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CASE REPORT

Clinical response in metastatic castration-resistant prostate cancer (mCRPC) cases treated with supra-physiological doses of testosterone: Bipolar androgen therapy

Senji Hoshi[1] | **Vladimir Bilim**[2] | **Kiyotsugu Hoshi**[1] | **Takuya Nakagawa**[3] | **Sadanobu Sato**[3] | **Rie Sakagami**[3] | **Masato Konno**[3] | **Takashi Kudo**[3] | **Kenji Numahata**[3] | **Isoji Sasagawa**[1]

[1]Department of Urology, Yamagata Tokushukai Hospital, Yamagata, Japan

[2]Department of Urology, Kameda Daiichi Hospital, Niigata, Japan

[3]Department of Urology Yamagata, Prefectural Central Hospital, Yamagata, Japan

Correspondence
Vladimir Bilim, Department of Urology Kameda Daiichi Hospital, Niigata, Japan.
Email: vbilim@zoho.com

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Abstract

Androgen deprivation therapy is a standard of care for metastatic prostate cancer. A paradoxical approach utilizing high doses of testosterone in castration-resistant prostate cancer patients demonstrated clinical responses. Here, we report on four heavily pretreated Japanese patients (including one patient on hemodialysis) successfully treated with supra-physiological doses of testosterone.

KEYWORDS

bipolar androgen therapy, metastatic castration-resistant prostate cancer, prostate cancer, testosterone injection

1 | INTRODUCTION

Androgen deprivation therapy (ADT) is a standard of care for metastatic prostate cancer (PCa), however, eventually, all men relapse. Docetaxel has long been the only agent demonstrated to improve overall survival in castration-resistant prostate cancer (CRPC) patients.[1] Multiple new agents with various actions including cabazitaxel, sipuleucel-T, radium-223, and PARP inhibitors prolong media survival by a few months. New androgen receptor-axis-targeted agents (ARAT) have improved the prognosis of men with CRPC patients. Although ARAT improves survival in CRPC patients,[2] they remain incurable and eventually progress. A new approach to hormonal therapy is necessary. It has been reported that the growth of some PCa cells can be inhibited by supraphysiologic levels of androgens.[3] High doses of testosterone (T) are administered monthly, and the supraphysiologic T level is followed by a rapid drop to castration levels during each cycle of therapy.[3] This was called "bipolar androgen therapy" (BAT). Although the mechanisms of BAT are currently poorly understood, clinical responses have now been observed in men with PCa treated with high doses of T. Although several clinical trials using BAT have been reported,[4,5] its application for CRPC is still controversial. BAT is an appropriate therapy in men with CRPC, particularly in patients with low-to-moderate metastatic burden. However, biochemical responses are observed in approximately one-third of the patients.[6,7] Moreover, there is concern that BAT can worsen clinical symptoms, especially in patients with a high metastatic burden.[8] We report on 4 heavily pretreated CRPC patients successfully treated with supra-physiological doses of T.

2 | CASE PRESENTATION

Patients' clinicopathological data are summarized in Table 1. At the time of BAT initiation, all patients had castrate T levels.

2.1 | Case 1

A 60-year-old man with end-stage renal disease on hemodialysis three times a week with iPSA 40.5 ng/ml and prostate biopsy GS 5+5 was found to have prostate cancer bone metastasis (right pelvic bone, chest, and lumbar spine) and bladder invasion (cT4N0M1b). He was initially treated with MAB (LHRH analog plus bicalutamide 80 mg qd) since June 2014. Two years later, he was diagnosed with CRPC (PSA 4 ng/ml) and enzalutamide 80 mg was added to LHRH analog in July 2016. Diabetic nephropathy progressed to end-stage renal disease, and hemodialysis was started in October 2017. High pro-GRP (160 pg/ml) was detected, and the emergency of therapy-induced neuroendocrine prostate cancer component was supposed. CRPC progressed during enzalutamide treatment and testosterone enanthate 250 mg IM was started in August 2018 and repeated every 4 weeks. Then, the patient was re-challenged with bicalutamide, which resulted in a drastic PSA decreased to 1.5 ng/ml and pro-GRP decreased to 97.8 pg/ml. PSA continues to stay at low levels for 20 months. LHRH injections and bicalutamide are being continued as well as testosterone enanthate 125 mg IM 4 weeks (Figure 1A). There are no new bone lesions as well as no other detectable metastases or regrowth of the primary prostatic tumor. He has radiological SD on the CT scans.

2.2 | Case 2

A 59-year-old man with iPSA 9.7 ng/ml and prostate biopsy GS 4+3 was diagnosed with locally invasive PCa (cT3aN0M0). He underwent radical retropubic

TABLE 1 Patients' clinicopathological data

	Age at diagnosis	Age at start of T	iPSA ng/ml	Biopsy GS	Pre-T PSA ng/ml	T start
1	60	67	40.5	5+5	1.4	August 2018
2	59	72	9.7	4+3	197	May 2021
3	65	78	15.7	4+5	8.26	May 2021
4	71	79	350	4+4	59	May 2021

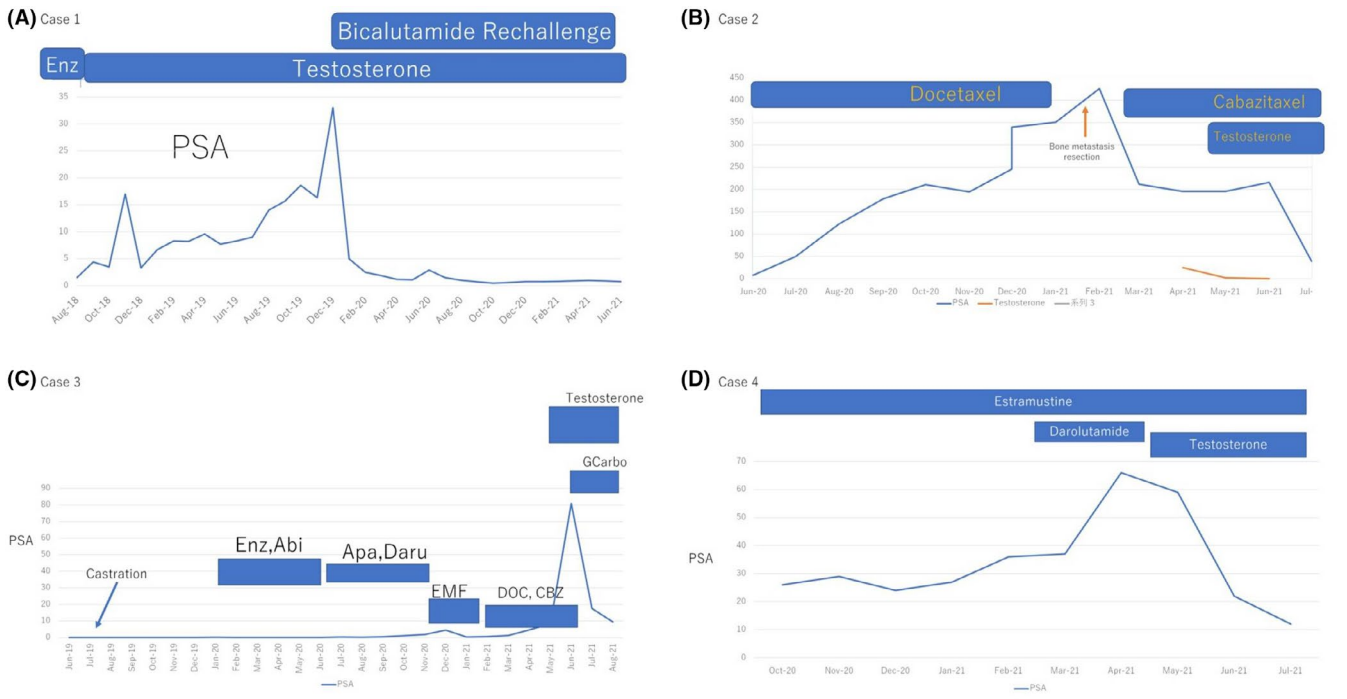

FIGURE 1 Clinical course of the patients. The *x*-axis is time (months), the *y*-axis is PSA (ng/ml)

prostatectomy (RRP) and then salvage EBRT. As he progressed to CRPC (PSA 8.4 ng/ml) chemical castration was started, and then, enzalutamide was added to the treatment. Bone metastasis appeared and radium chloride (223Ra) 6 injections were done followed by EBRT to the left femur (30 Gy). Then, resection of the left femur with femoral head prosthesis implantation was performed because of the left leg pain. AS PSA increased (50.2 ng/ml) docetaxel was started and then switched to cabazitaxel. Testosterone enanthate 250 mg IM was started in May 2021 resulting in a more than a fourfold decrease in PSA (Figure 1B). He also had a partial response of bone metastasis 6 months since the beginning of BAT (Figure 2).

2.3 | Case 3

A 65-year-old man with iPSA 15.7 ng/ml and prostate biopsy GS 4+5 without distant metastasis underwent RRP. The pathological diagnosis was pT3bN1 (a single positive right obturator LN). MAB was started right after the operation. Bicalutamide was switched to flutamide and then to estramustine followed by enzalutamide. PSA increased steadily reaching 0.84 ng/ml, and pararectal LN metastasis was diagnosed by PET-CT. The metastasis was surgically resected. PSA decreased to 0.03 ng/ml. The patient was sequentially treated with enzalutamide, abiraterone, apalutamide, darolutamide, estramustine, docetaxel, and cabazitaxel. PSA gradually increased to 8.26 ng/ml. Testosterone enanthate 250 mg IM was started in May 2021 with initial PSA flare to 80.87 ng/ml because of liver, retroperitoneal, and pelvic lymph node metastasis then drop to 17.56 ng/ml. The patient is now being treated with monthly T with triweekly injections of gemcitabine and carboplatin (Figure 1C). CT revealed PR in the liver and LN metastasis (Figure 3).

2.4 | Case 4

A 71-year-old man with iPSA 350 ng/ml underwent prostate biopsy and pathological diagnosis was PCa GS 4+4. Prostate MRI revealed extracapsular invasion. CT scan revealed enlarged left internal iliac LN, but no distant metastasis. Chemical castration with degarelix injection was performed, and MAB was started by adding bicalutamide, which was sequentially switched to flutamide, enzalutamide, and abiraterone. Five years since the beginning of the therapy the patient opted for surgical treatment and underwent RRP. The pathological diagnosis was T3bN1 with 5 out of 21 LN having metastasis. Following the operation, ADT was continued using enzalutamide. PSA increased and salvage EBRT (70 Gy) was done. A whole-body MRI revealed multiple spine bone metastasis and multiple LN metastasis. BMA denosumab was started. Enzalutamide was switched to estramustine followed by darolutamide. PSA increased to 66 ng/ml. Testosterone enanthate 250 mg IM was started in May 2021 followed by a drastic decrease in PSA (Figure 1D).

3 | DISCUSSION

Here, we presented 4 heavily pretreated (including RRP, EBRT, metastasectomy, and radium chloride) CRPC patients successfully treated with supra-physiological doses of T. Although it is widely accepted that T promotes prostate cancer growth, it was hypothesized that rapid cycling of T levels from high supra-physiological to castration levels result in clinical improvement. It has been shown that in a xenograft mice model androgen caused growth suppression of androgen-independent tumors. Furthermore, these tumors became androgen sensitive by androgen stimulation and the growth of androgen-stimulated

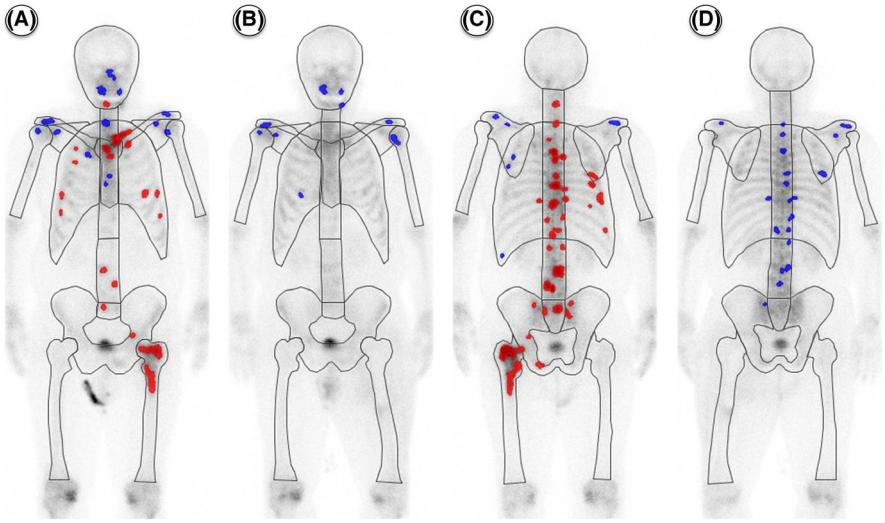

FIGURE 2 Bone scintigraphy revealed a partial response of bone metastasis. Scintigrams before T administration in May 2021 (A, C) and 6 months later (B, D). A, C present anterior and B, D posterior view

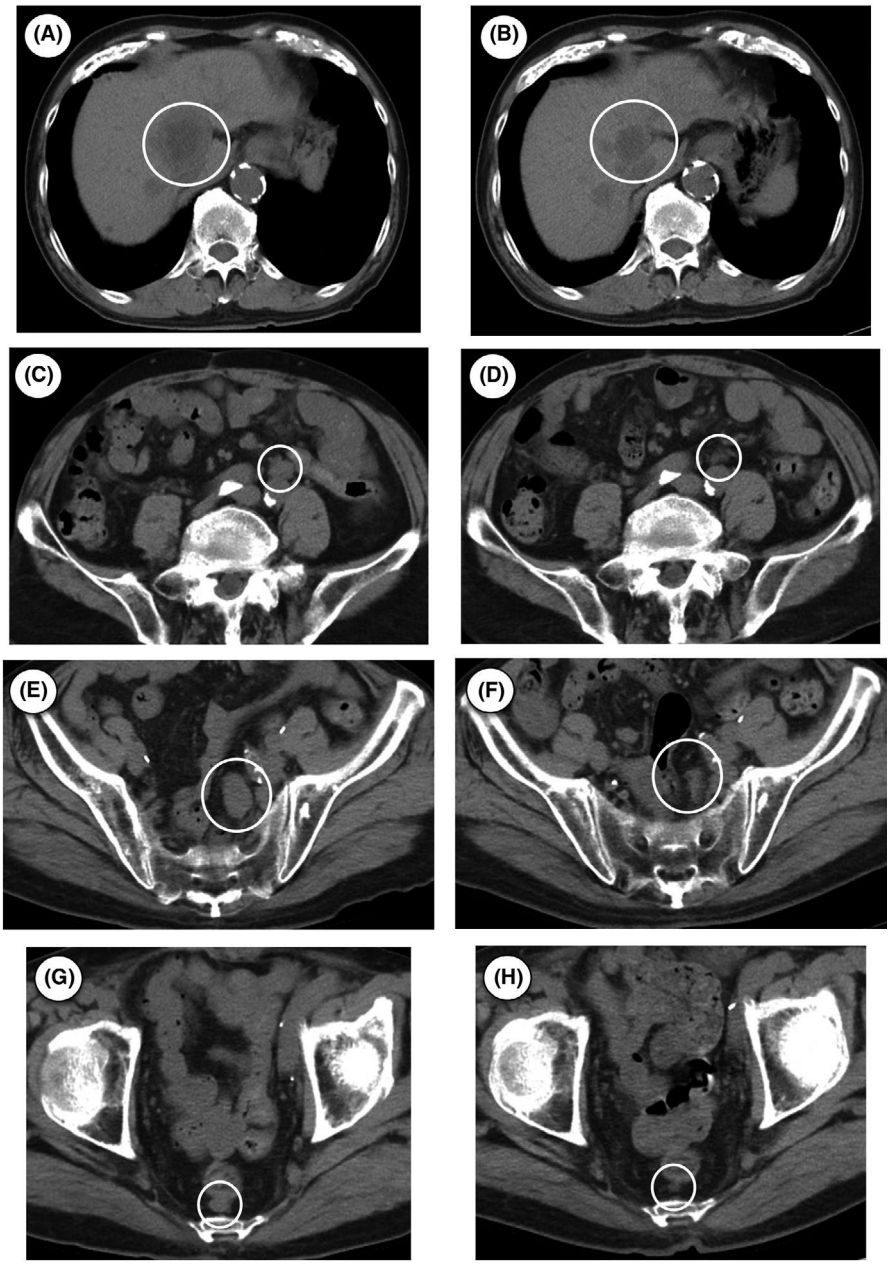

FIGURE 3 CT revealed PR in liver S4 (A, B), retroperitoneal, and pelvic LN metastasis (C, D, E, F). CT scans were taken before T administration in May 2021 (A, C, E) and 2 months later (B, D, F)

tumors could be restrained by androgen ablation.[9] In mice experiments, it was also demonstrated that low T levels stimulated and higher T levels inhibited PCa cell growth. Castrate T levels are not sufficient to support PCa cell growth.[10] Androgen suppressed the growth of androgen-independent LNCaP subline by inducing cell cycle arrest.[11]

Several clinical trials using BAT have been reported.[4,5] In phase II study enrolling asymptomatic mCRPC, BAT was shown to be a safe therapy that resulted in responses in asymptomatic men with mCRPC and also resulted in re-sensitization to enzalutamide in most patients.[7] In phase II study enrolling asymptomatic mCRPC patients, BAT showed clinical activity in mCRPC patients and was effective in resensitizing to ARAT.[5] A randomized phase II study comparing BAT versus enzalutamide demonstrated clinical activity and safety of BAT and confirmed that BAT can sensitize CRPC to subsequent antiandrogen therapy.[4]

Although precise molecular mechanisms driving responses to high doses of T are needed to be determined, the following possible mechanisms have been proposed. BAT led to a decrease in AR copy number and mutations presumably due to transcriptional repression of AR including AR variants. BAT also induced alterations in DNA repair genes.[6] Ligand-driven activation of AR by supra-physiological doses of T may result in growth inhibition due to cell cycle arrest and apoptosis.[12] These are most likely caused by DNA double-strand breaks, DNA

dysfunction, and mitotic distress.[12] Another proposed mechanism includes the disruption of AR-mediated DNA licensing.[12] Thus, the mechanism of BAT-induced inhibition of PCa cell growth and death is multimodal.

The patients in this series had been heavily pretreated and had a poor prognosis. The first patient was re-challenged with bicalutamide, which resulted in a drastic PSA decrease that lasts for more than 3 years. Bicalutamide, enzalutamide, and abiraterone re-challenge after T treatment have been reported.[13] This is the first report on T treatment in Japanese patients and a CRPC patient with CRF on hemodialysis. The second patient progressed on docetaxel and cabazitaxel resulting in PSA stabilization only. A steeper decline in PSA was observed after T injections. The third patient is being successfully treated with gemcitabine and carboplatin after T injections, although he previously has failed to respond to estramustine, docetaxel, and cabazitaxel. In the fourth patient, one-fifth fold decrease in PSA levels was observed.

The limitation of this case series report is a short duration of BAT in cases 2–4.

Adverse events (AE) of T injections include musculoskeletal pain, impaired liver function, increased hemoglobin, hypertension, breast tenderness, nausea, pruritus, edema, urinary obstruction, myocardial infarction, and pulmonary embolism. In our cases, no such AEs have occurred.

4 | CONCLUSION

Although further studies, including unveiling molecular mechanisms and clinical trials, are necessary, we can conclude that administration of supra-physiological doses of T with a rapid drop to castration levels (BAT) might resensitize cancer cells to non-steroidal antiandrogens and restore resistance to other treatment modalities including ARAT and cytotoxic chemotherapy.

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CONFLICT OF INTEREST
The authors have no conflict of interest in the subject matter or materials discussed in this manuscript.

AUTHOR CONTRIBUTIONS
SH, VB, KH, TN, SS, RS, MK, TK, KN, and IS made substantial contributions to conception and acquisition of data. SH conceived of the study. SH and VB reviewed the literature, analyzed and interpreted the data, drafted and revised the manuscript. IS gave organization support to the study and interpreted the data. All authors read and approved the final version of the manuscript.

CONSENT
Written informed consent was obtained from the patients for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor in Chief of this journal upon request.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID
Vladimir Bilim https://orcid.org/0000-0002-2334-1671

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