Serial bipolar androgen therapy (sBAT) using cyclic supraphysiologic testosterone (STP) to treat metastatic castration-resistant prostate cancer (mCRPC)

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During prostate carcinogenesis, molecular changes occur in prostate epithelial cells such that their Androgen Receptor (AR) protein expression increases significantly (i.e. >5 fold). This elevated AR expression perverts AR-dependent transcriptional programming from a growth suppressor to an oncogenic stimulator of malignant growth (1-3). Due to this malignancy acquired addiction to AR transcriptional programming, androgen deprivation therapy (ADT), which lowers serum testosterone (T) from 600 to <100 ng/dL, not only inhibits prostate cancer cell proliferation, but also results in transcriptional reprogramming that induces cancer cell death (4).

Unfortunately, metastatic prostate cancer patients eventually develop resistance to primary castration therapy in addition to secondary hormone-based therapies such as abiraterone and/or enzalutamide. The most common mechanism for the development of resistance is via an adaptive “auto-regulation” that increases AR protein expression by >30-fold (5). This increase results in sufficient AR accumulation in the nuclei of castration-resistant prostate cancer (CRPC) cells to induce by mass action the AR-dependent transcriptional programming needed to both inhibit their death and stimulate their proliferation despite castrate levels of androgen.

While this adaptive increase in AR provides a growth advantage under ADT conditions, it creates the potential for an “induced synthetic lethality” in these malignant cells. The basis for this induced synthetic lethality is derived from the fact that the half-life of the AR protein is more than doubled when fully occupied by androgen (5). Thus, when high AR-expressing CRPC cells are cycled from low (i.e., <100 ng/dL) to supraphysiologic (>700 ng/dL) androgen (SPT), the resultant fully ligand-occupied AR protein is stabilized, driving its accumulation in the nucleus to such a high level that it now “paradoxically” suppresses proliferation and induces cell death (5-10).

Several complementary mechanisms for the paradoxical effect of SPT have been described. Using both in vitro cell lines and in vivo xenograft models Isaacs et al. demonstrated that AR is a DNA licensing factor that plays a critical role in DNA replication and must be degraded as a cell goes through the cell cycle (11). These studies also documented that treatment with SPT saturates ligand binding to the AR, maximizing the amount of ligand-bound AR in the nucleus and stabilizing it against degradation, thus inhibiting DNA relicensing, which results in cell death in the subsequent cycle (12,13). In independent studies, Haffner et al. documented that treatment of CRPC cells
Overall, sBAT has been translated clinically in metastatic CRPC patients progressing on second line hormone therapies (i.e., abiraterone and/or enzalutamide) through intramuscular administration of 400 mg of T cypionate every 28 days to rapidly raise serum T to supraphysiologic levels >1,500 ng/dL by 2 days post-injection with a decline to near castrate level (~100 ng/dL) by 28 days post-injection, Figure 2. Overall, sBAT has produced minimal side effects and shown clinical responses in ~25% of patients (20-23). These positive results raise the issue of how to increase both the frequency and extent of clinical benefit resulting from the sBAT regimen. The fundamental therapeutic basis of sBAT is the mandatory requirement for rapid, adaptive auto-regulation of AR and its transcriptome by CRPC cells during the rapid extreme changes in androgen concentrations. Therefore, we are presently testing whether the therapeutic benefit of sBAT can be increased by combining it with appropriately timed transcriptional inhibitors targeting different, but complimentary epigenetic regulators to disrupt the adaptive transcriptional reprogramming by CRPC cells needed for their survival and proliferation during rapid extreme changes in androgen concentrations. Therefore, we are presently testing whether the therapeutic benefit of sBAT can be increased by combining it with appropriately timed transcriptional inhibitors targeting different, but complimentary epigenetic regulators to disrupt the adaptive transcriptional reprogramming by CRPC cells needed for their survival and proliferation during rapid extreme changes in androgen concentrations.
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Figure 2 Serum testosterone concentrations during serial bipolar androgen therapy (sBAT) clinical regimen. Testosterone cypionate was provided via intramuscular (IM) injection of 400 mg every 30 days. This results in serial cycling between supraphysiologic and castrate levels of serum testosterone on a monthly schedule.

Figure 2

Serum testosterone concentrations during serial bipolar androgen therapy (sBAT) clinical regimen. Testosterone cypionate was provided via intramuscular (IM) injection of 400 mg every 30 days. This results in serial cycling between supraphysiologic and castrate levels of serum testosterone on a monthly schedule.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work ensuring that questions related to the accuracy or integrity of all parts of the work are appropriately investigated and resolved. All animal procedures were approved by the Johns Hopkins University School of Medicine Institutional Animal Care and Use Committee.

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