

# CASE REPORT

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## A case of advanced prostate cancer controlled for the long term by flutamide after bicalutamide failure

Tomoaki Muramatsu, Yasuhito Funahashi, Akiyuki Yamamoto, Naoto Sassa,  
Yoshihisa Matsukawa, and Momokazu Gotoh

*Department of Urology, Nagoya University Graduate School of Medicine, Nagoya, Japan*

### ABSTRACT

Currently, the early introduction of new antiandrogens is popular for castration-resistant prostate cancer (CRPC). However, adverse events can be severe and their costs are high. Here, we present a patient with CRPC in whom flutamide controlled disease progression for 10 years. This case report shows that conventional alternative antiandrogens are cost effective and are still an important option for the treatment for CRPC.

Keywords: flutamide, bicalutamide, long-term, prostate cancer

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### INTRODUCTION

Androgen deprivation therapy is the pivotal treatment for patients with advanced prostate cancer. Complete androgen blockade therapy, which is a combination of an antiandrogen and medical or surgical castration, is usually given to patients with metastatic prostate cancer. Although complete androgen blockade therapy is effective in approximately 80–90% of patients, most patients become refractory within several years.<sup>1</sup> After failure of the first-line treatment, the disease progresses to the uncontrollable state in most cases. Here, we report a patient with metastatic prostate cancer treated by complete androgen blockade, in whom a second-line antiandrogen therapy with flutamide was effective for 10 years after failure of the first-line bicalutamide treatment. This is the case which conventional alternative antiandrogen controlled disease progression for the longest period.<sup>2,3</sup>

### CASE REPORT

A 73-year-old man had been referred to our hospital with lumbago 13 years earlier. He had a history of benign prostatic hyperplasia and was taking tamsulosin hydrochloride 0.2 mg/day.

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Corresponding Author: Yasuhito Funahashi, MD, PhD

Department of Urology, Nagoya University Graduate School of Medicine, 65 Tsuruma-cho, Showa-ku, Nagoya 466-8550, Japan.

Tel: +81-52-744-2985, E-mail: [yfunahashi@med.nagoya-u.ac.jp](mailto:yfunahashi@med.nagoya-u.ac.jp)

His blood pressure was 151/51 mmHg, pulse was 72 beats per minute and regular, and his temperature was 36.5°C. The abdomen was soft, flat and non-tender. His neurological examination was normal. His Eastern Cooperative Oncology Group Performance Status was 0.

Laboratory testing showed a hemoglobin level of 15.2 g/dL, platelet count of 147,000 mm<sup>3</sup>, creatinine level of 0.8 mg/dL, alkaline phosphatase at 347 IU/L, and C-reactive protein of 0.03 mg/dL. His serum prostate specific antigen (PSA) level was 1,790 ng/mL, and bone scintigraphy revealed multiple areas of bone accumulation in the collar bone, ribs, and vertebrae (Fig. 1a). Abdominal computed tomography revealed invasion of the rectum by prostate tumor and swelling of the bilateral obturator lymph nodes (Fig. 1b). A transrectal prostate biopsy confirmed adenocarcinoma with a Gleason score of 4+5 (Fig. 2), and his clinical stage was diagnosed as cT4N1M1b, stage D2. He started first-line androgen deprivation therapy with 80 mg/day bicalutamide and a luteinizing hormone-releasing hormone agonist 1 year after the initial visit. After his serum PSA decreased to a nadir of 0.211 ng/mL at 13 months, it increased to 6.84 ng/mL, although the metastatic bone lesions and lymph nodes had shrunk. Then, bicalutamide was discontinued, and he was switched to the second-line antiandrogen flutamide (250 mg/day). Thereafter, the PSA decreased to below the detection limit of 0.008 ng/ml by 11 months after starting the flutamide, a level that was maintained for 10 years. The metastatic lesions in the obturator lymph nodes and bone did not return. He had no clinical symptoms, such as general fatigue or liver dysfunction throughout the treatment period. In addition, he did not need to take other drugs, due to side effects.



**Fig. 1** Bone scintigraphy and Abdominal CT

**Fig. 1a:** Bone scintigraphy; the <sup>99m</sup>Tc-MDP uptake was increased in the clavicle, ribs, and vertebrae indicating multiple bone metastases (arrowheads).

**Fig. 1b:** Abdominal CT; the bilateral obturator lymph nodes are enlarged (arrowheads).

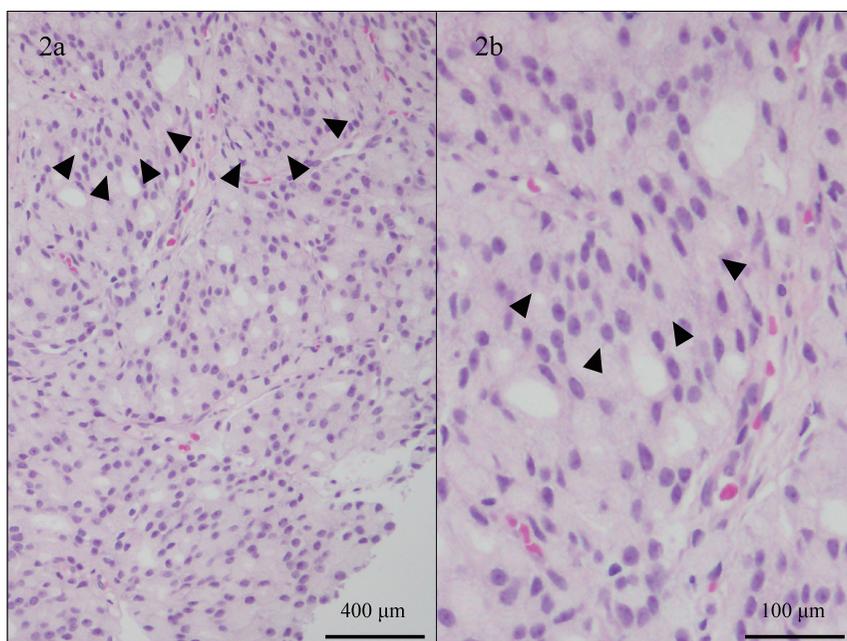


Fig. 2 Histopathological findings of the prostate biopsy  
H&E staining confirmed adenocarcinoma with a Gleason score of 4+5. (Arrowheads indicate Gleason 5 component.) Scale bars (a) 400  $\mu\text{m}$ , (b) 100  $\mu\text{m}$

## DISCUSSION

A switch of antiandrogen in androgen deprivation therapy is effective in some patients with metastatic prostate cancer. Suzuki et al reported that 142 of 232 patients (61.2%) with metastatic prostate cancer had decreased PSA levels in response to an alternative antiandrogen after a treatment failure with first-line complete androgen blockade therapy.<sup>4</sup> Further, Jackson et al reported that 27 of 50 patients (54%) with metastatic prostate cancer had  $\geq 50\%$  decrease of PSA by switching from bicalutamide to flutamide.<sup>5</sup> However, the response to the second-line antiandrogen is usually temporary. To our knowledge, no case has been reported in which the second-line antiandrogen controlled the disease progression for the long-term after failure of the first-line antiandrogen therapy for advanced prostate cancer.

Some studies analyzed predictive factors to determine whether alternative antiandrogen therapy is effective after failure of first-line bicalutamide therapy. Kamiya et al developed a nomogram to predict a PSA decrease  $\geq 50\%$  in response to alternative anti-androgen therapy.<sup>6</sup> They reported that the following five independent factors predicted the effectiveness of second-line anti-androgen therapy, including PSA, hemoglobin, and CRP at the initial diagnosis, a PSA nadir to the first-line hormone therapy, and the Gleason sum score. The PSA of our case at the initial diagnosis was 1,720 ng/mL, hemoglobin was 15.2 g/dL, CRP was 0.03 mg/dL, the PSA nadir to first-line hormone therapy was 0.211 ng/mL, and the Gleason sum score was 9. Therefore, he had a 65% probability of a  $\geq 50\%$  decrease in PSA in response to alternative anti-androgen therapy.

Bicalutamide and flutamide have different mechanisms of action.<sup>7</sup> Bicalutamide is involved in dissociation of the androgen receptor and has a remarkably high inhibitory effect on androgen receptor activation via the protein kinase A pathway compared to flutamide. Flutamide has

a several-fold greater inhibitory effect on transcription of the androgen receptor than that of bicalutamide.

After the failure of first-line androgen deprivation therapy, early introduction of novel treatments (abiraterone, enzalutamide, or docetaxel) has become the standard.<sup>8</sup> However, various adverse events are frequently observed for new antiandrogens such as hypertension, constipation, fatigue, loss of appetite, and adrenal dysfunction, while they are rare for flutamide. This case was predicted to respond to an alternative antiandrogen at a probability level of 65% based on the nomogram of Kamiya et al. A conventional alternative anti-androgen remains a significant option for castration-resistant prostate cancer for cases with good prognostic factors or side effects difficult to manage and a rare incidence of adverse events.

### CONFLICTS OF INTEREST

The authors have nothing to disclose.

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