



GLUCOCORTICOIDS AND TREATMENT OF PROSTATE CANCER: A PRECLINICAL AND CLINICAL REVIEW

MARWAN FAKIH, CANDACE S. JOHNSON, AND DONALD L. TRUMP

Glucocorticoids have been used for a substantial period to treat patients with advanced androgen-independent prostate cancer (AIPC). Although known for their anti-inflammatory activity, glucocorticoids have antitumor activity in various hematologic malignancies. The role of glucocorticoids as antineoplastic agents in epithelial tumors is less well defined. Their use in these tumors has been strictly palliative.

Glucocorticoids have been widely used in the treatment of advanced prostate cancer and have served as the "standard" therapy arm in several randomized studies. Although multiple studies of glucocorticoid use in prostate cancer have been conducted, their therapeutic role remains unclear. We review the information regarding the mechanisms underlying glucocorticoid antitumor effects in prostate cancer and critically review the results of clinical trials using these agents.

MECHANISMS OF ACTIVITY

The cytotoxic effect of glucocorticoids in hematologic cells is well defined.¹⁻⁴ Glucocorticoids bind to a cytosolic receptor that localizes to the nucleus, leading to a variety of transcriptional modifications. This ultimately results in upregulation of multiple caspases, leading to apoptotic cell death.⁵ Glucocorticoids do not induce apoptosis in prostate cancer cells, yet growth inhibitory effects are well documented.^{6,7} We have demonstrated direct antiproliferative effects in the hormone-refractory human PC-3 and rat Mat-Ly-Lu cell lines as

measured by cell cycle arrest and modulation of the cdk inhibitors, p21 and p27. The mechanisms of this growth inhibitory effect are not clear. However, several mechanisms have been postulated.

SUPPRESSION OF ADRENAL ANDROGEN SECRETION

Glucocorticoids may exert an antitumor effect on androgen-independent prostate cancer by suppression of adrenal androgens. Low-dose glucocorticoids produce negative feedback on the pituitary gland, leading to a decrease in both testicular and adrenal androgens.^{8,9} Plowman *et al.*¹⁰ reported on 17 orchiectomized patients with progressive prostate cancer who were treated with hydrocortisone 30 mg/day. A significant decrease in testosterone, androstenedione, and dihydroandrostenedione (DHEAS) levels was noted with therapy. Similarly, Tannock *et al.*¹¹ noted a decrease in testosterone, androstenedione, and DHEAS levels in association with low-dose prednisone therapy (7.5 to 10 mg daily) in surgically or medically castrated patients with advanced prostate cancer. Symptomatic relief was associated with a decrease in the adrenal androgen levels. Eight of 13 patients who had a decrease in DHEAS levels by 1 $\mu\text{mol/L}$ or greater had improvement in pain and only 1 of 8 patients with unchanged or increased DHEAS levels had symptomatic improvement.

PARACRINE/AUTOCRINE FACTOR MODULATION

Glucocorticoids can inhibit prostate cancer cell growth by modulating cellular growth factors such as lipocortin, tumor growth factor beta-1 (TGF β -1), urokinase-type plasminogen activator (uPA), and interleukin-6 (IL-6).

LIPCORTIN

Glucocorticoids mediate their anti-inflammatory effects in part by way of lipocortin, a member of the annexin family (calcium and phospholipid-binding proteins).^{12,13} Lipocortin gene transcription is upregulated by glucocorticoids, resulting in in-

Supported by grants from the Mary Hillman Jennings Foundation and CaPCURE. D. L. Trump and C. S. Johnson receive research funding from Bristol Myers Squibb, Aventis, and D-Novio.

From the Departments of Medicine, Division of Hematology-Oncology and Pharmacology, University of Pittsburgh School of Medicine; and University of Pittsburgh Cancer Institute, Pittsburgh, Pennsylvania

Reprint requests: Donald L. Trump, M.D., Department of Medicine, University of Pittsburgh Cancer Institute, Montefiore University Hospital, N 723, 200 Lothrop Street, Pittsburgh, PA 15213

Submitted: January 30, 2002, accepted (with revisions): March 28, 2002

creased cellular levels. Lipocortin is subsequently secreted from the cells to mediate its anti-inflammatory effects at the membrane level by inhibiting phospholipase A2.^{14,15} Lipocortin also mediates, at least in part, the antiproliferative effects of glucocorticoids. Carollo *et al.*⁶ showed that the inhibitory effect of dexamethasone on androgen independent PC-3 cells is completely abolished if the cells are incubated with sheep antihuman lipocortin antibodies. The mechanism through which lipocortin mediates its antiproliferative effect is not well defined.

TRANSFORMING GROWTH FACTOR BETA-1

TGF- β 1 is a member of a group of dimeric peptides that modulate multiple cellular functions, including extracellular matrix expression, differentiation, and cellular proliferation.¹⁶ TGF- β 1 has dual inhibitory and stimulatory effects on the growth of prostate cancer. Hsing *et al.*¹⁷ treated both tumorigenic (NRP-154) and nontumorigenic (NRP-152) rat prostate cell lines with TGF- β 1. TGF- β 1 induced cell death by apoptosis in both cell lines. The effects were enhanced by dexamethasone and inhibited by insulin growth factor-1. Dexamethasone increased TGF- β 1 mRNA expression in androgen-insensitive PA-III prostate cancer cell lines in association with growth inhibitory effects.¹⁸ Co-treatment of PA-III with TGF- β 1 antibody reversed the dexamethasone antiproliferative effects. This suggests that the inhibitory role of dexamethasone may be mediated by TGF- β 1.¹⁸ Barrack¹⁹ and Morton and Barrack,²⁰ on the other hand, showed that TGF- β 1 was implicated in tumor progression. They showed that although TGF- β 1 had no inhibitory effects on the growth of the hormone-independent, rat prostate Mat-Ly-Lu cancer cell line, it stimulated motility and fibronectin expression.²⁰

UROKINASE-TYPE PLASMINOGEN ACTIVATOR

uPA, a serine protease, is implicated in the progression of various malignancies, including prostate cancer. Serum uPA levels are higher in patients with metastatic prostate cancer than in those with localized disease.²¹ uPA increases the invasiveness and stimulates tumor migration and growth when expressed in hormone-responsive human prostate LNCaP cell lines.^{22,23} Furthermore, uPA has direct stimulatory effects on osteosarcoma cells and may play an important role in the pathophysiology of blastic lesions in prostate cancer.²⁴⁻²⁶ Dexamethasone downregulates uPA mRNA and its protein expression in both PC-3 and PA-III cell lines.²⁴ By downregulating uPA, glucocorticoids may inhibit the growth and invasiveness of prostate cancer

INTERLEUKIN-6

Recently, Nishimura *et al.*²⁷ showed that dexamethasone had growth inhibitory effects on the DU-145 AIPC human cell line. These inhibitory effects were associated with a dose-dependent up-regulation of inhibitor of kappa B ($\text{I}\kappa\text{B}\alpha$) a key inhibitor of nuclear factor-kappa B (NF- κB). A subcellular localization evaluation of DU-145 cells pretreated with dexamethasone confirmed the loss of NF- κB nuclear localization. NF- κB is an important regulator of several cytokines, including IL-6.²⁸ It is believed that loss of nuclear compartmentalization of NF- κB leads to inhibition of IL-6 secretion, thus leading to a favorable growth inhibitory effect. Consistent with this hypothesis is the inhibition of DU-145 cell growth by IL-6 antibodies, as well as the fourfold decrease in IL-6 levels in patients treated with low-dose dexamethasone.²⁷

SUPPRESSION OF ANDROGEN-DEPENDENT TRANSCRIPTION

Androgen and glucocorticoid receptors share a significant degree of homology, especially in their DNA-binding domain (DBD). Both receptors bind through their DBD to a common DNA site termed the hormone receptor element. AR, GR, and MR (mineralocorticoid receptors) bind to hormone receptor element as homodimers. Although these receptors bind to the same DNA site, they result in different transcriptional activities. Factors other than DBD-hormone receptor element interaction determine the specificity of the transcriptional activity. Chen *et al.*²⁹ has recently demonstrated that GR and AR can associate through their DBD to form a heterodimer. This heterodimer formation results in an inhibitory effect on androgen-specific transcription *in vitro*. This transcriptional inhibition can lead to inhibition of the necessary downstream events for the growth of prostate cancer cells. These results should be extrapolated with caution, because it has not been shown yet that GR and AR form heterodimers *in vivo*.

GLUCOCORTICOID-DRIVEN CELLULAR PROLIFERATION

Although the data discussed above point to an inhibitory effect of glucocorticoids on prostate cancer cell lines, a stimulatory effect has been also documented. Zhao *et al.*³⁰ described two cell lines (MDA PCa 2a and 2b) derived from bony metastases of a patient with progressing prostate cancer despite hormonal therapy. These cells carry a mutated AR (L701H and T877A) that has a high affinity to cortisol and cortisone. Both cortisol and cortisone resulted in enhanced cellular proliferation and prostate-specific antigen (PSA) secretion in these two cell lines.³⁰ Chang *et al.*³¹ studied the

effects of various endogenous and synthetic glucocorticoids on LNCaP prostate cancer cell line (AR T877A mutant) growth and PSA secretion. Both 11-deoxycorticosterone (DOC) and dexamethasone stimulated the AR-dependent PSA secretion. Furthermore, DOC was able to stimulate cellular growth at physiologically achievable levels, and dexamethasone seemed to have only a modest agonistic effect. These effects were mediated through the mutated T877A AR.

CLINICAL UTILITY OF GLUCOCORTICOIDS IN AIPC

Despite the limited preclinical data regarding the mechanism of their inhibitory effects on prostate cancer cell growth, glucocorticoids are used extensively in the treatment of AIPC. Miller and Hinman³² were the first to report on the clinical activity of glucocorticoids in AIPC. Ten patients with advanced prostate cancer who had progressed despite prior orchiectomy and estrogen therapy were treated with cortisone 50 to 200 mg/day. Subjective symptomatic improvements were noted in 8 of 10 patients.³² Since this initial publication, multiple studies have evaluated single-agent glucocorticoids in the treatment of AIPC. These studies have ranged from retrospective analyses to Phase III trials.

RETROSPECTIVE AND PHASE II TRIALS

Phase II and retrospective studies before 1995 did not use PSA as a marker of disease activity and relied on subjective response criteria (Table I).^{11,33,34} Tannock *et al.*¹¹ evaluated retrospectively in 28 patients and prospectively in 37 patients, the palliative effects of daily prednisone 7.5 to 10 mg. All enrolled patients had symptomatic bony metastases with evidence of disease progression despite orchiectomy and/or estrogen therapy. Of 28 patients analyzed retrospectively, 7 had improvement in pain and reduced requirements for analgesics lasting a median of 5 months. In 37 patients evaluated prospectively, 14 patients (38%) had improvements in pain and a leveling or a decrease in their analgesic requirements for at least 1 month. The reduction in pain was associated with improvements in quality of life (QOL). The clinical benefits lasted 3 to 30 months in 7 patients. Alkaline phosphatase and acid phosphatase were evaluated in this study but did not show any evidence of correlation with clinical response.

Patel *et al.*³⁴ treated patients with prostate cancer and measurable disease that had progressed despite orchiectomy or estrogen therapy with low-dose dexamethasone. Fifty-eight patients were randomized to receive either megestrol acetate or

plex response criteria that involved evaluations of multiple variables (bone scan, computed tomography, chest radiography, pain evaluation, acid phosphatase, weight, performance status, alkaline phosphatase, and hemoglobin). Two of 29 patients on the dexamethasone arm had evidence of disease regression each lasting 359 and 512 days. Twenty-one patients had stable disease at a median of 86 days. The median survival on the dexamethasone arm was 246 days.

Studies conducted since 1995 used PSA as a marker for response (Table I). PSA is not a perfect response endpoint, but it is agreed as an indicator of biologic activity.^{35,36} The Prostate-Specific Antigen Working Group has developed guidelines for using PSA as a measurement of outcome. Only a PSA decrease of more than 50% with a sustained decrease for 4 weeks is considered a PSA response.³⁶ Such a decrease has been associated with an extension in overall survival in several studies.^{37,38}

Storlie *et al.*³⁹ retrospectively evaluated 38 patients who had progressive disease despite orchiectomy and were treated with 0.75 mg dexamethasone two or three times a day. They reported a 63% subjective symptomatic improvement and a 79% PSA decrease of more than 50%. The median time to biochemical progression in responders (PSA increases of greater than 50%) was 245 days (range 99 to 660). Thirty-five percent of PSA responders had some evidence of bony disease regression and none of the nonresponders did. The study included only patients who had adequate follow-up. Thus, the study has potentially excluded nonresponders with early dropout because of disease progression.³⁹

Kelly *et al.*⁴⁰ conducted a Phase II trial in which 30 patients with AIPC were treated with hydrocortisone 40 mg/day. Suramin was added to the treatment regimen at the time of PSA progression. All patients must have had evidence of disease progression and documented castrate testosterone levels before entry on study. Patients who were taking flutamide had to have the drug discontinued; they were entered on trial only if they showed disease progression after flutamide withdrawal. Six patients (20%) had a decrease in PSA of more than 50% and the median duration of the decline was 16 weeks. One patient had a PSA decline of 99% lasting more than 52 weeks and 1 patient had PSA and bone scan stabilization lasting more than 44 weeks.

Sartor³⁷ retrospectively reviewed the results of 29 consecutive patients with AIPC treated with prednisone 10 mg twice daily. All patients had to have a rising PSA despite adequate androgen ablation to be entered in the trial. Flutamide withdrawal was ruled out as a possible confounding variable in all accessible patients. Ten (34%) of 29

TABLE 1. Phase II and retrospective studies evaluating glucocorticoids in the treatment of progressive hormone-resistant prostate cancer

Study	Patients (n) and Treatment	Entry Criteria	Objective Responses and Post-Therapy PSA Decline	MST and TTP (mo)	Quality of Life and Subjective Responses
Tannock <i>et al.</i> , ¹¹ 1989, prospective study	37; prednisone 7.5–10 mg	Failed orchiectomy and/or estrogen therapy	NA	—	38% had improvement in pain score at 1 mo; 19% had sustained improvement in pain for 3–30 mo
Patel <i>et al.</i> , ³⁶ 1990, prospective study	29; dexamethasone 0.75 mg BID	Failed orchiectomy or diethyl-stilbestrol therapy	2/29 objective responses (decrease in measurable disease)	MST 6.7	—
Nishiyama, ⁴¹ 1998, prospective study	7; low-dose dexamethasone 1.5–0.5 mg/day	Patients with orchiectomy or LHRH therapy with progression after secondary hormonal therapy withdrawal	4/7 (PSA decrease of >90%) after 3 mo of therapy	TTP 3–11	—
Sartor, ³⁷ 1998, retrospective study	29; prednisone 10 mg BID	Failed orchiectomy or LHRH agonist	34% (PSA decrease of >50%)	MST 12.8; median TTP 2	—
Storlie <i>et al.</i> , ³⁹ 1995, retrospective study	38; low-dose dexamethasone 0.75 BID/TID	Failed orchiectomy; progressive disease	PSA response: 79% had a PSA decrease >50% (not confirmed at 4 wk)	—	63% had symptomatic improvement
Kelly <i>et al.</i> , ⁴⁰ 1995, prospective study	30; hydrocortisone 25 mg QAM and 15 mg QPM	Progressive AIPC	20% (PSA decrease of >50%); 1 Pt had >99% PSA decrease	—	—
Weitzman <i>et al.</i> , ⁴² 2000, prospective study	12; dexamethasone 20 mg PO Q6 × 3 Q3 wk	Progressive AIPC	0% PSA response	—	—
Nishimura <i>et al.</i> , ⁴³ 2000, prospective study	37; dexamethasone 0.5–2 mg QD	Progressive AIPC	62% PSA response (>50% decrease confirmed in 4 wk)	MTP 9	11/18 had improvement in pain

Key: PSA = prostate-specific antigen; MST = mean survival time; TTP = time to progression; NA = not available; BID = twice daily; LHRH = luteinizing hormone-releasing hormone; TID = three times daily; Q = every; Pt = patient; PO = orally; AIPC = androgen-independent prostate cancer; QD = every day; MTP = median time to progression.

patients achieved a PSA decline of more than 50%. Patients who had more than a 50% decline in their PSA level had a median survival time (MST) of 17.4 months compared with 12.8 months in the overall patient population. The median progression-free survival was 2 months; however, 14% had a progression-free survival of more than 6 months. Although the PSA response rate of 34% was higher than what has been reported with a daily 10-mg prednisone regimen, the retrospective nature of the study and the small number of patients limited result interpretation. The results of the study, however, suggest an association between a decline of more than 50% in PSA and prolonged survival.

Nishiyama⁴¹ evaluated in a small prospective study 16 patients with bony metastases in whom hormonal therapy had failed. All patients had been treated with orchiectomy or a luteinizing hormone-releasing hormone analogue in combination with chlormadinone acetate, estramustine, or flutamide. Patients underwent hormonal withdrawal before study entry. Seven patients progressed despite hormonal withdrawal and were treated with dexamethasone 1.5 mg daily. Three of these patients had a PSA response of more than 50%, and all responses lasted more than 6 months.

Weitzman *et al.*⁴² evaluated a high-dose intermittent schedule of dexamethasone in patients with progressive prostate cancer despite androgen ablation. Twelve patients were treated with 20 mg dexamethasone every 6 hours for three doses repeated every 3 weeks. None of the patients had a decrease in PSA of more than 50%. Although the number of patients was small, these data suggest a lack of efficacy of an intermittent schedule using glucocorticoids.

Most recently, Nishimura *et al.*⁴³ evaluated, in a prospective trial, the use of low-dose dexamethasone in AIPC. Thirty-seven patients with a rising PSA and castrate testosterone levels were treated with daily dexamethasone 0.5 to 2 mg. Forty-nine of these patients had symptomatic metastases on entry. The median pretreatment PSA was 38 ng/mL (range 2.4 to 3570). Antiandrogens were discontinued at least 4 weeks before initiation of dexamethasone. Twenty-three patients (62%) had a PSA decline of more than 50% that was sustained for more than 4 weeks. Four of the responders had decreasing PSA after antiandrogen withdrawal and before the start of dexamethasone. The median time to PSA progression in the responders was 9 months. The MST in the PSA responders was 22 months versus 8 months in the nonresponders. The favorable results seen in this trial were, at least partially, influenced by the responses to antiandrogen withdrawal and perhaps the relatively low vol-

PHASE III TRIALS

Glucocorticoids have served as the control arm in several Phase III trials of cytotoxic or hormonal therapies (Table II). Tannock *et al.*⁴⁴ randomized 161 symptomatic patients with AIPC to mitoxantrone plus prednisone or prednisone alone at 10 mg/day and evaluated QOL as an endpoint. They described a 12% palliative response in patients receiving single-agent prednisone. The PSA level decreased by more than 50% in 22% of patients, but these responses were not reconfirmed in 4 weeks. Osoba *et al.*⁴⁵ analyzed this same patient population for health-related QOL.⁴⁵ Patients receiving prednisone had a significant improvement in health-related QOL scores at 6 weeks. This statistical significance was lost at 12 weeks of therapy.

Kantoff *et al.*³⁸ randomized 242 patients with AIPC to mitoxantrone plus hydrocortisone or hydrocortisone 45 mg daily and evaluated the survival and response rates as endpoints. The MST in the hydrocortisone arm was 12.6 months, and the median time to progression (MTP) was 2.3 months. Twenty-two percent of patients had a maximal PSA decrease of more than 50%. Patients who had a maximal decrease in PSA responses of more than 50% had a significantly higher MST (20.5 versus 10.3 months). This study did not show a statistically significant difference between the two arms in survival or quality-of-life (QOL) measures.

Gregurich⁴⁶ randomized 120 asymptomatic patients with progressive hormone-resistant prostate cancer to mitoxantrone plus prednisone or prednisone 5 mg twice daily. A PSA decrease of more than 50% occurred in 24% of patients on the prednisone arm. The MTP in the prednisone arm was 3.8 months, significantly lower than in the combination arm. The overall survival was equivalent in both arms.

Small *et al.*⁴⁷ randomized 460 patients with symptomatic, metastatic AIPC to low-dose suramin plus hydrocortisone or hydrocortisone 40 mg daily. The primary endpoint of the trial was the evaluation of pain and analgesic use as primary indicators of response. Twenty-eight percent of patients receiving single-agent hydrocortisone had a pain response and 8% had both a pain response and a decrease in opioid analgesic use. The PSA level decreased by more than 50% in 16% of patients receiving single-agent prednisone, and the MST was 9.2 months.⁴⁷

Fossa *et al.*⁴⁸ randomized 201 patients with symptomatic AIPC to receive prednisone 5 mg four times a day or flutamide 250 mg 3 times a day. The subjective response was assessed on the basis of the performance status, reduction in analgesic use, and reduction of the pain score (World Health Organization criteria). At 6 weeks of therapy, the subjec-

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.