Case Report

The Achievement of Long-Term CRPC Control in a Patient with Enzalutamide-Induced Nausea and Fatigue after Overcoming the Adverse Events with a Temporary Drug Holiday

Takashi Kawahara^a Yasuhide Miyoshi^a Masahiro Yao^b Hiroji Uemura^a

^aDepartments of Urology and Renal Transplantation, Yokohama City University Medical Center, Yokohama, Japan; ^bDepartment of Urology, Yokohama City University Graduate School of Medicine, Yokohama, Japan

Keywords

Enzalutamid · Xtandi · Drug holiday

Abstract

While the overall survival of patients with castration-resistant prostate cancer (CRPC) has been prolonged by enzalutamide, a considerable number of patients suffer from enzalutamide-induced nausea and fatigue. An 86-year-old male patient who started enzalutamide (160 mg) for CRPC treatment, experienced nausea and vomiting approximately 2 weeks after the start of treatment. Enzalutamide treatment was stopped for two weeks, then restarted enzalutamide at a half-dose (80 mg); the dose was then increased to 120 mg. He remained free from any adverse events and showed good CRPC control for 53 months. We herein report the case of a patient with enzalutamide-induced nausea and vomiting, whose symptoms were overcome and in whom long-term CRPC control was achieved following a temporary drug holiday.

© 2019 The Author(s)
Published by S. Karger AG, Basel

Introduction

Enzalutamide is widely used to treat all statuses of castration-resistant prostate cancer (CRPC) including non-metastatic, metastatic chemotherapy naïve, and post-chemotherapy CRPC (PROSPER, PREVAIL, AFFIRM) [1–3]. Although enzalutamide was shown to be effective in the treatment of CRPC, fatigue are reported as adverse events by 33–36% of enzalutamide-treated patients [2, 3]. In daily clinical practice, drug holidays, changing the timing of drug intake, and Chinese herbal medicine are used to treat fatigue, nausea, decreased appetite, dysgeusia, and other adverse effects induced by enzalutamide [4]. We herein report a case of enzalutamide-induced nausea and vomiting in which the patient's symptoms were overcome by a temporary drug holiday, allowing for the long-term control of CRPC.

Case Presentation

An 86-year old man was referred to our hospital due to an elevated serum PSA level (502 ng/mL). A prostate needle biopsy revealed a Gleason Score of 4 + 5 = 9 adenocarcinoma. Bone scintigraphy revealed bone metastasis, without lymph-node or organ metastasis. In April 2016, leuprolerin and bicalutamide were introduced. The patient's serum PSA level decreased to 0.38 ng/mL but gradually re-elevated, leading to the introduction of flutamide. Flutamide significantly reduced his serum PSA level, but was withdrawn due to severe fatigue. In February 2015, two weeks after the initiation of enzalutamide treatment, the patient experienced nausea and vomiting, and presented to our hospital as an emergency case.

After stopping enzalutamide for one week, the patient's nausea and fatigue subsided. Enzalutamide was restarted at a half-dose (80 mg), which was gradually increased to 120 mg without any adverse effects. We recommended increasing the dose to 160 mg; however, the patient indicated that he wished to continue treatment at a dose of 120 mg. At the time of writing, the patient's PSA level remains below 0.01 ng/mL without any adverse effects for 53 months (Fig. 1).

Discussion

Enzalutamide is widely used as a 2nd generation anti-androgen drug. Its effectiveness has been confirmed by the PROSPER, PREVAIL, and AFFIRM studies [1–3]. In these studies, vomiting (all grades) was reported in 1.7 and 6.9% in PREVAIL and AFFIRM study respectively. These adverse effects are usually low grade; however, their management is important due to their high incidence and the impact on the daily life of the patient during long-term treatment.

Basch et al. showed that the severity of most patients' symptoms was evaluated as lower by clinicians, underscoring the importance of patient-reported outcomes [5]. Especially in relation to appetite, the difference was higher than the other symptoms who received solid malignant diseases treatment. In the case of decreased appetite, most clinicians rated the severity lower than the patient. Thus clinician should care in mind about these symptoms which related to overall health status.

The management of enzalutamide-induced adverse events is especially important for patients who have obtained good CRPC control. The reported management strategies include a temporary drug holiday, the prescription of herbal medicine, and changing the timing of enzalutamide intake from morning to before sleep at night [4]. In our case, the patient's nausea

and vomiting were overcome with a temporary drug holiday and enzalutamide was restarted. The patient has not experienced any adverse events in the 4 years since enzalutamide was restarted.

In the present case, the enzalutamide-treated patient showed long-term CRPC control for 53 months after the drug holiday. The median overall survival time of CRPC patients with bone metastasis is reported to be 21.3 months [6]. On the other hand, most urologists experience cases in which long-term control of CRPC can be achieved with one medication added to androgen deprivation therapy. If a prescribed medicine shows good efficacy in the treatment of CRPC, then it is important to manage adverse events with the aim of continuing the medicine is important. In the present case, the patient initially showed enzalutamide-induced fatigue and nausea; however, these adverse events were overcome and the patient is currently free from adverse events at 53 months after restarting enzalutamide.

Availability of Data and Material

Due to ethical restrictions, the raw data underlying this paper are available upon request to the corresponding author.

Statement of Ethics

Written informed consent to participate and for publication was obtained from the patient for ethics approval. A copy of the written consent form is available for review from the Editor-in-Chief of this journal.

Disclosure Statement

The authors declare no conflicts of interest.

Funding Sources

None.

References

- 1 Hussain M, Fizazi K, Saad F, Rathenborg P, Shore N, Ferreira U, et al. Enzalutamide in Men with Nonmetastatic, Castration-Resistant Prostate Cancer. *N Engl J Med*. 2018 Jun;378(26):2465–74.
- 2 Scher HI, Fizazi K, Saad F, Taplin ME, Sternberg CN, Miller K, et al.; AFFIRM Investigators. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med*. 2012 Sep;367(13):1187–97.
- 3 Beer TM, Armstrong AJ, Rathkopf D, Loriot Y, Sternberg CN, Higano CS, et al. Enzalutamide in Men with Chemotherapy-naïve Metastatic Castration-resistant Prostate Cancer: Extended Analysis of the Phase 3 PREVAIL Study. *Eur Urol*. 2017 Feb;71(2):151–4.
- 4 Tomonori Minagawa TD, Toshiro Suzuki, Manabu Ueno, Takashi Nagai, Teruyuki Ogawa, Hideo Kiyokawa, Osamu Ishizuka. Effectiveness of Hochuekkito (Japanese herbal medicine) for general fatigue after introduction of enzalutamide in three cases of castration-resistant prostate cancer. *Jpn J Urol*. 2019;110:5.

- 5 Basch E. The missing voice of patients in drug-safety reporting. *N Engl J Med*. 2010 Mar;362(10):865–9.
- 6 Kawahara T, Ninomiya S, Miyoshi Y, Yao M, Uemura H. Changing the enzalutamide form from a capsule to a tablet improves the adherence of medicine intake: A case of a significant decrease in the prostate-specific antigen level and improvement in radiographic findings. *IJU Case Reports*. 2019;2(3):143–5.

Fig. 1. Clinical course.