

Case Report

# Stunning Response with Low-Dose Enzalutamide after Abiraterone Acetate Failure in a Patient Diagnosed with Metastatic Castration-Resistant Prostate Cancer: A Case Report

Luigi Rossi<sup>a</sup> Giuseppe Cimino<sup>b</sup> Elisa Gozzi<sup>a</sup> Marsela Sinjari<sup>a</sup>  
Martina Brandi<sup>a</sup> Serena Ceddia<sup>a</sup> Antonella Cosimati<sup>a</sup>  
Lucrezia Raimondi<sup>a</sup> Antonella Fontana<sup>c</sup> Luca Filippi<sup>d</sup> Oreste Bagni<sup>d</sup>  
Gian Paolo Spinelli<sup>a</sup>

<sup>a</sup>UOC of Oncology – ASL Latina – Distretto 1, University of Rome “Sapienza”, Aprilia, Italy;

<sup>b</sup>Department of Cellular Biotechnology and Hematology, University of Rome “Sapienza”, Rome, Italy; <sup>c</sup>Department of Radiotherapy, Santa Maria Goretti Hospital, Latina, Italy;

<sup>d</sup>Department of Nuclear Medicine, Santa Maria Goretti Hospital, Latina, Italy

## Keywords

Metastatic castration-resistant prostate cancer · Abiraterone · Enzalutamide · PSA · Bone metastases

## Abstract

We report a case of an elderly patient with metastatic castration-resistant prostate cancer, initially treated with abiraterone acetate (1,000 mg/day) combined with LH-RH antagonist, prednisone (10 mg/day), and zoledronic acid to manage bone metastases. In consideration of his poor performance status, radiological and biochemical progression of the disease, we decided to switch abiraterone to enzalutamide (160 mg/day). Due to adverse events, we reduced enzalutamide to a dose of 80 mg/day. Currently, the disease is under control despite the use of a low dose of enzalutamide.

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## Introduction

In developed countries, prostate cancer is now the second most commonly diagnosed malignancy in men and the fifth leading cause of cancer death in men worldwide, with a 5-year overall survival (OS) rate of 13.6% in patients aged >75 years [1, 2].

Correspondence to:  
Luigi Rossi, [dr.rossi@ymail.com](mailto:dr.rossi@ymail.com)

As prostate cancer cells are dependent on androgen receptor signalling for continued growth, androgen deprivation therapy (ADT) is the cornerstone of treatment for metastatic prostate cancer [3]. However, most patients sooner or later become refractory to this treatment developing a castration-resistant disease which is currently incurable [4, 5].

Therapeutic options for metastatic castration-resistant prostate cancer (mCRPC) have been the subject of intensive studies and investigation and, over the last few years, the prognosis for patients diagnosed with mCRPC has improved thanks to the introduction of novel agents.

The addition of an androgen receptor-targeting agent to ADT has become standard care for these patients, as has been demonstrated in phase III trials with the superiority of combined treatment over ADT alone in terms of OS and progression-free survival (PFS) [6–8].

To date, the treatment of mCRPC includes cytotoxic chemotherapy, radiotherapy, abiraterone acetate, and more recently enzalutamide.

Enzalutamide (previously MDV3100) is a novel oral second-generation non-steroidal androgen receptor inhibitor that was found to improve OS, extending time until progression of disease or death and survival in patients with mCRPC who had not received previous chemotherapy [9–12].

Here, we describe a rare case of a pre-treated patient with multiple bone metastases diagnosed with mCRPC, who experienced dramatic responses with resounding clinical benefit to a low-dose of enzalutamide after abiraterone acetate-failure with a decline in prostate-specific antigen (PSA) and durable radiological response of bone disease with low toxicity.

## Case Report

A 78-year-old man initially presented to our Oncology Unit with an elevated PSA level of 23.3 ng/mL.

Patient subsequently underwent a transrectal ultrasound guided prostate biopsy which revealed high-risk adenocarcinoma of the prostate with a Gleason score 5 + 5 = 10 involving 60% of the tested tissue.

Metastatic workup consisting of bone scan showed abnormal concentrations at the level of sacroiliac bones and some metameries of possible reference to repetitive osteoblastic lesions.

To manage bone metastases, the patient had been treated with zoledronate (4 mg).

He was then started on ADT (combined androgen blockade therapy using an anti-androgen drug and LH-RH agonist) with leuprolide, as a monthly dose and bicalutamide (150 mg/day) with disease control for 22 months and progressive decrease in PSA value up to 0.22 ng/mL.

Due to progressive increase in PSA values up to 62.11 ng/mL, treatment was switched to Abiraterone (1,000 mg/day) combined with LH-RH antagonist and prednisone (10 mg/day).

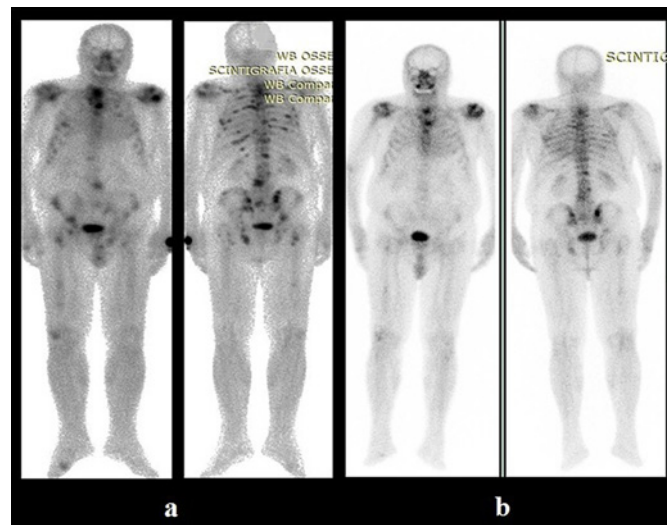
After 3 months of administration of abiraterone, he showed progressive increase in PSA values up to 444 ng/mL, worsening of clinical conditions as asthenia, anorexia, edema and onset of widespread pain.

The patient had performance status (PS) with an Eastern Cooperative Oncology Group Grade (G) 2/3.

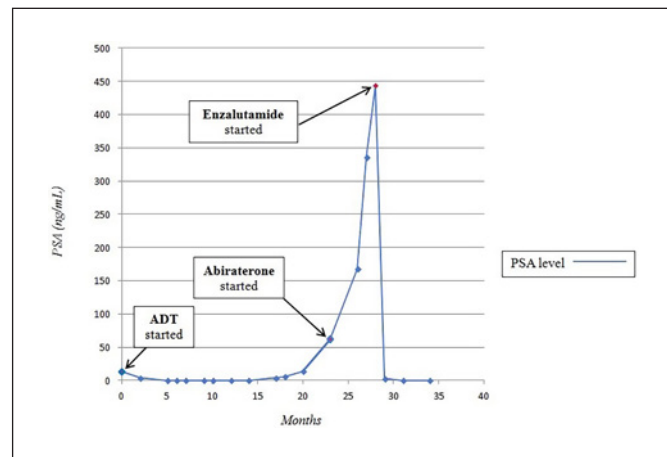
A bone scan was performed showing increased bone lesions (Fig. 1a).

As a result of poor control of disease with abiraterone, treatment with enzalutamide (160 mg/day) was started.

After 1 month of the administration of enzalutamide, PSA decreased to 3 ng/mL, with improvement in clinical conditions (PS 0) and near-disappearance of pain (Fig. 2).



**Fig. 1.** **a** Pretreatment bone scintigraphy. **b** Posttreatment bone scintigraphy.



**Fig. 2.** PSA level over the course of the treatment.

The patient experienced general fatigue while receiving enzalutamide treatment. We evaluated the patient’s general fatigue and clarified the quantitative information about this. The patient continued treatment with reduced dosage because of fatigue (80 mg/day). After the administration of reduced dosage of enzalutamide, PSA decreased to 0.3 ng/mL, and the patient reported noticeable improvement in fatigue. A bone scan was performed and showed a favorable response to treatment with overall reduction of pathological bone uptake (Fig. 1b). Treatment with enzalutamide, first at full dosage and then at a reduced dosage, has shown good disease control and a significant improvement in the patient’s clinical condition. At time of writing, patient is continuing treatment with enzalutamide with excellent disease control.

### Discussion

According to the new classification (ISUP 2014), there are 5 Grade Groups and our patient falls into Grade Group 5 because he had Gleason score 10 (5 + 5).

Gleason grade is one of the most important prognostic factors of outcome for patients affected by adenocarcinoma of the prostate and is used to choose the best management and therapy for the patient. Recognizing a high Gleason grade (patterns 4 and 5) and therefore a

Gleason score of 8 to 10 is fundamental for the patient, because these are the most aggressive and often lethal types of cancer [13].

Our patient had a high Gleason grade, and he was already metastatic to the bones since the diagnosis. He was in therapy with ADT, we added zoledronic acid, but after a few months he developed clinical, biochemical and radiological progression of the disease.

Most men with advanced disease can stop responding to traditional ADT and are defined as having castration-resistant prostate cancer (CRPC). CRPC is defined by disease progression despite androgen depletion therapy (ADT) and may present as either a continuous rise in serum PSA levels, the progression of preexisting disease, and/or the appearance of new metastases. Still it is important to maintain serum levels of testosterone (<50 ng/dL) [14].

Until recently, standard first-line therapy for patients progressing on ADT was chemotherapy regimens based on docetaxel plus prednisone. However, today new agents for CRPC such as abiraterone acetate (henceforth referred to as abiraterone) or enzalutamide have dramatically changed clinical outcomes for patients.

Abiraterone is an inhibitor of CYP17A1, an enzyme essential in the process of androgen synthesis, which can be upregulated in mCRPC. Enzalutamide is a potent androgen receptor inhibitor developed for its capacity to overcome androgen receptor overexpression, an adaptive mechanism implicated in the development of mCRPC [15].

A COU-AA-302 phase 3 trial tested the use of abiraterone acetate plus prednisone versus placebo plus prednisone and it demonstrated that OS for men with chemotherapy-naive metastatic CRPC was significantly longer with abiraterone acetate and prednisone than with placebo and prednisone (HR 0.79%; 95% CI 0.66–0.95). The main specific side effects were hypokalemia, hypertension, edema, and cardiac events [16].

Enzalutamide was tested against placebo in the PREVAIL trial in men with chemotherapy-naive metastatic CRPC, either with or without visceral disease, low- or high-volume bone disease or lymph node only disease; it was demonstrated that enzalutamide improved OS (HR 0.71; 95% CI 0.60–0.84). The most common adverse events included fatigue, back pain, constipation, and arthralgia although only 0.6% of enzalutamide-treated patients experienced a seizure [12].

These drugs have never been compared head to head, and clinical trials showed their similar activity, so either drug can be used as first-line treatment for metastatic CRPC (mCRPC) [15].

Our patient has no clinical history of seizure, and he is not affected by diabetes; considering there were no co-morbidities that could guide the choice of treatment, we decided to start therapy with abiraterone. After only 3 months of therapy without any benefit and with an important clinical, biochemical and radiological progression of disease, we discontinued abiraterone and started therapy with enzalutamide. He could have benefited from chemotherapy with docetaxel but his PS was very poor and there was no possibility to start chemotherapy.

The optimal sequence or combination of these new agents (abiraterone, enzalutamide, docetaxel, cabazitaxel, radium-223 and sipuleucel-T) is unknown; it depends on the extent of disease, patient comorbidities and preferences and drug availability (for example, sipuleucel-T is not available in Italy) [17].

In November 2019, *The Lancet* published the first randomized, head-to-head comparison study of abiraterone plus prednisone and enzalutamide. For the patients, it was possible to cross to the alternative drug at progression, so the trial was able to compare both treatment sequences and the second-line activity of both drugs. Patients were randomly assigned to group A, receiving abiraterone 1,000 mg once daily plus prednisone 5 mg orally twice daily until PSA progression, followed by crossover to enzalutamide 160 mg orally once daily or to group B, receiving the opposite sequence.

Primary endpoints were time to second PSA progression and PSA response ( $\geq 30\%$  decline from baseline) on second-line therapy. OS was one of several secondary endpoints. Time to second PSA progression was longer in group A than in group B (median 19.3 months vs. 15.2 months). Regarding the second primary endpoint, PSA responses to second-line therapy, were seen in 36% of patients in group A and 4% of patients in group B. Median OS was 28.8 months versus 24.7 months, group A versus group B, respectively. This trial was the first one to show an advantage for using a sequencing strategy of both drugs: abiraterone plus prednisone followed by enzalutamide had a longer time to PSA progression than the opposite sequence, so this treatment sequence is preferred and can result in improved clinical benefit. It is important to know that there are interesting trials about the optimal sequencing of taxanes and androgen receptors inhibitors but they are ongoing (NCT02254785 and NCT04015622), and there are only inconclusive data [15].

To our astonishment, after only 1 month of therapy with enzalutamide, we observed reset of PSA from 444 ng/mL to 3 ng/mL (Fig. 2, in this simple graph, we summarize the trend of PSA level in the history of the patient's disease) and the bone scan showed a global reduction of pathological uptake. He referred only fatigue G2–3 so we decided to halve the dosage of enzalutamide to 80 mg/day.

Today the patient no longer reports diffuse bone pain and fatigue, with a marked improvement in his quality of life.

In the literature, we found only a few articles that analyze benefits of low-dose enzalutamide; one of these, published in April 2020, compared low-dose enzalutamide ( $\leq 80$  mg per day) with standard dose (160 mg per day) in mCRPC. A PSA decrease of  $\geq 50\%$  at 12 weeks was observed in 67% patients versus 45% with standard dose. Furthermore median PFS was 11.2 months versus 11.9 months ( $p$  value 0.612) for patients receiving low dose and the standard dose respectively. The authors concluded that low-dose enzalutamide in elderly, symptomatic, poor-PS patients with metastatic disease was associated with the high response rate and survival compared to standard dose [18].

Moreover, in a retrospective Caribbean study, published in May 2019, the authors concluded that low dose of enzalutamide (80 mg/day) was efficient in a large proportion of patients included in the study, and they underlined that the time to 50% PSA reduction was 57 days (range 26–119) [19].

In the future, it would be interesting to identify clinical and molecular factors predictive of response to enzalutamide, in particular in elderly and frail patients who cannot benefit from chemotherapy.

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### Statement of Ethics

The authors declare that ethics approval was not required for this case report. Written informed consent was obtained from the patient for publication of this case and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this *Journal*.

### Conflict of Interest Statement

The authors declare no conflict of interest.

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### Author Contributions

Rossi Luigi: conceptualization.

Cimino Giuseppe: methodology.

Gozzi Elisa: writing-original draft preparation.

Sinjari Marsela: writing-original draft preparation.

Brandi Martina: formal analysis and investigation.

Ceddia Serena: formal analysis and investigation.

Cosimati Antonella: writing-review and editing.

Raimondi Lucrezia: critical revision.

Fontana Antonella: project administration.

Filippi Luca: data curation and validation.

Bagni Oreste: resources and supervision.

Spinelli Gian Paolo: final approval of the version to be published.

All authors have read and agreed to the published version of the manuscript.

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