Case Reports in Oncology

Case Rep Oncol 2024;17:537–542
DOI: 10.1159/000538124
Received: December 21, 2023
Accepted: February 17, 2024
Published online: April 4, 2024

Case Report

Long-Term Efficacy and Safety of Enzalutamide Monotherapy in Elderly Patients with Metastatic Castration-Resistant Prostate Cancer: A Case Report

Tomas Pokrivcak[a, b] Jiri Navratil[a, b] Alexandr Poprach[a, b] Michal Stanik[a, b] Igor Kiss[a, b]

[a]Masaryk Memorial Cancer Institute, Brno, Czech Republic; [b]Faculty of Medicine, Masaryk University, Brno, Czech Republic

Keywords
Enzalutamide · Metastatic castration-resistant prostate cancer · Aged 75 and over · Comorbidity

Abstract
Introduction: Prostate cancer is one of the most common cancers in men. Despite the sharp rise in incidence, mortality is decreasing. ARTA preparations are preferred options for asymptomatic or mildly symptomatic patients with mCRPC. The use of enzalutamide in elderly patients with mCRPC is risky and depends on a number of factors. An increased risk of falls and fractures has been shown. ***Case Presentation:*** We present a case report of an elderly patient with mCRPC treated with enzalutamide with very good long-term tolerance and efficacy. ***Conclusion:*** Despite the older age, no reduction of therapy was necessary in the patient due to good tolerance. Administration of enzalutamide in full doses resulted in a very good effect of therapy.

Correspondence to:
Tomas Pokrivcak, tomas.pokrivcak@mou.cz

Case Rep Oncol 2024;17:537–542
DOI: 10.1159/000538124

Introduction

Enzalutamide is an oral nonsteroidal antiandrogen belonging to the androgen receptor axis target agent (ARTA) group of drugs. The mechanism of action is based on direct blocking of androgen binding to the androgen receptor (AR), inhibition of translocation of the AR complex to the nucleus, and inhibition of androgen-stimulated gene expression [1]. The efficacy of enzalutamide in metastatic castration-resistant prostate cancer (mCRPC) has been confirmed in a number of studies. In the AFFIRM trial, a significant prolongation of overall survival (OS) was demonstrated in patients with mCRPC after chemotherapy [2]. In the PREVAIL study, enzalutamide significantly improved progression-free survival (PFS) and OS among men with chemotherapy-naive mCRPC [3]. The efficacy of enzalutamide in mCRPC was also demonstrated in the TERRAIN study, where PFS was prolonged compared to active treatment bicalutamide [4]. Among adverse effects, studies of enzalutamide have described an increased incidence of fatigue, hypertension, falls, and fractures [5]. In elderly patients in poorer condition, this toxicity may be limiting. The aim of our communication is to share our experience with long-term use and toxicity of enzalutamide in an elderly patient. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000538124).

Case Presentation

A 70-year-old patient presented in December 2007 for a positive prostate biopsy. Due to the finding of prostate adenocarcinoma with GS 2 + 3 in sextant biopsy and PSA 5 ng/mL, the initial finding was concluded as low-risk prostate cancer. Variants of the next procedure were discussed with the patient – radical prostatectomy, radiotherapy with curative intent, and active surveillance. From the options offered, the patient chose radical prostatectomy, which was performed laparoscopically in January 2008. Subsequently, the patient was followed up. Over a period of 6 months, PSA levels gradually progressed from 0.08 to 0.22 ng/mL. With regard to the findings, postoperative radiotherapy to the pelvis and prostate bed was indicated. A total dose of 60.0 Gy was applied until November 2008. Grade 2 proctitis and grade 1 cystitis developed as adverse events. After the end of radiotherapy, the PSA level dropped to 0.02 ng/mL. Subsequently, the patient was followed up by the urologist. Due to PSA progression to 0.24 ng/mL in August 2012, luteinizing hormone-releasing hormone (LHRH) agonist therapy was started. Administration of LHRH was started in August 2012. Despite continuous LHRH administration and castrating testosterone levels, biochemical progression occurred in May 2017 – three subsequent PSA rises were present at least 1 week apart, while the final PSA level was above >2 ng/mL. The follow-up examination included choline PET/CT with findings of local recurrence at the site of prostatectomy and lymphadenopathy in the pelvis and left groin. The finding was concluded as mCRPC. With respect to asymptomatic findings and good condition of the patient with ECOG 1 performance status, treatment with enzalutamide was started. Already after 3 months of treatment with enzalutamide at the standard dosage of 160 mg/day, a significant decrease in PSA from 2.23 to 0.079 ng/mL was observed. The control choline PET/CT showed regression of pathological accumulation at the post-prostatectomy site and reduction of pathological nodules in the small pelvis and left groin. Due to the effect of therapy and good tolerance, the established treatment with enzalutamide was continued. PSA levels continued to decline to 0.008 ng/mL in December 2018. According to control choline PET/CT, a complete response was confirmed. Despite the patient's advanced age, enzalutamide therapy was without adverse effects. With the help of a

general practitioner, we regularly monitored risk factors for coronary heart disease and bone metabolism. Other control PSA levels showed a stationary level below 0.008 ng/mL, the last value in June 2023. Duration of complete response also repeatedly confirmed on follow-up choline PET/CT scans, the last one in November 2022. Therefore, enzalutamide therapy was continued until the present time.

Discussion

Prostate cancer is one of the most common cancers in men. About 1 man in 8 will be diagnosed with prostate cancer during his lifetime. The increase in incidence is related to the incidental detection of cancer during transurethral resections indicated for prostatic hypertrophy and biopsies performed in asymptomatic patients with PSA elevation. Despite the sharp rise in incidence, mortality is decreased [6]. One of the main factors behind this trend is the improvement in the treatment of prostate cancer in advanced stages. Treatment of mCRPC depends on the manifestations of the disease and the patient's condition. In the case of a symptomatic patient with mCRPC, docetaxel is the preferred chemotherapy. ARTA preparations (enzalutamide, abiraterone) are preferred options for asymptomatic or mildly symptomatic patients with mCRPC. In both cases, continuation of androgen deprivation therapy is necessary – LHRH agonists/antagonists or orchiectomy. In the case of dissemination to the bones, prevention of bone events by application of bone-modifying agents (BMAs) is also advisable. Enzalutamide was introduced into practice in 2012 following its Food and Drug Administration (FDA) approval. The recommended dose is 160 mg (4 capsules of 40 mg) in one daily dose. Dose reduction is recommended only if grade 3 or higher toxicity occurs. No dose adjustment is necessary for patients with mild to moderate renal or hepatic impairment. The efficacy of enzalutamide in mCRPC has been confirmed in a number of studies – AFFIRM, PREVAIL, TERRAIN [2–4]. A direct comparison of the efficacy of ARTA agents – enzalutamide versus abiraterone acetate in a prospective study has not yet been performed. In a retrospective analysis, Tagawa et al. [7] compared the efficacy of enzalutamide and abiraterone in mCRPC in 3,174 patients from the Veterans Health Administration (VHA) database. Enzalutamide reduced the risk of death by 16% compared to abiraterone (95% CI: 0.76–0.94, p = 0.0012). The OS was also prolonged by 3.2 months (29.0 for enzalutamide vs. 25.9 for abiraterone). Similar results were presented by Scailteux et al. [8] in her analysis in the *American Journal of Epidemiology*. Retrospectively, they compared the overall survival of 10,308 patients with mCRPC on first-line palliative therapy for mCRPC. Enzalutamide reduced the risk of death compared to abiraterone by 10% (95% CI: 0.85–0.96) and prolonged median OS by 2.5 months (34.2 months vs. 31.7 months). The profile of adverse events leading to the need for hospitalization for abiraterone and enzalutamide was also analyzed in this group of patients. Among 11,534 patients, a higher incidence of renal insufficiency (IRR 1.42, 95% CI: 1.01–2.00), hepatopathy (IRR 3.06, 95% CI: 2.66–3.53), and atrial fibrillation (IRR 1.12, 95% CI: 1.05–1.19) was observed with abiraterone. In contrast, a number of meta-analyses have described a higher incidence of hypertension with enzalutamide compared with abiraterone [5, 9]. In a retrospective analysis, Schultz et al. [10] analyzed the relationship between cumulative exposure to corticosteroids and the risk of developing adverse events in 9,425 chemonaive patients with mCRPC. Patients receiving corticosteroids were at higher risk of developing adverse effects and had a faster onset compared to those not receiving corticosteroids. The amount of risk was significantly associated with the amount of corticosteroid dose. In high corticosteroid cohort, patients received a cumulative corticosteroid dose of >2.0 mg, corresponding to >5.6 mg per day for 360 days. In medium corticosteroid cohort, patients received a cumulative corticosteroid dose of

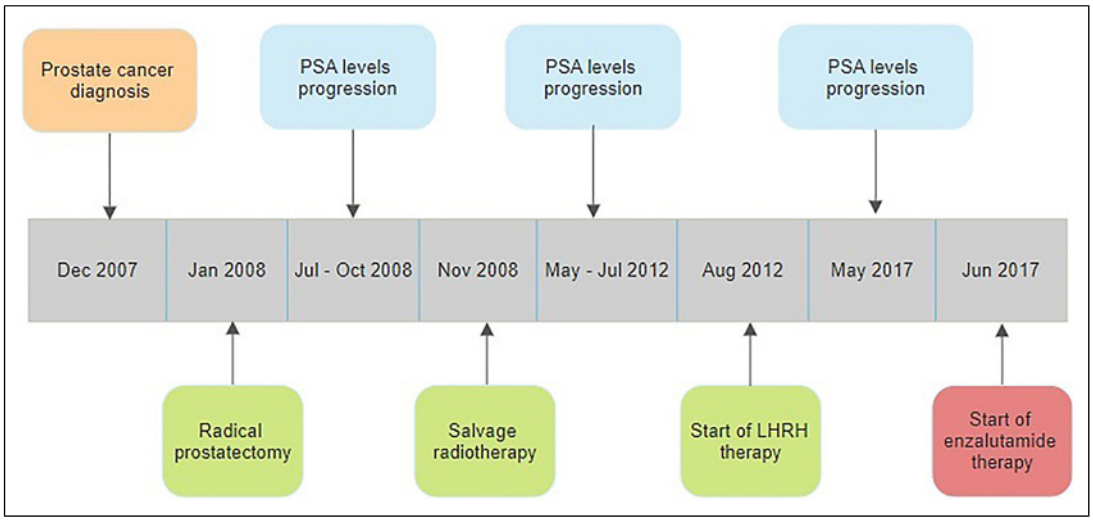

Fig. 1. Adapted and modified from Schultz et al. [10].

0.5–2.0 gm, corresponding to 1.4–5.6 mg per day for 360 days, and in low corticosteroid cohort, patients received a cumulative corticosteroid dose of <0.5 gm, corresponding to <1.4 mg per day for 360 days. Already low cumulative exposure to corticosteroids was associated with an increased risk of developing serious adverse events such as fractures, infections, or acute cardiovascular events. Corticosteroid doses were standardized to prednisone-equivalent doses (see Figure 1). Long-term treatment with androgen deprivation therapy leads to loss of bone density and the risk of developing osteoporosis with a high risk of fracture, especially in elderly patients. This risk obviously increases with use of corticosteroid and increases with the duration of treatment. Prevention of skeletal-related events (SREs) is a very important part of comprehensive oncological care. BMA, like the bisphosphonate zoledronic acid and the RANKL inhibitor denosumab, decrease SRE. SRE mean pathologic fracture, spinal cord compression, palliative radiation therapy of bone, and hypercalcemia. SRE is correlated to a decreased quality of life, increased pain, and shortened survival in PCa patients. We have strong recommendation to use these drugs in patients with mCRPC with bone metastasis to decrease the risk of SRE [11]. Different situation is in patients without bone metastasis, when we regularly do not use BMA. Especially for these patients, the prevention of osteoporosis is very important. Calcium supplementation in combination with vitamin D is necessary. In this meaning, enzalutamide has an advantage to using without prednisone. In an attempt to reduce toxicity, Vinh-Hung et al. [12] compared the administration of reduced and full-dose enzalutamide in patients over 75 years of age. They analyzed a total of 59 patients, of which 16 patients took a reduced dose of enzalutamide 80 mg/day compared to 43 patients with a standard dose of 160 mg/day. Patients in the enzalutamide-reduced group were significantly older with a median age of 84.6 (74.9–93.8) years. The median PSA in these patients at the start of enzalutamide therapy was 59.2 (11.0–1,058.3) µg/L. Bone-only metastases were present in 11 patients, dissemination to lymph nodes was demonstrated in 2 patients, and combined bone and lymph node involvement was observed in 3 patients. Median PFS was 11.2 months versus 11.9 months for patients receiving the standard dose ($p = 0.612$). A reduced dose of enzalutamide in patients over 75 years of age has shown efficacy comparable to the standard dose. In 20% of men, prostate cancer is diagnosed after the age of 75 [13]. Elderly patients and those with multiple comorbidities are not proportionally included in large randomized trials [14]. Because older patients tend to have more medical comorbidities and less physical functional reserve, they may benefit from

Case Rep Oncol 2024;17:537–542
DOI: 10.1159/000538124

tailored approaches to treatment [15]. Currently, clinical trials in prostate cancer are more focusing on several key antigens for antibody-drug conjugate therapy, especially STEAP1, TROP2, PSMA, CD46, and B7-H3. These targets are chosen due to their overexpression in prostate cancer cells compared to normal cells. Despite existing limitations, antibody-drug conjugate represents a promising and valid approach for prostate cancer treatment [16]. Treatment targeting on PSMA, especially conjugates with lutetium, has been used in clinical practice yet and changing the treatment guidelines. The preliminary results of the another ADC are encouraging, but further studies are needed to fully establish the efficacy and safety of ADC in the treatment of prostate cancer. Moreover, very interesting research is on the microbiota and his role in cancer's hallmarks through various mechanisms. However, there is still limited specific information about the role of the gastrointestinal and genitourinary microbiome in prostate cancer, particularly regarding its medical treatment and pathogenesis. The complexity of prostate cancer etiology, the potential influence of microbiota on cancer development and treatment, and the need for further research in this area [17]. But we have first clinical trials yet, which use live biotherapeutic product consisting mainly of a single strain bacteria to affect a gut microbiome. This study has shown potent anti-tumorigenic efficacy pre-clinically and reports signals of immune modulatory changes from flow cytometry analysis in treatment-naïve patients with confirmed cancer, including prostate cancer [18]. It is fascinating how microorganisms in the prostate cancer microenvironment may use complex mechanisms and networks to regulate the occurrence and development of prostate cancer [19].

Conclusion

Despite the older age, no reduction of therapy was necessary in the patient due to good tolerance. Administration of enzalutamide in full doses resulted in a very good effect of therapy.

Statement of Ethics

This retrospective review of patient data did not require ethical approval in accordance with local guidelines. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

This study was supported by MH CZ – DRO (MMCI, 00209805).

Author Contributions

T.P. and J.N. wrote the manuscript. A.P., M.S., and I.K. supervised the findings of this work. All authors discussed the results and contributed to the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

References

1 Tran C, Ouk S, Clegg NJ, Chen Y, Watson PA, Arora V, et al. Development of a second-generation antiandrogen for treatment of advanced prostate cancer. Science. 2009;324(5928):787–90. doi: 10.1126/science.1168175.
2 Scher HI, Fizazi K, Saad F, Taplin ME, Sternberg CN, Miller K, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med. 2012;367(13):1187–97. doi: 10.1056/NEJMoa1207506.
3 Beer TM, Armstrong AJ, Rathkopf DE, Loriot Y, Sternberg CN, Higano CS, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med. 2014;371(5):424–33. doi: 10.1056/NEJMoa1405095.
4 Shore ND, Chowdhury S, Villers A, Klotz L, Siemens DR, Phung D, et al. Efficacy and safety of enzalutamide versus bicalutamide for patients with metastatic prostate cancer (TERRAIN): a randomised, double-blind, phase 2 study. Lancet Oncol. 2016;17:153–63. doi: 10.1016/S1470-2045(15)00518-5.
5 Iacovelli R, Ciccarese C, Bria E, Romano M, Fantinel E, Bimbatti D, et al. The cardiovascular toxicity of abiraterone and enzalutamide in prostate cancer. Clin Genitourin Cancer. 2018;16(3):e645–53. doi: 10.1016/j.clgc.2017.12.007.
6 Taitt HE. Global trends and prostate cancer: a review of incidence, detection, and mortality as influenced by race, ethnicity, and geographic location. Am J Mens Health. 2018;12(6):1807–23. doi: 10.1177/1557988318798279.
7 Tagawa ST, Ramaswamy K, Huang A, Mardekian J, Schultz NM, Wang L, et al. Survival outcomes in patients with chemotherapy-naive metastatic castration-resistant prostate cancer treated with enzalutamide or abiraterone acetate. Prostate Cancer Prostatic Dis. 2021;24(4):1032–40. doi: 10.1038/s41391-021-00318-3.
8 Scailteux LM, Campillo-Gimenez B, Kerbrat S, Despas F, Mathieu R, Vincendeau S, et al. Overall survival among chemotherapy-naive patients with castration-resistant prostate cancer under abiraterone versus enzalutamide: a direct comparison based on a 2014–2018 French population study (the SPEAR cohort). Am J Epidemiol. 2021;190(3):413–22. doi: 10.1093/aje/kwaa190.
9 Lee HY, Chen HL, Teoh JYC, Chen TC, Hao SY, Tsai HY, et al. Abiraterone and enzalutamide had different adverse effects on the cardiovascular system: a systematic review with pairwise and network meta-analyses. Prostate Cancer Prostatic Dis. 2021;24(1):244–52. doi: 10.1038/s41391-020-00275-3.
10 Schultz NM, Penson DF, Wilson SD, Song Y, Yang H, Ramaswamy K, et al. Health care resource utilization and costs associated with corticosteroid use in patients with castration-resistant prostate cancer: an administrative Claims analysis. J Manag Care Spec Pharm. 2019;25(8):889–97. doi: 10.18553/jmcp.2019.19109.
11 Mollica V, Rizzo A, Rosellini M, Marchetti A, Ricci AD, Cimadamore A, et al. Bone targeting agents in patients with metastatic prostate cancer: state of the art. Cancers. 2021;13(3):546. doi: 10.3390/cancers13030546.
12 Vinh-Hung V, Natchagande G, Joachim C, Gorobets O, Drame M, Bougas S, et al. Low-dose enzalutamide in late-elderly patients (≥75 years old) presenting with metastatic castration-resistant prostate cancer. Clin Genitourin Cancer. 2020;18(6):e660–8. doi: 10.1016/j.clgc.2020.03.019.
13 Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. CA Cancer J Clin. 2022;72(1):7–33. doi: 10.3322/caac.21708.
14 Riaz IB, Islam M, Ikram W, Naqvi SAA, Maqsood H, Saleem Y, et al. Disparities in the inclusion of racial and ethnic minority groups and older adults in prostate cancer clinical trials: a meta-analysis. JAMA Oncol. 2023;9(2):180–7. doi: 10.1001/jamaoncol.2022.5511.
15 Sedrak MS, Gilmore NJ, Carroll JE, Muss HB, Cohen HJ, Dale W. Measuring biologic resilience in older cancer survivors. J Clin Oncol. 2021;39(19):2079–89. doi: 10.1200/JCO.21.00245.
16 Rosellini M, Santoni M, Mollica V, Rizzo A, Cimadamore A, Scarpelli M, et al. Treating prostate cancer by antibody-drug conjugates. Int J Mol Sci. 2021;22(4):1551. doi: 10.3390/ijms22041551.
17 Rizzo A, Santoni M, Mollica V, Fiorentino M, Brandi G, Massari F. Microbiota and prostate cancer. Semin Cancer Biol. 2022;86(Pt 3):1058–65. doi: 10.1016/j.semcancer.2021.09.007.
18 Lythgoe M, Dama P, Frampton AE, Pickford E, Tookman L, Cunnea P, et al. Immune modulation and the oral live biotherapeutic product, MRx0518, in treatment-naïve patients with cancer: updated safety data. J Clin Orthod. 2023;41(16_Suppl):3145. doi: 10.1200/jco.2023.41.16_suppl.3145.
19 Che B, Zhang W, Li W, Tang K, Yin J, Liu M, et al. Bacterial lipopolysaccharide-related genes are involved in the invasion and recurrence of prostate cancer and are related to immune escape based on bioinformatics analysis. Front Oncol. 2023;13:1141191. doi: 10.3389/fonc.2023.1141191.