Beyond androgen-deprivation therapy: High-dose testosterone as a potential therapy in enzalutamide-resistant prostate cancer

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Background: Second-generation anti-androgen therapies profoundly suppressed the growth of castration-resistant prostate cancer (CRPC). However, CRPC cells developed resistance by up-regulating androgen signaling through overexpression and amplification of androgen receptor (AR), and expression of AR variants independent of ligands. Recent reports suggested that AR overexpression represented a therapeutic vulnerability that are sensitive to high-dose testosterone (high-T, supra-physiological), resulting in cell growth inhibition. In this study, we will to molecularly dissect the mechanism underlying high T-induced cell growth inhibition in enzalutamide-resistant (ENZR) tumor using patient-derived xenograft (PDX) models.

Methods: PDXs (LuCaP series) were implanted in castrated SCID mice and treated with enzalutamide. When tumors grew on enzalutamide, mice were randomized to control and high-T arms. Tumor responses were monitored. Tumors were collected at D5 (day 5, early time point), and at the end of study (EOS) for molecular, intra-tumoral androgens and immunohistochemical analyses.

Results: High-T therapy significantly inhibited tumor progression in LuCaP 35CR-ENZR and LuCaP 96CR-ENZR, but not in LuCaP 77CR-ENZR and LuCaP 58CR-ENZR. High-T elevated serum and intratumoral T to a comparable level in responders vs. non-responders, suggesting T availability was not associated with high-T responsiveness. Interestingly, DHT level was increased in serum but not in the tumor. Although High-T unambiguously decreased both AR and ARv7 gene expression, nuclear AR protein level remained high and this was accompanied by an upregulated canonical AR program. In contrast, an ARv7 program was downregulated in both responders and non-responders, suggesting a shift towards canonical AR transcription program upon high-T treatment in ENZR CRPC. In an attempt to molecularly differentiate responders vs non-responders, unbiased pathway analysis of RNAseq showed genes associated with cellular assembly and organization, DNA replication and repair, and p21-mediated cell cycle progression were drastically inhibited by high-T exclusively in responders.

Conclusion: Our data showed that continuous high-T therapy inhibited the progression of a unique subset of ENZR CRPC. Despite universal increase in AR signaling and decrease in ARv7 program in both responders and non-responders upon high-T treatment, inhibition of genes associated with cellular organization and DNA replication and repair were only evident in responders, highlighting a unique AR transcription program in responders to high-T.

Conflict of interest: None