Prostate Specific Antigen Levels and Clinical Response to Low Dose Dexamethasone for Hormone-Refractory Metastatic Prostate Carcinoma

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Background. **It has been suggested that suppression of adrenal androgens may provide benefit to patients with metastatic prostate cancer refractory to initial hormonal therapy (e.g., orchiectomy).**

Methods. **The records of 38 patients with metastatic prostate cancer that had progressed after orchiectomy who were placed subsequently on low dose dexamethasone (DXM) with no other concurrent therapy (36 patients received 0.75 mg twice daily and two received 0.75 mg three times daily) were reviewed. Symptomatic status, prostate specific antigen (PSA) measurements, and available radiographic assessments were recorded. Bone scans were reviewed by an independent, blinded evaluator.**

Results. **Symptomatic improvement was experienced by 24 patients (63%), 20 (83%) of whom also had decreases in PSA. Prostate specific antigen values decreased in 30 patients (79%) with decreases 50% or greater and 80% or greater in 23 (61%) and 13 (34%) patients, respectively. Of the 23 patients with PSA decreases 50% or greater, 8 (35%) had radiographic evidence of disease regression, 5 (22%) were stable, 7 (30%) had disease progression, and 3 (13%) did not have serial radiographic exams. Flutamide was discontinued shortly before DXM treatment for 2 of the 23 patients.**

Conclusions. **Low dose DXM may produce important symptomatic improvement and decreased PSA levels in the majority of patients with hormone-refractory prostate cancer. In addition, a substantial percentage of those patients with decreases in PSA also will have radiographic evidence of disease regression. These results suggest the need for additional prospective controlled studies of DXM as a therapy for hormone-refractory prostate cancer.** ***Cancer*** **1995;76:96–100.**

Key words: prostatic neoplasms, prostate specific antigen, dexamethasone, orchiectomy, metastatic neoplasms.

Most patients with metastatic prostate carcinoma will show some response to first-line hormonal therapy in the form of surgical ablation of testicular androgens (orchiectomy) or gonadal suppression (estrogens, progestins, luteinizing hormone–releasing hormone agonists, or antiandrogens).[1,2] However, the majority of patients with metastases will experience disease progression within 2 years after initial hormonal therapy. The mean survival of these patients is less than 1 year after relapse.[2]

The biologic significance of adrenal androgens in prostate cancer refractory to primary hormonal ablation was recognized as early as 1945, when Huggins et al.[3] reported the effects of bilateral adrenalectomy in four patients whose disease had progressed after orchiectomy. Harper et al.,[4] in 1974, examined the conversion of adrenal androgens to dihydrotestosterone in the prostate. Based on that study, it has been estimated that, after ablation of testicular androgens, adrenal androgens could provide as much as one-fifth the original stimulus for prostatic cell growth.[1] The role of adrenal androgen production has been a major focus of second-line hormonal therapies directed at inhibition of adrenal androgen biosynthesis (e.g., aminoglutethimide, ketoconazole, spironolactone), as well as peripheral blockade of adrenal androgen effects (e.g., flutamide and cyproterone acetate).[2,5,6]

The use of low dose corticosteroids to suppress the pituitary–adrenal axis in advanced prostate cancer has been another approach to limit adrenal androgen production. The concept of "medical adrenalectomy" with high dose cortisol for patients with advanced prostate cancer was introduced by Miller and Hinman in 1954.[7] Several studies have demonstrated that suppressive doses of corticosteroids combined with testicular andro-

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gen ablation produces lower serum androgen levels and better clinical response than testicular androgen ablation alone.[8,9] Although there are also reported studies of low dose corticosteroids used alone as second-line therapy after failure of primary hormonal therapy, we are not aware of previously published work that systematically examines prostate specific antigen (PSA) levels in men with hormone-refractory prostate cancer receiving low dose corticosteroids as single agent therapy. We present our results with 38 patients with metastatic prostate cancer refractory to orchiectomy who received low dose dexamethasone (DXM) as single-agent therapy with PSA levels as a marker of disease status.

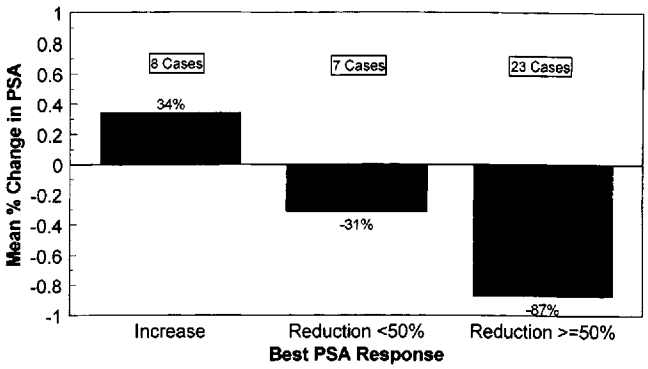

Figure 1. PSA response to low dose dexamethasone in 38 patients with progressive metastatic prostate cancer despite orchiectomy.

Methods

We retrospectively reviewed 38 patients treated at the Mayo Clinic in Rochester, Minnesota, between 1987 and 1992 who fulfilled the following criteria: (1) prior orchiectomy for metastatic prostate cancer; (2) progression of disease after initial response to orchiectomy; (3) secondary hormonal therapy with low dose DXM (usually 0.75 mg twice daily); (4) no other therapy concurrent with DXM during the period of response (including radiation); (5) initial PSA ≥10 ng/ml and on a rising trend at start of DXM; and (6) serial PSA measurements obtained during DXM therapy (usually 4–6 month intervals). Patients who had received DXM but who did not meet the above criteria were excluded.

Prostate specific antigen measurements were used to determine response to therapy, with best response being the lowest PSA level recorded during therapy and progression being the first sustained rise in PSA above the lowest measurement. Prostate specific antigen responses were categorized into three groups: (1) increase above initial value, (2) decrease of <50% of initial value, and (3) decrease of ≥50% of initial value (regression). Symptomatic status and available imaging corresponding to the date of the lowest PSA were used for comparison of biochemical to symptomatic and radiographic response. Symptomatic response as recorded in the patient history by the examining physician was categorized as improved, unchanged, or worse than at the beginning of DXM therapy. Serial bone scans were reviewed by a blinded nuclear medicine physician and graded on the same scale. In cases of heterogeneous response, bone scans were graded based on overall level of tumor activity. Because of the limitations of the retrospective study design, no attempt was made statistically to determine any specific correlations, and data are reported as descriptive results only.

Results

Twenty-seven (71%) of the patients in this study had metastatic prostate cancer at the time of diagnosis, whereas in four cases metastases were detected at 15, 20, 26, and 122 months after initial diagnosis. In seven cases, information regarding initial staging was unavailable. The mean age at time of diagnosis was 68 years (range, 49–85 years). All of the patients had orchiectomy as primary therapy for metastatic disease. Nineteen had failed at least one other form of pharmacotherapy, and 25 had had radiotherapy before a trial of low dose DXM. The range of previous pharmacotherapies included megesterol acetate, flutamide, diethylstilbesterol, and leukocyte A human interferon. All patients had progressive disease clinically and biochemically when DXM was begun. The mean PSA at the start of therapy was 238 ng/ml (range, 14.4 to 1430 ng/ml), and only two patients had PSA levels below 20 ng/ml (17.5 and 14.4 ng/ml). Thirty-six patients received DXM 0.75 mg twice daily, and two received 0.75 mg three times daily.

Biochemical responses are shown in Figure 1. After initiation of DXM, 30 (79%) of the patients in the study had lowered PSA levels. In 23 patients (61%), the PSA level dropped to less than 50% of the original value, with a mean time to best response of 90 days (range, 39–309 days). Both of the patients receiving DXM 0.75 mg three times daily were in this group. Thirteen patients (34%) had a greater than 80% decrease in PSA. For eight patients (21%), the PSA level rose.

Of the 38 patients studied, 24 (63%) had symptomatic improvement; 20 of these 24 (83%) had concomitant lowering of PSA levels. Overall, 67% of patients with lowered PSA levels also had symptomatic improvement, and 93% had either improvement or stability of symptoms. Of the eight patients with PSA increases, four (50%) had improvement of symptoms, two (25%) had stable symptoms, and two (25%) had progressive symptoms (Table 1).

The mean time to biochemical progression for those patients with a greater than 50% decrease in PSA was 245 days (range, 99–660 days). In the subgroup with a >80% reduction, the mean time to progression was 327

Table 1. Comparison of Symptomatic to Prostate Specific Antigen Response to Dexamethasone in Refractory Metastatic Prostate Cancer

	Symptomatic response			
PSA response*	*Improved*	*Stable*	*Worse*	*Total (%)*
Increase	4	2	2	8 (21)
Reduction <50%	7	0	0	7 (18)
Reduction 50–79%	4	6	0	10 (26)
Reduction ≥80%	9	2	2	13 (34)
Total (%)	24 (63)	10 (26)	4 (11)	

PSA: prostate specific antigen.

* A total of 67% of patients with decreases in PSA had improvement of symptoms; 93% of patients with decreases in PSA had stable or improved symptoms.

days (range, 151–659 days) versus 165 days (range, 99–110 days) for those with a 50%–79% reduction. One patient in the responder group was lost to follow-up on day 123 before progressing biochemically. Two patients died of unspecified causes before biochemical progression at days 161 and 108. For two patients, DXM was discontinued despite biochemical response on days 78 and 219, because these patients were judged to have progressive disease based on other parameters (one had worsening symptoms and the other had a worsening bone scan).

Of the 23 patients with decreases in PSA ≥50%, 8 (35%) had radiographic evidence of disease regression (of whom 6 were evaluated by bone scan and two by radiograph only), 5 (22%) were stable, and 7 (30%) had disease progression (Table 2). Three (13%) of these patients did not have serial radiographic exams. Among the seven patients with PSA decrease <50%, none had radiographic evidence of disease regression, two (29%) were stable, and five (71%) had disease progression. Of the eight patients with increases in PSA, none had radiographic evidence of regression, three (38%) were stable, and five (62%) had disease progression. In summary, 67% of patients with PSA increase or only partial response had radiographic evidence of disease progression, and none had regression. However, 35% of patients with ≥50% decrease in PSA had radiographic evidence of disease regression, and 57% had either stability or regression of disease (Fig. 2). In light of recent reports of PSA decreases after flutamide withdrawal, it should be noted that four patients had had flutamide discontinued shortly before starting DXM.[10] Two of the patients had PSA decreases ≥50% (with flutamide stopped within 1 day of the start of DXM), and two patients had PSA decreases <50% of initial PSA value (one with flutamide stopped 1 day and the other 9 days before the start of DXM). Five other patients had had flutamide discontinued before other pharmacotherapies before DXM, of whom three had progression, one stability, and one regression of disease after flutamide was discontinued.

Discussion

Several studies reported use of low dose corticosteroids alone as second-line therapy after failure of primary hormonal therapy. Plowman et al.[11] in 1987 demonstrated that hydrocortisone (30 mg daily) alone produced more suppression of adrenal androgen secretion than hydrocortisone plus aminoglutethimide. Similar results with hydrocortisone (20 mg twice daily) were reported by Dowsett et al.[12] in 1988. Tannock et al.[13] in 1989 demonstrated a correlation of symptomatic relief with lowered serum adrenal androgens in 37 patients

Table 2. Comparison of Radiographic Assessment of Disease Status to Prostate Specific Antigen Response to Dexamethasone in Patients With Refractory Metastatic Prostate Cancer

	Radiographic response				Imaging	
PSA response*	*Improved*	*Stable*	*Worse*	*Unknown*	*Bone scan*	*X-ray*
Nonresponder group (n = 15)						
Increase	0	3	5	0	6	2
Reduction <50%	0	2	5	0	3	4
Total (%)	0	5 (33)	10 (67)	0		
Responder group (n = 23)†						
Reduction 50–79%	4	1	2	3	3	4
Reduction ≥80%	4	4	5	0	10	3
Total (%)	8 (35)	5 (22)	7 (30)	3 (13)		

PSA: prostate specific antigen.

* A total of 67% of nonresponder group had radiographic evidence of disease progression and none had evidence of disease regression; 35% of responder group had radiographic evidence of disease regression.

† Two patients in responder group had flutamide discontinued shortly before dexamethasone therapy.

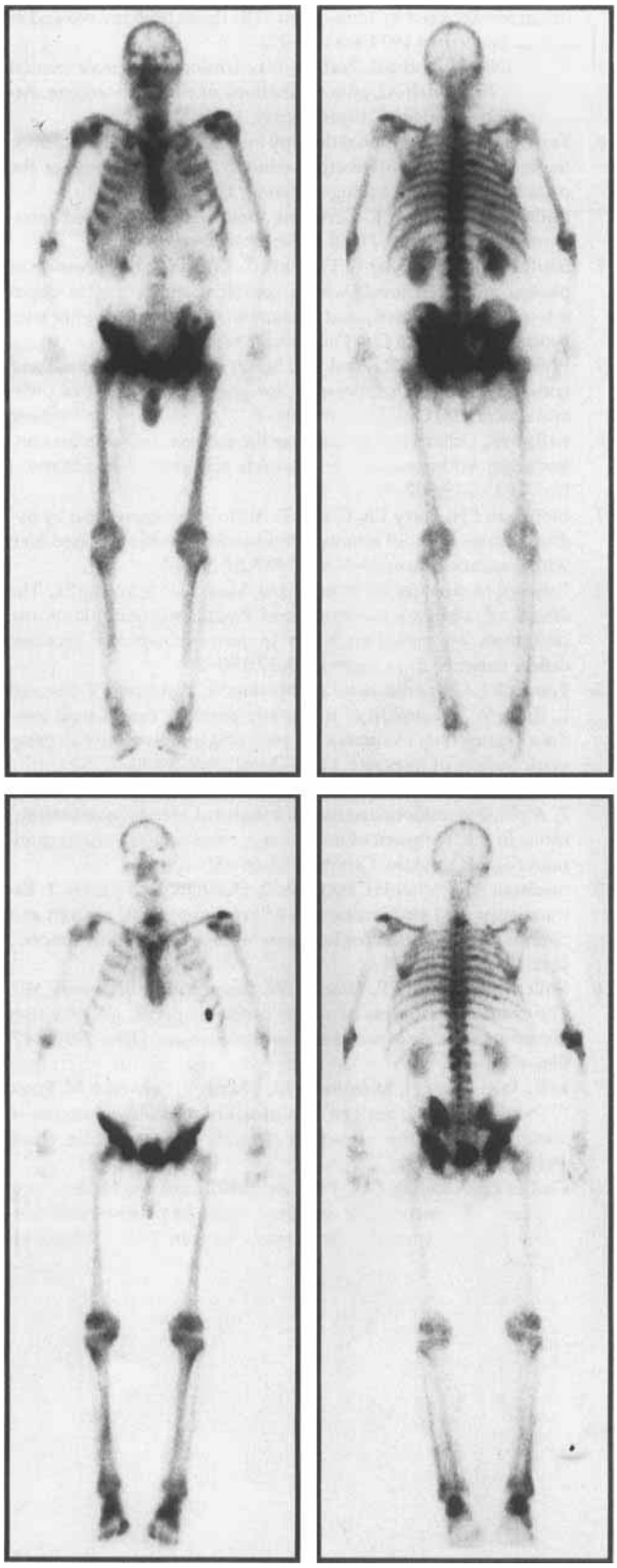

Figure 2. Bone scans (anterior and posterior views) of a patient with progressive metastatic prostate cancer despite orchiectomy. (Top panels) Day 1 of dexamethasone, when PSA measured 1430 ng/ml. (Bottom panels) Day 309, when PSA reached a nadir of 1.2 ng/ml. The apparently new rib lesion actually corresponds to a rib contusion sustained just before the follow-up bone scan.

with advanced prostate cancer treated with low dose prednisone (7.5–10 mg daily) who were no longer responding to primary hormone ablation. However, these investigators were unable to verify objective disease regression with prostatic acid phosphatase levels, X-rays, or bone scans. Patel et al.[14] reported in 1990 that of 23 patients with hormone-refractory prostate cancer receiving low dose DXM (0.75 mg by mouth twice daily), 2 had objective disease regression and the remaining 21 had clinically stable disease for a mean duration of 86 days. None of these studies examined clinical response to DXM in the context of PSA levels.

Although objective assessment of disease status in metastatic prostate cancer presents some difficulty, serum PSA is elevated in 90% of patients with hormone-refractory disease.[15] Miller et al.[16] in 1992 demonstrated that serum PSA is a sensitive monitor of objective response to primary hormonal ablation. In addition, Kelly et al.[17] demonstrated that decreasing PSA levels in response to treatment correlate with better survival. Gerber and Chodak[18] in 1990 demonstrated a significant correlation between symptom improvement and decreased serum levels of PSA in response to ketoconazole and prednisone in 15 patients with hormone-refractory metastatic prostate cancer. Of 12 patients with bone pain and/or other symptoms of progressive disease, 9 (75%) experienced symptomatic relief, which, with one exception, was accompanied by decreased PSA levels.

Although ours is a retrospective study with inherent limitations, numerous conclusions can be drawn from our data. First, it is clear that low dose DXM may produce important symptomatic improvement in patients with hormone-refractory prostate cancer, an unfortunately large and challenging patient population. Whether this effect is produced by actual regression of disease or by independent actions of systemic steroids is unclear. That most symptomatically improved patients also had significant decreases in PSA in the absence of any other form of antitumor therapy suggests some effect on their underlying disease. Although it is unclear whether the decrease in PSA represents disease regression or some independent effect of DXM on PSA production, a substantial proportion of patients who responded to DXM symptomatically and biochemically also had radiographic evidence of disease regression. These results are in agreement with other investigators'

findings that substantial PSA reductions do correlate with tumor response.

The design of the current study had numerous limitations. As a retrospective chart review, it lacks any form of control group. Also, the large percentage of responders (symptomatic and biochemical) may represent a selection bias in that some patients who did not respond well to DXM might not have returned for initial follow-up and thus been excluded from the study. In addition, because there were no consistent objective symptomatic criteria, determination of symptomatic response was dependent on the subjective impression of the examining physician as recorded. The radiographic assessment of disease status was also not uniform among these patients. Twenty-two (58%) patients had serial bone scans, most of whom were in the responder group. However, 13 (34%) had serial X-rays, usually to view a particular region that was producing symptoms and not to assess overall tumor status. Last, although serial PSA measurements were monitored over relatively consistent intervals, follow-up intervals were generally in the range of several months rather than weeks, which makes determination of time to regression and time to progression less accurate. Despite these limitations, the results of the current study suggest that low dose DXM may effect tumor regression, as evidenced by symptomatic improvement, improvement in radionuclide bone scans, and substantial decreases in PSA levels. Additional, carefully controlled prospective studies of DXM for patients with hormone-refractory prostate cancer are warranted.

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