Failure to achieve castrate level of serum testosterone during luteinizing hormone-releasing hormone agonist therapy in a patient with prostate cancer

Yoko Koh, Atsunari Kawashima, Takeshi Ujike, Akira Nagahara, Kazutoshi Fujita, Hiroshi Kiuchi, Ryoichi Imamura, Yasushi Miyagawa, Norio Nonomura and Motohide Uemura

We report the failure to achieve castrate level of serum testosterone during luteinizing hormone-releasing hormone agonist therapy in a patient with prostate cancer. A 76-year-old man was admitted to our hospital for evaluation of an elevated serum prostate specific antigen (PSA) level (191.10 ng/ml) in August 2011. He was diagnosed with T3aN0M1b prostate adenocarcinoma. A combined androgen blockade using luteinizing hormone-releasing hormone agonist (the 1-month depot of leuprorelin acetate) and antiandrogen was administered. Due to liver dysfunction, antiandrogens, both bicalutamide and flutamide, were stopped. The 1-month depot was switched to the 3-month depot in May 2013, but the patient complained of induration and abscess at the infection site. Leuprorelin acetate was replaced by goserelin acetate. Because no adverse event appeared after injection of the 1-month depot of goserelin acetate, the 3-month depot was administered in October 2013. The PSA level increased gradually, and the testosterone level was greater than 50 ng/dl, that is, above castrate range. The 3-month depot of both leuprorelin acetate and goserelin acetate was not effective for this patient. For this reason, the 1-month depot of leuprorelin acetate was started resulting in a rapid decrease in PSA and testosterone levels. Thereafter, androgen depriving therapy could be continued. Androgen deprivation therapy is the standard treatment for patients with advanced prostate cancer and luteinizing hormone-releasing hormone aims to suppress serum testosterone to castrate range. We recommend assessing the serum testosterone levels during luteinizing hormone-releasing hormone agonist therapy for monitoring treatment efficacy and verifying progression when the PSA level increases.

Keywords: androgen deprivation therapy, castration, luteinizing hormone-releasing hormone agonist, prostate cancer, testosterone

Departments of ¹Urology and ²Urological Immuno-Oncology, Osaka University Graduate School of Medicine, Osaka, Japan

Correspondence to Atsunari Kawashima, MD, PhD, Department of Urology, Osaka University Graduate School of Medicine, 2-2 E4 Yamadaoka, Suita, Osaka 565-0871, Japan
Tel: +81 6 6879 3531; fax: +81 6 6879 3539; e-mail: kawashima@uro.med.osaka-u.ac.jp

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Introduction
Androgen deprivation therapy (ADT) is the standard treatment for patients with advanced prostate cancer. It is important to suppress serum testosterone levels at castrate range continuously, and luteinizing hormone-releasing hormone (LH-RH) agonists are the key drugs for achieving this. Herein, we report a case in which LH-RH agonist therapy failed to maintain castrate levels of testosterone in a patient with metastatic prostate cancer.

Case report
A 76-year-old man was admitted to our hospital complaining of an elevated serum prostate specific antigen (PSA) level. Serum PSA was 191.10 ng/ml. The digital rectal examination disclosed a hard nodule in the right lobe of the prostate. Five of the six biopsy cores revealed adenocarcinoma of the prostate, with Gleason score of 4 + 5 = 9. Magnetic resonance imaging showed extraprostatic extension (Fig. 1) and bone scintigraphy showed multiple bone metastases (Fig. 2). The tumor-node-metastasis staging was cT3aN0M1b. He was 164.9-cm tall, weighed 59.2 kg and his BMI was 22.0 kg/m². He was being given warfarin potassium and atenolol for atrial fibrillation and hypertension, respectively.

A combined androgen blockade initiated in August 2011 consisted of bicalutamide (80 mg/day) and the 1-month depot of leuprorelin acetate (3.75 mg/month). In March 2012, PSA decreased gradually to 0.12 ng/ml. However, PSA rose to 1.27 ng/ml in July 2012. Since antiandrogen withdrawal syndrome was not observed after 1 month discontinuation of bicalutamide, flutamide started resulting in a rapid decrease in serum PSA levels to 0.02 ng/
ml. Flutamide was discontinued due to liver dysfunction (aspartate aminotransferase 446 IU/l, alanine aminotransferase 538 IU/l, total bilirubin 23.9 µmol/l) in December 2012. The 1-month depot of leuprorelin acetate was continued without signs of increasing PSA level. In May 2013, the 1-month depot was switched to the 3-month depot of leuprorelin acetate. Three months later, the patient complained of induration and abscess of the injection site, which was accompanied by PSA elevation (0.1 ng/ml). The 3-month depot of leuprorelin acetate was not effective and the 1-month depot of goserelin acetate was administered in September 2013. Because the PSA level decreased to 0.03 ng/ml one month later, the 3-month depot of goserelin acetate was then administered. PSA levels in the patient gradually increased, to the point that his testosterone level was near normal range. The PSA and testosterone levels decreased one month after the third and fourth infections of the 3-month depot of goserelin acetate, but increased 3 months later. They reached 11.41 ng/ml and 297 ng/dl, respectively, in September 2014 (Fig. 3).

Computed tomography and bone scintigraphy showed no disease progression. Subsequent treatment with the 1-month depot of leuprorelin acetate achieved castrate level of testosterone, and the PSA level decreased. Twelve months later, the patient developed castration-resistant prostate cancer and enzalutamide was initiated. Both the 1-month depot of leuprorelin and enzalutamide have been continued successfully for 4 years.

**Discussion**

ADT is the standard treatment for patients with advanced prostate cancer since Huggins and Hodges reported prostate cancer was influenced by androgens [1]. Medical castration has been commonly used instead of bilateral orchietomy. LH-RH agonists and antagonists are available to suppress serum testosterone levels. But there is no consensus regarding acceptable serum testosterone levels during ADT. The NCCN (National Comprehensive Cancer Network), EAU (European Association of Urology) and AUA (American Urological Association) guidelines recommend castrate levels of testosterone are less than 50 ng/dl by definition [2–4]. In our case, the 1-month depot of leuprorelin acetate decreased PSA level below 0.03 ng/ml, but the 3-month depot of goserelin acetate failed to maintain the castrate level of testosterone over the course of 3 months. We did not measure the serum testosterone level during the 1-month depot of leuprorelin acetate, so it is unknown whether the 1-month depot could achieve medical castration.

There are some case reports in which LH-RH analogues fail to suppress serum testosterone levels, and several possible explanations were suggested [5–12]. Hypothetically,
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changes in the LH-RH receptors, the existence of antibodies against the agonists or unknown interactions with other medicines were considered. Offelein and Cornum [13] correlated the failure to achieve castrate testosterone with obesity. Ogan et al. reported LH-RH agonists failed to decrease serum testosterone levels due to the concomitant presence of a functional pituitary adenoma secreting FSH and LH [14]. Another explanation could be an incorrect administration or a faulty batch of the agonists, but this is unlikely since this phenomenon was observed across multiple sites. It was also proposed that the absorption of LH-RH agonists was blocked or that they were rapidly metabolized. Matsuda et al. reported two cases of low serum concentration of goserelin acetate; however, the mechanism is unclear. In this case, since we did not measure the serum concentration of goserelin, we can only speculate regarding this possibility.

If the PSA level is rising during androgen-depriving LH-RH agonist therapy, it does not necessarily mean castration-resistant progression. In such cases, it is important to measure serum testosterone directly to assess whether the patient has achieved castration state. If the testosterone level is over 50 ng/dl, the question becomes how to treat the patient. Orchiectomy is often proposed as one option. If the patient refuses orchiectomy, it is recommended to add an antiandrogen, or change to another formulation of LH-RH agonists or LH-RH antagonists [13]. In conclusion, if patient PSA levels increase in spite of LH-RH agonist therapy, serum testosterone levels should be measured to determine whether the prostate cancer has truly advanced to a castration-resistant state. Monitoring serum testosterone is also a useful metric to confirm treatment efficacy.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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