Original Paper

Urologia Internationalis

Urol Int 2002;68:10–15

Received: September 19, 2000
Accepted: April 20, 2001

Prostate-Specific Antigen Levels and Prognosis in Patients with Hormone-Refractory Prostate Cancer Treated with Low-Dose Dexamethasone

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Key Words

Hormone-refractory prostate cancer · Dexamethasone · Prostate-specific antigen response · Palliative effect

Abstract

Objective: The efficacy of low-dose dexamethasone (DXM) therapy in patients with hormone-refractory prostate cancer (HRPC) was evaluated. ***Patients and Methods:*** Prostate-specific antigen (PSA) response and survival following DXM therapy were analyzed in 27 Japanese patients exhibiting HRPC. Concurrent therapies and antiandrogen withdrawal syndrome, which may affect PSA levels and palliative effects, were excluded from the study. A dose of 1.5 mg of DXM was administered, and androgen deprivation therapy was maintained during DXM therapy. A decline in PSA levels of at least 50% from baseline was considered a significant PSA response. Prognostic factors for PSA response and survival were examined by univariate and multivariate analyses. ***Results:*** A significant PSA response was observed in 16 of the 27 cases (59.3%). Median survival period of patients exhibiting significant PSA response was 15.9 months and was significantly longer than that of patients demonstrating a decline in PSA of less than 50% (median 7.7 months, $p < 0.0001$). Effect on pain control also correlated with the significant PSA response. No meaningful prognostic factors for PSA response were detected; however, a PSA decline of greater than 50% was the prognostic factor for survival. ***Conclusion:*** DXM therapy remains one of the most beneficial treatment modalities in patients with HRPC.

Introduction

Hormone-refractory prostate cancer (HRPC) comprises a heterogeneous group of patients. Clinical responses to second-line hormonal manipulations usually vary in this group of patients [1, 2]. Combined androgen blockade (CAB), antiandrogen withdrawal syndrome (AWS), estramustine phosphate (EMP), adrenal androgen inhibitors and glucocorticoids are indicated in patients with HRPC as second-line hormonal therapies [1, 2]. In recent years, new regimens, such as the combination of glucocorticoid and mitoxantrone [3, 4] and of EMP and docetaxel [5, 6], have been evaluated. Among these treatment options, glucocorticoid therapy has been shown to be an advantageous treatment modality due to its considerable prostate-specific antigen (PSA) response and palliative effects. Several reports have been published de-

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scribing the clinical effects of hydrocortisone, prednisone and dexamethasone (DXM) [7–11]. However, there have been few studies in which complicating factors, including AWS or external beam radiotherapy (EBR) that may potentially affect serum PSA levels and/or palliative effects, were excluded. In the present study, the effects of low-dose DXM in patients with HRPC were examined in terms of PSA decline, survival and improvement of pain scale as end points.

Patients and Methods

Between August 1997 and November 1999, 34 patients who had failed to prior hormonal therapies, such as androgen deprivation therapy using LHRH agonist (goserelin acetate), CAB (goserelin plus flutamide) or EMP, were treated with low-dose DXM in our institute. Twenty-seven of the 34 cases met the following criteria and were included in the study: (1) patients presenting with hormone-refractory metastatic prostate cancer which had failed to respond to prior hormonal therapies; (2) concurrent therapies, including whole pelvis radiation or systemic chemotherapy were not performed, and (3) AWS influences were excluded at the initiation of DXM therapy. In order to confirm AWS, DXM therapy was initiated following the repeated measurements of serum PSA after the discontinuation of flutamide. At least two measurements were made, separated by at least 2 weeks. AWS was observed in 1 of the 27 cases displaying a PSA decline of greater than 50% over 3 months. Serum PSA levels were measured by the Tandem-R assay. DXM was administered at a total dose of 1.5 mg/day (1 mg morning, 0.5 mg evening). The dosage was decreased to 1 mg/day over the 3 months following initiation of the therapy. Androgen deprivation therapy (ADT), utilizing goserelin acetate, was maintained during DXM administration. Serum PSA levels and Eastern Cooperative Oncology Group (ECOG) pain scale [12] were evaluated every 4–8 weeks. PSA responses were calculated as maximum decrease from baseline, and decreases in serum PSA levels of greater than 50% were considered as significant responses. Biochemical (PSA) failure to DXM therapy was defined as

Table 1. Prior treatments and background factors in patients treated with DXM

Background						
			Range (median), n = 27			
Age at initial diagnosis, years old			56–88 (71)			
PSA at initial diagnosis, ng/ml			18.0–3,100 (388.0)			
Gleason sum			5–9 (7)			
Time-to-PSA failure in first-line hormone therapy, months			2.7–48.9 (11.7), average 14.9 (95% CI, 10.7–19.1)			
Time-to-initiating DXM therapy from initial diagnosis, months			6.6–66.0 (22.4), average 28.0 (95% CI, 21.8–34.1)			
Prior treatments						
first-line		second-line		third-line		fourth-line
LHRH	10	CAB	3 (2)	DXM	3 (3)	
		CAB+EBR	1 (1)	DXM	1 (0)	
		EMP	2 (2)	DXM	2 (1)	
		EMP+EBR	1 (0)	DXM	1 (0)	
		DXM	2 (2)			
		CT[b]+EBR	1 (1)	EMP	1 (0)	DXM 1 (0)
CAB	15	EMP	9 (3)	DXM	8 (4)	
				CT[b]	1 (1)	DXM 1 (1)
		EMP+EBR	1 (0)	DXM	1 (0)	
		DXM	4 (3)			
		EBR	1 (0)	DXM	1 (0)	
LHRH + CT[a]	2	CAB	2 (1)	DXM	1 (1)	
				EMP+EBR	1 (0)	DXM 1 (1)

LHRH = LHRH agonist (goserelin); CAB = combined androgen blockade (goserelin + flutamide); CT[a] = systemic chemotherapy using vincristine, ifosphamide, peplomycin; CT[b] = CDDP, ifosphamide, epirubicin; EMP = estramustine phosphate; DXM = dexamethasone; EBR = external beam radiotherapy for whole pelvis (54–63 Gy).

Numbers in parentheses show patients in whom PSA decline of greater than 50% was observed.

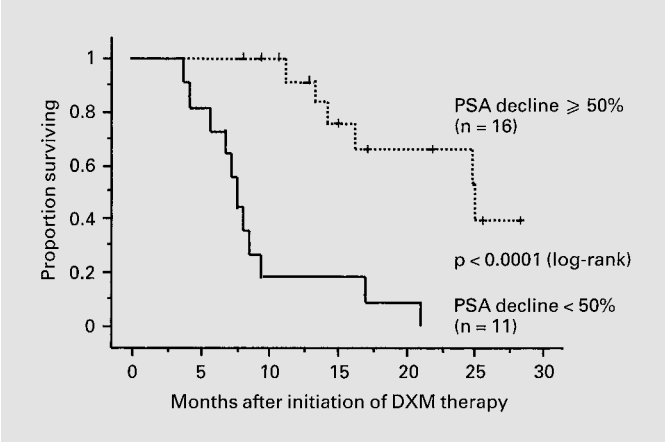

Fig. 1. Cause-specific survival rate following DXM therapy. Median survival period in patients who achieved a PSA decline of greater than 50% was 15.9 months. On the other hand, that in patients with a PSA decline of less than 50% was only 7.7 months. Two-year survival rate in these groups was 66 and 0%, respectively. The significant difference was seen between the two groups by log-rank test.

an increase in PSA levels of greater than 50% from nadir PSA levels on repeated measurements [13, 14]. Palliative effects were evaluated by ECOG pain scale [12]. An improvement of greater than one grade was considered meaningful. The correlation between significant PSA response, survival and background factors, including Gleason sum, response duration to first-line hormonal therapies and prior treatments, were analyzed by univariate (χ^2 test) and multivariate (Cox proportional hazards model) analyses.

Results

Twenty-seven patients were included in this evaluation. Patient characteristics and prior treatments are summarized in table 1. LHRH agonist, CAB and LHRH agonist plus systemic chemotherapy were employed as first-line therapies in 10, 15 and 2 cases, respectively. Time-to-PSA failure in first-line therapy ranged from 2.7 to 48.9 months (median 11.7). Time-to-initiation of DXM therapy from initial diagnosis ranged from 6.6 to 66.0 months (median 22.4). CAB, EMP or DXM was used as second-line therapies in 9 patients failing to respond to ADT. One patient underwent the combination of chemotherapy and EBR to whole pelvis. PSA response (greater than 50% decline) to second-line hormonal treatments was observed in 7 of the 9 cases (77.8%). In 10 of 15 cases displaying failure of first-line CAB therapy, EMP was employed as a second-line treatment. However, PSA response was observed in only 3 of 10 cases (30%). DXM was used as second-, third- or fourth-line hormone therapy in 6, 18 and 3 cases, respectively. Eight of 27 patients underwent combined endocrine treatment or systemic chemotherapy and EBR. However, these therapies were not concurrently performed during DXM therapy (table 1).

At initiation of DXM therapy, median PSA level was 75 ng/ml (range 5.5–639 ng/ml) and median extent of disease (EOD) score was 3 (range 1–4). Maximum PSA decline from baseline varied from 0 to 98.7%. Average PSA decline was 52.2% (95% CI, 37.1–67.3%). Of the 27 cases, 16 (59.3%) exhibited a PSA decline of at least 50%. Eleven of the 16 cases achieved a PSA decline of at least 80%. No PSA decline was observed in 6 cases (22.2%) whereas 4 patients (14.8%) achieved a PSA decline of less than 25%. The remaining patient displayed a PSA decline of between 25 and 50%. Nadir PSA levels ranged from 0.1 to 639 ng/ml (median 28.8). Normal levels were restored (<4 ng/ml) in 7 of the 27 cases (25.9%). Median period to PSA nadir was 14 weeks (range 2–76), and median response duration to DXM evaluated by PSA levels was 5.4 months. Median survival after DXM therapy was 13.1 months (average 14.3, 95% CI 11.4–17.2 months). Overall follow-up period from the initial diagnosis was 13.6–94.7 months (median 40) (table 2). The correlation between PSA response and survival period after DXM therapy was apparent. That is, median survival of patients displaying a PSA decline of at least 50% was 15.9 months (n = 16, average 17.9, 95% CI 14.4–21.4 months). In contrast, the median survival of patients achieving a PSA decline of less than 50% was 7.7 months (n = 11, average 9.1, 95% CI 5.9–12.3 months). A significant difference was observed between the two groups of patients ($p < 0.0001$, log-rank). However, there were no significant differences between the patient groups exhibiting PSA decline of greater than or less than 80% ($p = 0.0728$, log-rank) (fig. 1).

Analgesic medication was required in 21 of the 27 patients (77.8%). Narcotic analgesics (morphine sulfate) and non-steroidal anti-inflammatory drugs (NSAIDs) were administered in 9 and 12 patients, respectively, prior to DXM therapy. Five of the 9 cases became free from narcotics for a median period of 10.6 months. Six of the 12 cases became free from analgesic medication for a median period of 14 months. A close correlation between significant PSA response and pain improvement was observed. That is, 8 of the 11 cases (72.7%) with favorable pain control demonstrated a PSA decline of greater than 50% ($p = 0.0299$, χ^2).

Table 2. Patient characteristics and PSA response after initiating DXM therapy (n = 27)

Parameters	Range (median)	Average, 95% CI
Age at initiation of DXM	60–91 (72)	
Bone scan positive	27	
EOD score at initiation of DXM	1–4 (3)	
CT scan positive (soft tissue)	4	
PSA at initiation of DXM, ng/ml	5.5–639 (75.0)	125.5, 74.5–176.5
PSA nadir during DXM, ng/ml	0.1–639 (28.8)	79.1, 29.1–129.1
Time-to-PSA nadir, weeks (n = 21)	2–76 (14)	18.8, 7.5–45.1
Maximum PSA decline, %	0–98.7 (56.6)	52.2, 37.1–67.3
<25%	10 (37.0%)	
25 ≦25<50%	1 (3.7%)	
50≦ <80%	5 (18.5%)	
≧80%	11 (40.7%)	
Time-to-PSA failure after DXM, months	1.0–21.5 (5.4)	6.4, 4.6–8.3
Survival period after DXM, months		
All (n = 27)	3.8–28.7 (13.1)	14.3, 11.4–17.2
PSA decline ≧ 50% (n = 16)	8.1–28.7 (15.9)	17.9, 14.4–21.4
PSA decline < 50% (n = 11)	3.8–21.4 (7.7)	9.1, 5.9–12.3
Overall follow-up period, months	13.6–94.7 (40.0)	42.3, 35.6–49.0

Table 3. Prognostic factors for significant PSA response (≧50% decline) and survival after initiating DXM therapy

Parameters	PSA decline ≧50%	Survival period after DXM	
	univariate analysis[a] p value	univariate analysis[b] p value	multivariate analysis[c] hazards ratio p value
Prior EBR, + vs. –	0.0535	0.0003	2.81, 0.5642
Prior EMP, + vs. –	0.2388	0.9699	2.13, 0.1007
Gleason sum, ≦ 6 vs. ≧7	0.2321	0.0912	2.09, 0.4970
Response duration to first-line therapy, <352 vs. ≧352 days	0.0540	0.0639	1.80, 0.7155
PSA at DXM start, <75 vs. ≧75 ng/ml	0.3095	0.7499	2.24, 0.4214
PSA decline, <50% vs. ≧50%	–	<0.0001	2.70, 0.0055

EBR = External beam radiotherapy, EMP = estramustine phosphate, DXM = dexamethasone.

[a] Univariate analysis: χ^2 test, PSA decline <50% vs. ≧50%.

[b] Univariate analysis: log-rank test.

[c] Multivariate analysis: Cox proportional hazards model.

Main adverse effects of DXM therapy include weight gain and steroid face. However, only 2 patients were forced to discontinue DXM therapy despite significant PSA responses at 12 and 15 months, respectively. One patient was excused as a result of progressive congestive heart failure. The second case presented with exacerbation of diabetes mellitus.

Background factors, which may affect PSA response and survival following DXM therapy, were analyzed by univariate and multivariate analyses. By univariate analysis, no meaningful factors for PSA decline of greater than 50% were detected. Significant factors impacting survival period following DXM therapy were prior history of EBR ($p = 0.003$, log-rank) and PSA decline of greater than 50% ($p < 0.0001$, log-rank). By multivariate analysis, PSA decline of greater than 50% was the sole meaningful prognostic factor for survival period ($p = 0.0055$, Cox proportional hazards model) (table 3).

Table 4. PSA response rate to glucocorticoid (GC) therapy in the literature

Group (first author)	Types of GC, doses (per day)	PSA decline ≧50%	Response duration months	Median survival after GC, months all, PSA responder[a]
Harland, 1992 [10]	Hydrocortisone, 40 mg	8/15 (53%)	Mean 6.0	ND
Kelly, 1995 [7]	Hydrocortisone, 40 mg	6/30 (20%)	Median 4.0	ND
Kantoff, 1999 [4]	Hydrocortisone, 40 mg	25/116 (22%)	Median 2.3	12.6, 20.5
Tannock, 1996 [3]	Prednisone, 10 mg	12/54 (22%)	ND[b]	50% at 10 months
Sartor, 1998 [9]	Prednisone, 20 mg	10/29 (34%)	Median 2.0, Mean 2.8	12.8, 17.4
Storlie, 1995 [8]	Dexamethasone, 1.5 mg	23/38 (61%)	Mean 8.1	ND
Nishiyama, 1998 [15]	Dexamethasone, 1.5 mg	4/7 (57%)	Range 3–11	ND
Small, 2000 [11]	Hydrocortisone, 40 mg	37/230 (16%)	ND	9.3, ND
Present study	Dexamethasone, 1.5 mg	16/27 (59%)	Median 5.4, Mean 6.4	13.1, 15.9

[a] PSA responder = PSA decline of at least 50%; [b] ND = not described.

Discussion

As second-line treatment for HRPC, antiandrogen (flutamide or bicalutamide) is indicated in patients who have failed to respond to first-line ADT. Otherwise EMP may be indicated for such patients. In cases in which CAB therapy has failed, AWS should be considered initially. Thereafter, second- or third-line hormonal therapies, such as adrenal blocking agents or glucocorticoids, should be considered. The efficacy of glucocorticoid therapy in HRPC patients involving hydrocortisone [4, 7, 10, 11], prednisone [3, 9] or DXM [8, 15] has been examined. In those reports, PSA response rate (decline of at least 50%) varied from 16 to 60%, and time-to-progression or time-to-PSA failure ranged from 2 to 8 months. Sartor et al. [9] noted that PSA response rate (decline of greater than 50%) was elevated in patients treated with higher doses of glucocorticoids; that is, treatment with prednisone at 20 mg/day versus prednisone at 10 mg/day, or hydrocortisone at 30 mg/day. PSA response rate was higher in patients treated with DXM (57–61%) than in those treated with prednisone or hydrocortisone (table 4). However, all studies employing DXM, including the present study, are of a retrospective nature. On the other hand, PSA response rates in prospective trials involving hydrocortisone or prednisone were 16–22% [3, 4, 11]. In the present study, PSA response was correlated to survival following DMX therapy. Significant differences were observed between patients displaying PSA decline of greater than 50% and those exhibiting PSA decline of less than 50%. In contrast, no meaningful differences were observed for patients displaying PSA decline of greater than 80% versus less than 80%. It is well known that PSA decline does not correlate with tumor regression or longer survival in all cases of HRPC. Given this inconsistency, it is appropriate to evaluate both PSA changes and palliative effects in clinical trials involving HRPC patients [3, 4, 11]. Evidence exists, however, which suggests that patients exhibiting a PSA decline of greater than 50% demonstrate longer survival than those displaying no significant PSA response. The present study is such an example [4, 9]. As a result, it is important to predict which patients are most likely to benefit from glucocorticoid therapy. Petrylak et al. [16] reported that prior history of chemotherapy and/or whole pelvis radiation affected PSA response in trials employing EMP plus docetaxel. Prior history of EBR and response duration to first-line hormonal therapy may be important factors; however, they did not reach the significance as prognostic factors for PSA response in the present study. Patients with no prior EBR and longer response duration to first-line hormonal therapy may benefit from DXM therapy. However, due to the retrospective nature of the present study, it is inappropriate to draw definite conclusions when attempting to predict PSA response.

Glucocorticoid therapy for patients presenting with HRPC has been shifting from monotherapy to combination therapy with mitoxantrone [3, 4]. This combination therapy has become the standard modality for symptomatic HRPC patients; however, no significant effect on sur-

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