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The Role of Testosterone in the Treatment of Castration Resistant Prostate Cancer

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Abstract

Most men with metastatic prostate cancer who are treated with androgen deprivation therapy will eventually develop castration-resistant disease. In this review, we examine the molecular mechanisms that constitute castration resistance and how these processes may be exploited using testosterone-based therapies. We detail how the utilization of super-physiologic doses of testosterone at regular intervals, followed by a rapid clearance of testosterone through continued chemical castration, also known as bipolar androgen therapy, offers an especially promising therapeutic approach. We investigate the historical basis for this modality, detail recent early phase clinical trials that have demonstrated the feasibility and efficacy of this treatment, and describe an ongoing clinical trial comparing this modality to a currently accepted standard of care, enzalutamide, for castration-resistant prostate cancer. Finally, we explore how this treatment modality will continue to be refined in the near future.

Keywords

bipolar androgen therapy; castration resistant prostate cancer; testosterone therapy

Introduction

Drs. Charles Huggins and Clarence Hodges first demonstrated the role of androgens in the physiology and treatment of metastatic prostate cancer in 1941, a discovery that eventually garnered Huggins the Nobel Prize in Medicine and Physiology.[1] Androgen deprivation therapy remains a highly effective first line treatment for metastatic prostate cancer. Most patients treated with systemic androgen deprivation, however, eventually develop castration resistant prostate cancer (CRPC) that progresses rapidly despite ongoing systemic hormone suppression. The median survival for patients with metastatic CRPC ranges from approximately 12.1 to 27.0 months depending on a patient's individual risk status.[2, 3] A patient's risk stratification is closely correlated with performance status, sites of metastatic disease, narcotic requirements, and laboratory abnormalities, including lactate dehydrogenase, hemoglobin, prostate specific antigen (PSA), and albumin levels.[2, 3] Androgens and androgen receptor signaling have pleiotropic effects on prostate carcinoma

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cell survival, proliferation, and various forms of death via the programmed cell death pathway and cell cycle arrest.[4, 5] This increased understanding has been accompanied by the development of novel approaches to treating patients with CRPC, including bipolar androgen therapy (BAT), a therapeutic approach in which super-physiologic doses of testosterone are delivered at regular intervals, only to be followed by a rapid clearance of testosterone as androgen levels are once again reduced to levels consistent with castration.[6–8] In this review, we discuss what is currently understood about mechanisms of resistance to anti-androgen therapy, clinical experiences to date with the use of testosterone therapy for the treatment of CRPC, and ongoing efforts in both translational and clinical medicine to refine testosterone-based approaches for the treatment of CRPC.

Molecular mechanisms of androgen ablation

Multiple molecular mechanisms account for the effects of androgen ablation on prostate cancer cell death. Androgen deprivation for the treatment of hormone-sensitive prostate cancer primarily acts through the programmed cell death pathway, a mechanism that ultimately results in cell cycle arrest and apoptosis in prostate cancer cells.[4, 5] Xenografted model systems have demonstrated that testosterone disrupts the cellular machinery involved in DNA replication and that the molecular effects of androgen ablation occur rapidly after the onset of therapy, with the proportion of prostate cancer cells progressing from G_0 through the S phase plummeting nearly 100 fold within 48 hours of treatment initiation.[4, 9] How do these replicative processes stall? On a molecular level, androgen receptors (AR) constitute a component of the replication complexes (RCs) that assemble at specific sites within the genome. In prostate carcinoma cells, these complexes serve as licensing factors that ensure each segment of the genome is replicated only once. The factors are recycled after each cell division.[10] Initially, androgen deprivation in castration sensitive prostate carcinoma cells rapidly diminishes the pool of receptors that are available for incorporation into RCs, cellular division ceases as these critical factors are depleted, and cell death rapidly occurs via numerous mechanisms, including, but not limited to, up-regulation of transforming growth factor-beta1 (TGF-β1), alteration of the prostatic microenvironment, and degeneration of the prostatic microvasculature.[11–20]

Molecular mechanisms of castration resistance

The majority of patients treated with androgen ablation will eventually develop castration resistant cancer. Multiple molecular mechanisms account for castration resistance. In many patients, the pool of AR mRNA and available full length ARs increases in a manner independent of exogenous androgen levels as castration resistance develops.[10, 21–24] The levels of intracellular ARs present in patients with CRPC may eventually increase to values 30 to 90 times greater than amounts seen in patients without CRPC.[24] This pool of ARs enables cellular division to proceed by binding to RCs despite exogenous testosterone levels that persist at amounts consistent with castration.[10] This up regulation of ARs and persistently elevated rates of cellular division in the setting of continued androgen ablation is driven by multiple processes, including stimulation by adrenal androgens,[22] an increased capacity for CRPC cells to convert adrenal androgens to testosterone and dihydrotestosterone,[25] an upregulation of alternate signaling pathways within the cell,[23, 26]

increased levels of intracrine steroidogenesis that enable intracellular androgens to approach levels seen in eugonadal patients,[27, 28] an increased sensitivity of the AR to lower levels of androgens,[28] splicing alterations that result in upregulated, truncated receptors that are activated in the absence of ligands,[24, 28] and mutations within the AR that result in AR antagonist resistance and/or conversion of AR antagonism to agonism. To date, the alternative androgen pathway has been targeted via the development of drugs such as abiraterone acetate, which inhibits CYP17, a component of the adrenal androgen synthesis pathway, and AR antagonists such as enzalutamide, which directly inhibits the androgen receptor from translocating to the cellular nucleus where it engages in DNA binding and cellular signaling.[29] These agents have both achieved modest successes for patients with metastatic CRPC.[29–31]

The development of testosterone-based approaches for the treatment of castrate resistant prostate cancer in preclinical models

While great efforts have focused on suppressing the growth of CRPC by maintaining castration-equivalent androgen levels and simultaneously blocking other molecular targets along the androgen signaling axis, parallel projects have utilized super-physiologic androgen doses to exploit unique susceptibilities within CRPC cells and subsequently delay disease progression.[24] This approach was first utilized with modest success in murine xenografts during the late 1990s,[24, 32] and a similar body of evidence has emerged using supraphysiologic doses of estrogen for refractory estrogen-receptor positive breast cancer.[33–35] Multiple mechanisms may account for the potential utility and anti-cancer effects of super-physiologic testosterone doses in the treatment of CRPC. First, super-physiologic testosterone disrupts the recycling of ligand-bound ARs within the nucleus of the cell, as ligand bound ARs are unable to be degraded within the cell or serve as licensing factors. This deficiency prevents the cellular cycle from progressing through mitosis, which in turn induces apoptosis.[24, 36] Secondly, super-physiologic testosterone directly damages DNA through the recruitment of topoisomerase Iiβ and ARs, a process that results in double stranded DNA breaks and subsequent cell death.[7, 8] This process also recruits the cell's DNA repair machinery, including Ku70, Ku80, PARP1, ATM, and DNA-dependent protein kinase (DNA-PK) to the sites of the genetic damage.[7, 37–41] Bipolar androgen therapy dose schedules have intermittently been combined with cytotoxic therapies in studies designed to target DNA-repair machinery as well as to preferentially act upon cycling cells brought into cycle via testosterone therapy.[42] Optimizing the selection and dosing schedule of cytotoxic therapies targeted at molecular DNA repair machinery delivered in concert with testosterone-based therapies will be an area of active research in the future as greater experience is garnered with testosterone-based therapeutic approaches.

Clinical experience utilizing testosterone replacement for the treatment of castration resistant prostate cancer

There is a significant body of evidence dating back to the 1960s detailing the use of testosterone replacement for the treatment of CRPC. Early experiences with testosterone therapy included patients with heterogeneous disease patterns and varying degrees of

hormone sensitivity, including men with hormone naïve disease who had been previously untreated, patients with hormone-sensitive disease, and men with CRPC.[43] The results from these studies were often discouraging as patients frequently experienced pain flares at sites of bony disease shortly after the initiation of treatment.[44] Patients in these series were provided varying levels of testosterone replacement at doses ranging from normal physiologic to super-physiologic amounts. Testosterone administration was often accompanied by an ensuing rise in the patients' PSA levels, only to be followed in many cases by a rapid decline in PSA and symptom relief. Unfortunately, patients treated with testosterone therapy uniformly experienced progressive disease, at which point the testosterone was often withdrawn in order to achieve androgen levels consistent with castration. Interestingly, patients often experienced regression of their cancers at the time of repeat androgen deprivation.[45, 46]

Early phase clinical trials examining bipolar androgen therapy

Early clinical experiences informed the development of more contemporary early phase clinical studies by Szmulewitz et al. and Morris et al. investigating the utilization of transdermal testosterone for the treatment of metastatic CRPC in men with low burdens of disease. Men in both studies demonstrated good tolerance of the regimen, with only 1 out of 27 enrolled patients, a patient in the Szmulewitz study who experienced grade 4 cardiac toxicity, experiencing grade 3 or 4 toxicity. An additional patient enrolled in the Morris study experienced a worsening of a pre-existing spinal lesion and subsequent cord compression before being taken off study.[44] A minority of men enrolled in both studies experienced declines in their PSA levels, with 20% of patients in the Szmulewitz study and 33% of patients in the Morris study experiencing PSA declines. No differences in mortality or progression were detected given the early phase nature of the studies and small sample sizes (results summarized in Table 1). The majority of patients in both studies did not experience a symptomatic flare of disease or progression in response to the administration of transdermal testosterone. This lack of a symptomatic flare, as was frequently observed in patients treated with testosterone in earlier, less rigorous, studies, reiterated the safety of utilizing super-physiologic testosterone dosing as a therapeutic approach for CRPC.[47, 48] Of note, the testosterone regimen in both studies achieved, on average, eugonadal levels of testosterone as opposed to the super-physiologic levels that were observed in preclinical models. No statistically significant correlation between transdermal dose of testosterone and time to disease progression was observed, although this conclusion must be analyzed in the context of the small sample sizes of these studies.[44, 49]

Ongoing clinical trials examining bipolar androgen therapy

The aforementioned early phase studies informed the development of a phase I pilot study, the Testosterone Revival Abolishes Negative Symptoms, Fosters Objective Response and Modulates Enzalutamide Resistance (TRANSFORMER) study, examining the safety and efficacy of the administration of super-physiologic doses of testosterone via intramuscular (IM) injection in combination with oral etoposide. Oral etoposide has minimal activity in metastatic CRPC as a single agent, with a median overall survival of 31 weeks in a small early phase clinical trial,[50] however, oral etoposide was combined with BAT in order to

theoretically maximize the cytotoxic effects of any double stranded DNA breaks that occurred via testosterone administration. Inclusion criteria included men with metastatic CRPC, castrate-level testosterone levels for one year, and rising PSA levels and/or limited disease burden, defined as 5 or less bony metastases and 10 or less total metastatic sites. The results of this pilot study were promising. Overall, 14 patients were enrolled, and the treatment was well tolerated. A minority of patients experienced grade 3 or 4 toxicities, including neutropenia (6.3% of patients) and pulmonary embolism (12.5%). One death secondary to neutropenic sepsis/pneumonia occurred (6.3%). Unlike the earlier phase I studies from Szmulewitz et al. and Morris et al. that utilized transdermal testosterone, the TRANSFORMER pilot study group achieved super-physiologic serum testosterone levels two days after intramuscular injection, with patients experiencing an average testosterone level of >1500 ng/dL, well above the upper range of normal (700 ng/dL). Overall, 50% of patients experienced a decline in PSA. In total, 100% of the 10 patients who completed BAT cycling and who then proceeded to subsequent androgen-ablating therapies (abiraterone, enzalutamide, bicalutamide, or nilutamide) experienced declining PSAs in response to second line treatments. This result suggested BAT may potentially re-activate the androgen signaling axis in prostate cancer cells that were previously deemed castration resistant.[51]

This pilot study informed the Phase 2 portion of the TRANSFORMER clinical trial. The trial opened in January 2015 and is currently randomizing patients between two treatment arms, with one group of patients receiving super-physiologic testosterone injections on a 28-day schedule and the other group receiving daily doses of 160 mg of oral enzalutamide on a 28-day cycle. Of note, the BAT arm does not include etoposide or any other cytotoxic chemotherapy. The primary study outcome is radiographic progression free survival with secondary outcomes that include PSA trends, radiographic response, time to PSA progression, and the frequency of adverse events. Crossover is allowed at time of progression, and response rates to second-line treatments after crossover will be calculated as part of the secondary analysis (i.e., response rates for patients receiving enzalutamide after progressing on BAT). Quality of life will also be monitored as a secondary outcome after anecdotal evidence in the early phase studies from Szmulewitz and Morris, as well as the TRANSFORMER pilot study, demonstrated improvements in functional status, patient well-being, libido, and sexual function for patients receiving BAT.[44, 49, 52] The omission of a classic cytotoxic agent directed at molecular DNA repair mechanisms in the phase 2 portion of the TRANSFORMER study will significantly inform the interpretation of the study's results and subsequent trial design. A promising result in the phase 2 portion of TRANSFORMER, for example, will likely result in the omission of classically cytotoxic therapies on the BAT-based arm of any subsequent randomized phase 3 trial. In theory, this omission may improve the overall safety profile of the BAT arm as compared to the comparator, although it is important to note that BAT in combination with etoposide was already especially well tolerated in the TRANSFORMER pilot study. Secondly, a promising result in the phase 2 portion of the TRANSFORMER study would suggest that BAT monotherapy is sufficient to achieve clinically relevant levels of cytotoxicity even in the absence of a potentially synergistic cytotoxic therapy such as etoposide. A natural extension of this conclusion, however, would be to further refine BAT-based approaches in a systematic, rational manner by combining these therapies with cytotoxic agents targeted at

molecular DNA repair mechanisms in an attempt to further improve the clinical outcomes that may be achieved with BAT therapy alone.

Conclusion

Most men with metastatic prostate cancer who are treated with first line androgen deprivation therapy will eventually develop castration-resistant disease. Mechanisms of resistance to androgen deprivation include alternative sources of androgens, such as the adrenal glands,[22] the increased ability for CRPC cells to convert adrenal androgens to testosterone and dihydrotestosterone,[25] utilization of alternative signaling pathways within the cell,[23, 26] increased intracrine steroidogenesis,[27, 28] enhanced sensitivity of the androgen receptor to low level androgens,[28] splicing alterations that result in upregulated, truncated receptors that are activated in the absence of ligands,[24, 28] and mutations within the AR that result in AR antagonist resistance and/or conversion of AR antagonism to agonism. Small case series including men with both androgen sensitive disease and CRPC,[43, 45–48, 53–57] phase I clinical trials,[44, 49] and the TRANSFORMER pilot study have demonstrated that these mechanisms of androgen deprivation resistance may be exploited using testosterone based therapies, including bipolar androgen deprivation therapy.[51] Preclinical models have suggested that the efficacy of testosterone therapy stems from its ability to directly act as a cytotoxic agent by inducing double stranded DNA breaks as well as by disrupting licensing of ligand-bound androgen receptors within prostate cancer cells.[7, 8, 24, 36] These experiences informed the ongoing phase 2 TRANSFORMER study examining BAT as compared to enzalutamide for men with low-volume metastatic CRPC. TRANSFORMER is scheduled to complete accrual in December 2018.[52] The study notably omits a classic cytotoxic agent, such as etoposide, from the BAT arm, and the ability to combine classic cytotoxics with testosterone-based therapies in an effort to achieve therapeutic synergy will remain an active area of investigation in the near future.

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Table 1

Early phase clinical trial experience with testosterone-based therapies.[44, 49, 51]

Author	Accrual	Median Age	Median PSA (ng/mL) at Enrollment	% Achieving PSA Decrease	Time to Progression (Days)	Etoposide included?
Szmulewitz *et al.*	15	73	11.1	20	63(14–672)	No etoposide
Morris *et al.*	12	65	9.1	58	86 (27–250)	No etoposide
Schweizer *et al.*	14	71	21.7	50	221 (95 – 454)	Etoposide included