Nature Reviews Urology | Published online 3 Jan 2018; doi:10.1038/nrurol.2017.223

PROSTATE CANCER

Rapid testosterone cycling reverses castration resistance

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Bipolar androgen therapy (BAT) can induce clinical responses in men with metastatic castration-resistant prostate cancer (mCRPC) and can resensitize tumours to enzalutamide. Thus, BAT could be used in sequence with androgen-ablative treatments to improve outcomes for men with this disease.

Promising data from a pilot study indicated that BAT alone (in which levels of circulating androgens are rapidly cycled between supraphysiological and castration concentrations) induced clinical responses in men with mCRPC. This observation caused researchers to hypothesize that BAT could exploit the adaptive androgen receptor (AR) upregulation that occurs during antiandrogen therapy.

For this multicohort, single-centre, open label, phase II trial of BAT, investigators recruited patients with mCRPC whose disease had progressed whilst they were receiving therapies directed against the AR, such as enzalutamide. The BAT regimen consisted of 400 mg intramuscular testosterone cypionate on day 1 of a 28-day cycle with continuous gonadotropin hormone-releasing hormone agonist therapy until disease progression (serum PSA levels 25% higher than baseline after three BAT cycles). After disease progression and a 28-day washout period, participants could proceed to 160 mg oral enzalutamide daily. The co-primary end points were investigator-assessed 50% reductions in serum PSA (PSA_{50}) level from baseline for BAT and enzalutamide treatment (baseline PSA concentration set at initiation of respective treatment). Secondary end points were safety, tolerability, PSA progression-free survival (PFS), clinical or radiographic PFS, objective response in measurable lesions, metabolic studies, and quality of life (QOL) measures.

Overall, 30 patients were recruited to this trial. All men had previously received enzalutamide and were refractory to this therapy. All participants received at least one cycle of BAT, with a median of six cycles being administered. In total, 30% of patients achieved a PSA_{50} during BAT; among the patients with RECIST-evaluable lesions, 50% had a partial or complete response. Median PFS on BAT was 3.3 months and median clinical or radiographic PFS was 8.6 months. The most common (in 10% of patients) grade 3–4 adverse event during BAT was hypertension, three grade 3–4 adverse events were potentially attributable to testosterone, and transient pain flares occurred in two men. No dose-limiting toxicities, dose adjustments, or treatment-related deaths occurred. Overall QOL did not differ between baseline and after three BAT cycles, but IIEF scores significantly increased.

In total, 70% of patients who completed BAT proceeded to enzalutamide treatment rechallenge. Of patients receiving enzalutamide rechallenge, 15 achieved a PSA_{50}. Median PFS for this group of patients was 5.5 months and median clinical or radiographic PFS was 4.7 months. The low-grade adverse events that occurred during enzalutamide treatment were consistent with previous reports. Serious adverse events were experienced by five patients, but were not assessed as being probably, likely, or definitely related to treatment. No patient deaths occurred.

Analysis of circulating tumour cell (CTC) and AR-V7 status showed that response to BAT occurred in 31% of men who were CTC-negative at baseline, 27% who were CTC-positive and AR-V7-negative, and 33% who were CTC-positive and AR-V7-positive. Response to enzalutamide rechallenge occurred in 60% of men who were CTC-negative at baseline, 55% who were CTC-positive and AR-V7-negative, and none who were CTC-positive and AR-V7-positive.

These results support the hypothesis that rapid cycling of androgens using BAT in the setting of prostate cancer progression could be clinically beneficial to men with mCRPC. Furthermore, BAT can resensitize resistant disease to enzalutamide therapy. Currently, two further studies on BAT in the post-abiraterone setting and for newly CRPC are ongoing and will add to our knowledge regarding the clinical utility of BAT.

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ORIGINAL ARTICLE Teply, B. A. Bipolar androgen therapy in men with metastatic castration-resistant prostate cancer after progression on enzalutamide: an open-label, phase 2, multicohort study. *Lancet Oncol.* http://dx.doi.org/10.1016/S1470-2045(17)30906-3 (2017)

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