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Bipolar androgen therapy as platform for personalized medicine in castration-resistant prostate cancer

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Abstract

Background Bipolar androgen therapy (BAT) with supraphysiologic testosterone (SPT) could be a therapeutic platform to keep the "endocrine interference" going in men with castration resistant prostate cancer CRPC Davis ID., et al(N Engl J Med 38:121-31, 2019), Denmeade SR, Sena LA, Wang H, Antonarakis ES, Markowski MC (Oncologist 28:465-73, 2023). This concept, scientifically developed by the Johns Hopkins group, has been tested in several clinical trials Denmeade SR, Isaacs JT (Prostate 70:1600-7, 2010).

Case presentation This case report details the diagnosis and novel treatment with BAT during the course of disease of a 68-year-old male patient with primary metastatic prostate cancer identified in November 2019. After treatment failure of standard therapy this patient commenced with SPT given intramuscularly at four weeks intervals and concurrent androgen deprivation throughout treatment with BAT (Fig. 1). He responded clinically with stable disease and without serious toxicity.

Keywords Bipolar androgen therapy, Castration-resistant prostate cancer, Personalized medicine

1 Introduction

Bipolar Androgen Therapy (BAT) is an emerging treatment strategy for metastatic castration-resistant prostate cancer (mCRPC), based on the paradoxical concept that supraphysiologic testosterone (SPT) can induce tumour stress and re-sensitize cancer cells to androgen receptor (AR)-targeted therapies [4]. Androgen-deprivation therapy has traditionally served as the cornerstone of treatment for men with metastatic prostate cancer. Nevertheless, emerging evidence has challenged this paradigm. For instance, clinical studies have demonstrated a paradoxical inhibitory effect of SPT on the growth of CRPC xenografts [5, 6]. Building on these observations, subsequent investigations into androgen receptor (AR) biology revealed that AR amplification occurs in up to 50% of patients with advanced disease [7–9]. In addition, AR may crosstalk with thyroid hormones thereby sustaining growth and proliferation [10].

These findings underscore a critical adaptive mechanism: resistant prostate cancer cells upregulate AR activity despite ongoing castration and AR-targeted therapies. Considering this, novel strategies such as BAT have gained attention. BAT involves rapid cycling between supraphysiological testosterone exposure and androgen deprivation, thereby disrupting tumour adaptation to chronically low androgen levels. Importantly, this approach exploits a fundamental function of AR—its role in regulating the cell cycle and DNA replication. Indeed, AR binding to DNA can induce cellular stress and trigger cell cycle arrest [11].

Taken together, these insights highlight a paradigm shift in understanding AR signalling and its therapeutic implications, paving the way for precision medicine in CRPC management.

Prior case reports have documented sustained clinical responses to BAT, even in heavily pretreated patients [12]. This case is presented to highlight several notable findings and to underscore the biological plausibility of re-establishing androgen dependence in CRPC.

Unlike in the United States, where BAT has been explored in multiple clinical trials [3, 13, 14], it remains a relatively unknown systemic therapy in Norway. BAT may offer a valuable therapeutic platform to maintain "endocrine interference" in men with mCRPC, a concept originally introduced by Huggins and Hodges and later expanded upon by the Johns Hopkins group [3, 6].

Our patient exhibited a genomic profile characterized by an overrepresented DNA damage repair (DDR) signature and features of BRCAness, making him a strong candidate for BAT. Denmeade and colleagues have proposed that AR activity and BRCAness, identified through Mann-Whitney ranking of gene expression signatures, may predict responsiveness to BAT [9].

This case report details the diagnosis and novel treatment approach using BAT in a 68-year-old male patient diagnosed with primary metastatic prostate cancer (mPCa) in November 2019.

The patient had no family history of prostate cancer. Initial pathological analysis revealed a Gleason score of 9 (Grade Group 5) across all 10 biopsy cores. Morphological examination identified intraductal carcinoma (IDC) as the predominant pattern, with focal cribriform architecture and perineural invasion.

The pretreatment prostate-specific antigen (PSA) level was 41 ng/mL. Multiparametric MRI (mpMRI) and PSMA-PET/CT imaging revealed tumour spread to pelvic lymph nodes and a solitary metastasis in a thoracic vertebra. The disease was staged as cT3bN1M1a + b. Immunohistochemical analysis of the primary tumour showed intact mismatch repair (MMR) protein expression, negative PD-L1 staining, and focal CD3 positivity. Cell morphology and flow cytometry confirmed concurrent hairy-cell leukemia (HCL). AE1/AE3 cytokeratin and NKX3.1 expression supported bone infiltration by prostate cancer cells.

Prior to initiating long-term androgen deprivation therapy (ADT), whole-exome sequencing was performed (NGS). A bioinformatics pipeline was applied to identify acquired single nucleotide variants and short insertions and deletions (indels) in the tumor sample. Sequence reads from the blood (control) and tumor samples were initially aligned to the human reference genome (build b37 with an added decoy contig) using BWA-mem v0.7.15 [15]. Germline variants (SNVs/InDels) were identified with

Illumina's DRAGEN pipeline (software version 01.011.308.3.3.11) on the existing read alignment of the control (blood) sample.

Clinically relevant genomic alterations were identified in DDR genes including *ATM* and *BARD1*, along with a dominant SBS3 mutational signature, subclonal *PTEN* mutations, and fusion transcripts involving *BRCA2* and *PIK3*. Based on tumour board recommendations, the patient received combined ADT and high-energy photon beam radiotherapy to the primary tumour. After four months of ADT, complete testosterone suppression was achieved by adding the second-generation AR inhibitor enzalutamide to goserelin during and after radiotherapy [1].

Due to COVID-19-related delays, fiducial gold markers were placed in April 2020, followed by image-guided conformal radiotherapy (74 Gy) from May to June 2020. At the end of radiotherapy, the patient's PSA nadir was 0.44 ng/mL. Follow-up MRI scans showed signal changes consistent with a positive response in bone marrow metastases, as well as regression of the prostate tumour and lymph node involvement. A 18 F-PSMA-PET (210 MBq intravenously) scanned the patient from head to lower extremities 2 h after injection. In the PET images no metastatic bone lesions were detected. Reduced uptake was noted in the prostate and pelvic lymph nodes.

By August 2020, PSA had declined to < 0.03 ng/mL, and the patient continued dual androgen blockade with goserelin and enzalutamide. In March 2021, rising PSA levels prompted discontinuation of enzalutamide. Given the patient's BRCAness profile (*BRCA2* fusion, *ATM* and *BARD1* alterations), olaparib—a PARP inhibitor—was initiated as second-line personalized therapy in April 2021 [16]. Since the patient had a second malignancy, HCL, a reduced starting dose was given. The patient experienced a sustained response for 23.8 months, with manageable hematologic toxicity affecting thrombocytes (CTCAE grade 1) and hemoglobin levels. However, the decrease in hemoglobin could have been associated with long-term use of ADT.

In February 2023, PSA levels rose again, although the patient remained in good clinical condition. A PSMA-PET scan performed at the same time with 197 MBq 18 F-PSMA and image registration 2 h later showed no metastatic lesions or local recurrence. He was enrolled in a basket trial evaluating BAT using standardized SPT (400 mg) administered intramuscularly [3], alongside continued ADT. The first BAT cycle (March–May 2023) stabilized PSA levels without notable side effects (Fig. 1). A PET scan in May (188 MBq 18 F-PSMA) showed weak PSMA uptake in retroperitoneal lymph nodes.

AR-V7 splice variant analysis, performed before and during enzalutamide treatment, revealed AR-V7 positivity—a marker often associated with resistance to AR-targeted therapies.

The second BAT cycle began in September 2023, incorporating the STEP-UP therapy concept (NCT04363164), with ARi added 28 days after each SPT injection. By October 2023, AR-V7 was no longer detectable, suggesting restored AR responsiveness.

A third BAT cycle (December 2023–March 2024) included darolutamide in step-up doses, resulting in low PSA levels. A fourth cycle (May–November 2024) combined SPT, ARi, and olaparib, followed by a fifth BAT cycle in December 2024.

In January 2025, PET/CT imaging (195 MBq 18 F-PSMA) showed increased disease activity with moderate uptake of PSMA in pelvic lymph nodes and new PSMA uptake in mediastinal lymph nodes. In addition, the PET images raised suspicion of spread to the bone. We have used several biomarkers, neuron-specific enolase in case

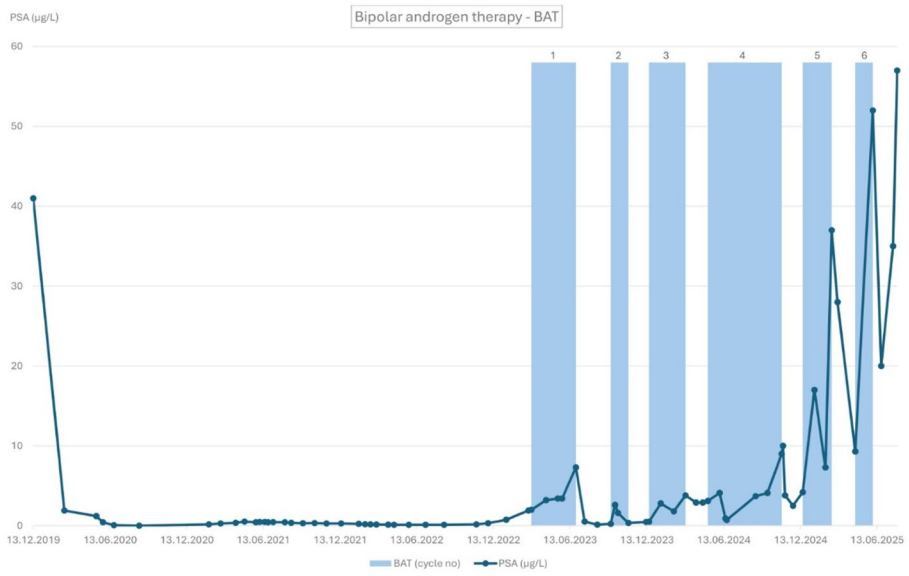

Fig. 1 Course of PSA from diagnosis and during ADT treatment and BAT cycles in blue bars. BAT-cycle1: SPT + ADT; BAT-cycle2: SPT + ADT + Enzalutamide; BAT-cycle3: SPT + ADT + Darolutamide, BAT-cycle4: SPT + ADT + Olaparib, BAT-cycle5: SPT + ADT + Olaparib, BAT-cycle6: SPT + ADT (self-administered)

of neuroendocrine PC development and tried to measure ctDNA. Circulating free DNA analysis via FoundationOne® revealed only a *BRAF* mutation, likely related to the patient's HCL. Olaparib was reintroduced in February 2025, but PSA rose to 37 ng/mL. After discontinuation of PARPi, PSA declined to 29 ng/mL and further to 9.3 ng/mL four weeks later. No clinically significant toxicity was observed upon addition of olaparib.

In May 2025, PSA increased again, and the patient self-administered SPT. PSMA-PET/CT with 201 MBq 18 F-PSMA confirmed radiologic disease progression. The progression-free interval was 26 months. In a patient with mCRPC treated with BAT, a notable progression-free interval of 26 months was achieved. Following biochemical progression—evidenced by a PSA level of 54 ng/mL and suspicious PSMA imaging—a therapy switch was recommended. The patient subsequently underwent radioligand therapy and, at the most recent follow-up, remained alive with an overall survival of 73 months from diagnosis.

2 Discussion

The patient's prolonged disease stability likely reflects a combined therapeutic effect, although the individual contributions of BAT and concurrent agents cannot be definitively distinguished. To date, all BAT studies have excluded patients with symptomatic disease, particularly those experiencing bone pain. Reported adverse events have primarily involved musculoskeletal discomfort and hormonal effects, such as breast tenderness, hot flushes, and gynecomastia. In our asymptomatic patient, we did not employ validated instruments to assess side effects or health-related quality of life. Nevertheless, we observed improved functional performance and reduced fatigue during BAT treatment.

Notably, the patient had a durable initial response to enzalutamide, and in the second BAT cycle, AR responsiveness was successfully rechallenged with enzalutamide. Notably, this has been described in BAT phase 2 trials. In the RESTORE trial, over 50% of

patients previously treated with enzalutamide responded to ARi reintroduction following BAT [14]. Similarly, the TRANSFORMER trial demonstrated a 78% response rate to enzalutamide after progression on abiraterone and BAT [13].

Monitoring treatment efficacy using PSA alone is challenging when multiple agents are administered concurrently. In this case, AR-V7—a splice variant associated with resistance to AR-targeted therapies—was used as a biomarker. It has been shown that SPT can inhibit the expression of the ligand-dependent AR variant, AR-V7 [17]. After SPT, tumours regained sensitivity to AR-targeted agents, suggesting functional modulation of AR-V7 rather than an incidental change [2].

The variant was initially detected but became undetectable following enzalutamide rechallenge, suggesting a contextual AR remodelling accounting for the BAT effect.

The addition of ARi to ADT resulted in a durable clinical response. This approach is currently being evaluated in the STEP-UP trial (NCT04363164), and was applied in our patient with darolutamide, leading to significant PSA decline and a prolonged progression-free interval.

SPT can repress genes involved in DNA repair. NGS performed on biopsies from PCa patients receiving BAT revealed that patients with "BRCAness" were more likely to exhibit clinical response to BAT. Although the patient initially responded well to olaparib during the fourth BAT cycle, reintroduction of olaparib in the fifth cycle led to rising PSA levels, which subsequently declined after PARPi withdrawal. This pattern may reflect remodelling of DDR pathways and a loss of BRCAness, as previously described in other malignancies [18].

3 Conclusion

Resistance to androgen receptor (AR) blockade in castration-resistant prostate cancer (CRPC) is paradoxically associated with sustained AR signalling. In this case, the clinically asymptomatic patient exhibited PSA expression in response to supraphysiologic testosterone (SPT), and Bipolar Androgen Therapy (BAT) achieved over two years of clinical benefit without clinical side effects. These findings support the potential of BAT as a promising treatment strategy and warrant its consideration in selected patients with CRPC.

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Data availability
All processed molecular data of the tumour biopsy and R code for the transcriptome analysis are available through the following DOI: [**https://doi.org/10.5281/zenodo.4596571**](https:/doi.org/10.5281/zenodo.4596571) .

Declarations

Ethics approval and consent to participate
This work contains genomic findings approved by the institutional tumour board (em professor Eivind Hovig, dr. Kjetil Berner).

Consent for publication
The listed authors, Wolfgang Lilleby, Hans Geinitz and Samuel Denmeade have substantially contributed to the article and accepted the final version.

Competing interests
The authors declare no competing interests.
The study was conducted according to the guidelines of the Declaration of Helsinki (in its most recently amended version). All procedures followed were in accordance with the ethical standards as required by national law. The patient gave his written consent to publish his case.

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