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

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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.

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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, leuprorelin 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 Flutamide significantly reduced his serum PSA level, but was withdrawn due to severe fatigue.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, clinicians 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.

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**Fig. 1.** Clinical course.