Abiraterone is able to block AR activation induced by accumulating precursor hormones resulting from CYP17A1 inhibition

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Background & Aim

Although metastatic prostate cancer (PC) responds well to androgen ablation therapy, progression towards castration resistant PC (CRPC) occurs within 3 years. Despite low circulating levels of testosterone (T) in CRPC patients under hormonal therapy, the androgen receptor (AR) is still active, indicating its remaining role as target in the treatment of CRPC. We previously demonstrated that conversion of adrenal androgens into T, rather than intratumoral de novo steroidogenesis, is the major source of T in CRPC tumours [1]. Adrenal androgens are synthesized from progesterone (Prog) and pregnenolone (Preg) by the enzyme CYP17A1. Clinical trials have demonstrated that the CYP17A1 inhibitor Abiraterone (Abi) can increase survival in CRPC patients even after chemotherapy [2]. The blockade of CYP17A1, however, may lead to accumulation of precursor hormones that have the potential to activate the AR [3].

AIM: In this preclinical study, we tested if Abi is able to inhibit CRPC growth in vitro and whether resulting accumulation of precursor hormones can drive PC progression.

Results

In DuCaP BIC-B, progesterone can induce growth despite adequate CYP17A1 blockade

DHT-induced growth is inhibited at higher concentrations of Abiraterone

Progestosterone induces AR regulated gene expression which can be blocked by Abi

Precursor hormones induce AR translocation

Materials & Methods

- Castration resistant clones were generated by treatment of CPRC. We previously demonstrated indicating its remaining role as target in the treatment of CRPC.
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- Gene expression levels of AR target gene PSA was assessed by qRT-PCR.
- HEF3B cells with a GFP-tagged AR were used to study AR translocation under similar conditions.

Conclusion

High levels of Prog comparable to those found in patients during treatment with a CYP17A1 inhibitor can potentially activate AR-regulated cell growth in AR-overexpressing CRPC in vitro. Although treatment with Abi may lead to high precursor hormone levels in serum, its anti-androgenic properties may prove sufficient to block precursor hormone-induced AR activation.

References


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