patient was initiated at the recommending starting dose of 25 mg/m^2 IV q3wks 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 from 300 ng/dL 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 to 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 patients that had progressed after hormonal manipulation. Mitoxantrone in combination with prednisone was compared to prednisone alone in a randomized study published by Tannock *et al* in 1996.¹ Treatment with mitoxantrone and prednisone (as compared to prednisone alone) led to improved disease palliation, but no benefit in survival was identified. Nearly a decade later, two randomized, phase III studies were published, demonstrating an overall survival (OS) benefit with docetaxel-based therapy as compared to 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 overall survival (OS) of 25.8 months, as

compared to 21.7 months with placebo ($P=0.03$). 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 (as compared to placebo) improved median OS from 10.9 months to 14.8 months ($P<0.001$). Recently presented phase III data for MDV3100 (a novel anti-androgen that blocks nuclear translocation of androgen receptor) also suggest an improvement in overall survival in this setting (18.4 months vs 13.6 months, $P<0.0001$).⁶ Radioisotopes may also play a role in the docetaxel-refractory patient – the phase III ALSYMPCA study assessed radium-223 vs placebo in patients with bone metastases who were either docetaxel-refractory or docetaxel-ineligible; a survival benefit of 2.8 months was demonstrated.⁷

Nevertheless, cytotoxic chemotherapy still plays a critical role in the post-docetaxel space. Cabazitaxel is a novel taxane that differs structurally from docetaxel by the presence of two methoxy side moieties substituting for hydroxyl groups, which leads to improved cellular retention as compared to docetaxel.⁸ Cabazitaxel 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 v 12.7 months, $P<0.001$), 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% CI 0.61-1.08) in patients < 65, as compared to 0.62 (95% CI 0.50-0.78) in patients ≥ 65.

Although no studies to date directly compare abiraterone and cabazitaxel in docetaxel-refractory patients, editorial comments have suggested favoring the former option due to toxicity considerations.¹¹ The patient cited herein, who received cabazitaxel therapy at the age of 80 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 in the post-docetaxel space. Firstly, the study identified a high rate of grade ≥ 3 neutropenia (82%), with 8% of patients developing 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 above 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 over the age of 65, 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 as compared to docetaxel.

In addition to safety considerations, therapeutic decision-making in the post-docetaxel space 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 on OS of 2.7 months as compared to control. In contrast, abiraterone showed a 3.9 month improvement in OS as compared to control. The nature of controls is a key consideration – cabazitaxel was compared to mitoxantrone, whereas abiraterone was compared to placebo. Again, acknowledging the caveats of cross-trial comparisons, the metaphorical “bar” was likely higher in TROPIC, where an active cytotoxic therapy was employed as a comparator.

Prior therapies may also compromise the efficacy of post-docetaxel therapies. Ryan *et al* reported a phase II experience assessing abiraterone in 33 patients with mCRPC, 19 of whom had received prior therapy with abiraterone.¹² PSA declines 50% were observed less frequently in patients who had prior ketoconazole as compared to patients who were ketoconazole-naïve (47% vs 64%, respectively). Notably, since prior ketoconazole therapy was an exclusion criterion for both the pre- and post-docetaxel phase III evaluations of abiraterone for mCRPC, the benefit of abiraterone in the post-ketoconazole setting (i.e., 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 therapy for this disease.

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