ELSEVIER

EFFECT OF PREDNISONE ON PROSTATE-SPECIFIC ANTIGEN IN PATIENTS WITH HORMONE-REFRACTORY PROSTATE CANCER

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ABSTRACT

Objectives. To evaluate the effects of prednisone on prostate-specific antigen (PSA) in a cohort of patients with "hormone-refractory" prostate cancer.

Methods. Data were collected from 29 consecutive patients with hormone-refractory progressive prostate cancer who were treated with 10 mg of prednisone orally two times a day. Patients were included in this analysis only if other factors known to influence PSA levels (antiandrogen withdrawal, radiation, and/or other concomitant anticancer therapies) were definitively excluded as potentially confounding variables.

Results. The mean and median PSA decline after initiating prednisone was 33% (95% confidence interval [CI] 20% to 46%) and 24% (range 0% to 99%), respectively. Ten patients (34%) had a PSA decline of more than 50% and 4 patients (14%) had PSA declines of more than 75%. The average and median time for progression-free survivals were 2.8 (95% CI 1.7 to 3.8) and 2.0 (range 0 to 11) months. Four (14%) patients had PSA declines lasting 6 months or more. Median survival was 12.8 months. Additional analyses indicated that a PSA decline of more than 50%, compared with less than 50%, was associated with a longer survival. Toxicities included steroid myopathy (n = 4), new-onset diabetes (n = 1), and dyspnea (n = 1).

Conclusions. Prednisone (10 mg orally two times a day) can decrease PSA by more than 50% in approximately one third of patients with hormone-refractory progressive prostate cancer. On the basis of comparisons with other data sets, we hypothesize a dose-response relationship between glucocorticoid dose and PSA decline.

UROLOGY **52:** 252–256, 1998.

Glucocorticoids have significant palliative activity in patients with metastatic prostate cancer whose previous therapy with surgical or medical orchiectomy failed. This activity in post-orchiectomy prostate cancer was initially recognized in the 1950s.[1] Since that time, various glucocorticoids at a wide range of doses have been used in patients. Clear efficacy has been documented in some patients when using palliative end points.[2]

In recent years investigators have recognized that hormone-refractory prostate cancer is comprised of a relatively heterogeneous group of patients.[3] In fact, a significant proportion of these hormone-refractory patients may respond to secondary hormonal manipulations as measured by changes in objective markers such as prostate-specific antigen (PSA) decline and/or tumor shrinkage.[3,4] The PSA changes after glucocorticoid treatment are frequently difficult to interpret in the literature because of confounding variables such as radiation therapy,[5] adrenal suppressive therapies,[6] suramin,[7,8] or other concomitant therapies.[9] In addition, not all studies[10] examining PSA changes after glucocorticoids were initiated before recognition of antiandrogen withdrawal as a potentially active therapeutic maneuver.[11]

Since the advent of PSA testing and the recognition of the flutamide withdrawal as a potentially confounding variable, only four trials using regular PSA monitoring to ascertain glucocorticoids effects in patients with hormone-refractory progressive prostate cancer have been published. Two trials used low doses of hydrocortisone (30 to 40 mg/day) before suramin treatments[12,13]; another report used prednisone at 20 mg/day but included only 8 patients[14]; a recent report used 5 mg of pred-

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Submitted: November 10, 1997, accepted (with revisions): February 23, 1998

0090-4295/98/$19.00

nisolone orally two times a day.[15] Additional series using glucocorticoid therapy have been reported in abstract form, but many details regarding these series are incomplete.[16,17] In this report, we review our experiences with prednisone 20 mg/day (10 mg two times a day) in patients with progressive prostate cancer despite medical or surgical orchiectomy. No confounding variables known to effect PSA were present in any patient. No patients had concomitant treatment with radiation therapy, antiandrogen withdrawal, or any other known confounding variables such as ketoconazole, suramin, aminoglutethimide, or chemotherapy. The effects of prednisone on PSA are emphasized because these data are limited in the peer-reviewed literature.

MATERIAL AND METHODS

Patients were included in this review only if antiandrogen withdrawal could conclusively be excluded as a confounding variable. No patients had concomitant treatment with any medication or modality. All patients had been previously treated with surgical or medical castration (luteinizing hormone-releasing hormone [LHRH] analogue) and had evidence of a rising PSA at least 10 ng/mL above the previous nadir before initiating prednisone therapy. Thus all patients were classified as having hormone-refractory progressive prostate cancer. Twenty-nine consecutive patients meeting these criteria are included in this analysis.

Treatment consisted solely of 10 mg of oral prednisone prescribed two times a day. If patients had previously received an LHRH analogue, this therapy was continued at the same dose as before. Serum PSA determinations were made at baseline (within 1 week of starting prednisone) and serially thereafter at each clinic visit. Patients were typically scheduled in clinic every 4 weeks. PSA responses were calculated according to the method of Tannock and colleagues,[11] ie, the maximum observed decrease from baseline.

We note that both Hybritech and Abbott assays were used to determine serum PSA levels in these studies. Although each patient consistently used only one methodology, there is the possibility of significant interpatient PSA variation because different assays were used.

In analyzing the PSA response duration, progression was defined as a PSA rise of 10 ng/mL or more that was sustained on repeated measurements 2 or more weeks apart. We note that this is a more conservative criterion than that used by some investigators, ie, many analyses have required a PSA rise of 50% or greater than the nadir (or baseline) before declaring progressive disease.

In addition to PSA end points, symptomatic end points were also evaluated. Patient symptoms of weight loss, pain, decreased appetite, and fatigue were routinely documented in the chart. Formal quality of life assessments were not performed. Because pain management with narcotic and nonnarcotic medications were optimized at each clinic visit, the investigators believe that improvements in symptomatic end points may or may not be attributed to prednisone.

Potential statistical differences between survival curves were assessed by the log-rank test or by multivariate approaches using a Cox proportional hazard analysis.[18]

TABLE I. ***Patient treatments before initiating prednisone***

Treatment	No. of Patients
Medical or surgical castration	29
Prior antiandrogens	17
Bicalutamide	2
Flutamide	15
Initial CAB	6
Subsequent CAB	11
External beam radiation	13
Chemotherapy	3
Vitamin A	2
Megace	2
Ketoconazole	1
Prednisone	1
Intravenous radiation	1

KEY: CAB = combined androgen blockade using a combination of an antiandrogen and medical or surgical castration.

RESULTS

A total of 29 consecutive patients were included in this analysis. A review of prior therapies administered to these patients (see Table I) indicated that all patients received prior orchiectomy or regular injections of an LHRH agonist. Seventeen patients had received prior antiandrogen therapy in addition to medical or surgical castration. Six of these patients had received antiandrogens as part of initial hormonal therapy; 12 patients received antiandrogens after progression of disease was initially documented. Radiation was previously administered to 12 patients. All patients completed radiation at least 1 month before starting prednisone. Chemotherapy had been previously administered to 3 patients and megestrol acetate to 2 patients; miscellaneous therapies had been administered in several other cases. When taken together, 13 patients had been pretreated with only one previous hormonal therapy (orchiectomy or LHRH analogues), 13 patients had been treated with two hormonal therapies (antiandrogens + medical/surgical orchiectomy), and 4 patients had been treated with three or more hormonal therapies before prednisone. Flutamide withdrawal was not considered a hormonal therapy in this compilation.

Pretreatment characteristics of the patient population included the following (see Table II): median patient age was 71 years, median Eastern Cooperative Oncology Group (ECOG) performance status was 1, median PSA was 158 ng/mL, and median hemoglobin was 11.6 g/dL. Twenty-six patients had previously documented metastatic disease on a bone scan (n = 19), a computed tomography scan (n = 2), or both scans (n = 5); 2 patients did not have a bone scan available for review, and 1 patient had a negative bone scan.

TABLE II. *Patient population in the prednisone study*

Total population	29
Bone scan positive	24
CT scan positive (soft tissue)	7
Age (median yr)	71 (range 50–85)
Performance status (median)*	1 (range 0–3)
Hemoglobin (median g/dL)	11.6 (range 7.4–14.2)
Alkaline phosphatase (median U/L)	134 (range 57–2260)
PSA (median ng/mL)	158 (range 13–768)

Key: CT = computed tomography; PSA = prostate-specific antigen.
** According to the criteria established by the Eastern Cooperative Oncology Group (ECOG).*

TABLE III. *PSA responses after initiating prednisone*

PSA decline (average)	33% (95% CI 20%–46%)
PSA decline (median)	24% (range 0%–99%)
≥25% declines	14/29 (48%)
≥50% declines	10/29 (34%)
≥75% declines	4/29 (14%)

Key: PSA = prostate-specific antigen; CI = confidence interval.

Twenty-six of the 29 patients had symptoms of some type including pain, loss of appetite, fatigue, and/or weight loss. Taken together, the majority of patients in this study had symptomatic, metastatic hormone-refractory prostate cancer.

PSA responses are noted in Table III. The average PSA decline compared with baseline was 33% (95% confidence interval [CI] 20% to 46%); the median PSA decline was 24%. The range of PSA declines varied from 0% to 99%. Of the 29 patients, 14 (48%) achieved a PSA decline of at least 25%, 10 (34%) achieved a PSA decline of at least 50%, and 4 (14%) achieved a PSA decline of at least 75% less than baseline. From an alternative point of view, 4 patients achieved a PSA decline of at least 25% and less than 50%, 6 patients achieved a PSA decline of at least 50% and less than 75%, and 4 patients achieved a PSA decline of at least 75%. No PSA decline was documented in 10 patients; 4 patients had a documented PSA decline of less than 25%.

The mean progression-free survival as determined by PSA was 2.8 months (95% CI 1.7 to 3.8 months); the median progression-free survival was 2.0 months (see Table IV). The range of progression-free survival was 0 to 11 months. Of the 29 patients, 20 patients had a PSA progression-free survival of at least 2 months, 10 patients had a PSA progression-free survival of at least 4 months, and 4 patients had a progression-free survival of at least 6 months.

Of the 26 symptomatic patients, 23 had improved appetite, weight gain, or pain relief. Because pain management was optimized concomitantly, the contributions of prednisone and/or pain management cannot be accurately ascertained.

TABLE IV. *Progression-free survival after initiating prednisone*

Duration (average)	2.8 months (95% CI 1.7–3.8)
Duration (median)	2.0 months (range 0–11)
Duration ≥2 months	20/29 (69%)
Duration ≥4 months	10/29 (34%)
Duration ≥6 months	4/29 (14%)

Key: CI = confidence interval.

Analysis of survival revealed that the median survival after starting prednisone was 12.8 months. The 25th and 75th percentiles for survival were 6.4 and 21.4 months, respectively. To examine the relationship between PSA changes and survival, survival was calculated for cohorts stratified by various percentages of PSA decline (Table V). Comparisons of survival for each cohort were then performed by log-rank testing. No differences in survival were noted for patients having a PSA decline of greater than 25% versus less than 25%. For patients having PSA declines of greater than 50% versus less than 50%, however, median survival differences of 17.4 versus 10.5 months ($P = 0.027$) were noted. The median survival of patients with a PSA decline of greater than 75% was 27.2+ months; however, only 4 patients achieved this particular end point (making statistical analyses inappropriate).

A multivariate analysis of PSA response (greater than 50% decline) was then performed and included the following independent variables: age, performance status, baseline hemoglobin, baseline alkaline phosphatase, and previous antiandrogen use. None of these variables predicted PSA declines of greater than 50% in these patients.

A multivariate analysis of survival using Cox proportional hazards was performed on the following pretreatment laboratory variables: alkaline phosphatase (greater than 140 IU/L), hemoglobin (greater than 12 g/dL), PSA (greater than 100 ng/mL), or age (greater than 70 years). In this small study, none of these pretreatment variables were associated with survival.

A review of prednisone-induced toxicities revealed 4 cases of proximal muscle weakness compatible with steroid-induced myopathy, 1 case of new-onset diabetes in a man with no history of glucose intolerance, and 1 case of new-onset shortness of breath and edema in a patient subsequently found to have heart failure and a left ventricular ejection fraction of less than 30%.

TABLE V. *Relationship between PSA decline and survival*

PSA Decline (%)	No. of Patients	Median Survival (25th to 75th Percentile)	*P* Value
PSA <25	15	11.7 mo (5.7–17.6)	0.131
PSA >25	14	14.8 mo (10.3–21.7)	
PSA <50	19	10.5 mo (5.9–15.9)	0.027
PSA >50	10	17.4 mo (12.8–30.5)	

Key: PSA = prostate-specific antigen.
P value determined by log-rank testing.

TABLE VI. *PSA response rates comparing 20 and 10 mg/day of prednisone and 30 mg/day of hydrocortisone*

	P 20 mg/day (%)*	P 10 mg/day (%)†	HC 30 mg/day (%)‡
25% declines	14/29 (48)	25/54 (46)	5/22 (23)
50% declines	10/29 (34)	12/54 (22)	2/22 (9)
75% declines	4/29 (14)	5/54 (9)	0/22 (0)

Key: P = prednisone; HC = hydrocortisone.
Note: The Tannock et al. *study was uncontrolled for antiandrogen withdrawal until midway in their study; thus, their response rates could potentially be inflated by the inclusion of flutamide withdrawal responses. Hydrocortisone (30 mg/day) is the glucocorticoid equivalent of 7.5 mg/day of prednisone.*
* *This study.*
† *Tannock* et al.[11]
‡ *National Cancer Institute data base.*

COMMENT

These data clearly indicate that prednisone can decrease PSA levels in some patients whose initial hormonal therapy with medical or surgical castration had failed. This review carefully excluded all patients with other known confounding variables. Prior hormonal therapy with an LHRH analogue or orchiectomy had failed in all patients. The average and median decline in PSA was relatively modest (33% and 24%, respectively); however, selected patients had a more robust PSA response. The average and median progression-free survival were also quite modest (2.8 and 2.0 months, respectively) and consistent with previously published data.[11] Symptomatic improvement was noted in most patients; however, pain management was optimized during each clinic visit, and this undoubtedly contributed to overall patient well-being.

There has been only one previously published study of prednisone at 20 mg/day in patients with metastatic prostate cancer whose previous therapy with surgical or medical orchiectomy had failed. In that study, 3 of 8 patients had a decline in PSA of greater than 50%.[14] Other details were not stated. These limited data are consistent with the data reported in this study.

PSA changes induced by 30 mg of oral hydrocortisone a day (20 mg every AM, 10 mg every PM) in a similar group of patients with hormone-refractory prostate cancer (without confounding variables) are available from a data base established at the National Cancer Institute (Bethesda, Md). On analyzing PSA changes according to the same method used herein (the method of Tannock *et al.*[11]), 30 mg/day of hydrocortisone induced PSA declines of at least 25% in 5 of 22 (23%) patients, at least 50% in 2 of 22 (9%) patients, and declines of at least 75% in 0 of 22 (0%) patients (see Table VI).

PSA changes after 5 mg of prednisone orally two times a day were published by Tannock and colleagues.[11] This trial did not recognize antiandrogen withdrawal as a potentially active therapy until midway through the study; thus, response rates may be in part attributable to this maneuver. In the Tannock *et al.* report, a PSA decline of at least 25% was noted in 25 of 54 (46%) patients, a 50% or more decline was noted in 12 of 54 (22%) patients, and a 75% or more decline was noted in 5 of 54 (9%) patients. As noted above, our method of calculating PSA changes was exactly the same as that used by Tannock and colleagues. A comparison of these data is shown in Table VI.

A recent study evaluated the effects of 5 mg of prednisolone orally two times a day in patients with hormone-refractory prostate cancer.[15] The investigators stated that 55% of patients achieved a PSA decline; however, the percentage of patients achieving a greater than 25%, greater than 50%, or greater than 75% decline in PSA was not stated. After the first patient visit (6 weeks after treatment), patient follow-up was conducted at an interval of every 3 months. Differences in both data reporting and patient follow-up make these data difficult to compare with the other studies cited herein.

Analysis of our data indicates that prednisone

can decrease PSA in patients whose previous therapy of antiandrogens had failed. This suggests that antiandrogens and glucocorticoids are non-cross resistant in action, raising the possibility that the mechanism of glucocorticoid action in this disease may extend beyond adrenal suppression.

The exact mechanism of PSA decline cannot be determined from these or other studies. We note, however, that in vitro studies in a PSA-secreting human prostate cancer cell line do not suggest that PSA secretion is directly altered by glucocorticoids.[19] Furthermore, our in vitro experiments (data not shown) detected no effects of glucocorticoids on in vitro prostate cancer cell line cellular growth. These data suggest that the effects of glucocorticoids may be indirect, perhaps being mediated by glucocorticoid-induced inhibition of neovascularization.[20] We conclude that additional experiments are necessary to understand the mechanism of glucocorticoid action in patients with prostate cancer.

Our analysis of patient survival leads us to hypothesize that PSA declines of greater than 50% may be useful in predicting a relatively prolonged survival. We note that previously published investigations have made similar conclusions when using landmark methods of analysis.[21]

Although the studies of PSA response rates with various glucocorticoids cannot readily be compared because of potential patient selection biases and other factors, note that the percentage of patients with PSA declines is higher in patients receiving higher doses of glucocorticoids (Table VI). These data suggest the possibility that a dose-response curve for glucocorticoids may be present in patients with hormone-refractory prostate cancer. It is also possible that differences between prednisone and hydrocortisone may contribute to the differences in observed outcome. We note that no prospective trial has ever compared various doses and schedules of glucocorticoids in this patient population. We suggest that randomized studies should be performed to establish the optimal dose, schedule, and route of glucocorticoid administration.

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