

Cabazitaxel Rechallenge at Prostate-Specific Antigen Relapse After Previous Cabazitaxel and Docetaxel Chemotherapy: Case Report

Christina J. Perry, Santhanam Sundar

Clinical Practice Points

- Docetaxel is recommended as first-line chemotherapy in patients with castration-refractory prostate cancer. The choice and order of treatments in patients whose disease progresses either before or after receiving docetaxel is still being evaluated.
- We report the first case of rechallenge treatment with cabazitaxel in an elderly man who had also been previously rechallenged with docetaxel and diethylstilbestrol (DES). The patient had 17 cycles of cabazitaxel in total, with no significant cumulative toxicity and no significant dose-limiting toxicities.
- Reintroduction of hormones or chemotherapeutic agents to which a response has previously been observed should be considered in selected patients with castration-refractory prostate cancer.

Clinical Genitourinary Cancer, Vol. 10, No. 3, 207-9 © 2012 Elsevier Inc. All rights reserved.

Keyword: Cabazitaxel, Prostate cancer, Rechallenge

Introduction

Cabazitaxel is a new member of the taxane group and is not cross-resistant with docetaxel. *In vitro* it has been shown to promote tubulin assembly and also to stabilize microtubules against depolymerization as successfully as docetaxel.¹ Cabazitaxel has recently been shown to improve survival in patients with prostate cancer who have previously been treated with docetaxel.²

We report the first case of cabazitaxel rechallenge in a patient with prostate cancer. He received 10 cycles of cabazitaxel initially in the TROPIC trial and then a further 7 cycles in the Early Access Programme after the publication of the TROPIC trial results. Of significance, our patient was more than 80 years of age and was also rechallenged with docetaxel and diethylstilbestrol (DES).

Case Report

An 83-year-old man was initially diagnosed with metastatic prostate cancer in July 2004 when he presented with a pathologic fracture of his right hip. He was found to have a prostate-specific antigen (PSA) level of 12,000 $\mu\text{g/L}$, and a bone scan revealed multiple bone

metastases. He was given goserelin (a luteinizing hormone-releasing hormone [LHRH analogue]), and his PSA level fell dramatically to 16.4 $\mu\text{g/L}$ in June 2005.

After 14 months of treatment, his PSA level began to rise to 44.5 $\mu\text{g/L}$, and DES with aspirin prophylaxis was added. One month later, in October 2005, he became short of breath and a computed tomographic (CT) scan confirmed lung metastases. Although his PSA level had fallen to 14.7 $\mu\text{g/L}$, visceral metastatic disease was present and he was given first-line palliative chemotherapy with a combination of docetaxel and prednisolone; DES was discontinued. He completed 6 cycles of docetaxel and had an excellent PSA response, with his pretreatment PSA level of 14.7 $\mu\text{g/L}$ falling to a posttreatment PSA nadir of 3.7 $\mu\text{g/L}$. He continued receiving prednisolone alone for 14 months, with a slowly rising PSA level until July 2007. In addition, he experienced neck pain and was treated with a single 8-Gy fraction of radiotherapy in April 2007.

On reaching a PSA peak of 14.4 $\mu\text{g/L}$, his prednisolone was gradually reduced and he was rechallenged with DES and aspirin because of the encouraging response observed previously with DES rechallenge.^{3,4} Again, his PSA level rose slowly over 14 months, his DES was stopped, and he was entered into the TROPIC trial comparing mitoxantrone with cabazitaxel. He received 10 cycles of cabazitaxel starting in October 2008, had a modest PSA response (falling from 25.6 $\mu\text{g/L}$ before cabazitaxel administration to 18.0 $\mu\text{g/L}$ after cabazitaxel therapy) and had stable disease on his posttreatment CT scan.

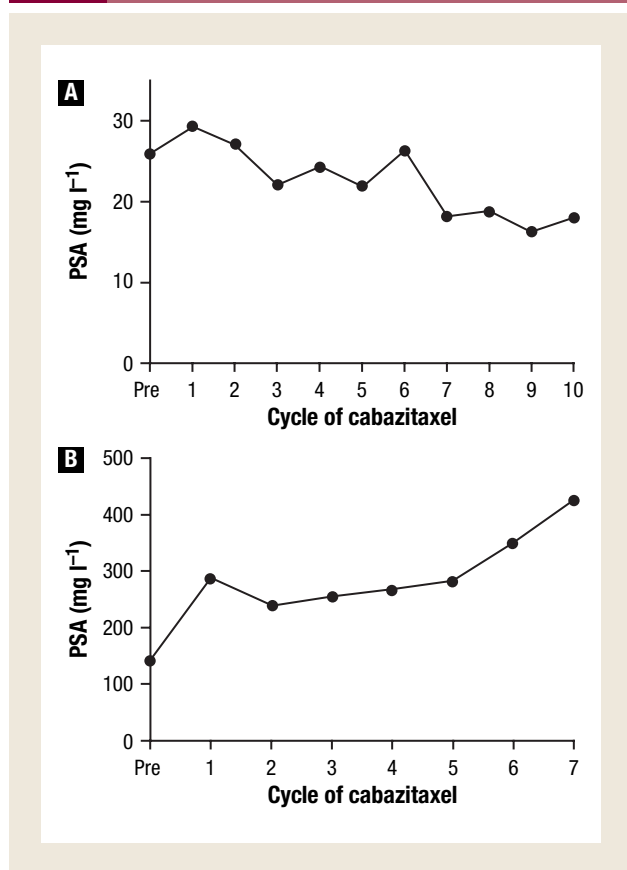
Department of Clinical Oncology, Nottingham City Campus, Nottingham University Hospitals NHS Trust, Nottingham, United Kingdom

Submitted: Dec 12, 2011; Accepted: Jan 14, 2012; Epub: Mar 23, 2012

Address for correspondence: Christina J. Perry, MBChB (Hons), Department of Clinical Oncology, Nottingham City Campus, Nottingham University Hospitals NHS Trust, Hucknall Road, Nottingham, NG5 1PB, UK
Fax: 0115 8405879; e-mail contact: cperry@doctors.org.uk

Cabazitaxel Rechallenge at PSA Relapse

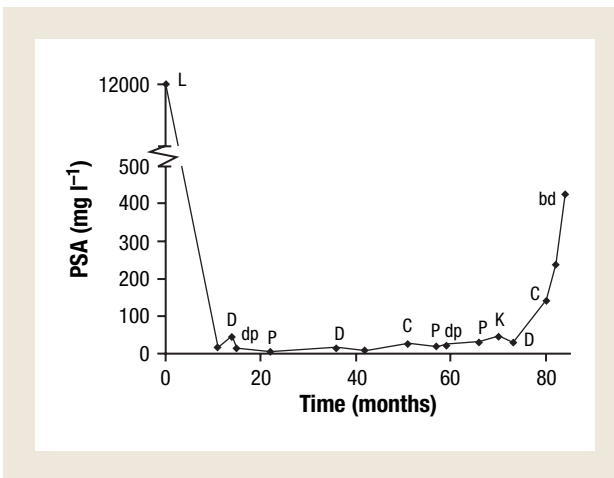
Figure 1 PSA Response to Cabazitaxel. A, Prostate-Specific Antigen (PSA) Response in TROPIC Trial. B, PSA Response in Early Access Programme



He tolerated cabazitaxel very well and on completion was given maintenance prednisolone (Figure 1A).

Two months later, in June 2009, his PSA level began to rise (21.8 $\mu\text{g/L}$) and he was rechallenged with docetaxel and prednisolone. He completed 9 cycles in January 2010, with a PSA level of 30.2 $\mu\text{g/L}$ and a stable CT scan after treatment. He was again given maintenance prednisolone until PSA progression (46 $\mu\text{g/L}$) in May 2010, when his prednisolone was replaced with ketoconazole, hydrocortisone, and fludrocortisone. After 2 months of this treatment, his liver function test results deteriorated and all 3 drugs were stopped. He also experienced lower back pain and received an 8-Gy single fraction of radiotherapy to his lumbar spine in June 2010. He was rechallenged with DES and aspirin with dexamethasone in August 2010 when his PSA level was 29.6 $\mu\text{g/L}$. After 5 months, his PSA level rose again (141 $\mu\text{g/L}$), and his treatment was changed to prednisolone before he again received cabazitaxel in March 2011, but this time he participated in the Early Access Programme. He tolerated cabazitaxel well; initially his PSA level was stable and he gained significant symptomatic benefit. He received 7 cycles of cabazitaxel, but this was discontinued as his PSA level started to rise (425 $\mu\text{g/L}$) (Figure 1B). Bicalutamide was started in combination with dexamethasone and he was given a further single 8-Gy fraction of palliative radiotherapy to his cervical and lumbar spine for pain in August 2011. He died 3 months later. Overall, our patient with metastatic prostate cancer at

Figure 2 PSA Response to Treatment



Abbreviations: bd = bicalutamide and dexamethasone; C = cabazitaxel and prednisolone; D = diethylstilbestrol; dp = docetaxel and prednisolone; K = ketoconazole, hydrocortisone, and fludrocortisone; L = LHRH agonist goserelin; P = prednisolone.

diagnosis had excellent clinical and biochemical disease control for over 7 years. Figure 2 demonstrates his PSA response to treatment over the 7 years after diagnosis.

Discussion

Docetaxel is well established as first-line chemotherapy in patients with castration-refractory prostate cancer.⁵ The TAX 327 study demonstrated a survival benefit with docetaxel administration once every 3 weeks compared with both weekly docetaxel and mitoxantrone in this setting. All regimens were given in combination with prednisolone. Median survival was 19.2 months with docetaxel given every 3 weeks compared with 17.8 months with weekly treatment and 16.3 months with mitoxantrone.⁶

In patients whose disease progresses either before or after receiving docetaxel treatment, there was no standard choice of therapy before the publication of phase 3 cabazitaxel trial results and most recently abiraterone⁷ and alpharadin trial results.^{8,9} Widely used treatment options include further hormone treatment or second-line chemotherapy with agents such as mitoxantrone. Rechallenge with docetaxel has also been explored as an option. Several studies have investigated rechallenge with docetaxel in patients who have responded to or had stable disease with first-line docetaxel treatment. A 50% PSA response rate in the order of 38% to 48% has been reported, as has an overall survival of 16 months.^{10,11} Di Lorenzo et al conducted a small phase II trial of rechallenge with docetaxel, again in patients who had a response or no progression with first-line docetaxel. Their results were less favorable but still demonstrated a 50% PSA response rate of 24.5% and overall survival of 13 months.¹²

Recent interest has involved the use of cabazitaxel in patients with metastatic hormone-refractory prostate cancer. The TROPIC trial (a phase III randomized trial) compared mitoxantrone given every 3 weeks vs. cabazitaxel (every 3 weeks) in combination with prednisolone in patients whose disease progressed either during or after first-line treatment with docetaxel. Median survival was 15.1 months in men who received cabazitaxel compared with 12.7 months in

those who received mitoxantrone (hazard ratio, 0.70; 95% confidence interval, 0.59-0.83; $P < .001$). The main adverse effects recorded were neutropenia and diarrhea, which were higher in the cabazitaxel group.² Cabazitaxel is currently not available to National Health Service patients in the United Kingdom, and the outcome of the current review under development by the National Institute of Health and Clinical Excellence (NICE) is expected in February 2012.¹³ Our patient initially received cabazitaxel in the TROPIC trial² and then in the Early Access Programme.¹

We describe the case of a man who was initially diagnosed in his late 70s with metastatic prostate cancer and whose disease had been controlled for 7 years with a combination of hormone treatment and chemotherapy. Of note he had been rechallenged with DES, steroids, docetaxel, and cabazitaxel. This is the first report in the literature, to our knowledge, of rechallenge with cabazitaxel. At the time of rechallenge with cabazitaxel he was heavily pretreated and in his early 80s and yet tolerated treatment very well. This case highlights several key points. First, in selected patients with metastatic prostate cancer, a durable long-term response can be achieved with multiple lines of both hormone and cytotoxic treatments. Second, our case demonstrates that rechallenge with a drug to which a response has previously been documented may be beneficial. Finally, we draw attention to the observation that carefully selected older patients with metastatic prostate cancer can gain substantial benefit from hormone and chemotherapy treatment, including rechallenge treatment, and should not be excluded from these options or clinical trials based purely on age.

Conclusion

In selected patients with castration-refractory prostate cancer, the use of multiple lines of both hormone and chemotherapy treatment can achieve a durable clinical and biochemical response. Rechallenge treatment with an agent to which a response has been previously demonstrated should be considered. Further studies are needed to establish the role of rechallenge treatment with cabazitaxel in this cohort of patients.

Disclosure

Dr Sundar has attended Sanofi-Aventis advisory board meetings and has received honoraria, conference sponsorship, and research funding from Sanofi-Aventis. All other authors state that they have no conflicts of interest.

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