Metastatic Castration-Resistant Prostate Cancer: Two Case Reports of Dramatic Response with Abiraterone Acetate in Patients Heavily Pretreated with Chemotherapy

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Key Words

Abiraterone acetate · Metastatic castration-resistant prostate cancer · Cytochrome P450 c17 · Prostate-specific antigen · Chemotherapy

Abstract

Metastatic castration-resistant prostate cancer (mCRPC) with visceral involvement requires new, effective and safe treatments after chemotherapy failure. The CYP17A1 inhibitor abiraterone acetate has been approved as a treatment for mCRPC, both after docetaxel chemotherapy and more recently for patients who are not responding to chemotherapy. In published studies, most patients previously treated with docetaxel had received a limited number of lines of chemotherapy and a small proportion of these patients presented with visceral metastases. We report two mCRPC patients with extensive visceral disease, who were heavily pretreated with chemotherapy. They experienced major responses to treatment with abiraterone acetate. For both patients, responses to abiraterone were noticeable within 1 month, encompassing a marked regression of visceral metastases and a decrease in prostate-specific antigen. The clinical benefit of abiraterone was maintained for at least 6 months and the treatment was well tolerated.

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Introduction

In Europe and other developed countries, prostate cancer is the most common cancer in men, and it ranks third overall in terms of mortality (behind lung cancer and colon cancer) [1]. Metastatic prostate cancer is initially treated with androgen deprivation therapy (ADT), but most patients eventually become refractory to this treatment and develop castration-resistant disease. Therapeutic options then include cytotoxic chemotherapy, symptomatic care with narcotic analgesics, and radiotherapy to dominant sites of bone pain. More recently, abiraterone acetate was added to this armamentarium.

The development of treatments for castration-resistant prostate cancer (CRPC) has been the subject of intensive investigation. Accumulating data emphasize that ‘castration-resistant’ tumors retain a clinically relevant degree of hormone sensitivity and highlight the continued importance of androgen axis activation in advanced tumors [2, 3]. Accordingly, therapeutic strategies designed to more effectively reduce androgen activity were required to improve clinical efficacy and prevent disease progression.

Androgen production primarily occurs in the testes and adrenal glands, but in men with CRPC, the tumor tissue is an additional source of androgens [4]. Abiraterone acetate is the first oral treatment for metastatic CRPC (mCRPC) that inhibits androgen production at all three sources [5]. Abiraterone is a selective inhibitor of androgen biosynthesis that potently blocks cytochrome P450 c17 (CYP17), a critical enzyme in testosterone synthesis [6, 7].

Abiraterone acetate is approved, in combination with prednisone or prednisolone, for the treatment of mCRPC in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen. Results of a pivotal phase 3, randomized, placebo-controlled, multicenter study [8] showed that in a prespecified interim analysis, after a follow-up of 12.8 months, treatment with abiraterone acetate in combination with prednisone or prednisolone resulted in a 35% reduction in the risk of death (HR = 0.65; 95% CI: 0.54, 0.77; $p < 0.001$) and an improvement of 3.9 months in the median overall survival (14.8 vs. 10.9 months) compared to placebo plus prednisone or prednisolone. In an updated analysis (with a follow-up period of 20.2 months), results were consistent with those from the interim analysis with a 4.6-month improvement in the median overall survival between the two arms [15.8 vs. 11.2 months (HR = 0.74)] in favor of abiraterone acetate [9].

In this trial, 90% of the patients had bone metastases and a good performance status (PS). Moreover, only 30% of the patients had received 2 lines of chemotherapy before abiraterone and no patient had 3 or more lines. Thus, it is important to report therapeutic experience in patients treated with a high number of prior cytotoxic therapies, as regularly seen in the clinic. Here, we describe 2 heavily pretreated patients with extensive visceral mCRPC, who experienced dramatic responses to abiraterone with a decline in prostate-specific antigen (PSA) and response of visceral disease. These cases illustrate the possibility of achieving meaningful responses with low toxicity with abiraterone in aggressive mCRPC despite significant exposure to chemotherapy.

Case 1

In April 2004, a 58-year-old male presented with a PSA of 17.9 ng/ml, T3 and Gleason 7 (3 + 4) prostate adenocarcinoma. He underwent pelvic lymph node ablation, showing an invasion of the right ilio-obturator nodes. A bone scan as well as a thoraco-abdominal CT were normal. The patient was treated with prostatic (70 G) and pelvic (50 G) radiation

therapy, followed by gosereline acetate (10.8 mg every 3 months for 6 months). His post-treatment PSA nadir was 1 ng/ml in July 2004.

In October 2007, progression occurred with an increase in PSA, CT showing enlarged lumbo-aortic nodes as well as lumbar bone metastases. The patient began ADT with gosereline acetate (10.8 mg every 3 months) and bicalutamide 50 mg/day from June 2007 to December 2007, followed by spine radiation therapy. In January 2008, as PSA progressed, docetaxel (75 mg/m² every 3 weeks with prednisone 10 mg daily/6 cycles) was started. A partial response was obtained, and ADT was resumed after chemotherapy. In January 2009, while PS was 1, a new progression occurred with bone pain, radiographic progression (bone, liver, hydronephrosis) as well as PSA increase. A mitoxantrone/prednisone treatment was proposed (10 mg/m², 3 cycles), but treatment was poorly tolerated and the disease continued to progress.

From 2009 through 2011, the patient received a total of 5 separate regimens for his progressing metastatic disease: zoledronic acid, stilboestrol, oral vinorelbine (80 mg weekly, 6 cycles), docetaxel (60 mg/m², 3 cycles), and carboplatin/VP16 (3 cycles: carboplatin AUC 4 and VP16 100 mg/m² for C1, carboplatin AUC 4 and VP16 80 mg/m² for C2 and carboplatin AUC 3.75 and VP16 75 mg/m² for C3). However, the disease progressed and PS deteriorated to 3.

In March 2011, a named-patient treatment with abiraterone was started at a dose of 1,000 mg/day together with prednisone 10 mg/day. Before abiraterone, PSA was 504 ng/ml and PS was 3; main metastatic lesions were located in the bones, lumbo-aortic nodes, liver, urinary tract (hydronephrosis) and lungs. Moreover, the patient had ascite and lower limb edema.

Quickly after abiraterone initiation, the patient had a sharp clinical improvement (PS 1). Biological response (PSA decrease at 281 ng/ml) was obtained after 1 month of treatment. No side effects were attributed to abiraterone treatment. After 3 months of treatment, radiological partial response was achieved (fig. 1) and PSA was 54 ng/ml with PS 1.

In August 2011, PS deteriorated, lower limb edema increased, and the patient died.

Case 2

In 2000, a 49-year-old man presented with prostate adenocarcinoma with PSA at 6 ng/ml and Gleason score of 7 (3 + 4). He underwent a radical prostatectomy with pelvic lymph node ablation. After radical prostatectomy, the patient was staged pT2N0, but surgical margins were positive and intraprostatic lymphovascular invasion was diagnosed with no invasion of capsule or seminal vesicles. Gleason score was confirmed.

In September 2007, PSA monitoring showed an increase at 57 ng/ml. A CT showed enlarged iliac lymph nodes without metastases. Bicalutamide was started and PSA decreased to 1.2 ng/ml. In August 2008, upon increase in PSA, the patient began ADT (leuprolide 45 mg every 6 months). PSA dropped, but 1 year later, in August 2009, PSA was at 122 ng/ml and a CT showed retroperitoneal node enlargement. The patient began chemotherapy with docetaxel (75 mg/m² every 3 weeks with prednisone 10 mg daily – 10 cycles). Partial node response was obtained and PSA dropped to 15 ng/ml after 10 cycles of docetaxel. In September 2010, progression was evident with bone and lung metastases and PSA at 666 ng/ml. Zoledronic acid was given and a second line of chemotherapy was proposed with cisplatin + VP16 (CDDP 75 mg/m² and VP16 100 mg/m² for C1, CDDP 67.5 mg/m² and VP16 90 mg/m² from C2/6 cycles). Stabilization was obtained until May 2011 when PSA rose to 1,069 ng/ml together with bone pain. PS was good at 0. A named-patient treatment with

Dupuy et al.: Metastatic Castration-Resistant Prostate Cancer: Two Case Reports of Dramatic Response with Abiraterone Acetate in Patients Heavily Pretreated with Chemotherapy

abiraterone was started at a dose of 1,000 mg/day together with prednisone 10 mg/day. After 1 month of abiraterone, PSA dropped to 143 ng/ml. Abiraterone was well tolerated. In December 2011, the patient remained in very good shape (PS 0, and PSA 14.8 ng/ml). A CT showed response of lung lesions (fig. 2). Then, the disease remained stable until May 2012 with a bone scan indicating progressive bone metastases, while CT lung and node lesions remained stable. In August 2012, PSA was at 2,025 ng/ml and abiraterone was stopped. Chemotherapy was resumed with cabazitaxel (25 mg/m² – 3 cycles). Tolerance was good and PSA dropped to 1,208 ng/ml after C2.

Discussion

As yet, little information has been made available on the efficacy of abiraterone for the treatment of mCRPC patients presenting with visceral metastases after several lines of chemotherapy. Both these cases illustrate abiraterone efficacy in heavily chemotherapy-pretreated patients. In 1 case, 5 different chemotherapy regimens were given within 3 years, and 2 regimens were used in the other patient. Both patients received a first line of chemotherapy with docetaxel. However, the response achieved was modest and short-lived. The following lines of chemotherapy were used on an empirical basis as there is no standard of treatment for subsequent chemotherapy lines.

In both patients, efficacy of abiraterone was obtained within 1 month. Efficacy was characterized by sustained visceral metastatic response and a marked decrease of PSA. One out of the 2 patients had an important PS deterioration before abiraterone, with a sharp improvement of PS under abiraterone treatment. Clinical benefit with abiraterone was maintained for 6 months in the first case and 1 year in the second case.

Although the 2 cases reported here are somehow different and possibly presenting with worse clinical features and more advanced disease compared to the patients included in the abiraterone post-docetaxel phase III trial [8], we observed a marked clinical benefit in our patients. In the published trial, 70% of the patients had received only one line of chemotherapy, and 90% of the patients had a PS of 0 or 1; 29% of the patients presented with visceral metastases at baseline, and an objective response rate of 14% (RECIST) was obtained.

The PS 3 status of 1 of our patients and its marked improvement is also to be noted as most cancer studies limit patient inclusion to those with good PS. The safety of abiraterone was excellent in both cases; in particular, no mineralocorticoid side effects were observed. Both patients were simultaneously treated with zoledronic acid, without any safety issue. Finally, a recent study found that the number of previous chemotherapy regimens was a predictive factor of low response to abiraterone [10]; this is not confirmed by the 2 patient cases reported here.

Conclusion

These two clinical observations illustrate that heavily treated mCRPC patients can derive substantial and durable benefits from abiraterone. The benefits were obtained in terms of visceral metastatic response, PSA response and PS improvement. Abiraterone tolerance was excellent.

Conflicts of Interest

The authors state that they have no conflict of interest that might impair the impartiality of this scientific work.

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Fig. 1. Case 1: CT partial response 3 months after abiraterone initiation .

Dupuy et al.: Metastatic Castration-Resistant Prostate Cancer: Two Case Reports of Dramatic Response with Abiraterone Acetate in Patients Heavily Pretreated with Chemotherapy

Fig. 2. Case 2: CT major response 6 months after abiraterone initiation .