Prostate Cancer

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INVITED REVIEW

Glucocorticoids and prostate cancer treatment: friend or foe?

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Glucocorticoids have been used in the treatment of prostate cancer to slow disease progression, improve pain control and offset side effects of chemo- and hormonal therapy. However, they may also have the potential to drive prostate cancer growth via mutated androgen receptors or glucocorticoid receptors (GRs). In this review we examine historical and contemporary use of glucocorticoids in the treatment of prostate cancer, review potential mechanisms by which they may inhibit or drive prostate cancer growth, and describe potential means of defining their contribution to the biology of prostate cancer.

INTRODUCTION

Glucocorticoids are a class of steroidal hormones comprised of physiologic hormones produced by the adrenal cortex (e.g. cortisol) and synthetic analogs (e.g. prednisone) that bind to the glucocorticoid receptor (GR). Glucocorticoids regulate a broad range of critical processes, including the response to physiologic stress and the regulation of inflammation and glucose metabolism. While cortisol and its derivatives, such as prednisone, have mixed glucocorticoid and mineralocorticoid effects, other analogs, such as dexamethasone, are essentially pure GR agonists. A partial list of glucocorticoids used in the clinical treatment of prostate cancer is shown in both **Figure 1** and **Table 1**.

GR is structurally similar to the other members of its nuclear receptor subfamily, including the receptors for mineralocorticoid, progesterone and androgen. The shared modular components of these receptors are comprised of an N-terminal transactivation domain, DNA binding domain, hinge region and C-terminal ligand binding domain. [1]Coregulators bind to the AF1 domain within the N-terminus and control transcriptional activity. The DNA binding domain contains two zinc finger motifs responsible for recognition and binding of target DNA sequences termed glucocorticoid-responsive elements. The C-terminal ligand binding domain forms a hydrophobic pocket for binding ligand. In addition, nuclear localization signals exist in the DNA binding domain and the ligand binding domain.

In its inactive form, GR is a cytosolic transcription factor bound by a number of chaperone proteins. When ligand binding occurs, the chaperone proteins are released, exposing nuclear localization signals and facilitating translocation to the nucleus. Glucocorticoid action in the nucleus depends on whether it forms a homodimer or a heterodimer with proinflammatory transcription factors (e.g. activator protein 1 or nuclear factor-kappa B). Binding to the latter represses inflammatory activity and results in the anti-inflammatory effect of glucocorticoids.

Although the majority of glucocorticoid effects in humans are mediated through regulation of gene transcription, non-genomic effects have also been described.[2] Each GR isoform can be post-translationally modified. For example, the predominant isoform, GR-α, can serve as a regulator of transcription and protein stability, depending on its phosphorylation state. How GR isoform expression and phosphorylation modulates relevant activity in prostate cancer treatment remains largely unexplored.

GLUCOCORTICOIDS IN PROSTATE CANCER TREATMENT

The antineoplastic effects of glucocorticoids will be discussed in detail in section of antineoplastic effects. In addition to antineoplastic effects, glucocorticoids have also been extensively used to offset the toxicities of chemotherapy, including nausea and emesis from many agents, hypersensitivity reactions and peripheral edema from taxanes[3] and hyperaldosteronism from abiraterone.[4] Virtually all patients with CRPC who receive docetaxel, cabazitaxel or abiraterone treatment will receive steroids, frequently on a continuous basis for months to years. The toxicities of long-term glucocorticoids have been well described, and include hyperglycemia, osteoporosis, glaucoma, immunosuppression, hypertension, myopathy and gastritis, with the severity largely dependent on dose and duration.

ANTINEOPLASTIC EFFECTS

Glucocorticoid effects on androgens

The use of glucocorticoids in prostate cancer derives from the exquisite sensitivity of prostate cancer to manipulation of testicular and adrenal androgens. Suppression of androgen synthesis and blockade of androgen receptor (AR) signaling are among the most effective approaches to treating locally advanced and metastatic prostate cancer. Since the earliest days of hormonal therapy, steroidal hormones (including estrogens, progestins and glucocorticoids) have

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played a role in the treatment of prostate cancer, primarily to suppress androgen synthesis.[5] The effect of these steroidal hormones has been postulated to be through feedback inhibition of the hypothalamic/pituitary axis, with subsequent suppression of testicular and adrenal androgen synthesis.[6-8]

The importance of suppressing adrenal androgens has become apparent recently, as the role of these hormones in driving prostate cancer progression has been recognized. Multiple lines of evidence demonstrate that prostate cancer progressing despite castrate testosterone blood levels (defined as testosterone < 50 ng dl^{−1}) is often driven by intratumoral androgen signaling, and is more appropriately labeled 'castration resistant' prostate cancer (CRPC).[9] Thus, despite absence of testicular androgen production, prostate cancer tumor tissue metabolizes adrenal androgens (e.g. androstenedione and dehydroepiandrosterone) into testosterone and dihydrotesterone. Dehydroepiandrosterone and androstenedione also have weak direct agonist activity for the AR, and can provide AR activation independent of metabolism to testosterone and dihydrotestosterone. The potential role for glucocorticoids in the androgen regulation of prostate cancer was first suggested when adrenalectomy was shown to provide additional clinical benefit in men with prostate cancer refractory to orchiectomy or diethylstilbestrol, the stage of disease formerly considered 'hormone refractory'.[10] Glucocorticoids were initially found to suppress total androgen levels in healthy men, and their potential utility in suppressing adrenal androgens in men with prostate cancer was quickly recognized.[11]

A number of single arm, phase II studies in CRPC were conducted in order to define the optimal type and dose of glucocorticoid for suppression of adrenal androgens (see section of clinical studies). By and large, these studies demonstrated substantive activity of glucocorticoids, and this data strongly supports the theory that CRPC

Figure 1: Glucocorticoid structures.

Table 1: Glucocorticoids used in prostate cancer therapy

Name	Glucocorticoid potency	Mineralocorticoid potency	Dosing in treatment of prostate cancer
Hydrocortisone/cortisol	1	1	20-30 mg qAM, 10 mg qPM
Prednisone	3.5–5	0.8	10-20 mg daily
Dexamethasone	25–80	0	0.5-2 mg daily, 8 mg q 8 h prior to docetaxel

remains hormonally regulated and that hormonal manipulation continues to be critical to prostate cancer biology even in the latest stages of the disease.

GLUCOCORTICOID-STIMULATED TUMOR GROWTH THROUGH NUCLEAR RECEPTOR INTERACTIONS

The potential for glucocorticoids to promote rather than suppress prostate cancer growth has been raised by the structural similarity of both receptors and ligands of the nuclear receptor superfamily which include GR, AR, mineralocorticoid and progesterone receptor. Consistent with the homology of their DNA binding domains, the response elements for each of these receptors can be recognized by ligand-bound receptors in specific experimental settings, suggesting that ligands and receptors can regulate the same signaling pathways.[12] Thus, it is plausible that under selection pressure, AR could broaden its ligand specificity to include ligands of the closely related steroid receptor superfamily, including GR. Mutation of the ligand binding domain of AR occurs in the setting of androgen deprivation in men with CRPC, and allows AR signaling to proceed via binding to glucocorticoids, estrogens and progestins.[13–15] For example, glucocorticoids can activate AR signaling in cells transfected with AR with the T877A mutation, although not at concentrations typically achieved in the serum of patients treated with glucocorticoids for prostate cancer.[16] Despite the existence of these AR mutations, their clinical importance was unclear for men with early CRPC due to their relative rarity.[17]

GR may be able to substitute for AR even in the absence of AR mutations in specific experimental settings. In cells engineered to overexpress GR, glucocorticoids have been shown to activate a transcriptional program that overlaps significantly with genes induced by AR activation.[18] Surprisingly, the effect of glucocorticoids depended on the specific androgen context. Whereas in androgen-replete conditions, glucocorticoids had partial antagonist effect on AR, in androgen-deplete conditions glucocorticoids had agonist effect on AR. Therefore, the GR may be able to maintain AR signaling in androgen-deprived environments by inducing a transcriptional program closely resembling the transcriptional program activated by AR. Further evidence that nuclear receptor superfamily members may regulate similar transcriptional programs comes from the finding that the transcription factor FOXA1 regulates differential binding of both GR and AR to the same, or closely opposed, enhancer elements, and thus serves as a critical regulator of GR and AR function in prostate cancer.[19]

Preliminary studies also suggest that GR may play an important role in resistance to the AR antagonist enzalutamide.[20] Cells selected *in vitro* for enzalutamide-resistance were interrogated with cDNA array analysis and revealed dramatically upregulated GR levels compared to parental cells. Knockdown of GR in the enzalutamide-resistant cells partially abrogated resistance to enzalutamide. In summary, GR activation may induce a transcriptional program that overlaps with the transcriptional program induced by AR in androgen-deprived conditions and in this manner, may contribute to the development of resistance to enzalutamide-mediated AR blockade.

Androgen-independent modulation of tumor growth
Beyond glucocorticoid suppression of adrenal androgen production, direct antiproliferative effects of glucocorticoids have also been demonstrated in multiple tumor types, including prostate cancer. A common theme in these studies has been the finding that glucocorticoids suppress or induce cytokines regulating prostate cancer growth, including transforming growth factor -β, interleukin (IL)-6 and IL-8. Glucocorticoids upregulate the antiproliferative cytokine
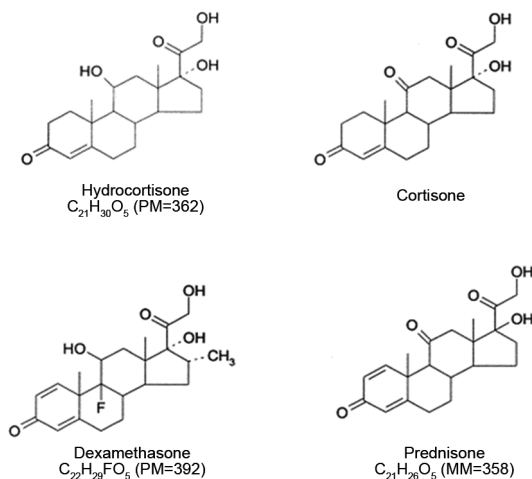
transforming growth factor-β and its receptors *in vitro*, in a GR-dependent manner and mediate suppression of prostate cancer cell growth.[21–23] IL-6 drives prostate cancer growth through AR-dependent and -independent mechanisms in prostate cancer cells.[24] Exposure to dexamethasone suppresses IL-6 levels both *in vitro* and in patients with CRPC, potentially through disruption of nuclear factor-kappa B signaling.[23,25] In these and other preclinical experiments, suppression of IL-6 blocks cell proliferation and tumor growth, suggesting that IL-6 inhibition is a potentially important mechanism for GR-mediated tumor suppression.[26,27] Of interest, dexamethasone suppression of IL-6 has also been associated with decreased GR expression *in vitro* and *in vivo*, suggesting that chronic dexamethasone exposure may lead to downregulation of GR.[25]

Glucocorticoids can regulate tumor angiogenesis and lymphangiogenesis in multiple xenograft models, which may be critical to proliferation and metastasis. Glucocorticoids have been shown to suppress vascular endothelial growth factor and IL-8 in xenograft models with a reduction in vascular endothelial growth factor as well as decreased microvessel density and tumor growth.[28] These androgen-independent effects of glucocorticoids may play relevant roles in GR-mediated tumor suppression, although the clinical correlations are less robust than GR-mediated effects on androgen production.

CLINICAL STUDIES

The activity of glucocorticoids in CRPC is illustrated by a select list of phase I/II studies shown in **Table 2**.[29–39] Glucocorticoids induced prostate-specific antigen (PSA) responses in 20%–60% of patients, depending on the extent of prior treatment and the type of glucocorticoid used. A substantial proportion of patients also derived symptomatic benefit, with declines in pain scores, decreased opioid use and more limited evidence for an improvement in overall quality of life.[31] Glucocorticoid use in these studies was continuous and relatively low dose to minimize the potential morbidity, particularly in an older patient population with significant comorbidities. The importance of continuous versus pulse administration is illustrated by a small study that evaluated PSA response to a lead-in cycle of high dose pulse dexamethasone which mimicked dosing used with

docetaxel, with no PSA responses in the first cycle of treatment.[40] More recently, patients whose prostate cancer progressed during treatment with the CYP17 inhibitor abiraterone, and who were not receiving concurrent corticosteroids were treated with dexamethasone as salvage therapy. This was based on the hypothesis that upstream androgenic precursors (e.g. deoxycorticosterone or progestins) could activate AR, and therefore suppression of adrenocorticotropic hormone would reduce production of these androgenic precursors by the adrenal glands. Approximately 30% of patients had subsequent PSA declines of 50% or greater after dexamethasone treatment, suggesting that glucocorticoids can induce responses in a setting in which suppression of adrenal precursors (e.g. dehydroepiandrosterone) is maximal.[41] These studies suggested a moderate, but definable level of response of CRPC to glucocorticoids.

The defined level of antineoplastic activity and common use of glucocorticoids in the treatment of CRPC led to the use of glucocorticoids in the control arms of multiple randomized studies (**Table 2**). The initial randomized studies demonstrating the benefit of mitoxantrone in the treatment of CRPC used glucocorticoids alone as the control arm and glucocorticoids combined with mitoxantrone as the experimental arm. In these studies, 22% patients receiving glucocorticoids in either of the control arms (hydrocortisone 40 mg daily or prednisone 10 mg daily) experienced PSA declines of ≥ 50%.[33,34] Similarly, in a randomized study of flutamide *vs* prednisone in patients with CRPC, significant declines (≥50%) in PSA were seen in 21% of patients, with 56% of patients receiving prednisone experiencing a subjective response to therapy.[35] In the registration studies of abiraterone, prednisone (10 mg d⁻¹) was the control arm and in the phase III studies testing placebo with prednisone against abiraterone with prednisone in chemotherapy-naïve men with CRPC[37] or in men with progression after docetaxel.[39] In both studies prednisone had clinical benefits, including PSA declines (10% post-docetaxel, 24% pre-docetaxel) and radiographic responses (by Response Evaluation Criteria in Solid Tumors) of 3% and 16%, respectively.

Docetaxel with concurrent prednisone is an FDA-approved therapy for patients with prostate cancer[42] and, to date, there have been no docetaxel-based combinations which have improved on docetaxel with prednisone in phase III studies in patients with CRPC.[43–45] Although the

Table 2: Clinical trials utilizing glucocorticoids in the treatment of prostate cancer

Reference	n	Glucocorticoid	Disease state	Study arms	Result
Tannock *et al*.[29]	37	Prednisone 10 q.d	Chemotherapy naïve	Single arm	40% improved QOL
Kelly *et al*.[30]	30	Hydrocortisone 40 mg q.d	Chemotherapy naive	Single arm	20% PSA response
Storlie *et al*.[31]	38	Dexamethasone 0.7 mg b.i.d	Chemotherapy naïve	Single arm	79% improved symptoms 61% PSA response
Venkitaraman *et al*.[32]	102	Dexamethasone 0.5 mg q.d	Chemotherapy naïve	Single arm	49% PSA response
Tannock *et al*.[33]	81	Prednisone 10 q.d	Chemotherapy naïve	Mitoxantrone+ prednisone *vs* prednisone	Prednisone arm: 22% PSA response
Kantoff *et al*.[34]	123	Hydrocortisone 30 mg AM, 10 mg PM	Chemotherapy naïve	Mitoxantrone+ hydrocortisone *vs* hydrocortisone	21.5% PSA response 4% radiographic response
Fossa *et al*.[35]	101	Prednisone 20 mg q.d	Chemotherapy naïve	Flutamide *vs* prednisone	21% PSA response 56% subjective response
Shamash *et al*.[36]	133	Dexamethasone 2 mg q.d	Chemotherapy naïve	DES+Dex *vs* Dex	50% PSA response
Ryan *et al*.[37]	542	Prednisone 5 mg b.i.d	Chemotherapy naive	Abiraterone+ prednisone *vs* prednisone	24% PSA response rate 16% RECIST response
Sternberg *et al*.[38]	315	Prednisone 10 mg q.d	Docetaxel refractory	Satraplatin+ prednisone *vs* prednisone	12% PSA response
de Bono *et al*.[39]	398	Prednisone/prednisolone 5 mg b.i.d	Docetaxel refractory	Abiraterone+ prednisone *vs* prednisone	10% PSA response 3% RECIST response

QOL: quality of life; PSA: prostate specific antigen

underlying assumption has been that the comparison regimens would be at least equivalent to docetaxel/prednisone in achieving response and survival advantages, several studies have demonstrated inferior survival when prednisone was not included in the treatment arm. In the ASCENT-II study, calcitriol with docetaxel on a weekly schedule was compared to prednisone with docetaxel administered every 3 weeks. The study was stopped when an interim analysis demonstrated that median overall survival was 17.8 months in the calcitriol/docetaxel arm *vs* 20.2 months in the docetaxel/prednisone arm (*P* = 0.002).[43] The VITAL-2 study, which compared the GVAX prostate cancer vaccine combined with docetaxel to docetaxel with prednisone was stopped after enrollment of 400 patients when survival in the experimental arm was inferior to that in the docetaxel/prednisone arm. At study termination, median survival in patients treated with docetaxel/GVAX was 12.2 months, *vs* 14.1 months in those who received docetaxel/prednisone (*P* = 0.0076).[46] There were no differences in deaths due to treatment in either of these studies. Although not definitive, these studies suggest that glucocorticoids may provide clinical benefit beyond reduction of taxane-related toxicities when administered with docetaxel.

Several studies have been carried out to evaluate the contribution of glucocorticoids and GR in resistance to androgen deprivation and next generation AR axis targeting agents. A post hoc analysis of the phase III AFFIRM study of placebo *vs* enzalutamide in patients with metastatic CRPC after prior docetaxel[47] was carried out to evaluate the impact of glucocorticoid use at study entry on overall survival. Glucocorticoid use was not mandated by protocol but was allowed at study entry and during study therapy and approximately one-third of patients were receiving glucocorticoids at study entry. Patients receiving glucocorticoids had a significantly higher number of poor prognostic features, and overall survival was substantially worse in patients receiving glucocorticoids at study entry in both the placebo (9.3 *vs* 15.8 months) and enzalutamide treated (12.3 *vs* OS not reached) groups. Using Cox proportional-hazards modeling and stepwise removal of the factors which provided the greatest impact on survival, the use of glucocorticoids remained a statistically significant factor associated with worse survival, with a hazard ratio of 0.54 (no glucocorticoid *vs* glucocorticoid) at study entry.[48] This analysis suggested that the use of glucocorticoids in patients with CRPC previously treated with docetaxel was associated with inferior survival (independent of other known prognostic factors) and may be driving an adverse biology.

A second analysis was carried out in a similar patient dataset from COU-301, a phase III randomized study of prednisone with placebo *vs* prednisone with abiraterone in patients with metastatic CRPC after prior docetaxel.[49] Glucocorticoid use was mandated by protocol and patients enrolled had presumably received glucocorticoids as part of their prior therapy with docetaxel. Similar to the AFFIRM study, 33% of patients were receiving glucocorticoids at time of study entry, and the group who enrolled while receiving glucocorticoids had a statistically higher frequency of factors previously defined as carrying worse prognosis: liver metastases, performance status of 2, multiple prior chemotherapies, Gleason score 8 or above, elevated lactate dehydrogenase, low albumin and greater opioid use at baseline (*P* < 0.005, glucocorticoid use *vs* no use). Patients receiving glucocorticoids at entry in COU-301 also had inferior overall survival irrespective of study arm, including prednisone/placebo (9.3 *vs* 12.7 months) and prednisone/abiraterone (13.4 *vs* 17.3 months). A multivariate Cox regression model was used with a stepwise removal to identify the prognostic factors for overall survival. In the final model, glucocorticoid use did not add significant prognostic impact on overall survival. Factors that were directly correlated with

glucocorticoid use included shorter time from last administration of docetaxel, ECOG (Eastern Cooperative Oncology Group) performance status of 2 and an analgesia score of ≥ 2 (all *P* < 0.05) at entry into study. These findings are consistent with the hypothesis that patients taking glucocorticoids at time of enrollment were generally sicker, thus providing an explanation for their inferior outcomes. It is difficult to reconcile the results of these two studies without pooling the datasets and performing exactly the same modeling analysis on both trials. The shared conclusion is that patients who entered each study receiving glucocorticoids from their physicians were sicker and had worse prognostic features. Whether there is a true difference in the effect of glucocorticoids on resistance to these two agents which target the AR axis remains uncertain.

Several observations are worthy of additional comment. First, patients with CRPC treated in randomized studies with glucocorticoids do not appear to have dramatic decrement in functional status with treatment initiation, and in some cases have PSA responses and symptomatic improvement, suggesting that glucocorticoids are not driving an adverse biology in the majority of patients with CRPC. Second, the number of patients who demonstrate glucocorticoid withdrawal responses appears limited, although this has not been closely evaluated. Third, very limited information is currently available from tissue samples acquired directly from patients with CRPC to suggest that GR upregulation or mutation of AR is a frequent event. Further studies are necessary to answer the question of whether glucocorticoids or GR are mediating progression in specific subsets of patients with CRPC. It will be important to determine the frequency of GR upregulation, as well as activating AR mutations in the ongoing analyses of CRPC using exome sequencing and RNAseq through the efforts of the AACR-PCR-SU2C dream teams (http://www.standup2cancer.org/dream_teams/view/precision_therapy_for_advanced_prostate_cancer). Studies are also ongoing to determine both tissue and clinical effects of abiraterone administration without concurrent glucocorticoids. While we await additional data, glucocorticoids will continue to be a standard component of therapy in patients with CRPC.

COMPETING INTERESTS

All authors declare no competing interests.

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