



Abiraterone-Induced Rhabdomyolysis in Prostate Cancer: A Report of Two Cases and Review of the Literature

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Abstract

Background: Abiraterone is a hormone targeted treatment that is used along with the standard androgen deprivation therapy for castration-resistant prostate cancers and has recently been proven to improve survival outcomes when used for castration-sensitive prostate cancers as well. However, to date, there is little literature on a fatal complication of this medication, which is rhabdomyolysis.

Patient Description: We report a case series of two patients, a 72-year-old and an 80-year-old male, both with metastatic castration-resistant prostate cancers who developed rhabdomyolysis within a few weeks of starting Abiraterone. Both individuals showed significant recovery shortly after discontinuation of Abiraterone.

Conclusion: This case highlights the importance of recognizing rhabdomyolysis early in patients started on Abiraterone, as this serious complication may be more common than previously suspected. This association becomes particularly important clinically now that there will be an increased frequency in the use of Abiraterone given recent studies showing its benefits when started early for patients with castration-sensitive prostate cancers as well.

Introduction

Castration Resistant Prostate Cancer (CRPC), defined as disease progression while on Androgen Deprivation Therapy (ADT), as evidenced by increasing PSA, new metastasis or progression of existing metastasis, is commonly treated with novel hormone targeting agents, such as Abiraterone and Enzalutamide, in addition to continuation of ADT. Recently, the LATITUDE trial supports the addition of Abiraterone to ADT for castration-sensitive prostate cancer (CSPC) as well, which could mean that Abiraterone will be used more frequently in early prostate cancers [1]. Since the CYP17A1 inhibitor Abiraterone became FDA approved in 2011 for the treatment of CRPC, there has been few case reports in the literature of an association between the drug and rhabdomyolysis. Considering that the mortality rate of rhabdomyolysis can be as high as 30%, it is important to bring awareness of this association as early recognition and discontinuation of this agent could prevent long term complications [2].

We present two cases of patients with CRPC started on Abiraterone who developed rhabdomyolysis within the first few weeks of treatment initiation. Fortunately, the association with Abiraterone was recognized immediately, and the medication was discontinued, leading to resolution of rhabdomyolysis without further complications for these individuals. This report serves to identify patients who are most at risk for the development of Abiraterone-induced rhabdomyolysis, and to recognize that perhaps this complication is more common than previously suspected.

Case Presentation 1

A 72-year-old Caucasian male with a history of essential hypertension, type II diabetes, prior strokes with residual neurologic deficits, recently diagnosed and treated for non-muscle invasive bladder cancer and prostate cancer (Gleason 8) with widespread metastasis to the bone presented to an outside hospital with generalized weakness after a couple of weeks of starting standard dose Abiraterone with prednisone.

The patient underwent radical prostatectomy at the time of diagnosis 12 years ago, with salvage radiation therapy for a biochemical relapse 2 years later. He developed metastatic disease to the bone and retroperitoneal lymph nodes 3 years ago, for which he was treated initially with a combination of Androgen Deprivation Therapy (ADT) with leuprolide acetate and bicalutamide, followed by discontinuation of bicalutamide and short-term benefit due to withdrawal effect. Due to rising

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PSA and poor performance status, he was started on Abiraterone with prednisone. However, within the first few weeks of being on treatment, his performance status declined further and presented to an outside hospital for evaluation.

On admission to the hospital, he was found to have progressively worsening weakness, rigidity and muscle pain. He had an EMG study showing myopathy with membrane instability, Creatinine Kinase (CK) elevated to 24,918, transaminitis with AST being 550 and ALT being 331, acute renal insufficiency with Creatinine of 3.0 from baseline Creatinine of 1.2, and urinalysis showing a significant amount of blood without RBCs. All these findings were concerning for rhabdomyolysis, with the most likely etiology attributed to Abiraterone as he has not started on any other medication or has not had any strenuous activity. Abiraterone was discontinued and patient started on high dose steroids, aggressive hydration with marked improvement in his rigidity and strength. After hospital discharge, his aforementioned lab abnormalities resolved, and his strength continued to improve with physical therapy. He has initiated treatment with the androgen-receptor antagonist Enzalutamide, and has been tolerating it well thus far, without recurrent episodes of the rhabdomyolysis.

Case Presentation 2

An 80-year-old Caucasian male with stage 3 chronic kidney disease and metastatic prostate cancer presented the hospital with abdominal pain, discovered to have pyelonephritis and a mild case of rhabdomyolysis in the setting of being for two months on Abiraterone and prednisone for castrate resistant prostate cancer.

The patient underwent in an outside facility neoadjuvant chemotherapy and ADT, followed by radical prostatectomy and lymph node dissection for high risk prostate cancer (Gleason 9) fifteen years prior to this presentation. He remained on Leuprolide intermittently for persistently elevated PSA levels and upon seeking second opinion; he underwent staging evaluation that revealed metastatic disease to the bones, as well as pelvic and retroperitoneal lymphadenopathy. At this time, Abiraterone and prednisone were added to the Leuprolide, and had been tolerating that regimen well for several weeks up until he developed weakness along with abdominal pain and nausea that lead him to present to the ED.

On admission to the hospital, he had a CT of the abdomen and pelvis for work up of his abdominal pain that showed perinephric stranding, as well as urinalysis concerning for pyelonephritis. He developed hematuria but given the concomitant generalized weakness, he had a gradually up-trending CK and Creatinine, concerning for new onset rhabdomyolysis. He was empirically treated with Vancomycin and Zosyn and narrowed to Ciprofloxacin when his urine culture sensitivities resulted. He was on Crestor prior to admission for hyperlipidemia, which was discontinued, and he was given IV fluids. Initially, the Abiraterone was continued as it was felt that the antibiotics were the possible cause of his rhabdomyolysis; however, despite the previously mentioned interventions, his CK up-trended to 4,219 and his Creatinine increased to 3.4, from a baseline of 1.2. At this time, the Abiraterone was discontinued. On discharge, the CK and Creatinine had normalized, and he never had recurrence of any of those symptoms.

One month later, he was restarted on the Abiraterone given that the lab abnormalities had resolved, however, this was discontinued shortly after as he started developing abdominal pain concerning

that he will have recurrent event. Patient enrolled on an institutional radiation oncology protocol for treatment of oligometastatic disease and in conjunction with single agent Leuprolide is maintaining an almost undetectable PSA level.

Discussion

According to the American Society of Clinical Oncology, recommended treatment for CRPC includes continuing androgen deprivation therapy indefinitely, along with targeted therapies, such as Abiraterone/Prednisone or Enzalutamide, or bone-targeted therapies with radium-223, which have all shown to improve overall survival, quality of life, with the reported toxicity. Systemic chemotherapy with a docetaxel-based regimen could also be offered in the right patient population but is associated with increased toxicities [3]. Furthermore, Taylor et al. performed a retrospective multivariate analysis of 341 patients from four clinical trials of secondary therapy for CRPC and found that when Abiraterone or Enzalutamide was combined with continued ADT, patients had a median survival benefit of 2-6 months compared to those without ADT, supporting the recommendation to continue ADT [4].

In addition to the survival benefits of Abiraterone for CRPC, the 2017 phase III LATITUDE trial recently supports its use for castration-sensitive prostate cancers. When comparing ADT, Abiraterone and prednisone to the standard ADT for men with newly diagnosed metastatic prostate cancer, Fizazi et al. [1] reported a 38% lower chance of death in the Abiraterone group. Abiraterone also more than doubled the median time of when the cancer progressed, from 14.8 months to 33 months. These findings could support more frequent use of Abiraterone for early metastatic prostate cancers.

Moreover, a systematic review and meta-analysis on 2,283 patients with CRPC from 10 trials showed that Abiraterone significantly prolonged overall survival, radiographic progression free survival, and time to progression without any unexpected toxicities [5]. Furthermore, the STAMPEDE trial found that men with locally advanced or metastatic prostate cancer who were treated with ADT and Abiraterone/Prednisone compared to ADT alone had 71% improvement in the time to treatment failure, correlating to 37% improvement in overall survival [6].

Despite its effectiveness in treating CRPC, Abiraterone's mechanism of action can largely contribute to the risk for rhabdomyolysis that has been underreported. Abiraterone is a CYP17A1 inhibitor that functions by blocking production of androgens in the prostate, testicles and adrenal glands. It works by inhibiting cytochrome P450 17 alpha-hydroxylase (CYP17), which in turn decreases cortisol production, as well as the intended effect of decreasing androgen production. This decrease in cortisol leads to an increased production of ACTH and mineralocorticoids by removing the negative feedback effect from the cortisol, which in turn can lead to hypokalemia. Hypokalemia is a known major adverse effect of abiraterone but is also a major risk factor for rhabdomyolysis [7-8].

Rhabdomyolysis is caused by muscle breakdown, which leads to leakage of proteins, electrolytes and myoglobin into the bloodstream, leading to complications such as acute kidney injury. Risk factors include advanced age, chronic kidney disease, diabetes, hypokalemia, dehydration, recreational drugs, severe exertion, trauma or crush injuries, certain viral infections, and prescription drugs like statins and antipsychotics [9]. It is critically important for internists and oncologist prescribing all the aforementioned medications to be

aware of the precipitating and pre-existing factors that are fairly common in this patient population. The aim of this case reports is to enrich the literature given that there is lack of reporting of this potentially life-threatening condition that is reversible with early recognition and treatment.

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