

Case Report

Combination of 5 α -reductase inhibitor with combined androgen blockade (CAB) as a novel cytoreductive regimen before prostate brachytherapy: Ultra-CAB

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Abstract: We report a first case of using a 5 α -reductase inhibitor (5ARI) and combined androgen blockade (CAB) as a cytoreductive regimen before prostate brachytherapy. Prostate volume reduction with CAB is limited to approximately 40% in most cases, making it difficult to meet anatomical constraints to perform these procedures in cases with large prostate volume. With the added administration of 5ARI, further volume reduction can be expected. Here, we describe this cytoreductive regimen used in a 63 year-old prostate cancer patient who became eligible to receive brachytherapy after dutasteride (0.5 mg daily) was added to CAB and prostate volume reduction of 57% was achieved.

Keywords: Combined androgen blockade (CAB), ultra-combined androgen blockade (UCAB), dutasteride, brachytherapy, 5 α -reductase inhibitor, prostate cancer

Introduction

Brachytherapy is one of the best treatment options in many patients with localized prostate cancer (PCa). Brachytherapy alone is an effective definitive therapy for low-risk PCa patients, but prostate volume is an important factor in terms of carrying out brachytherapy safely. Implantations to a large prostate may be more technically difficult with an increased risk of inadequate dose coverage and is considered a relative contraindication of brachytherapy. To overcome this problem, neoadjuvant androgen deprivation therapy (ADT) was introduced. In brachytherapy, it is often used to cytoreduce an enlarged prostate gland, however, 5 α -reductase inhibitors (5ARIs) have not been used in PCa patients undergoing brachytherapy.

Case presentation

A 63 year-old man presented with an elevated prostate specific antigen level of 4.94 ng/mL. Transrectal prostate needle biopsy was performed, and he was diagnosed with Gleason Score 3+4, 1/10 positive core, cT2aNOMO

prostate cancer. Transrectal ultrasonography (TRUS) of the prostate revealed a prostate volume of 73.2 cc, and the patient selected radiation therapy with prior androgen deprivation therapy as radical therapy. The pre-treatment free-testosterone level was 4.05 ng/mL. After 3 months of combined androgen blockade (CAB, goserelin and bicalutamide), the reduction effect was inadequate as prostate volume was only reduced to 44.0 cc, but since the patient aspired to receive brachytherapy, dutasteride, a 5 α -reductase inhibitor, was added. Two months after the administration of dutasteride (0.5 mg daily), his testosterone level dropped to 0.12 ng/mL, the luteinizing hormone level was < 0.1 mIU/mL, and the prostate volume was reduced to 31.5 cc, enabling brachytherapy to be carried out safely (**Figure 1**). D90 (the minimum dose received by 90% of the prostate volume) and V100 (the percent volume of the prostate receiving 100% isodose) a month after brachytherapy were 199.96 Gy and 98.92%, respectively. The patient had a preoperative International Prostate Symptom Score (IPSS) of 12, but his IPSS a year after brachytherapy remains at 11.

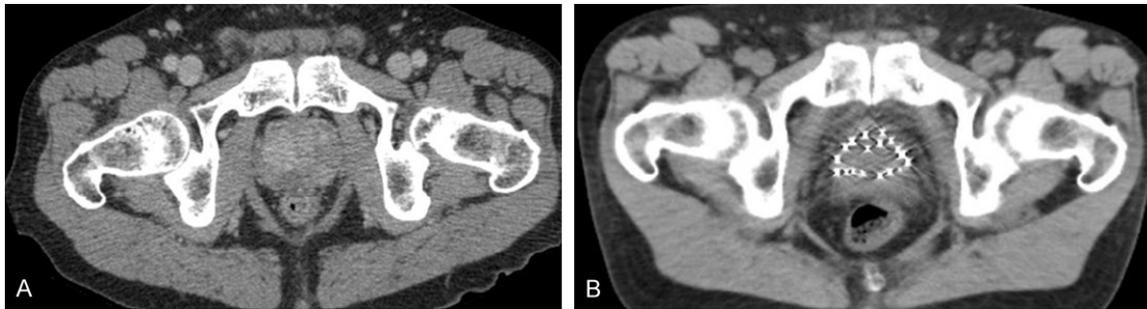


Figure 1. Computed tomography scan of the pelvis showing enlarged prostate before brachytherapy (A), and post-operative volume-reduced prostate after added administration of dutasteride to combined androgen blockade (B).

Discussion

Neoadjuvant ADT is often used in PCa patients undergoing brachytherapy in order to overcome anatomical limitations. Brachytherapy involves inserting needles through a transperineal template into the prostate gland to place radioactive seeds, and the prostate volume needs to be appropriate for the implantations. The American Brachytherapy Society (ABS) guidelines list prostate volume > 60 cc as one of the relative contraindications for TRUS-guided brachytherapy because of an increased frequency of pubic arch interference [1]. Brachytherapy is not absolutely contraindicated in patients with large prostate size, but the Japanese guideline sets an exit-standard from the radiation controlled area, making it difficult to carry out brachytherapy in a large prostate due to an increase in the number of seed implantations and increased radioactivity in the body. While the upper limit of prostate volume differs among institutions, at our institution, patients with a prostate volume less than 35 cc are eligible for brachytherapy.

With the emergence of these issues, ADT came into use. Previous studies have demonstrated that a 3-month course of ADT using luteinizing hormone-releasing hormone (LHRH) agonists with or without antiandrogens resulted in prostate volume reduction of approximately 40% on average [2]. However, all of these previous studies involved the use of LHRH agonists with or without antiandrogens, or antiandrogens alone, and none used 5ARIs. Merrick *et al.* first reported the use of dutasteride and bicalutamide as a cytoreductive regimen and have shown that prostate volume reductions are comparable to those in previous reports [3].

Our case is the first using both neoadjuvant CAB and 5ARI as a cytoreductive regimen before prostate brachytherapy. After 3 months of CAB alone, volume reduction of only 40% (44 cc) was achieved, but with the added administration of dutasteride (0.5 mg daily), we were able to achieve total volume reduction of approximately 57% (31.5 cc), and thereby satisfied the upper prostate volume limit for brachytherapy at our institution. The ABS guidelines state patients with a high IPSS for urinary irritative and obstructive symptoms are at increased risk of developing postimplant urinary retention and numerous studies have demonstrated a correlation between high IPSSs and increased toxicity after brachytherapy [1]. In our case, the patient's IPSS remained stable and he has not experienced exacerbation postoperatively without any toxicity.

Dutasteride is a 5 α -reductase inhibitor that blocks the conversion of testosterone to dihydrotestosterone in the prostate gland. There are two isoforms of 5 α -reductase, type I and type II, and dutasteride inhibits both isoforms. Following the findings of two large randomized, placebo-controlled trials, the Food and Drug Administration (FDA) reported the negative conclusions that finasteride and dutasteride do not have a favorable risk benefit profile for the proposed use of chemoprevention of prostate cancer in healthy men [4]. However, a recent study reported that 5ARIs were associated with significantly reduced risk of low- and intermediate-grade prostate cancer and were not associated with increased or decreased risk of high-grade or lethal prostate cancer [5]. As we have reported in the earlier studies, 5ARIs may have a potential risk of activating the initiation of DNA replication system [6, 7], and because the use

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of dutasteride is only intended to expect a cyto-reductive effect in our regimen, it should be used only for limited periods. The fact that further volume reduction was achieved in our case suggests that the inhibitory effect of local androgen with CAB is inadequate, and the addition of 5ARI helped further inhibition of androgen, leading to volume reduction.

Conclusion

By adding another inhibitor of androgen production to CAB, further prostate volume reduction could be achieved prior to brachytherapy. We are the first to report this cytoreductive regimen, and we have termed this therapy ultra-combined androgen blockade (UCAB).

Disclosure of conflict of interest

None.

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