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Transdermal square-wave testosterone therapy: A pilot trial in metastatic castration-resistant prostate cancer.

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Background: Metastatic castration-resistant prostate cancer (mCRPC) becomes resistant to anti-androgen therapies due to a variety of adaptive mechanisms. Intramuscular bipolar androgen therapy (BAT) which alternates between high and low testosterone (T) levels is therapeutically active in mCRPC and confers sensitivity to second-generation androgen receptor antagonists such as enzalutamide (ENZA). We hypothesized that transdermal T with sustained supraphysiologic T levels would lead to high response rates to ENZA in mCRPC. We also hypothesized Square-wave transdermal T therapy would be a safe alternative to BAT due to the ability to quickly withdraw therapy in the setting of symptoms. **Methods:** This was an open-label, single-site, phase 2 feasibility trial in men with asymptomatic mCRPC who had not previously received ENZA. Transdermal T was administered at a dose of 100 mg/day for a minimum of 12 weeks and until disease progression. Therapy was then switched to ENZA 160 mg/day until next disease progression. Patients who initially responded to T could receive a second course of transdermal T followed by ENZA, remaining on study until progression on both T and ENZA, or for the 12-month study duration, whichever was sooner. ADT was continued throughout. The primary endpoint of the study was feasibility. T dose was adjusted to achieve T levels between 900-1500 ng/dL. Secondary end points included PSA50 response rate (50% decline in PSA) and safety. **Results:** Fifteen patients were enrolled. Ten (66.7%) had Gleason >8 disease. Thirteen (86.7%) patients had bone metastases. Median baseline PSA was 11.73 ng/mL. Primary endpoint of feasibility based on patient recruitment and retention was met. The median testosterone level on T was 901.3 ng/dL (Range: 645.2 to 1171.1). Median time on therapy was 15.9 weeks on T and 25.9 weeks on ENZA. PSA50 was 13.3% on initial T therapy and 66.7% after switching to ENZA. Three (20%) patients did not initiate ENZA after T progression. Two desired to avoid androgen-related side effects and 1 initiated chemotherapy. No Grade 3 or higher adverse events (AEs) occurred on T and the most common AEs were weight gain, rash, and nipple sensitivity. **Conclusions:** Square-wave transdermal T alternating with ENZA is feasible and achieves adequate T levels in the treatment of asymptomatic mCRPC. Given the acceptable safety profile and quick reversibility, transdermal T warrants further exploration, and we have expanded enrollment to include higher risk patient populations. Clinical trial information: NCT03734653. Research Sponsor: Cancer League of Colorado and University of Colorado Cancer Center.