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INVITED RESEARCH HIGHLIGHT

Prostate Cancer

From bench to bedside: bipolar androgen therapy in a pilot clinical study

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Prostate cancer remains a leading cause of cancer death in Europe and the United States and is an emerging problem in Asia despite significant improvements in available treatments over the last few decades. Androgen deprivation therapy (ADT) has been the core treatment of advance-staged disease since the discovery of prostate cancer's androgen dependence in 1941 by Huggins *et al.*[1] Options for initial medical treatment include gonadotropin-releasing hormone analogues such as leuprolide (LHRH agonist) and degarelix (LHRH antagonist) and androgen receptor (AR) binding agents such as bicalutamide. Although most patients will initially respond to either surgical or medical castration, there is almost always progression to castration-resistant prostate cancer (CRPC) necessitating treatment with more novel agents.[2] However, even drugs such as abiraterone and enzalutamide, two next-generation agents used commonly in metastatic CRPC, have failed to demonstrate persistent efficacy in most patients.[3,4]

Emerging research has proposed several mechanisms of resistance to ADT including constitutively active AR splice variants, overexpression of AR, and mutations of the ligand-binding-domain of AR.[5] Preclinical studies published by Isaacs *et al.*[6] and Haffner *et al.*[7] on adaptive auto-regulation of AR and induction of DNA damage with testosterone therapy in CRPC cells provide a rationale for a novel approach to overcoming castration resistance: bipolar androgen therapy (BAT). By actively exposing cells with adaptive changes in AR function to supraphysiologic levels of androgen, nuclear AR loses the flexibility to be removed from origin of DNA replication sites thereby interrupting mitosis and causing tumor cell death. This is then followed by a return to a castrate level of testosterone leaving surviving cells with baseline low AR or adaptive down-regulated AR again vulnerable to cell death.

Translating this work from bench to bedside, Schweizer *et al.*[8] recently published their experience on CRPC patients treated with multiple sequential cycles of supraphysiologic androgen in the setting of ongoing ADT. This single-institution pilot study enrolled 16 asymptomatic CRPC patients with low-to-moderate burden metastatic disease, previously treated with chronic androgen ablation for over 1 year. Patients received three 28-day cycles of combination testosterone cypionate (d1, 400 mg intramuscular) and etoposide (d1–14, 100 mg oral), while continuing LHRH agonist therapy in order to suppress endogenous testosterone synthesis and allow rapid cycling. In this study, supraphysiologic testosterone levels (mean >1500 ng dl^{-1}) were achieved 2 days after injection in the majority of patients with a drop to ~600 ng dl^{-1} 2 weeks post- and to ~150 ng dl^{-1} 4 weeks post-treatment. No patient returned to a castrate level of <50 ng dl^{-1} 28 days after therapy initiation though many approached this level. The primary endpoint of the study was the rate of prostate-specific antigen (PSA) decline below baseline after three cycles of therapy. Radiographic disease was followed with computed tomography scans every 3 months and bone scans every 6 months. Patients with PSA trending down or ≤50% of pretreatment baseline continued on treatment until disease progression was seen.

Fourteen out of 16 patients completed the first three cycles of therapy; two patients dropped out of the study after a single cycle due to toxicity. Seven patients (50%) demonstrated a PSA response, 6 after the initial stage. Eight out of 10 (80%) patients with RECIST-evaluable soft tissue metastases at baseline did not progress on treatment with 1 CR, 4 PRs and 3 patients with stable disease. No patient had progressive bony metastatic disease per PCWG2 criteria. A *post hoc* analysis of PSA progression in patients with subsequent second-line ADT after BAT showed a 100% response and a reversal of anti-androgen resistance in two cases. Most adverse events were consistent with known side effects of etoposide. None of the patients developed new pain or skeletal events. In addition, quality of life improved in patients with intact sexual function before ADT as they had a return of sexual function during the study.

This pilot study showed that BAT was not only well-tolerated but demonstrated efficacy in the form of a PSA decline in 50% of patients with many also achieving a significant radiographic response. All patients who progressed responded to subsequent second-line hormonal therapies. These data reinforce the available preclinical studies supporting the potential of BAT to reverse resistance to androgen-ablative therapies. This trial also raises awareness of the potential value of chemotherapeutic agents such as etoposide that has previously demonstrated little clinical efficacy[9], but may have the potential of enhancing double-strand breaks when used in conjunction with BAT.

Though promising, there are several issues that warrant careful consideration. First, these results are not applicable to all patients with metastatic CRPC. Patients with symptomatic metastatic disease were excluded from this study given concerns of worsening of pain with high levels of testosterone. Additionally,

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patients on ADT for <1 year were not included given concerns about lack of a reasonable level of the adaptive AR. Second, while promising, the risk/benefit ratio of adding etoposide to BAT needs further evaluation especially as the majority of the detected toxicities could be attributed to etoposide.[10] So far, docetaxel-based chemotherapy has the strongest track record of efficacy in men with CRPC.[11] Additionally, cabazitaxel has demonstrated efficacy in patients pretreated with docetaxel. How to best sequence chemotherapy and hormonal therapies and which drug and dosage to choose for achieving maximum synergistic effects are among the essential questions to answer with future clinical trials. Potential clinical cross-resistance between taxanes, androgen-directed agents, and novel chemotherapeutic approaches require further elucidation.

Additionally, questions remain in terms of which patients are most likely to respond to BAT. In the authors' preclinical work, androgen rapidly eliminated AR variant expression in VCaP cells but not in CWR22-Rv1 cells. LNCaP cells with T877A-mutated AR and LAPC-4 cells with wild type AR show differential responses to androgen and nonsteroidal anti-androgen therapy.[12] Significant inter-tumor heterogeneity in terms of mutational profiles also complicates the potential broad application of this therapy.[13] Further genomic analyses will no doubt shed light on the efficacy of BAT and its potential pitfalls. Lastly, while the results of this pilot study are encouraging, a larger patient cohort with refined stratification and long-term follow-up is required before BAT can be widely accepted into clinical practice.

In conclusion, this initial clinical study shows encouraging results for BAT as a novel treatment for patients with metastatic CRPC. If its efficacy and safety are verified in future prospective clinical trials, BAT will be yet another valuable arrow in the Oncologist's quiver and a strong example of translating important findings from the bench to the bedside.

COMPETING INTERESTS

The authors declare no competing interests.

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