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Possible Mechanism of Dexamethasone Therapy for Prostate Cancer: Suppression of Circulating Level of Interleukin-6

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BACKGROUND. Glucocorticoids may have favorable effects on prostate cancer patients showing clinical and/or biochemical failure after androgen ablation. The efficacy and mechanisms of dexamethasone therapy as possible alternative endocrine therapy were investigated.

METHODS. Twenty five patients with prostate cancer treated by androgen ablation and showing a steady increase in serum prostate specific antigen (PSA) were treated with low-dose dexamethasone.

RESULTS. Of 25 patients, 11 demonstrated 50% or more decline of serum PSA and 9 showed improvement of pain on dexamethasone therapy. Of 8 patients who responded to dexamethasone thearpy, 5 had 80% or more decrease in serum interleukin-6 (IL-6). In contrast, none of 8 non-responders showed remarkable IL-6 suppression. Response of PSA was not correlated to the changes in serum dehydroepiandrosterone, dehydroepiandrosterone sulfate, or androstendione.

CONCLUSIONS. Significant suppression of serum IL-6, probably through inhibition of androgen-independent activation of androgen receptor, may be one of the mechanisms for the effect of dexamethasone therapy in prostate cancer patients with progressive disease. *Prostate 56: 106–109, 2003.*

KEY WORDS: **prostate cancer; androgen ablation; glucocorticoid; interleukin-6; prostate specific antigen**

INTRODUCTION

For the management of advanced prostate cancer, endocrine therapy by androgen ablation is generally effective as an initial treatment. However, when progression occurs after initial endocrine therapy, optimal therapy has not been established. Recently, it was demonstrated that antiandrogen withdrawal and administration of another antiandrogen or glucocorticoid might have favorable effects on patients who had been treated with androgen ablation and had shown clinical and/or biochemical failure [1–6]. Thus, "hormone-refractory" prostate cancer is thought to include patients with a spectrum of diseases. Based on these findings, Scher et al. [3] advocated new classification of hormonal sensitivity of prostate cancer: (i) hormone-naïve; (ii) androgen-independent and hormone-sensitive; and (iii) androgen-independent and hormone-insensitive. In the present study, the efficacy of dexamethasone as an alternative endocrine therapy is examined by responses in serum prostate specific antigen (PSA) and pain relief. In addition, the mechanisms of dexamethasone therapy are investigated.

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MATERIALS AND METHODS

A total of 25 patients with prostate cancer who had been treated with androgen ablation (surgical castration or LHRH agonist) and had shown biochemical failure (a steady increase in serum PSA) were included in the present study. Upon biochemical failure, the patients were treated with dexamethasone (initially 1.5 mg/day, then tapered to 0.5 mg/day). In patients treated with surgical or medical castration plus antiandrogen, antiandrogen withdrawal syndrome was assessed for at least 4–8 weeks by the cessation of the antiandrogen before dexamethasone therapy; and treatment with LHRH agonist was not discontinued. Serum PSA levels were determined with the Tandem-R PSA Assay (Hybritech, Inc., San Diego, CA). The clinical effect of dexamethasone therapy was evaluated based on improvement of pain. Patients who showed 50% or more decline of serum PSA and/or improvement of pain estimated by decrease in dose or change of analgesics were defined as responders to dexamethasone therapy. The changes in serum testosterone, dehydroepiandrosterone, dehydroepiandrosterone sulfate, androstendione, ACTH, cortisol and interleukin-6 (IL-6) were measured in relation to the effect of dexamethasone therapy.

Statistical Analysis

Statistical analysis was performed by the Mann–Whitney U-test and chi-square test. $P < 0.05$ was considered significant.

RESULTS

At initial diagnosis, histological examination of the tumor showed 3 well differentiated, 10 moderately differentiated, and 10 poorly differentiated adenocarcinomas. Histological grade of the tumor was unknown in two patients. The methods of initial endocrine therapy consisted of surgical or medical castration alone in 7, castration plus chlormadinone acetate in 11, castration plus flutamide in 6, and castration plus bicalutamide in 1. As second or third line endocrine therapy, alternative antiandrogen was administered; chlormadinone acetate in 4, flutamide in 7, and bicalutamide in 12. The duration of endocrine therapy ranged from 5 to 81 months with a mean of 27.4 months. Patients' ages at the start of dexamethasone therapy ranged from 47 to 82 years with a mean of 69 years. The median serum PSA level at dexamethasone therapy was 262 ng/ml with a range of 8.4–4,100 ng/ml.

TABLE I. Change of Serum PSA and Clinical Symptoms by Dexamethasone Therapy in Prostate Cancer Patients Who Showed Biochemical Failure

	Pain relief by dexamethasone therapy		
≥50% PSA decline	Effective	Not effective	No symptom
Yes	8	0	3
No	1	12	1
Total	9	12	4

Of 25 patients, 11 (44%) demonstrated 50% or more decline of serum PSA by dexamethasone therapy. The average duration of responding period was 5.1 (range: 1–8) months. Eight patients showing 50% or more decline of PSA and one patient without remarkable decline of PSA revealed improvement of pain relief (Table I). The response of dexamethasone therapy was not related to serum PSA levels at the start of therapy, the duration of previous endocrine therapy, or the previous occurrence of antiandrogen withdrawal syndrome (Table II).

Serum testosterone levels were suppressed to within the castrate range in all patients examined (data not shown). The response to dexamethasone therapy was

TABLE II. Comparison of Clinical Characteristics Between Responders and Non-Responders to Dexamethasone Therapy in Prostate Cancer Patients Who Showed Biochemical Failure

Factors	Responders[a]	Non-responders
Number of patients	12 (48%)	13 (52%)
PSA at dexamethasone therapy (ng/ml)	657.6 ± 645.6	774.1 ± 1172.3
Duration of endocrine therapy (months)	32.3 ± 26.6	23.0 ± 17.2
Previous antiandrogen withdrawal syndrome		
Yes	2	2
No	7	11
Not evaluable	3	0

[a]Responders: patients who showed 50% or more decline of serum PSA and/or improvement of pain.

not correlated with the changes in serum dehydroepiandrosterone, dehydroepiandrosterone sulfate, or androstendione, although some non-responders did not show significant suppression of adrenal androgens after dexamethasone therapy (data not shown). The change of serum IL-6 during dexamethasone therapy was evaluated in 16 patients. As shown in Figure 1, 5 of 8 responders to dexamethasone therapy demonstrated 80% or more decrease in serum IL-6 at 1 month from the start of dexamethasone. On the contrary, none of 8 non-responders showed remarkable IL-6 suppression (Fig. 2). There was an association between the response of dexamethasone therapy and 80% or more suppression of serum IL-6 ($P < 0.05$, chi-square test).

DISCUSSION

In the present study, the favorable effect of low-dose dexamethasone was demonstrated in a substantial number of patients who showed PSA failure after initial endocrine therapy. Some of the previous studies also reported the high rate of PSA response to glucocorticoid therapy in patients with progressive prostate cancer after androgen ablation [4–6]. Thus, it may be worthwhile to administer dexamethasone after confirming the antiandrogen withdrawal syndrome, since low-dose dexamethasone therapy does not have severe adverse effects.

The mechanism of dexamethasone therapy for hormone-refractory prostate cancer has been believed to be suppression of adrenal androgens. However, in the majority of patients in the present series, serum levels of adrenal androgens were suppressed by

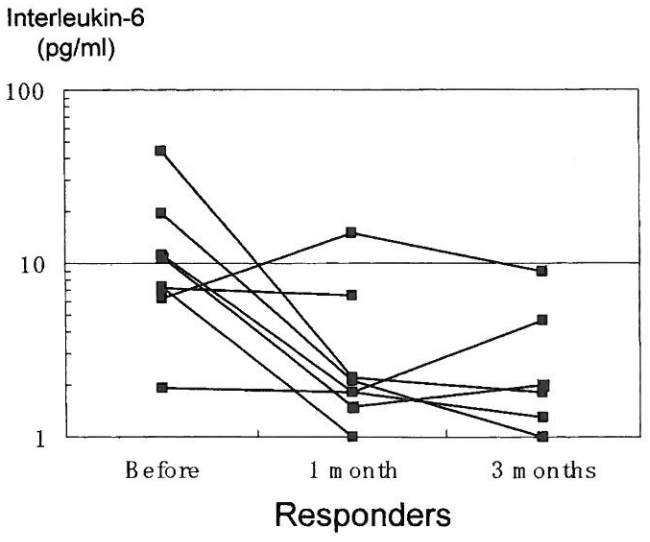

Fig. 1. Change of serum interleukin-6 (IL-6) following dexamethasone therapy. Each dot represents each patient. Responders to dexamethasone therapy (n = 8): patients who showed 50% or more decline of serum PSA and/or improvement of pain.

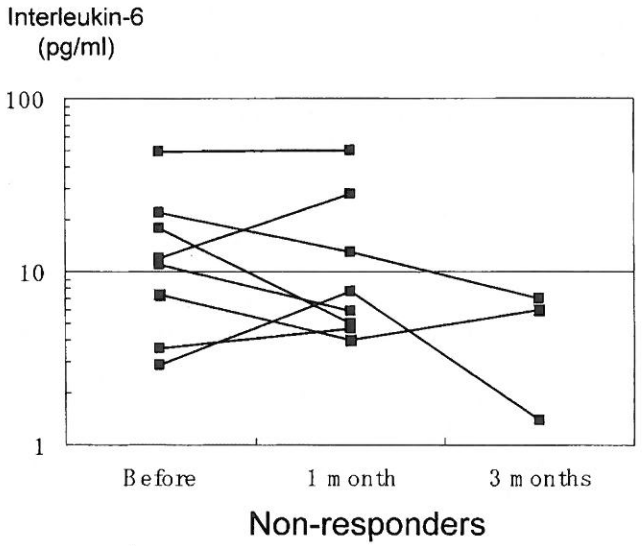

Fig. 2. Change of serum IL-6 following dexamethasone therapy. Each dot represents each patient. Non-responders to dexamethasone therapy (n = 8).

dexamethasone therapy irrespective of the response of dexamethasone therapy. In some of non-responders to dexamethasone therapy, no marked suppression of adrenal androgens was observed, probably due to low compliance with dexamethasone administration, since serum cortisol was not decreased very much.

The present study suggests another possible mechanism of dexamethasone action, that of significant suppression of IL-6. The direct effect of dexamethasone on prostate cancer cells has been suggested through NF-kappaB–IL-6 pathway [7]. However, circulating IL-6 is thought to be derived from many different cell types including monocytes, fibroblasts, endothelial cells, and possibly some of prostate cells [8]. IL-6 is known to be suppressed by glucocorticoids [9] and to stimulate the growth of the prostate cancer cell lines through its receptors in an androgen-independent manner [10–12]. In addition, recent reports have shown that IL-6 can activate the androgen receptor through a signal transducer and activator of transcription 3 (STAT3)-dependent pathway [13–15]. Circulating IL-6 levels are high in hormone-refractory prostate cancer patients [16], and serum IL-6 may be a good prognostic factor after androgen ablation therapy in prostate cancer patients [17]; the present study shows that remarkable suppression of serum IL-6 is closely related to the response to dexamethasone therapy. Since serum level of IL-6 was not related to serum PSA at the start of dexamethasone therapy in the present study, and both IL-6 producing and non-producing prostatic cancer cells have been reported in the literature [10], it seems unlikely that the decline of serum IL-6 simply resulted from reduction of IL-6

producing cancer cells. Therefore, the decrease in circulating IL-6 by dexamethasone administration may reflect inhibition of ligand-independent activation of the androgen receptor, resulting in inhibition of expression of androgen responsive genes.

The androgen receptor plays a key role in androgen-dependent proliferation of prostate cancer cells. Although the content of androgen receptor has been shown to be a prognostic indicator in prostate cancer patients treated by endocrine therapy, androgen-independent tumors can express the androgen receptor [18], suggesting that post-receptor pathways of cell proliferation are preserved in a number of prostate cancer cells. Therefore, it is likely that expression of other androgen-responsive genes which control androgen-dependent proliferation of cancer cells could be similarly inhibited by dexamethasone.

CONCLUSIONS

The favorable effect of low-dose dexamethasone was demonstrated in prostate cancer patients who showed PSA failure after initial endocrine therapy. Significant suppression of IL-6 may represent one of the mechanisms for the effect of dexamethasone therapy in prostate cancer patients showing biochemical failure. Since the present study was based on a small number of patients and the observation seemed preliminary, further investigations would be required to make final conclusions.

REFERENCES

1. Scher HI, Kelly WK. Flutamide withdrawal syndrome: Its impact on clinical trials in hormone-refractory prostate cancer. J Clin Oncol 1993;11:1566–1572.
2. Akakura K, Akimoto S, Furuya Y, Ito H. Incidence and characteristics of antiandrogen withdrawal syndrome in prostate cancer after treatment with chlormadinone acetate. Eur Urol 1998;33:567–571.
3. Scher HI, Steineck G, Kelly WK. Hormone-refractory (D3) prostate cancer: Refining the concept. Urology 1995;46:142–148.
4. Stolie JA, Buckner JC, Wiseman GA, Burch PA, Hartmann LC, Richardson RL. Prostate specific antigen levels and clinical response to low dose dexamethasone for hormone-refractory metastatic prostate carcinoma. Cancer 1995;76:96–100.
5. Nishiyama T, Terunuma M. Hormone/antihormone withdrawal and dexamethasone for hormone-refractory prostate cancer. Int J Urol 1998;5:44–47.
6. Nishimura K, Nonomura N, Yasunaga Y, Takaha N, Inoue H, Sugao H, Yamaguchi S, Ukimura O, Miki T, Okuyama A. Low doses of oral dexamethasone for hormone-refractory prostate carcinoma. Cancer 2000;89:2570–2576.
7. Nishimura K, Nonomura N, Satoh E, Harada Y, Nakayama M, Tokizane T, Fukui T, Ono Y, Inoue H, Shin M, Tsujimoto Y, Takayama H, Aozasa K, Okuyama A. Potential mechanism for the effects of dexamethasone on growth of androgen-independent prostate cancer. J Natl Cancer Inst 2001;93:1739–1746.
8. Hobisch A, Rogatsch H, Hittmair A, Fuchs D, Bartsch G Jr., Klocker H, Bartsch G, Culig Z. Immunohistochemical localization of interleukin-6 and its receptor in benign, premalignant and malignant prostate tissue. J Pathol 2000;191:239–244.
9. Ray A, Zhang D-G, Siegel MD, Ray P. Regulation of Interleukin-6 gene expression by steroids. In: Mackiewicz A, Koj A, Sehgal PB, editors. Interleukin-6-type cytokines. New York: Ann NY Acad Sci; 1995. pp 79–88.
10. Okamoto M, Lee C, Oyasu R. Interleukin-6 as a paracrine and autocrine growth factor in human prostatic carcinoma cells in vitro. Cancer Res 1997;57:141–146.
11. Chung TD, Yu JJ, Spiotto MT, Bartkowski M, Simons JW. Characterization of the role of IL-6 in the progression of prostate cancer. Prostate 1999;38:199–207.
12. Lou W, Ni Z, Dyer K, Tweardy DJ, Gao AC. Interleukin-6 induces prostate cancer cell growth accompanied by activation of STAT3 signaling pathway. Prostate 2000;42:239–242.
13. Hobisch A, Eder IE, Putz T, Horninger W, Bartsch G, Klocker H, Culig Z. Interleukin-6 regulates prostate-specific protein expression in prostate carcinoma cells by activation of the androgen receptor. Cancer Res 1998;58:4640–4645.
14. Chen T, Wang LH, Farrar WL. Interleukin 6 activates androgen receptor-mediated gene expression through a signal transducer and activator of transcription 3-dependent pathway in LNCaP prostate cancer cells. Cancer Res 2000;60:2132–2135.
15. Ueda T, Bruchovsky N, Sadar MD. Activation of the androgen receptor N-terminal domain by interleukin-6 via MAPK and STAT3 signal transduction pathways. J Biol Chem 2002;277:7076–7085.
16. Drachenberg DE, Elgamal AA, Rowbotham R, Peterson M, Murphy GP. Circulating levels of interleukin-6 in patients with hormone refractory prostate cancer. Prostate 1999;41:127–133.
17. Nakashima J, Tachibana M, Horiguchi Y, Oya M, Ohigashi T, Asakura H, Murai M. Serum interleukin-6 as a prognostic factor in patients with prostate cancer. Clin Cancer Res 2000;6:2702–2706.
18. Takeda H, Akakura K, Masai M, Akimoto S, Yatani R, Shimazaki J. Androgen receptor content of prostate carcinoma cells estimated by immunohistochemistry is related to prognosis of patients with stage D2 prostate carcinoma. Cancer 1996;77:934–940.