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Case Report

Changing the Timing of Enzalutamide Intake from Morning to before Sleep at Night Overcame Enzalutamide-Induced Dysgeusia

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Keywords
Enzalutamide · Xtandi · Dysgeusia · Taste alternation · Timing of intake

Abstract
Dysgeusia is an adverse effect caused by enzalutamide said to affect 1–5% of patients. 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. Case 1: A 72-year-old man developed castration-resistant prostate cancer (CRPC) and was administered enzalutamide. After six weeks of enzalutamide installation, he showed taste alternation, and consequently his dysgeusia increased to grade 2; we therefore changed the medicine intake time from morning to night just before sleep without dose reduction. Four weeks after changing the timing, his dysgeusia had improved. Case 2: A 63-year-old man had developed bone metastatic CRPC, so the combination of Ra-223 and enzalutamide (160 mg/body) was introduced. His serum PSA level had gradually decreased, but dysgeusia appeared, so we changed the timing of enzalutamide intake from morning to night just before sleep without dose reduction. One month after changing the timing, his dysgeusia had improved. We herein report two cases of enzalutamide-induced dysgeusia successfully treated by changing the timing of drug intake from morning intake to just before sleep.

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Introduction

In cancer treatment, many drugs cause dysgeusia as a major adverse effect [1]. Dysgeusia not only necessitates a reduction or stopping cancer treatment but also reduces the nutritional status of cancer patients, harming their poor prognosis. Enzalutamide has been shown to imbue a favorable prognosis in multi-phase CRPC [2–4]. However, some adverse effects, including nausea, fatigue, and dysgeusia, have been reported, as with other CRPC treatment drugs. Efforts to manage the side effects induced by enzalutamide are therefore needed [4, 5]. Dysgeusia affects 1% to 5% of patients receiving enzalutamide.

We herein report two cases of enzalutamide-induced dysgeusia successfully treated by changing the timing of drug intake from the morning to just before sleep.

Case Presentation

Case 1

A 72-year-old man was referred to our hospital for his bilateral hydronephrosis. His serum PSA level was 178 ng/mL, and bone scintigraphy showed multiple bone metastases. A prostate needle biopsy revealed a Gleason Score of 4 + 4 = 8. NSE, LDH, and ALP levels were also elevated. In July 2018, combined androgen blockade including leuprorelin and bicalutamide was introduced. Despite some decrease in the PSA level, the PSA nadir was not very low and tended to elevate again, so docetaxel was introduced for six courses. Despite docetaxel treatment, however, the PSA and NSE levels were not markedly decreased, so enzalutamide was introduced. After six weeks of enzalutamide installation, the patient showed Common Terminology Criteria for Adverse Events (CTCAE) grade 1 dysgeusia, which later increased to grade 2, so we changed the medicine intake time from the morning to the night just before sleep without dose reduction. Four weeks after changing the timing, his dysgeusia had improved (Fig. 1).

Case 2

A 63-year-old man was referred to our hospital for a further examination of his elevated PSA level (919 ng/mL). A prostate needle biopsy revealed a Gleason Score of 5 + 5 = 9. Bone scintigraphy and computed tomography (CT) revealed multiple bone metastases and axillary lymph node metastasis. In November 2017, he started combined androgen blockade including leuproreline acetate and bicalutamide (80 mg/body). His serum PSA level had decreased to 1.16 in March 2018 but gradually increased afterward, so leuprprelin was changed to degarelix, and bicalutamide was stopped. Bone scintigraphy revealed residual bone metastatic lesions, so combination therapy with Ra-223 and enzalutamide (160 mg/body) was introduced. His serum PSA level gradually decreased, but CTCAE grade 2 dysgeusia developed in March 2019. We speculated that the dysgeusia had been induced by enzalutamide. Because his dysgeusia was persistent and enzalutamide showed efficacy in reducing his PSA level, the timing of enzalutamide intake was changed from the morning to the night just before sleep without dose reduction. One month after changing the timing, his dysgeusia had improved (Fig. 2).

Discussion

Dysgeusia is a distortion in the sense of taste and is often associated with ageusia, which is a complete lack of taste, and hypogeusia, which is a decrease in taste sensitivity [6]. Dysgeusia can be induced by medication, psychological issues, and a loss of zinc, among other causes. In the present cases, the symptoms appeared between 6 weeks and 7 months after enzalutamide was introduced. On changing the timing of the enzalutamide intake, the symptoms recovered. We therefore speculated that dysgeusia was an enzalutamide-induced adverse event in our cases. A previous study showed that enzalutamide caused dysgeusia in around 1–5% of patients.

The large size of enzalutamide capsules makes oral intake difficult [7]. Furthermore, when enzalutamide capsules are taken, the blood concentration level of enzalutamide is rapidly increased, which might result in decreased appetite and nausea [7]. In June 2018, the form of the drug changed from capsule to tablet in Japan and Germany. We reported that patients who showed a low compliance with enzalutamide due to the difficulty associated with taking large capsules demonstrated an improved compliance and better cancer control when taking the drug in tablet form [7].

With the change of the drug form to a tablet form, the rapid increase in the blood concentration of enzalutamide no longer occurs; however, a considerable number of patients still report nausea and a decreased appetite as adverse events. 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 [8]. Taking the drug before sleep means that the blood concentration is higher when the patient has fallen asleep; thus, the patient does not feel or has a decreased feeling of fatigue and nausea. These methods are also used in the management of patients receiving anti-cholinergic agents for lower urinary tract symptoms [9].

The management of dysgeusia by supplying zinc or further assessment was reported, however, such assessments are useful only for dysgeusia. Changing the timing of intake timing might contribute to other adverse symptoms. We herein report two cases in which enzalutamide-induced dysgeusia was treated by changing the timing of enzalutamide intake from morning to night. Changing the timing of enzalutamide intake might improve dysgeusia induced by 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 and all methods were followed by the ethical standards of the Declaration of Helsinki.

Disclosure Statement

We declare no conflicts of interest

Funding Sources

None.

Author Contributions

TK, YM, HU are responsible for the concept and drafted the manuscript.
MY provided the intellectual content and critically reviewed the manuscript.

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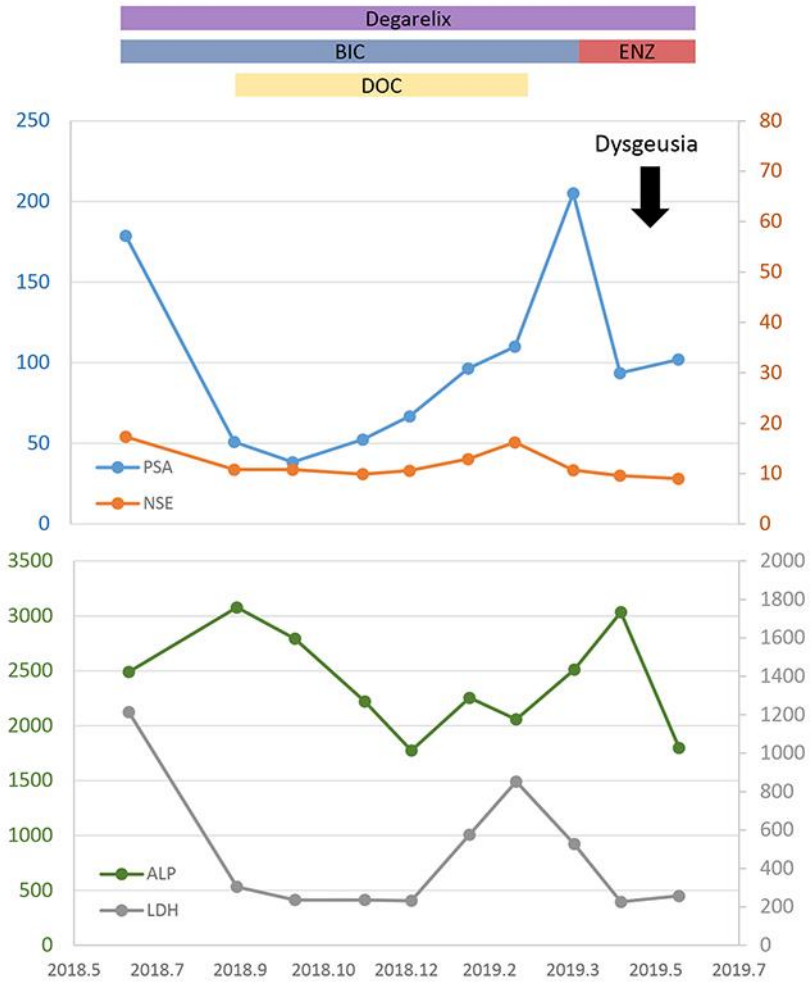

Fig. 1. Clinical course of case 1.

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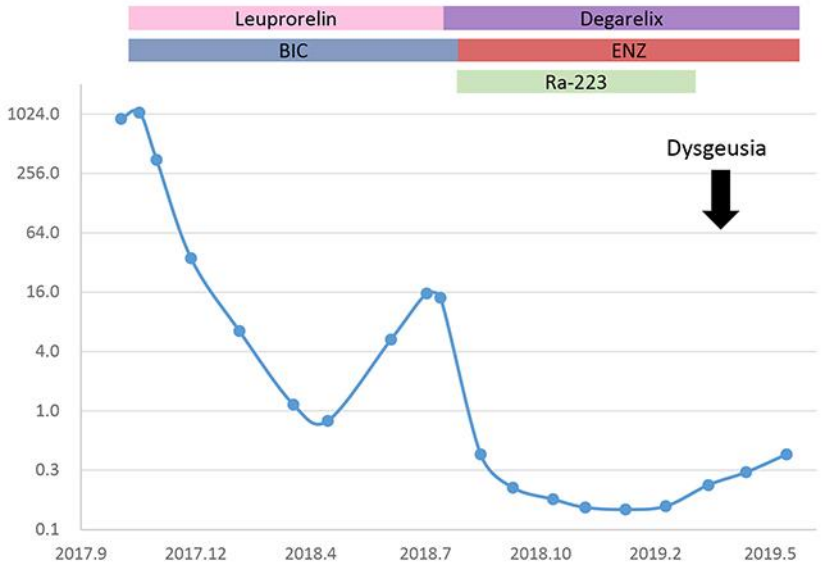

Fig. 2. Clinical course of case 2.