Dilated Cardiomyopathy after Sequential Therapy with Abiraterone and Enzalutamide

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Abstract

**Background:** Newer agents targeting the androgen signaling pathway, including abiraterone acetate (Zytiga) and enzalutamide (Xtandi), have led to survival improvements in the management of metastatic castration resistant prostate cancer (mCRPC). However, the short and long term impact of these agents on cardiovascular risk remains unclear. We present a case of non-ischemic cardiomyopathy after sequential therapy with abiraterone and enzalutamide.

**Case report:** An 81-year-old gentleman with a past medical history of mCRPC presented to medical oncology clinic with complaints of new onset of orthopnea and exertional dyspnea. Four weeks prior to this visit, he was started on enzalutamide 160 mg daily, after his disease progression following five months of abiraterone therapy. Clinical examination was consistent with heart failure. His 12 lead EKG revealed sinus tachycardia with a ventricular rate of 106, without acute ST-T wave changes. His cardiac enzymes were within normal limits. The Natriuretic peptides B-type (BNP) was 1,200 pg/mL. A 2D echocardiograph revealed diffuse hypokinesis with a left ventricle ejection fraction of 25% without regional wall motion abnormalities noted. A myocardial perfusion (MIBI) stress scan showed a dilated left ventricle with global hypokinesis. Left ventricle ejection fraction was calculated at 27%, diastolic volume at 208 mL, and end systolic volume at 152 mL. There were no focal perfusion defects. The overall clinical diagnosis was consistent with cardiomyopathy.

**Conclusion:** Urologists and medical oncologists should consider the cardiac side effects of the new generation androgen signaling inhibitors should be carefully monitored for evidence of cardiac toxicity.

**Keywords:** Abiraterone acetate (Zytiga); Enzalutamide (Xtandi); Cardiomyopathy; Prostate cancer; Androgen deprivation therapy

Introduction

For the last seventy years, androgen-deprivation therapy (ADT) has remained the cornerstone of metastatic prostate cancer treatment [1,2]. The relationship between ADT and cardiovascular disease risk is not a new story. Historically, diethylstilbestrol, a nonsteroidal estrogen, was used in treating metastatic prostate cancer but was abandoned because of excess cardiovascular and thromboembolic risk [3]. Since then, several studies have reported an association between ADT and an increased risk of cardiovascular events, including myocardial infarction and cardiovascular mortality [4-11]. Keating et al. [4] described an excess risk of myocardial infarction (MI), diabetes, and sudden cardiac death with ADT in a large cohort of men age 66 years or older. D’Amico et al. [8] analyzed data on 1,372 men from three randomized trials of ADT and found an earlier onset of fatal MI among ADT users age 65 years or older compared with nonusers age 65 years or older. Saigal et al. [10] reported excess cardiovascular morbidity with ADT use among 4,810 men age 65 years or older compared with controls with data from a population-based registry. Tsai et al. [11] identified 1,015 men on ADT in a clinical urologic database and demonstrated an increased risk of cardiovascular mortality with ADT. In addition, two population-based registries showed a possible association between ADT with heart failure in men with prostate cancer [12,13]. On Oct 20, 2010, The U.S. Food and Drug Administration (FDA) notified the manufacturers of the Gonadotropin-Releasing Hormone (GnRH) agonists, the most commonly used ADT, of the need to add new safety information to the Warnings and Precautions section of the drug labels [14].

Newer agents targeting the androgen signaling pathway including Abiraterone Acetate (AA) [15,16] and Enzalutamide (ENZA) [17,18], which take traditional ADT to a next level, have led to survival improvements in the management of metastatic castration resistant prostate cancer (mCRPC). However, the short and long term impact of these agents on cardiovascular risk remains unknown.

Here, we report a patient with mCRPC who developed severe congestive cardiomyopathy after sequential therapy with AA and ENZA that did not reverse after discontinuation of ENZA therapy. While a direct cause-effect relationship cannot be firmly established in this case report, patients who sequentially receive novel androgen signaling inhibitors should be carefully monitored for evidence of cardiotoxicity.

Case Report

81-year-old man with mCRPC presented with new onset of exertional dyspnea, paroxysmal nocturnal dyspnea, and orthopnea. There was no history of cardiac disease or similar symptoms prior to this admission. He denied fever, cough, sick contacts, recent travel, and pain on deep inspiration.

His prostate cancer was initially diagnosed in 1997 (PSA 27; clinical stage T2c; Gleason score 4+5). He underwent prostatectomy

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Received: July 05, 2016; Accepted: August 28, 2016; Published: August 31, 2016

Citation: Freeman B, Wang J (2016) Dilated Cardiomyopathy after Sequential Therapy with Abiraterone and Enzalutamide. Oncol Cancer Case Rep 2: 115. doi: 10.4172/2471-8556.1000115

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and lymph node dissection, which was aborted due to positive nodal involvement of prostate cancer. He was then treated with combined androgen deprivation therapy. Subsequently he developed biochemical recurrence in May 2002. He was then treated with hormone therapy including combined androgen deprivation therapy, later with estrogen therapy in 2006. He was eventually found with bony metastasis. He was treated on a Southwest Oncology Group Clinical trial (Taxotere plus-minus atrasentan) from March 26, 2008 through November 2008. Subsequently, he was treated with mitoxantrone and prednisone from January 2009 to October 2009. In January 2010, he was on a short course of ketoconazole and hydrocortisone which was stopped due to poor tolerance. Subsequently he had multiple lines of therapies including a phase I clinical trial using REVILIMID (lenalidomide) and cyclophosphamide (2010, four months), cabazitaxel (2011, five cycles) and sipuleucel-T prostate cancer therapy (2012, total 3 doses), AA (2012, five months). Unfortunately, he developed radiographic progressive disease while on AA (PSA increased from 4 to 117). AA was subsequently stopped and prednisone was tapered off. Four weeks prior to this visit ENZA was started.

On examination, the patient was an elderly Caucasian man who was fully alert and oriented, afebrile with blood pressure of 105/51, a pulse of 106 bpm, respiratory rate at 22 per minute and a SaO2 of 90% to 94%.

The patient reported tachycardia, but the rest of the physical examination was unremarkable. No petechiae or active bleeding was noted. Laboratory results revealed hemoglobin of 13.1 g/dL (MCV 92.4, RDW 14.5); white cell count of 6800/mm³ with an absolute neutrophil count (ANC) of 4200/mm³ and a platelet count of 279,000/mm³. Sodium: 144; Potassium: 3.9; Chloride: 110; CO₂: 27; BUN: 14; Creatinine: 0.93; Glucose: 108; Magnesium: 1.8; Calcium: 8.3; Cholesterol: 98; Triglycerides: 41; HDL Cholesterol: 37; LDL Cholesterol: 53; VLDL Cholesterol: 8; Chol/HDL Ratio: 2.6; PSA: 138.09 ng/mL. Troponin I was in normal range. The BNP was 1,200 pg/mL. A 12 lead EKG revealed sinus tachycardia with a ventricular rate of 106, but without acute ST-T wave changes. Urine analysis was normal. His chest X-ray showed patchy bibasilar opacities, which may represent atelectasis or pulmonary edema.

The patient was admitted to the oncology unit with a working diagnosis of suspected acute coronary syndrome. ENZA was stopped. A 2D echo revealed diffuse hypokinesis with a left ventricle ejection fraction of 25% without regional wall motion abnormalities. Cardiology was consulted. He was started on lasix, carvedilol, and lisinopril. A myocardial perfusion (MIBI) stress scan showed a dilated left ventricle with global hypokinesis. Calculated left ventricle ejection fraction (LVEF) of 27% (normal is >50%), and diastolic volume of 208 mL, and end systolic volume of 152 mL. No focal perfusion defect was observed. Overall, these findings were consistent with cardiomyopathy. Cardiac catheterization was not recommended by cardiology consultant due to the findings on Mibi Stress Test. His symptoms resolved with medical therapy and he was discharged on hospital day four in stable condition. No further cardiac symptoms were reported after six month follow up. A repeat Echocardiograph at 3 and 6 months showed LVEF remained stable at 25%.

**Discussion**

New anticancer therapies have led to a long life expectancy for many patients. However, treatment-related comorbidities have become an issue for long-term cancer survivors. In this report, we present a patient with mCRPC who experienced congestive heart failure probably related to a new androgen signaling inhibitor. In the current case, there were several risk factors for cardiovascular disease in this patient, including previous therapies with estrogen and mitoxantrone alongside long term hormonal therapy with GnRH agonist (leuprolide). However, the finding of normal LVEF (ECHO showed 55%) twelve months prior to this admission suggests the sequential use of new androgen targeting agents AA and ENZA likely contributed to his acute congestive heart failure. After a review of the literature, we conclude that this is the first reported case of non-ischemic cardiomyopathy that occurred after sequential use of AA and ENZA that has been reported.

ADT remains the cornerstone of metastatic prostate cancer. Current ADT includes GnRH agonists (such as leuprolide, goserelin), bilateral orchietomy, LH-RH antagonists (such as degarelix) and anti-androgen receptor blockers (such as flutamide and bicalutamide). Recent advances in our understanding of the critical role of the androgen receptor in the progression of CRPC have led to the development of a new generation of androgen signaling pathway inhibitors [15-18]. AA is a selective, irreversible and potent inhibitor of 17 a-hydroxylase and c17, 20-lyase, critical enzymes that catalyze two key steroid reactions in the testosterone synthesis pathway [19]. ENZA is a second generation androgen receptor inhibitor which targets multiple steps in the androgen-receptor-signaling pathway [20]. It competitively inhibits androgen binding to androgen receptors and differs from currently available anti-androgen agents in that it inhibits androgen receptor nuclear translocation, DNA binding, and co-activator recruitment. It has a greater affinity for the androgen receptor and has no known agonistic effects. The oral formulation and ease of administration of AA and ENZA make it ideal for urologists to prescribe, and the recent FDA approval of these agents for the treatment of pre-chemotherapy patients is expected to significantly increase the use of these agents among urologists (in addition to medical oncologists). While the novel androgen signaling inhibitor certainly pushes hypogonadism to an unprecedented level, studies on the impact of these novel agents on cardiovascular risk are currently lacking. While a direct cause-effect relationship between ENZA and congestive cardiomyopathy cannot be firmly established in one case report, the super-hypotestosteronemia after sequential therapy with AA and ENZA may be a plausible explanation to his new onset of congestive heart failure.

The underlying mechanisms of cardiovascular risk associated with ADT remains undetermined [21]. Current investigation on cardiovascular side effects focus on metabolic changes associated with ADT4, [9-11]. However, the direct impact of testosterone on hemodynamics should not be neglected. Androgen receptors are present in endothelial cells, vascular smooth muscle cells, and cardiomyocytes. Testosterone is important to myocardial contractility [22]. Testosterone acts on the vascular arterial wall where it induces vasodilation. This is a non-genomic and rapid onset effect that primarily involves the vascular smooth muscle cells, in which testosterone lowers the intracellular Ca²⁺ flux, secondary to interaction with voltage-operated calcium and potassium channels [22]. Testosterone also induces protein synthesis and hypertrophy in the cardiomyocytes through a receptor-specific interaction [23]. Castration in male rats reduced the expression of genes encoding the L-type Ca²⁺ channel, the Na⁺/Ca²⁺ exchanger, B₁-adrenoceptors, and myosin heavy chain subunits [24,25]. In parallel, cardiomyocyte contractile capacity deteriorated. In rats, testosterone improves coronary blood flow and increases both fractional shortening and peak myocardial oxygen consumption, thereby improving cardiac function [25]. Castration results in reduced ejection fraction and diastolic dysfunction, with alteration of the isoenzyme composition of the myosin heavy chain [26]. In humans, testosterone reduces blood pressure and enhances relaxation of brachial arteries; direct injection into coronary arteries produces dilatation and increased
coronary blood flow [27,28]. These vasodilatory effects of testosterone on coronary and other vasculature are confirmed by the findings that men with prostate cancer undergoing androgen-deprivation therapy experience an increase in central arterial pressure (reflecting stiffening of large arteries) [29]. Low circulating levels of testosterone may therefore contribute to the generalized increase in vascular tone found in patients with CHF and correlated positively with cardiac output [30]. Hypogonadism has been associated with increased cardiovascular risk. In a study by Khaw et al. [31] men with testosterone levels of at least 19.6 nmol/L had a 41% lower risk of dying in 10 years compared with men who had testosterone levels of 12.5 nmol/L or less; and for every 6 nmol/L increase in endogenous testosterone, the risk of death decreased 14%. In summary, since testosterone might have beneficial effects on the cardiovascular system and is protective in CHF, [32,33], ADT might indirectly impair cardiac function by decreasing or blocking testosterone.

Clinical trials involving AA and ENZA for the treatment of mCRPC reported low incidence of heart failure [15-18]. In the two randomized clinical trials, cardiac failure all grades, grades 3 or 4 were reported in 2.3%, 1.9% of patients who received AA [15,16]. The cardiac toxicity reported in ENZA trial was less than 1% [17,18]. However, clinicians should be aware there is a disconnection between the reported side effects and adverse effects observed in real world. Further, there appears to be a significant disconnect between the cardiac effects of cancer drugs and how they are reported in clinical trials [34]. These inconsistencies in adverse effects reporting are partly due to an inadequate method of measuring AEs such as CHF in clinical trials [34,35]. Studies of other drugs AA and ENZA likely have similar methodological problems (study designs did not incorporate such tests as echocardiography, brain natriuretic peptide and surveys of heart failure functional status) and are prone to the same underreporting of cardiovascular side effects. In addition, the onset of CHF from ADT may be delayed [36] and accumulative, which may not be captured by the short follow up within current system. Based on clinical experience, many believe cardiovascular risk in the patients taking ADT is likely underappreciated, and underestimated.

AA and ENZA obviously will play an increasingly important role in management of mCRPC, which take androgen deprivation to a new level. In addition to routine sequential use, there is an enthusiasm in combination of these agents to achieve more efficacious inhibition of the androgen signaling axis [37,38]. The efficacy of this combination over ENZA alone is being tested in the ALLIANCE phase 3 A031201 trial (ClinicalTrials.gov identifier NCT01949337). Limited data are available on the long term side effects associated with metabolic disturbances from novel endocrine agents, although the sequelae of castration are well described and could be worsened by longer sequential and combined use of additional endocrine treatments. The case reported here could serve as a cautionary note: physicians treating mCRPC should be mindful of side effects as increasing numbers of patients are started on the new generation of androgen signaling axis targeting agents, especially those with established cardiovascular disease and specific high-risk subgroups of patients. The side effects from sequential use of these novel agents such as cardiovascular morbidity should be carefully monitored and properly treated. Routine LVEF monitoring should be mandatory in clinical trials of any new therapeutics considered to carry risk for cardiac toxicity based on mechanism of action, or when a previous cardiac toxicity signal has been present.

Clinicians should not necessarily withhold ADT from men who might benefit from it in terms of cancer-specific survival, even in patients with a history of cardiac comorbidity after careful consideration of the risks and benefits. These patients with underlying cardiac disease should receive secondary preventive measures, including lipid-lowering, antihypertensive, glucose lowering, and antiplatelet therapy as appropriate.

**Conclusion**

AA and ENZA have been increasingly used in management of mCRPC, which take androgen deprivation to a new level. Patients who receive these agents should be carefully monitored for evidence of cardiac toxicity. Clinicians have to balance the potential therapeutic benefits of androgen deprivation against the long-term side effects. Better selection of patients, screening, monitoring, and modifying cardiovascular risk factors, may mitigate some of the adverse effects of long term ADT. Future trials of novel forms of endocrine therapy, as well as trials utilizing combination of these agents should prospectively assess cardiac function and stratify patients according to their comorbidities and individual’s cardiovascular risk.

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