Low Doses of Oral Dexamethasone for Hormone-Refractory Prostate Carcinoma

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BACKGROUND. Although glucocorticoids have been used to treat patients with hormone-refractory prostate carcinoma (HRPC), reports have varied regarding the types and doses of glucocorticoids used as well as their clinical benefits. In the current study, low doses of dexamethasone were investigated for their specific beneficial effects and the feasibility of long term treatment.

METHODS. Thirty-seven patients diagnosed with HRPC were treated with oral dexamethasone (0.5–2 mg/day). The patients ranged in age from 53–89 years (median, 74 years). Thirty-two patients, including 6 with lymph node metastases, had bone involvement whereas only 5 patients were found to have elevated serum prostate specific antigen (PSA) levels.

RESULTS. Twenty-three patients (62%) who received no other concomitant therapy demonstrated a decline in their serum PSA level of $\geq$ 50%, which was confirmed by a second PSA value obtained $\geq$ 4 weeks later. The median time to PSA progression was 9 months. Among 18 patients with bone pain, 11 (61%) had improvement and in 5 patients (28%) the pain became stable. Among 21 patients with interpretable bone scans, 4 (19%) showed improvement and 8 (38%) achieved stable disease. Both symptomatic and objective responses of bone metastases were correlated with declines in the serum PSA level of $\geq$ 50%. Ten patients achieved an increase in their hemoglobin level of at least 2 g/dL. Patients whose PSA level declined by $\geq$ 50% with therapy had significantly prolonged survival (median, 22 months). As pretreatment markers, a longer interval before the initial evidence of disease progression appeared was found to correlate significantly with posttherapy PSA declines of $\geq$ 75%. All side effects of the glucocorticoids were reported to be mild.

CONCLUSIONS. Low doses of dexamethasone were found to be beneficial in the treatment of HRPC, decreasing the severity of anemia and osseous disease as well as reducing serum PSA levels. A posttherapy serum PSA decline of $\geq$ 50% appears to be a reliable marker of improved survival with this therapy. ***Cancer* 2000;89: 2570–6.** *© 2000 American Cancer Society.*

KEYWORDS: prostate carcinoma, hormone-refractory, dexamethasone, prostate specific antigen.

Prostate carcinoma is the second leading cause of death in American men[1] and is a growing worldwide problem. The majority of patients with advanced prostate carcinoma will respond to testicular androgen blockades such as castration or luteinizing hormone-releasing hormone (LH-RH) analogue with or without antiandrogens. However, the median duration of response after hormonal therapy is < 2 years.[2,3] Once the disease becomes hormone-refractory, it is difficult to cure the patient because to our knowledge no effective therapy has been established.

To our knowledge to date no clinical trial has resulted in a clearly prolonged survival among patients with hormone-refractory prostate carcinoma (HRPC). Instead, a palliative role for cytotoxic chemother-

apy in the treatment of HRPC has been reported.[4,5] The antineoplastic agent mitoxantrone in combination with a corticosteroid (either prednisone or hydrocortisone) has shown clinical efficacy as palliative treatment in approximately 35–40% of patients diagnosed with HRPC.

The clinical efficacy of glucocorticoids in the treatment of patients with advanced prostate carcinoma has been reported previously.[6-10] Although subjective and objective response rates varied,[6] clear effects in patients with HRPC have been documented in terms of a decreased prostate specific antigen (PSA) level[7-9] or palliative activity.[10] Although to our knowledge the exact mechanism of action for decreasing the PSA level is not understood, suppression of adrenal androgens has been proposed. Indeed, adrenal androgens were reported to be suppressed in 22% of patients achieving a ≥ 50% decrease in the PSA level.[5] In addition, an antiinflammatory effect may play a key role in the palliation of pain from bone metastases.

There are several types of glucocorticoids that have been used in different doses for clinical trials. We chose dexamethasone for its very intense glucocorticoid activity with little mineralocorticoid activity. To our knowledge no reports to date have shown a clear dose-response effect for dexamethasone. Furthermore, high doses of dexamethasone possibly produce adverse effects such as Cushing syndrome. Therefore, we administered low doses of dexamethasone for the treatment of HRPC. In addition, we found oral administration to be the most attractive option for the majority of patients with HRPC in view of their advanced age and poor physical condition. The objective of this prospective study was to evaluate the clinical usefulness of oral dexamethasone in the treatment of patients with HRPC.

MATERIALS AND METHODS

Patient Selection

Thirty-seven patients were enrolled in this clinical trial performed at Osaka University Hospital, Kyoto Prefectural University Hospital, and three affiliated hospitals between January 1996 and November 1999. Informed consent was obtained from all patients in this study. Eligibility criteria included: HRPC, defined as serial rising PSA values on ≥ 3 occasions at least 2 weeks apart or radiologically detected new or extensive lesions; a castration level of serum testosterone while receiving hormonal therapy; a Karnofsky performance status (KPS) of ≥ 40%; and a life expectancy of ≥ 3 months.

Pretreatment characteristics of the patients are shown in Table 1. The age of the patients ranged from 53–89 years (median, 74 years). The majority of patients primarily had moderately to poorly differentiated adenocarcinoma of the prostate with metastases. Prior therapies are shown in Table 2. As a primary hormonal therapy, 36 patients received medical or surgical castration plus an antiandrogen, estrogen, or estramustine, whereas 1 patient received bicalutamide alone followed by estramustine. The antiandrogen was discontinued at least 4 weeks before the administration of dexamethasone. There were four patients who had demonstrated a decline in the serum PSA after antiandrogen withdrawal.

Estramustine-based chemotherapies were administered in 20 patients. Although 2 patients had re-

TABLE 1
Patient Characteristics

	Median (range)
Age (yrs) (n = 37)	74 (53–89)
Pretreatment PSA (ng/mL) (n = 37)	38 (2.4–3570)
Interval before initial evidence of disease progression (mos) (n = 37)	23 (3–48)
Karnofsky performance status (%) (n = 37)	80 (40–100)
Pretreatment hemoglobin level (g/dL) (n = 32)	11.8 (7.9–16.3)
(n = 37)	**No. of patients (%)**
Histologic grade of primary tumor	
Well differentiated adenocarcinoma	1 (3%)
Moderately differentiated adenocarcinoma	14 (38%)
Poorly differentiated adenocarcinoma	19 (51%)
Indeterminate	3 (8%)
Progressive disease site	
Bone	32 (86%)
Lymph nodes	6 (16%)
Prostate	5 (14%)
Biologic failure (PSA)	5 (14%)
Symptomatic status	
Bone pain	18 (49%)
Dysuria	4 (11%)

PSA: prostate specific antigen.

TABLE 2
Prior Therapies

(n = 37)	**No. of patients (%)**
Primary hormonal therapy	
LH-RH analogue plus other hormonal agents[a]	29 (78%)
Castration plus other hormonal agents[a]	7 (19%)
Antiandrogen alone	1 (3%)
Prior use of antiandrogen	15 (41%)
Prior radiation therapy	10 (27%)
Prior chemotherapy	
Estramustine plus other cytotoxic agents[b]	17 (46%)
Estramustine alone	3 (8%)

LH-RH: luteinizing hormone–releasing hormone.
[a] Other hormonal agents included chlormadinone acetate, estrogen, estramustine, and flutamide.
[b] Other cytotoxic agents included cyclophosphamide, 5-fluorouracil prodrug, and etoposide.

ceived estramustine combined with initial hormonal therapy, 18 received estramustine-based regimens for between 1–27 months (median, 3 months) after disease progression subsequent to initial hormonal therapy.

With regard to the sites of progressive disease that were evaluated by bone scan, computed tomography (CT), or magnetic resonance imaging (MRI), 32 patients had bone disease, 6 had lymph node involvement, and 5 had local disease progression (prostate) whereas 5 patients had only biochemical disease progression evaluated by PSA.

Assessability, Toxicity, and Response Criteria

In general, patients underwent a physical examination and laboratory studies including complete blood cell count, blood chemistry, and PSA at a minimum of every 4 weeks. Posttherapy PSA decline was used to determine primary response to therapy. The percentage of PSA decline and the time to PSA progression was calculated using the guidelines suggested by the PSA working group.[11] Both a PSA decline of $\geq$ 50% and a PSA decline of $\geq$ 75% were confirmed by a second PSA evaluation at least 4 weeks later. Because a decline in the serum PSA occasionally was observed after the dose escalation of dexamethasone in patients with an initial posttherapy PSA decline, no PSA decline after the dose escalation was considered to be treatment failure.

The difference from baseline to the highest hemoglobin level at least 4 weeks after treatment with dexamethasone was calculated in evaluable patients, who then were divided into 4 groups: those with a hemoglobin increase $\geq$ 2 g/dL, those with a hemoglobin increase $<$ 2 g/dL but $\geq$ 1 g/dL, those with a change in hemoglobin $<$ 1 g/dL, and those with a decrease in hemoglobin $\geq$ 1 g/dL.

Symptomatic response in terms of bone pain was assessed by comparing the analgesic dose at the time of the lowest PSA level after therapy and the pretreatment dose. The response was categorized as "improvement" (reduced analgesic dose), "stability" (the same analgesic dose), or "progression" (increased analgesic dose).

Chest X-ray, bone scan, CT scan, or MRI was performed according to the clinical evolution. If assessable, posttherapy bone scans were graded as "improvement" (a decrease in the number of lesions without the development of new lesions), "stability" (no change in the number of lesions without the development of new lesions), or "progression" (an increase in the number of lesions or the emergence of new lesions relative to the baseline scan). Measurable disease as assessed by CT scan and/or MRI was categorized as partial response (PR) (defined as an at least 50% reduction in the sum of the products of the greatest perpendicular dimensions), stable (either a $<$ 50% reduction or a $<$ 25% increase in the sum of the products of the greatest perpendicular dimensions without the appearance of new lesions), or progression (either an at least 25% increase in the sum of the products of the greatest perpendicular dimensions or the appearance of new lesions).

Toxicities were assessed every 4 weeks based on a medical history, physical examination, and laboratory studies. Dose reduction or discontinuation of dexamethasone was employed if a serious adverse effect developed.

Survival times were established from the date of study entry until the date of death or last follow-up. Survival rates were calculated using the Kaplan–Meier method and comparisons were made using the log rank test.

The associations between pretreatment or posttreatment parameters and posttreatment PSA decline were evaluated by the Mann–Whitney *U* test. A *P* value of 0.05 was taken to indicate statistical significance. All statistical analyses were performed using StatView software (SAS Institute Inc., Cary, NC).

Treatment

The treatment, which was administered on an outpatient basis, was comprised solely of oral dexamethasone starting from 0.5–1 mg/day. Patients typically received 0.5 mg twice daily whereas those with PSA failure alone received 0.5 mg once daily. If a patient had demonstrated an initial decline in PSA after dexamethasone therapy, a dose escalation of 0.5 mg/day was administered to observe further response when the PSA serially rose from the nadir. If a patient had no posttherapy decline in PSA on the initial two occasions, this therapy was discontinued. Thus, oral administration of dexamethasone was continued to a maximum of 2 mg/day until disease progression or unacceptable side effects. To prevent the rebound effects of dexamethasone withdrawal, the dose was reduced by 0.5–1 mg/day at least 2 weeks apart. All patients receiving an LH-RH analogue continued therapy.

RESULTS

Treatment

Five asymptomatic patients initially received 0.5 mg of dexamethasone once daily whereas the other patients received 0.5 mg twice daily. Limited dose escalation of dexamethasone was used in 25 patients 2–12 months after the start of therapy. The maximum doses varied from 0.5 mg/day in 2 patients to 1 mg/day in 13 patients, 1.5 mg/day in 19 patients, and 2 mg/day in 3 patients.

TABLE 3
PSA Decline after Dexamethasone Therapy

Initial PSA decline	No. of patients (%)	Time to PSA progression (mos) Median (range)	Further PSA decline (no. of patients) Dose escalation (No. of patients)
≥ 75%	19 (51%)	10 (6–21)	2/12
≥ 50%[a]	23 (62%)	9 (3–21)	3/16
< 50%	9 (24%)	3 (1–9)	2/9
Elevation	5 (14%)	0 (0)	—

PSA: prostate specific antigen.
[a] The row includes the number of patients with a decline in the prostate specific antigen ≥ 75%.

The duration of dexamethasone treatment ranged from 1–22 months (median, 7 months). Twenty-seven patients discontinued dexamethasone at the time of disease progression or the development of side effects and then underwent chemotherapy or symptom control.

Clinical Response

Biochemical responses evaluated by serum PSA levels are shown in Table 3. Twenty-three patients (62%) had a PSA decline of ≥ 50% and 19 patients (51%) had a PSA decline of ≥ 75%. Their median times to PSA disease progression were 9 months and 10 months, respectively. A greater decline in the PSA level was found to be correlated with a longer median time to PSA disease progression. Conversely, five patients demonstrated PSA elevation and then underwent other therapy. Those patients who had not shown a trend toward an increasing PSA value at the time of assessment were excluded from the assessment for the time to PSA disease progression.

Among the 25 patients who were treated with dose escalation, 5 experienced additional PSA declines.

Among the four patients who had experienced antiandrogen withdrawal syndrome, all had a PSA decline of ≥ 75% after dexamethasone therapy.

To assess the association between a PSA decline of ≥ 50% and clinical response in bone metastases, an assessment of bone pain and a bone scan were performed, as shown in Table 4. Among the 18 patients with symptomatic bone metastases, the majority with a PSA decline of ≥ 50% showed improvement in bone pain whereas 6 of 9 patients with a PSA decline of < 50% were found to have stability or progression in pain. Thus, the majority of symptomatic patients achieved improvement or stability of their bone pain. Among the 21 patients assessable for bone scan, 9 of 10 patients with a PSA decline of ≥ 50% showed improvement or stability whereas 8 of 11 patients with a PSA decline of < 50% were found to have progression based on bone scan changes. A PSA decline of ≥ 50% was associated significantly with a good outcome on both bone pain ($P = 0.0167$) and bone scan ($P = 0.0021$).

With regard to for measurable disease, five patients were assessable for metastatic lymph nodes. Among these patients, only 1 showed a PR with a PSA decline of ≥ 50%, 2 were considered stable (one with a PSA decline of ≥ 50% and the other without this decline), and 2 were found to have disease progression without this decline.

Because a significant number of patients experienced an improvement in anemia during therapy with dexamethasone, the posttherapy change in the hemoglobin level was evaluated as shown in Table 5. Thirty-two patients were assessable for a change in their hemoglobin level after dexamethasone therapy. Twenty-one patients (65%) had an increase in their hemoglobin level of at least 1 g/dL and 10 patients (31%) had an increase of at least 2 g/dL, whereas only 2 patients (6%), including 1 patient with rectal bleeding, demonstrated a decrease in their hemoglobin level of ≥ 1 g/dL. The majority of patients with a change in their hemoglobin level of < 1 g/dL had a hemoglobin level of ≥ 13 g/dL at baseline.

To determine any predictors of a better PSA response, pretreatment factors at baseline (age, KPS, interval before the initial evidence of disease progression, hemoglobin level, serum PSA, histologic grade, and bone pain) were stratified into 2 groups based on the level of PSA decline (≥ 50% vs. < 50% or ≥ 75% vs. < 75%). None of these pretreatment factors were found to be associated significantly with a PSA decline of ≥ 50% (data not shown). Conversely, as shown in Table 6, a longer interval before the initial evidence of disease progression (median, 32.5 months) was found to have a statistically significant association with a PSA decline of ≥ 75% ($P = 0.0217$). KPS was found to be of borderline statistical significance ($P = 0.0684$).

Survival Analysis

The overall survival time after dexamethasone treatment ranged from 3–28 months (median, 20 months). The 1-year and 2-year survival rates were 66% and 27%, respectively.

To determine whether a posttherapy PSA decline correlated with survival, overall survival rates were stratified by a posttherapy PSA decline of 50% and were analyzed as shown in Figure 1. The median survival times were 22 months in patients with a PSA decline of ≥ 50% versus 8 months in patients without this decline. The difference in the probability of survival between the two groups was statistically significant ($P = 0.0002$).

TABLE 4
Assessment of Bone Metastasis Stratified by PSA Decline

	Bone pain (n = 18)				Bone scan (n = 21)			
	No. of patients				No. of patients			
PSA decline	Improvement	Stability	Progression		Improvement	Stability	Progression	
≥ 50%	8	1	0	$P = 0.0167$	4	5	1	$P = 0.0021$
< 50%[a]	3	4	2		0	3	8	
Total (%)	11 (61%)	5 (28%)	2 (11%)		4 (19%)	8 (38%)	9 (43%)	

PSA: prostate specific antigen.
[a] The row includes the number of patients with an elevation in their prostate specific antigen level.

TABLE 5
Improvement in Anemia (n = 32)

Change in hemoglobin level	No. of patients (%)
Increase ≥ 2 g/dL	10 (31%)
2 g/dL > increase ≥ 1 g/dL	11 (34%)
Change < 1 g/dL	9 (28%)
Decrease ≥ 1 g/dL	2 (6%)

TABLE 6
Univariate Analysis of Pretreatment Markers for PSA Decline

	PSA decline		
Factor	≥ 75%	< 75%	*P* value
	Median		
Interval before initial evidence of disease progression (mos) (n = 37)	32.5	16.5	0.0217
Karnofsky performance status (%) (n = 37)	80	80	0.0684
Age (yrs) (n = 37)	76	72	0.0827
Pretreatment hemoglobin level (g/dL) (n = 32)	12.1	11.1	0.186
Pretreatment PSA level (ng/mL) (n = 37)	27	54	0.763
	No. of patients		
Histologic grade (n = 34)			
Well differentiated adenocarcinoma	1	0	
Moderately differentiated adenocarcinoma	8	6	0.259
Poorly differentiated adenocarcinoma	8	11	
Bone pain (n = 37)			
Symptomatic	7	11	0.608
Asymptomatic	9	10	

PSA: prostate specific antigen.

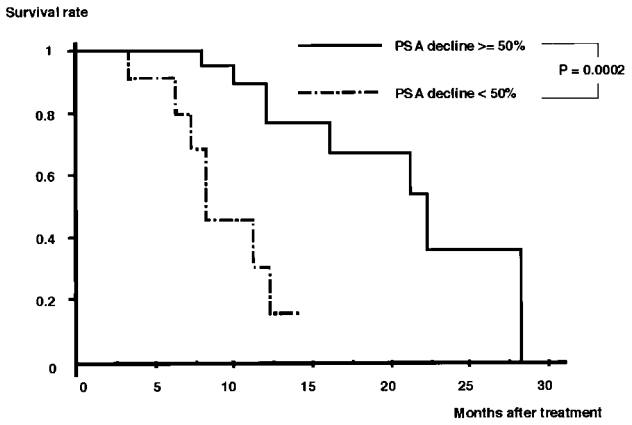

FIGURE 1. Overall survival stratified by 50% decrease in the prostate specific antigen (PSA) level; patients who achieved a posttherapy PSA decline of ≥ 50% (n = 23) versus those patients who did not (n = 14).

In addition, the overall survival rates stratified by a posttherapy PSA decline of 75% were analyzed. A statistical difference was observed between patients with a PSA decline of ≥ 75% and those without this decline ($P = 0.0234$). The median survival times were 22 months and 9 months, respectively. Because the follow-up period for patients with a PSA decline of > 75% was short (median, 11 months), their median survival time was the same as that of patients with a PSA decline of ≥50%.

To elucidate prognostic markers, survival rates stratified by pretreatment factors were compared. The factors examined included age (≥ 75 years vs. < 75 years), interval before the initial evidence of disease progression (≥ 12 months vs. < 12 months or > 24 months vs. ≤ 24 months), PSA (≥ 20 ng/mL vs. < 20 ng/mL), and bone pain (symptomatic vs. asymptomatic). Only freedom from bone pain was associated significantly with better survival ($P = 0.0133$), whereas the other factors had no statistical significance. Although it is not statistically significant, a long interval before the initial evidence of disease progression appeared to be associated with prolonged survival. For patients in whom this interval was > 24 months, the median survival difference was 22 months versus 16 months in patients in whom this interval was ≤ 24 months ($P = 0.0723$).

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