Bipolar Androgen Therapy (BAT) for men with Asymptomatic Castrate-Resistant Prostate Cancer: Updated results from the RESTORE study.

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BACKGROUND: Prostate cancer that progresses after abiraterone (Abi) or enzalutamide (Enza) is poorly responsive to further androgen ablative therapy. Paradoxically, we previously demonstrated in a pilot study that rapid cycling between the polar extremes of supraphysiologic and near-castrate serum testosterone concentrations (bipolar androgen therapy [BAT]) could induce tumor responses in asymptomatic men with castrate-resistant prostate cancer (CRPC). Preclinical and pilot study data suggested that exposure to BAT could also produce re-sensitization to androgen ablative therapies. Here, we performed a single-center, multi-cohort, phase 2 study (NCT02090114) to test the hypotheses that BAT produces clinical response and re-sensitization in patients with metastatic CRPC.
METHODS: Eligible patients had metastatic CRPC, with ≤2 previous second-line hormonal therapies, no prior chemotherapy, ECOG of 0-2, without high-risk lesions for tumor flare and, importantly, no bone pain from osseous metastases. Cohort A patients were those most recently progressing after Enza; Cohort B were those most recently progressing after Abi. Patients received BAT (intramuscular testosterone cypionate 400mg every 28 days) until progression/toxicity and were continued on LHRH-agonists. Upon progression after BAT, men were re-challenged with Enza (Cohort A) or Abi (Cohort B). The co-primary endpoints were 50% decline in PSA from baseline (PSA_{50}) for BAT and for Abi/Enza re-challenge. Results for the post-Abi cohort were reported along with the previously published data in the post-Enza cohort (Teply et al. Lancet Oncol. 2018;19:76-86). **RESULTS:** Overall, 58 patients received at least one cycle of BAT. For the combined post-Abi (n=28) and post-Enza (n=30) cohorts, 14 (24%; 95% CI 14-37%) of 58 patients achieved a PSA_{50} response to BAT ($p<0.0001$) and 27/58 (47%) had some PSA decline. In Cohort A, nine (30%; 95% CI 15-49%; $p<0{\cdot}0001$) of 30 patients, and in Cohort B, five (18%; 95% CI 7-36%; $p=0.02$) of 28 patients achieved a PSA_{50} response to BAT. Those treated previously with both Abi and Enza (6/21) showed no difference in PSA50 response to BAT vs prior monotherapy only (8/37). Overall, PSA50 response to post-BAT androgen ablation was 48%, with 71% (15/21) Enza- and 21% (4/19) Abi-treated patients undergoing re-sensitization. BAT was well-tolerated with most common grade 1-2 toxicities being joint pain, breast tenderness, edema and fatigue. 8 SAEs possibly attributable to BAT occurred in one patient each. Ten of 58 patients (17%) were AR-V7(+) at baseline; 9/10 became AR-V7(–) during BAT but all became AR-V7(+) again after re-challenge with Abi or Enza. **CONCLUSIONS:** BAT is a safe therapy that resulted in PSA_{50} and objective responses in asymptomatic men with metastatic CRPC, with frequent re-sensitization to Abi or Enza in patients undergoing re-challenge. Pending results from a randomized study comparing BAT with Enza (NCT02286921) will further define the potential clinical role for BAT in the management of CRPC.

Conflicts of Interest: None

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