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Original Article

Treatment of androgen-independent prostate cancer with dexamethasone: A prospective study in stage D2 patients

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Abstract

Purpose: In order to evaluate the efficacy of dexamethasone in the treatment of Japanese men with androgen-independent prostate cancer, a prospective study was conducted using prostate-specific antigen (PSA) as a primary end-point.

Methods: Nineteen Japanese men with stage D2 androgen-independent prostate cancer were registered and treatment was started. After ruling out anti-androgen withdrawal syndrome, they were treated with dexamethasone (1.5 mg daily). Patients were monitored for PSA, symptoms, radiologic response, survival rate, time to disease progression, time to treatment failure and complications.

Results: Prostate-specific antigen levels decreased in nine patients (50.0%); five (27.8%) showed a 50% or greater decrease and two (11.1%) showed an 80% or greater decrease. For the nine patients, the mean duration of PSA response was 7.3 months and the median duration was 2.1 months (range, 1.2–27.5+). Bone pain, which was noted in 13 patients at study entry, improved in seven patients (53.8%). Of nine patients who had serial radiographic examinations with bone scan, three (33%) showed partial response, two (22%) were stable and four (44%) showed disease progression. Treatment was well tolerated, except for one patient who suffered a severe pulmonary infection.

Conclusion: Dexamethasone decreased PSA levels and produced subjective symptomatic improvement in the patients with stage D2 androgen-independent prostate cancer.

Key words androgen-independent prostate cancer, dexamethasone.

Introduction

Initial hormonal treatment for advanced prostate cancer has a beneficial effect in the majority of patients. However, many patients eventually progress to androgen-independent disease. Once the cancer becomes androgen-independent, further systemic treatments achieve only modest benefits. It is not clear whether chemotherapy for such patients has an impact on the survival rate or palliation of symptoms. Corticosteroids may act through a variety of ways in patients with prostate cancer. Recently, the use of corticosteroids has been regarded as a treatment option which is minimally toxic, low cost and which demonstrates mild anticancer activity[1,2] and which has an apparent beneficial effect on quality of life.[3] Several studies have reported the use of corticosteroids alone as a second-line therapy following failure of primary hormonal therapy. Nishiyama and Terunuma recommended that patients whose disease continued to progress after discontinuation of oral hormonal agents should be treated with corticosteroids.[4] As a decline in

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PSA from baseline is related to survival in patients with androgen-independent prostate cancer,[5] in this trial we examined the effect of dexamethasone on PSA as a primary end-point of response for the patients with androgen-independent stage D2 prostate cancer.

Methods

Patients were eligible for this study if they had metastatic prostate cancer (stage D2) and had undergone no less than one prior anti-androgen treatment but had subsequent disease progression or disease exacerbation. Patients were required to have adequate hepatic and renal function; however, those with diabetes mellitus or active infectious disease were not eligible. Performance status had to be 0–3, and the patient's expected survival should have been over 3 months. Before entry into the trial, it was necessary that the patient's serum testosterone levels be less than 1 ng/mL to confirm repression of testicular androgen; also required was subsequent documented disease progression more than 4 weeks after stopping anti-androgen administration to rule out anti-androgen withdrawal syndrome. Continued use of luteinizing-hormone releasing hormone (LHRH) agonist was required for those who had not undergone orchiectomy. Dexamethasone was administered orally at a dose of 1.5 mg per day. The treatment was conducted for at least 12 weeks and continued unless disease progression or severe complications occurred.

From June 1997 to May 1999, 19 patients were registered for this clinical study. Patients ranged from 46 to 82 (median 72) years of age at study entry. Histologically, adenocarcinoma was initially diagnosed as well differentiated in two patients, moderately differentiated in eight and poorly differentiated in nine. The median duration from the initiation of first-line hormonal therapies to the study entry was 24.5 months (range, 6.3–96.3 months). Prior hormonal therapies were surgical castration in five patients, medical castration in 14, flutamide in 12, chloromadinone acetate in seven, and DES-P in 14. Other prior therapies, such as chemotherapy or radiation therapy, were estramustine in 17, intravenous chemotherapy in five, orally administered chemotherapy using VP-16 or fluorouracil in seven, and external beam radiation in five. All patients had bone lesions detected on radionuclide bone scans and elevated serum PSA (median 219.9, range 26.0–3503.0). Thirteen cases had bone pain that required some analgesic before the treatment. No other subjective complaints, such as loss of appetite or difficulty of urination, were recognized.

Prostate-specific antigen levels, as a primary end-point, were used to determine response to the therapy. Serum PSA levels were measured every 4 weeks and judged PSA response at 12 weeks after the initiation of the therapy or at the best response. The rates of PSA decline from baseline were classified into four groups: over 80%, from 50% to 80%, declined but under 50% and no decline. Disease progression was also defined as a continuous elevation of PSA in at least three consecutive measurements separated by more than 2 weeks each. In addition to the PSA end-point, radiographic findings and subjective symptoms, especially pain, were evaluated. Bone scan was performed at 12 weeks after the initiation of the therapy if possible. The patients were evaluated every 2 weeks for subjective symptoms: for pain with the necessity, kinds and volume of pain-relief drugs; for urinary voiding disorders with the International Prostate Symptom Score; and for other complaints with question and answer. Formal quality of life assessments were not performed. We regarded improvement in symptoms as attributable to dexamethasone in this study. The evaluation of complications was done by routine clinical examination, physical findings and blood and urine examination.

All patients consented to treatment after being informed about their condition, disease status, the treatment schedule, side-effects and expectation of treatment results.

Statistical analysis of survival curves was performed using the log–rank test.

Results

All patients were treated with dexamethasone for at least 12 weeks but one patient could not continue because of an infected decubitus and was excluded from the evaluation. Seventeen (89.5%) of the patients could be treated with dexamethasone in an outpatient clinic. Only two cases were treated in hospital in order to receive other medications for their cancer pain. Median duration of treatment was 6.2 months (range, 0.9–21.0+ months).

Of the evaluable 18 patients, a decline in PSA was recognized in nine (50%). The range of decline in PSA varied from 0% to 98.2%. Of the nine patients, five achieved at least 50% and two achieved at least 80% lower PSA than their prestudy baseline. In analyzing the PSA-response duration of the responders, progression was defined as a re-elevation of the PSA; median duration was 2.1 months and mean duration was 7.3 months (range, 1.2–27.5+ months). Patient characteristics and the PSA results are shown in Table 1. Of the

Table 1 Patients characteristics and the results of PSA

Case	Age (years)	Histology* (differentiation)	Castration	Prior hormone therapy	Chemotherapy/ radiation therapy	PSA decline rate (%)	Response duration (months)	Survival duration (months)	Survival outcome
1	46	Poor	Medical	DES	EPM, VP-16	21.0	1.3	20.4	Dead
2	64	Well	Medical	DES, flutamide	EPM, UFT	73.7	3.3	>13.1	Alive
3	70	Moderately	Medical	DES, flutamide	EPM	73.3	2.0	7.2	Dead
4	72	Poor	Medical	DES	EPM	25.8	3.8	5.5	Dead
5	82	Poor	Medical	DES, flutamide	EPM, XRT	Increase	0.0	2.5	Dead
6	79	Poor	Medical	DES, flutamide	EPM, VP-16, XRT	Increase	0.0	>11.3	Alive
7	76	Moderately	Surgical	CMA, DES	CDDP, IFM, EPM, UFT	Increase	0.0	6.1	Dead
8	70	Poor	Medical	CMA, flutamide	CDDP, IFM, EPM, UFT, VP-16, XRT	Increase	0.0	8.3	Alive
9	82	Poor	Medical	DES, flutamide	XRT	35.8	1.9	>3.0	Alive
10	82	Moderately	Surgical	DES	XRT	Increase	0.0	1.0	Dead
11	80	Moderately	Medical	DES, flutamide	EPM	70.9	2.9	7.8	Dead
12	71	Moderately	Medical	CMA, flutamide	EPM	84.3	>27.5	>27.5	Alive
13	79	Poor	Surgical	DES, flutamide	EPM, UFT	17.6	1.2	>12.2	Alive
14	63	Moderately	Surgical	DES, flutamide	CDDP, IFM, EPM, VP-16	Increase	2.2	7.0	Dead
15	65	Moderately	Medical	DES	EPM, VCR, IFM, PEP	Stable	0.0	17.2	Dead
16	75	Poor	Medical	CMA	EPM, CDDP, IFM	Increase	0.0	2.5	Dead
17	71	Well	Surgical	DES, flutamide	EPM	Drop out	Drop out	>6.1	Alive
18	66	Moderately	Medical	CMA	EPM, VCR, IFM, PEP	98.2	>26.1	>26.1	Alive
19	79	Poor	Medical	Flutamide	EPM	Increase	1.0	1.0	Dead

* All patients were stage D2.

PSA, prostate-specific antigen; DES, fosfestrol; CMA, chloromadinone acetate; EPM, estramustine phosphate; VP-16, etoposide; UFT, tegaful-uracil; XRT, radiation therapy; CDDP, cis-diamminodichloroplatinum; IFM, ifosphamide; VCR, vincristine; PEP, peplomycin.

nine patients who could be evaluated for bone scan findings at 3 months after the start of dexamethasone therapy, three showed partial response (PR), two showed no change (NC) and four showed progression (PD) in comparison with findings before therapy. Of the 12 evaluable patients with bone pain that required analgesia, two were able to decrease the dose and five were able to stop their analgesic. Overall, seven (58.3%) patients experienced subjective improvement in bone pain by using dexamethasone. In analyzing the duration of symptomatic improvement, the median duration was 3.0 months and the range was 1.3–7.3 months. Survival curves, as shown in Fig. 1, revealed a median survival after starting dexamethasone of 7.2 months. No statistical differences in survival were noted for those patients having a PSA decline of greater than 50% compared to less than 50% ($P = 0.132$). As complications, newly developed diabetes

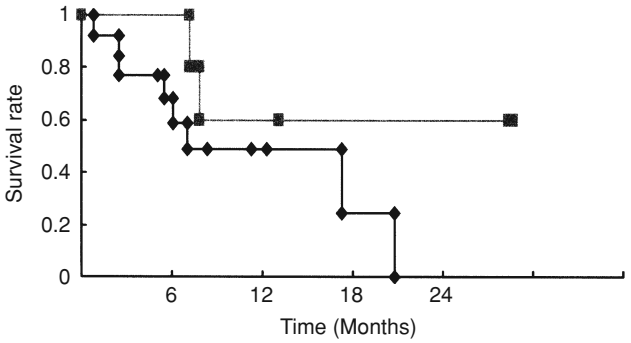

Fig. 1 Survival rate due to prostate-specific antigen (PSA) decline-rate. Decline in PSA of 50% or greater from baseline following dexamethasone treatment may show a tendency of survival improvement in patients with androgen-independent prostate cancer, although the statistical significance was not clear ($P = 0.132$). ■, Decline ≥ 50%, $n = 5$; ◆, decline < 50%, $n = 13$.

mellitus, which required insulin administration, was seen in one patient and both pneumo-cryptococcosis and a gastric ulcer were seen in another patient. The latter patient died due to pneumonia.

Discussion

The efficacy of glucocorticoids has been documented in some patients with hormone-refractory prostate cancer using palliative end-points.[3] Moreover, some reports show that glucocorticoids can decrease PSA levels and tumor size.[1,2,4,6,7] However, as Sartor *et al*. mentioned,[2] reported PSA changes with glucocorticoid treatment are frequently difficult to interpret because of confounding variables from concomitant therapies. Most reports investigating PSA change after therapy with glucocorticoids were initiated before recognition of the anti-androgen withdrawal syndrome as a potentially active therapeutic maneuver.[8] In addition, hormone-refractory prostate cancer is comprised of a relatively heterogeneous group of patients. Repression of the serum androgen level in hormone-refractory patients to the level of surgical castration should be confirmed, because some reports have shown that androgen re-elevation was observed in spite of the regular injection of LH-RH agonist.[9,10] For the present study, androgen-independent prostate cancer was defined as a disease that progressed despite a low level (1 ng/mL) of testosterone with medical or surgical castration; testosterone levels were confirmed in all patients. Additionally, previous treatment with anti-androgen had failed for all patients in this study. Our study was also performed after confirming the absence of anti-androgen withdrawal syndrome in these patients. These facts show that the cancers in our patients had re-growth under maximum androgen blockade (adrenal androgen suppression) when they entered this study. No confounding variables known to effect PSA were present in any patients as no concomitant treatment had been given. Our results clearly indicate that dexamethasone can decrease PSA levels in 50% of patients in whom maximum androgen blockade therapy has failed and that dexamethasone can contribute to subjective symptom improvement, especially bone pain, in a greater percentage of patients. This result suggests that anti-androgens and dexamethasone are non-cross resistant in action, raising the possibility that the mechanism of dexamethasone action in androgen-independent prostate cancer may extend beyond adrenal suppression.

The exact mechanism of PSA decline cannot be determined from our results. Montgomery *et al*. showed that glucocorticoids could not induce suppressive regulation on LNCaP cells in an *in vitro* study.[11] In addition, the effects of glucocorticoids may be indirect and may be mediated by an inhibition of neovascularization.[12] Further basic and clinical studies should be done to understand the mechanism of dexamethasone action in patients with androgen-independent prostate cancer.

Clinically, our series showed some effect on objective response and subjective symptoms, although previous ineffective treatments did not. In our small study, there were no statistically significant differences in survival rate among patients demonstrating PSA decline; however, Scher *et al*. reported that a decline in PSA of 50% or greater from baseline is related to survival in patients with androgen-independent prostate cancer.[5]

From these results, dexamethasone is expected to have a good effect on the quality of life of terminal-stage prostate cancer patients. We believe that a prospective study of dexamethasone for larger numbers of patients which both evaluates the response and investigates quality of life as a formal standard should be undertaken.

In conclusion, dexamethasone decreased PSA levels in half of the patients with stage D2 androgen-independent prostate cancer. Moreover, symptomatic improvement was recognized in over half of the patients.

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