

Square-Wave Transdermal Testosterone Followed by Enzalutamide in Metastatic Androgen Pathway Modulation Resistant Prostate Cancer (mAPMR): A Phase II Trial

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Background: Androgen Receptor overexpression in mAPMR creates a therapeutic vulnerability to supraphysiologic testosterone (SPT). SPT is typically delivered as bipolar androgen therapy (BAT), which rapidly cycles testosterone between supraphysiologic and near-castrate levels. However, IM testosterone cannot be rapidly withdrawn or easily titrated, and high peak levels may contribute to adverse events, including venous thromboembolism. We therefore hypothesized that transdermal (TD) testosterone could achieve supraphysiologic levels with greater dosing flexibility, favorable safety, antitumor activity, and androgen receptor pathway inhibitor (ARPI) resensitization. In the Square Wave T trial, we tested this approach by alternating TD testosterone with enzalutamide.

Methods: Square Wave T was a single-arm, single-center Phase 2 trial at the University of Colorado. Eligible patients had mAPMR with castrate testosterone (<50ng/dL) and remained on androgen deprivation therapy (ADT). Prior treatment with enzalutamide or apalutamide was not permitted, although any number of other prior therapies was allowed. Patients were excluded for disease posing unacceptable risk of testosterone induced tumor flare, active CNS disease, or clinically significant cardiovascular disease. Patients received transdermal 1% testosterone gel, initially 100mg daily (two 50mg packets). Testosterone was measured after 2 weeks, and dosing was adjusted to a target level of 900-1500 ng/dL, with further adjustments permitted on day 1 of each 4 week cycle. After at least 12 weeks, patients switched to enzalutamide for PSA, radiographic, or investigator assessed clinical progression.

Results: 30 patients were enrolled. The most common site of metastasis was bone (26, 87%). A small minority had visceral metastases (3, 10%). After beginning study treatment with TD testosterone, the median peak testosterone level was 1128 ng/dL (IQR 898-1433). During the testosterone treatment phase, 11% (3/27) of patients achieved a PSA50 response. Of the patients who switched to enzalutamide on study, 86% (19/22) achieved a PSA50 response relative to PSA at the time of therapy switch (19/22). When compared to baseline PSA levels, 45% (10/22) of patients achieved a PSA50 response during the enzalutamide treatment phase. After 12 weeks of testosterone therapy, median loss of fat mass was 1925 grams (IQR: 638-3114) and median gain of lean mass was 4210 grams (IQR: 2619-5331).

Conclusions: Transdermal testosterone reliably achieved supraphysiologic levels and was feasible to administer. Although PSA responses to testosterone were modest, subsequent enzalutamide produced frequent PSA responses, supporting ARPI resensitization after SPT. Testosterone was also associated with favorable changes in body composition, including increased lean mass and decreased fat mass. These findings support further study of transdermal "square wave" testosterone as a titratable alternative to BAT.

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