Case report

doi:10.5633/amm.2025.0315

Enzalutamide induced heart failure with reduced ejection fraction

Mirjana Todorović Mitić[1], Marija Todorović Marković[2], Ana Cvetanović[1,3], Milan Čevrljaković[1], Ljubomir Dinić[4,5]

[1]University Clinical Center Niš, Department for Oncology, Niš, Serbia

[2]Copenhagen University Hospital Rigshospitalet (A Highly Specialized Hospital in Denmark), Department for Cardiology, Copenhagen, Denmark

[3]University of Niš, Faculty of Medicine, Depratment for oncology, Niš, Serbia

[4]University of Niš, Faculty of Medicine, Department Surgery and Anesthesiology and reanimatology, Niš, Serbia

[5]University Clinical Center Niš, Department for Urology, Niš, Serbia

Contact: Mirjana Todorović Mitić

2a Zorana Radosavljevića Čupe str., 18000 Niš, Serbia

E-mail: mirjanatdrvc@gmail.com

Prostate cancer is the second most common malignancy in men and the second leading cause of cancer death. Patients unfit for surgery, with locally advanced or metastatic disease, require androgen-deprivation therapy.

In the past decade, Enzalutamide and Abirateron were established in prostate cancer treatment. Their safety profile and clinical evidence showed a significant possibility of cardiovascular complications. Heart failure is more common in patients treated with Abirateron. We report a case of a patient with heart failure induced by Enzalutamide. By reviewing the literature, we have found only two cases of Enzalutmaide induced heart failure.

Further research on the influence of novel anti-androgen therapy on the cardiovascular system, personalized evaluation of the cardiovascular system, and risk stratification for potential cardiovascular adverse events before initiating therapy, are needed.

Keywords: enzalutamide, heart failure, prostate cancer

Prikaz bolesnika

doi:10.5633/amm.2025.0315

Srčana insfucijencija sa redukovanom ejekcionom frakcijom uzrokovana enzalutamidom

Mirjana Todorović Mitić[1], Marija Todorović Marković[2], Ana Cvetanović[1,3], Milan Čevrljaković[1], Ljubomir Dinić[4,5]

[1]Univerzitetski klinički centar Niš, Klinika za onkologiju, Niš, Srbija

[2]Univerzitetska bolnica "Rigshospitalet" (Visokospecijalizovana bolnica u Danskoj), Kilinika za kardiologiju, Kopenhagen, Danska

[3]Univerzitet u Nišu, Medicinski fakultet, Katedra za onkologiju, Niš, Srbija

[4]Univerziteta u Nišu, Medicinski fakultet, Katedra za hirurgiju i anesteziologiju sa reanimatologijom, Niš, Srbija

[5]Univerzitetski klinički centar Niš, Klinika za urologiju, Niš, Srbija

Kontakt: Mirjana Todorović Mitić

Zorana Radosavljevića Čupe 2a, 18000 Niš, Srbija

E-mail: mirjanatdrvc@gmail.com

Karcinom prostate je drugo najčešće maligno oboljenje muškaraca i drugi vodeći uzrok smrti od malignih bolesti. Lečenje inoperabilnih pacijenata, pacijenata sa lokalno-uznapredovalom ili metastatskom bolešću zahteva primenu androgen-deprivacione terapije.

U protekloj deceniji u terapiju karcinoma prostate uvedeni su lekovi Enzalutamid i Abirateron. Bezbedonosni profil ovih lekova i podaci iz kliničke prakse ukazuju na značajan uticaj ovih lekova na pojavu kardiovaskularnih komplikacija. Srčana insuficijencija je češći neželjeni efekat Abiraterona. U ovom radu prikazujemo slučaj pacijenta kod koga je srčana insuficijencija uzrokovana Enzalutamidom. Pregledom literature pronašli smo dva slučaja srčane insfucijencije uzrokovane Enzalutamidom u svetu.

Neophodna su dalja istraživanja o uticaju nove anti-androgene terapije na kardiovaskularni sistem, personalizovani pristup proceni funkcije karidovaskularnog sistema i stratifikacije rizika za potencijalne kardiovaskularne neželjene efekte, pre započinjanja terapije.

Ključne reči: enzalutamid, srčana insufucijencija, karcinom prostate

Introduction

Prostate cancer has one of the highest incidences among malignant diseases and it has been estimated that more than 11% of males worldwide will have prostate cancer diagnosed during their lifetime. It is also responsible for nearly 50% of cancer deaths(1,2). It is estimated that 288,300 men will be diagnosed with prostate cancer and 34,700 men will die of the disease by the end of 2025 in the United States of America. With approximately 2300 to 2400 newly diagnosed cases annually, prostate cancer is the second most common malignancy (after lung cancer) and the third leading cause of cancer death (after lung and colorectal cancer) in Serbia (3). Although prostate cancer is highly prevalent, the 5-year relative survival rate for men with localized or locally advanced disease is outstanding, nearing 100%, and yet men with metastatic disease have a 5-year survival rate of only about 30% (4). The risk of developing prostate cancer increases with age and the median age at diagnosis is 67 years (2).

The etiology and pathogenesis remain unclear but are believed to be multifactorial and include: aging, ethnicity, hormonal, and genetic factors. Androgens are crucial in the development, maintenance, and progression of prostate cancer. In 80-90% of cases, increased androgen activity is present in the early stage of the disease. The incorporation of androgen deprivation therapies into the treatment strategy for prostate cancer has provided numerous benefits, including enhanced survival for patients with clinically localized or locally advanced disease and improved symptom management for those with advanced stages of the condition (2). First line androgen deprivation therapy (ADT) mechanism of action is blocking testosterone production by inhibition of the hypothalamic-pituitary-gonadal axis. There are different forms of ADT, and the most frequently used ones are gonadotropic releasing hormone (GnRH) agonists and antagonists. Most metastatic prostate cancer patients, treated with first-line ADT, eventually develop castration resistance, as quickly as 7 months after therapy initiation. In that manner, metastatic or non-metastatic hormone-sensitive prostate cancer (HSPC) is becoming castration (hormone) resistant prostate cancer (CRPC) which is associated with a lower survival rate and quality of life deterioration (6). In the past decade, novel hormonal therapy has been introduced as the primary treatment of advanced prostate cancer to overcome castration resistance. Abirateron acetate, enzalutamide, apalutamide and darolutamide are the key novel hormonal therapies that inhibit androgen receptor (AR) function by blocking its dimerization, nuclear translocation, and binding AR-dimers to AR and have been shown to improve overall survival when added to first-line ADT (7).

Cardiac adverse drug reactions and mortality incidence are higher in patients treated with GnRH analogs, especially in individuals with pre-existing cardiac conditions. Incorporating novel agents like enzalutamide and abiraterone into the treatment regimen further elevates cardiovascular risk (8). abiraterone and enzalutamide have been associated with a higher risk of hypertension, with abiraterone also linked to an increased incidence of heart failure (9). Prescribing information for abiraterone cites risks of cardiac arrhythmias, chest discomfort, and heart failure, while enzalutamide cites only cardiac ischemia risk (10,11).

Enzalutamide acts as a direct androgen receptor antagonist with greater affinity than first-generation antagonists. It also inhibits its nuclear translocation, thereby blocking the transcription of oncogenic genes essential for cancer growth and survival (12). It has been shown that adding enzalutamide to ADT increases overall survival and quality of life in patients who progressed during ADT (13). The efficacy of enzalutamide has also been investigated in patients with non-metastatic CRPC (defined as prostate-specific antigen (PSA) doubling time ≤10 months during ADT) (14).

There is an urgent need for further research on the pharmacovigilance of novel hormonal therapy in prostate cancer patients due to the high mortality rate caused by cardiovascular disease, rather than malignancy itself. A recent study done in 2021 showed a higher incidence of cardiac events in patients treated with abiraterone in contrast to the patients treated with enzalutamide and concluded that enzalutamide has a much better safety profile than abiraterone, especially in patients with cardiac comorbidities (15).

By reviewing the literature, we have found only two case reports of enzalutamide induced non-ischemic cardiomyopathy (8).

Case report

We present a case of a 75-year-old Caucasian man who was diagnosed with non-metastatic prostate cancer in 2010. He was experiencing dysuria for a couple of months before he scheduled an appointment with a urology specialist. The level of serum PSA was determined and it was increased with the absolute

value of 6.9 ng/ml. The urologist decided to perform a radical prostatectomy, as a primary diagnostic and treatment procedure, and it took place in December 2010. The pathology report indeed confirmed high-grade adenocarcinoma of the prostate gland, Gleason score 6, grade group 2, pT3N0 with positive limfo-vascular invasion, impaired capsule, and infiltration of adipose tissue as well as seminal vesicles. Due to tumor size and impaired capsule with infiltration of surrounding tissue, the tumor board decided to conduct postoperative radiation therapy. After completion of the treatment, in May 2011, with a total of 45 Gy of radiation dose, the patient started with a watchful waiting regimen. In May 2019, at his regular 6-month follow-up, an increased PSA of 12.76ng/ml was noted. Radiological findings, including thoracic, abdomen, and pelvic CT scans and bone scintigraphy were negative for loco-regional and distant metastases. He started with androgen deprivation therapy (LHRH agonist) and his PSA level decreased. Nevertheless, in March 2024, the PSA level started to rise again, with an absolute value of 44.29ng/ml. Imaging studies showed enlarged retroperitoneal lymph nodes (up to 32mm in diameter) and bone metastases. Since he had a medical history of well-controlled hypertension and atrial fibrillation and had undergone an operation for an aneurysm of the abdominal aorta back in 1997, we performed echocardiography before making a therapy decision. Initial findings were within normal, with an ejection fraction of 61% so we have decided to initiate enzalutamide along with LHRH agonist treatment. The patient started with enzalutamide therapy in July 2024.

In August 2024, 40 days after the initiation of enzalutamide, he was presented to the emergency room with acute onset shortness of breath, pain in the middle of the chest, peripheral edema, and fatigue. An echocardiogram demonstrated new cardiomyopathy with a reduced left ventricular (LV) ejection fraction of 26% and diffuse hypokinesis. Coronary angiography showed no significant arteriosclerosis. Enzalutamide was discontinued since it was the only preceding event before the onset of heart failure. He started guided heart failure therapy with beta-blocker (bisoprolol), angiotensin-converting enzyme inhibitor (ramipril), mineralocorticoid receptor antagonist (spironolactone), and sodium-glucose transport protein inhibitor (dapagliflozin). A control echocardiogram after one month showed improvement in left ventricular systolic function with an ejection fraction of 36%. Four months after enzalutamide discontinuation, the ejection fraction was 39%. He was still feeling fatigue, but less intense compared to the onset of the symptoms. The tumor board decided to continue LHRH agonist as

monotherapy since the patient is not symptomatic from his metastatic cancer and due to possible cardiotoxicity of other hormonal and chemotherapy agents.

Discussion

In the majority of cancer patients, death is caused by other reasons than malignancy itself. Around 45% of prostate cancer patients will die due to complications of anticancer therapy (16). In recent decades, prostate cancer treatment has advanced significantly, with the approval of numerous new therapies, including hormonal treatments (17). Resistance to androgen deprivation therapy (ADT) prompted the development of novel androgen receptor (AR) blockers, such as enzalutamide, apalutamide, and darolutamide, which have proven effective in the CRPC setting. These agents primarily work by inhibiting the interaction between androgens and AR, preventing AR nuclear translocation, or blocking AR-dependent gene transcription. These mechanisms ultimately reduce prostate cancer cell proliferation and tumor size but increase the possibility of the development of serious cardiovascular complications (18). Increased cardiovascular risk is reported in prostate cancer patients treated with ADT, abiraterone or enzalutamide. Hypermineralocorticism can be induced by abiraterone which further leads to hypokalaemia, hypertension, and edema. As a result of that, heart failure and atrial tachyarrhythmia may occur in patients treated with abiraterone (9).

Enzalutamide, an androgen receptor inhibitor, exhibits a higher binding affinity to androgen receptors compared to older inhibitors like bicalutamide. This characteristic is linked to improved clinical outcomes in patients with non-metastatic or metastatic castration-resistant prostate cancer (CRPC) compared to bicalutamide (19). Pathophysiology of QT prolongation, the most common cardiac adverse event of enzalutamide, is delayed rectifier potassium and sodium current, longer action potential duration, and appearance of afterdepolarizations (20). In a recent meta-analysis of prospective studies, enzalutamide was found to have a much better cardiac safety profile compared to abiraterone (21). A recent study done in 2021 showed a higher incidence of cardiac events in patients treated with abiraterone in contrast to the patients treated with enzalutamide and concluded that enzalutamide has a much better safety profile than abiraterone, especially in patients with cardiac comorbidities (15). Nevertheless, our patient did have cardiac adverse events due to enzalutamide therapy. By reviewing the literature, we have

found only two previously reported cases of enzalutamide induced heart failure with reduced ejection fraction.

A meta-analysis from 2018, which included 8660 patients with metastatic prostate cancer treated with enzalutamide found an increased incidence of hypertension among those patients (22). Another study by Shrestha B confirmed that the most common cardiovascular complication in patients treated with enzalutamide was hypertension (10.6%), followed by ischemic heart disease (1.88%) and atrial fibrillation (0.39%) (23).

Given the relatively high prevalence of cardiovascular complications associated with prostate cancer treatment, every patient must undergo a thorough clinical evaluation before initiating any anticancer therapy, including novel hormonal treatments. Treatment decisions should consider the patient's age, type of therapy, current and prior cardiovascular status, existing comorbidities, and concurrent medications. Regular cardio-oncology assessments are highly recommended, and existing cardiovascular conditions should be effectively managed and treated. Before starting therapy, patients should be screened for hypertension, dyslipidemia, and prediabetes/diabetes. Baseline electrocardiography and transthoracic echocardiography should be performed, with follow-up evaluations conducted before each new treatment phase. In the event of cardiovascular complications, management decisions should take into account the cancer prognosis (e.g., early-stage vs. metastatic disease), life expectancy, and the patient's preferences (24).

Conclusion

Prostate cancer has a very high prevalence among elder men, and it could potentially be even higher due to the increasing elderly population worldwide. Anti-androgen therapy remains the standard of care in the majority of PC patients. In the past decade, several new hormonal agents were introduced in the treatment of prostate cancer. Although very efficient, new hormonal therapy is associated with an increased risk of many complications, of which cardiovascular is the most severe. One of the proposed mechanisms of onset of hypertension, HF, ischemic heart disease, rhythm disturbances, and venous

thromboembolic disease, is exacerbation of the imbalance of the cardiovascular system due to hormonal and metabolic changes. Hereby we report a case of likely rare cardiovascular toxicity due to enzalutamide therapy, which typically has a safer cardiovascular profile among novel AR blockers. Literature review shows that abiraterone has more cardiovascular side effects than enzalutamide which more commonly causes hypertension. Further research on the safety profile of novel anti-androgen therapy as well as their impact on the cardiovascular system is needed and should encourage the development of comprehensive cardio-oncology programs. Our findings underline the importance of baseline screening and personalized evaluation of the cardiovascular system, risk stratification for possible cardiac adverse events fundamental analysis of potential risk or benefit, before therapy initiation.

REFERENCES:

1. Connolly RM, Carducci MA, Antonarakis ES. Use of androgen deprivation therapy in prostate cancer: indications and prevalence. Asian J Androl. 2012 Mar;14(2):177-86.
2. Crawford, E.D., Heidenreich, A., Lawrentschuk, N. et al. Androgen-targeted therapy in men with prostate cancer: evolving practice and future considerations. Prostate Cancer Prostatic Dis 22, 24–38 (2019)
3. Institute of public health of Serbia „Dr Milan Jovanović Batut": Maligni tumori u Republici Srbiji 2022.pdf. Available online. Last accessed February, 2025.
4. National Cancer Institute: SEER Stat Fact Sheets: Prostate. Bethesda, Md: National Cancer Institute. Available online. Last accessed February, 2025.
5. Mohler J.L., Antonarakis E.S. NCCN guidelines updates: management of prostate cancer. J Natl Compr Canc Netw. 2019;17(5.5):583–586
6. Fizazi K., Tran N., Fein L. Abiraterone acetate plus prednisone in patients with newly diagnosed high-risk metastatic castration-sensitive prostate cancer (LATITUDE): final overall survival analysis of a randomised, double-blind, phase 3 trial. Lancet Oncol. 2019;20(5):686–700
7. de Bono J.S., Logothetis C.J., Molina A. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med. 2011;364(21):1995–2005Bretagne M., Lebrun-Vignes B., Pariente A.
8. Kumar, A., Reddy, A. & Sekar, A. Enzalutamide induced non-ischemic cardiomyopathy. A case report and review of literature on anti-androgen therapy-related cardiovascular events. Cardio-Oncology 9, 9 (2023)
9. Bretagne M, Lebrun-Vignes B, Pariente A, Shaffer CM, Malouf GG, Dureau P, Potey C, Funck-Brentano C, Roden DM, Moslehi JJ, Salem JE. Heart failure and atrial tachyarrhythmia on abiraterone: A pharmacovigilance study. Arch Cardiovasc Dis. 2020 Jan;113(1):9-21
10. Janssen. ZYTIGA (abiraterone acetate): highlights of prescribing information https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210308s000lbl.pdf: Food and Drug Administration; 2018.

11. Pfizer. XTANDI (enzalutamide): highlights of prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/203415lbl.pdf : Food and Drug Administration; 2019

12. Culig Z. Molecular mechanisms of enzalutamide resistance in prostate cancer. Curr Mol Biol Rep. 2017;3(4):230–235

13. Hussain M, Fizazi K, Saad F, et al.: Enzalutamide in Men with Nonmetastatic, Castration-Resistant Prostate Cancer. N Engl J Med 378 (26): 2465-2474, 2018

14. Loriot Y, Miller K, Sternberg CN, et al.: Effect of enzalutamide on health-related quality of life, pain, and skeletal-related events in asymptomatic and minimally symptomatic, chemotherapy-naive patients with metastatic castration-resistant prostate cancer (PREVAIL): results from a randomised, phase 3 trial. Lancet Oncol 16 (5): 509-21, 2015

15. Cone EB, Reese S, Marchese M, Nabi J, McKay RR, Kilbridge KL, Trinh QD. Cardiovascular toxicities associated with abiraterone compared to enzalutamide-A pharmacovigilance study. EClinicalMedicine. 2021 May 6

16. Beyer D. C., McKeough T., Thomas T. (2005). Impact of short course hormonal therapy on overall and cancer specific survival after permanent prostate brachytherapy. Int. J. Radiat. Oncol. Biol. Phys. 61, 1299–1305.

17. Wilk M, Waśko-Grabowska A, Szmit S. Cardiovascular Complications of Prostate Cancer Treatment. Front Pharmacol. 2020 Dec 22;11:555475

18. Rice M. A., Malhotra S. V., Stoyanova T. (2019). Second-generation antiandrogens: from discovery to standard of care in castration resistant prostate cancer. Front. Oncol. 9, 801

19. Penson DF, Armstrong AJ, Concepcion R, Agarwal N, et al. Enzalutamide versus bicalutamide in castration-resistant prostate cancer: the STRIVE Trial. J Clin Oncol. 2016;34(18):2098–106.

20. Saigal CS, Gore JL, Krupski TL, Hanley J, et al. Androgen deprivation therapy increases cardiovascular morbidity in men with prostate cancer. Cancer. 2007;110:1493–500

21. Salem J.-E., Yang T., Moslehi J. J., Waintraub X., Gandjbakhch E., Bachelot A., et al. (2019). Androgenic effects on ventricular repolarization: a translational study from the international pharmacovigilance database to iPSC-cardiomyocytes. Circulation 140, 1070–1080

22. Lacovelli R, Ciccarese C, Bria E, Romano M, et al. The cardiovascular toxicity of Abiraterone and Enzalutamide in prostate cancer. Clin Genitourin Cancer. 2018;16(3):e645–53.

23. Shrestha B, Gouli S, Shrestha A. Abstract 16180: Cardiovascular adverse events associated with androgen receptor-targeted therapy used in the treatment of prostate cancer.

24. Curigliano G., Lenihan D., Fradley M., Ganatra S., Barac A., Blaes A., et al. (2020). Management of cardiac disease in cancer patients throughout oncological treatment: ESMO consensus recommendations. Ann. Oncol. 31, 171–190.