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Bipolar Androgen Therapy: A Paradoxical Approach for the Treatment of Castration-resistant Prostate Cancer

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Since Huggins and Hodges first described the palliative benefits of surgical or medical castration in 1941, the treatment of advanced prostate cancer has focused almost exclusively on inhibiting androgen receptor (AR) signaling (ARS) [1]. Often overlooked, however, is the fact that Huggins also postulated that treatment with excess androgens, a strategy he called "hormone interference", could also produce a therapeutic benefit [2]. The seemingly paradoxical ability of supraphysiologic androgen levels to inhibit prostate cancer growth has been demonstrated in multiple in vitro and in vivo studies. In addition, a number of case series recounting the benefits of testosterone (T) supplementation in prostate cancer patients have peppered the literature for more than half a century [3–6]. More recently, preclinical studies have shed light on the mechanisms underlying the antitumor effects of androgens [7–11]. These findings have renewed our interest in exploring high-dose T as a therapeutic strategy for men with advanced prostate cancer, and have provided the impetus for the development of a series of prospective studies testing intermittent high-dose T in the clinic, a therapeutic strategy we have termed *bipolar androgen therapy* (BAT).

As prostate cancer cells transition from a hormone-sensitive to castration-resistant state, one of the most frequently observed events is adaptive upregulation of AR expression [12]. It has been shown that AR upregulation drives resistance to ARS inhibition. However, such upregulation may also create a therapeutic liability. We and others have observed that a number of AR-overexpressing cell lines display blunted cell growth and cell death when exposed to supraphysiologic androgen levels [8,13–19]. Thus, at supraphysiologic levels, T is able to exert a pharmaceutical effect in AR-overexpressing prostate cancer cells that results in inhibition of prostate cancer growth. Cells that adaptively downregulate AR expression or that have low basal levels of AR may also be killed when T levels are allowed to rapidly drop back to castrate levels over a cycle of BAT.

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Studies exploring the mechanisms behind the paradoxical antitumor effects of supraphysiologic androgen levels have demonstrated that in high-AR cell lines, rapid transition from a castrate to a high-androgen environment induces transient double-strand DNA (dsDNA) breaks that can produce gene rearrangements such as *TMPRSS2-ERG* [7,11,13]. More recently, a clinical case report described an extreme response to BAT in a patient with germline mutations in the homologous recombination genes *BRCA2* and *ATM* [20].

Another potential mechanism underlying the antitumor effects of high-dose T is related to the role that AR plays as a DNA licensing factor in prostate cancer cells [9]. During the cell cycle, nuclear AR binds to origins of replication and participates in the formation of prereplicative complexes that allow DNA replication to proceed. Under normal conditions, AR is degraded from origins of replication and is absent during mitosis. Under high-androgen conditions, however, sufficient ligand-bound nuclear AR persists during mitosis, and probably interferes with DNA relicensing, leading to cell death in daughter cells.

Finally, differences in the AR transcriptome are present when high-AR cell lines are exposed to either high or low androgen concentrations [21]. Under high-androgen conditions, AR can repress a number of genes, including *AR* and those involved in androgen synthesis, DNA synthesis, and proliferation. Therefore, high-dose T may lead castration-resistant cells to transition from a more oncogenic transcriptome associated with castrate T levels to a high-androgen transcriptome that does not support cancer proliferation.

To exploit these mechanistic findings, we developed a mode of intermittent high-dose T therapy in the clinic termed BAT. We hypothesized that rapidly cycling between the polar extremes of near-castrate and supraphysiologic serum T (SPT) levels would prevent adaptive changes in AR expression, prolonging the length of time during which patients respond to this therapy. Furthermore, because recent studies have shown that the dsDNA breaks and apoptosis induced by high doses of androgens are transient, rapid cycling of T could result in repeated rounds of DNA damage, enhancing antitumor effects [22].

To date, BAT has yielded encouraging preliminary results in CRPC patients. In our first pilot study testing BAT combined with etoposide, we found that of the 14 patients completing at least the first 3 mo of therapy (response-evaluable cohort), 50% had PSA declines and 5/10 RESICT-evaluable patients had an objective soft-tissue response [13]. It is also notable that there was a high rate of response to subsequent ARS inhibitors (eg, abiraterone, antiandrogens), potentially indicating that BAT could effectively resensitize tumors to drugs inhibiting ARS. This observation provided justification for a study (NCT02090114; RESTORE) evaluating BAT in men after abiraterone or enzalutamide, with the co-primary endpoints of (1) response to BAT and (2) response to rechallenge with either abiraterone or enzalutamide. Preliminary results from the enzalutamide arm of the study have demonstrated a >50% PSA decline and an objective response in approximately one-third of patients. BAT was well tolerated, with low-grade musculoskeletal pain and breast tenderness being common side effects. On rechallenge with enzalutamide, ~50% of patients had a >50% PSA response. BAT is also able to suppress AR-V7 expression in most men with detectable AR-V7 in baseline CTC samples [23].

At present, BAT is being definitively tested in a large (n = 180) randomized trial (NCT02286921; TRANSFORMER) in asymptomatic CRPC patients who have failed on abiraterone. In this study, BAT is being compared to enzalutamide for the primary endpoint of progression-free survival. Patients are notably allowed to cross over following progression to the first therapy, with an important secondary endpoint being PSA progression-free survival on the second agent in order to further examine the question of the ability of BAT to resensitize tumors to ARS inhibitors.

As it stands, not all men respond favorably to treatment, and there is an urgent need to develop biomarkers able to discriminate between BAT responders and nonresponders. Candidate predictive biomarkers include high AR/AR-V7 expression and the presence of mutations in genes involved in DNA repair (eg, *BRCA1/2*, *ATM* and others). The case report of an extreme BAT responder with germline *BRCA2* and *ATM* mutations supports DNA damage as one potential mechanisms underlying response to high-dose T, while a second case report showing eradication of an *AR* copy gain (detected from ctDNA) and a clinical response to high-dose T supports AR levels as an important mediator of BAT's efficacy [20,24]. These hypotheses are actively being investigated in the RESTORE and TRANSFORMER trials.

Optimization of SPT-based therapies is still needed. While there is a strong rationale for an intermittent approach (ie, BAT), preclinical studies have demonstrated that continuous exposure to supraphysiologic androgen levels also has a robust antitumor effect. Clinical trials testing different dosing schedules are needed to determine if better modes for administration of SPT-based therapy exist. It also stands to reason that combinatorial SPT-based therapies may produce better outcomes. An emerging understanding of the mechanism of BAT inhibition have suggested that potential combinatorial strategies (eg, with PAPR inhibitors, platinum agents, proteasome inhibitors, immune checkpoint inhibitors) may be warranted, as are rational sequencing strategies (time-sequential therapies).

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