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INVITED RESEARCH HIGHLIGHT

Prostate Cancer

Reappraisal of glucocorticoids in castrate-resistant prostate cancer

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Recent reports and discussions of preclinical prostate cancer models have emphasized the possibility that enzalutamide resistance may be mediated by glucocorticoid receptors (GR).[1,2] In both *in vitro* and xenograft animal studies, it is possible to show that the GR is up-regulated in prostate cancer cell lines and that dexamethasone reverses enzalutamide induced growth inhibition. In these model systems, GR agonists can induce a subset of androgen receptor target genes including prostate-specific antigen. These investigators also report a correlation between GR expression in patient-derived prostate cancer specimens and clinical response to enzalutamide. The authors discuss the possibility that these findings have important clinical relevance. We note that the current clinical evidence for GR mediating drug resistance or disease progression in patients with castrate-resistant prostate cancer (CRPC) is very limited at best.

Withdrawal responses to antiandrogens, progestins, and various estrogens are not uncommon in CRPC[3] suggesting that under certain circumstances a wide variety of compounds interacting with steroid receptors can stimulate cancer growth in patients. After a careful literature search, we are unable to find a single reported case of a pure glucocorticoid withdrawal response. We also note that a glucocorticoid antagonist clinical trial in CRPC found no responses.[4]

Moreover, various glucocorticoids including prednisone, prednisolone, hydrocortisone, and dexamethasone confer clinical benefit to prostate cancer patients, demonstrated by both tumor marker declines[5–7] and palliative assessments.[8] The exact mechanism whereby glucocorticoids exert their positive effect is unknown but inhibition of steroidogenesis in steroid synthesizing tissues has been postulated.

Glucocorticoids play a positive role in the clinic, whether used as monotherapy as cited above or in combination with established therapies such as abiraterone, docetaxel, or cabazitaxel.[9] Additional clinical data suggest that prednisolone and dexamethasone, though both GR agonists, are distinct in their effects thus mitigating arguments that these effects are solely GR mediated.[10]

Taken together, although there are multiple potential interactions between glucocorticoids and prostate cancer, the story may be quite complex and context dependent. Studies of the benefits and potential harms of various glucocorticoids are warranted in prostate cancer patients.

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