THE PRELIMINARY RESULTS OF DOCETAXEL-PREDNISOLONE COMBINATION THERAPY FOR THE JAPANESE PATIENTS WITH HORMONE-REFRACTORY PROSTATE CANCER

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Between April 2004 and August 2005, we used docetaxel in combination with prednisolone to treat 14 patients with hormone-refractory prostate cancer (HRPC). Docetaxel was administered at a dose of 70 mg/m^2 once every 21 days and oral prednisolone 5 mg was administered twice daily concurrently on days 1–21. The treatment was continued until disease progression or unacceptable adverse events occurred. Prostate specific antigen (PSA) was used as a tumor marker. PSA response was defined as a reduction from baseline of at least 50% that was maintained for 4 weeks. Five patients had measurable soft tissue lesions, which were nodal metastases in 4 and liver metastasis in 1.

The median follow-up was 8.4 months. During follow-up, 5 patients died. The median treatment cycle was 7 cycles. Manifestations of hematologic toxicity included 11 patients (78%) with grade 3/4 neutropenia and only 1 with febrile neutropenia. Two patients with gastric hemorrhage and febrile neutropenia needed hospitalization. During follow-up, 8 patients (57%) achieved a PSA reduction from baseline of at least 50%. Three patients with nodal metastases and 1 patient with liver metastasis had partial response.

Combined docetaxel and prednisolone was shown to be effective and feasible in Japanese patients.
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Key words : Docetaxel, Prednisolone, Hormone-refractory prostate cancer

INTRODUCTION

The now widespread approach of measuring prostate specific antigen (PSA) has increased the detection of prostate cancer. About 10–20% of men with prostate cancer present with metastatic disease, and in many others, metastases develop despite surgery or radiotherapy. For patients with metastatic lesions androgen deprivation therapy (ADT) is the primary therapeutic approach for advanced prostate cancer. The initial response rate to ADT is 80 to 90%, but nearly all men develop progressive disease after an average of 18 to 24 months. The median survival of men with hormone-refractory prostate cancer is approximately 12 months[1]. Once the disease becomes hormone-refractory, it is very difficult to cure by other treatment modalities. Chemotherapy can reduce serum PSA levels in patients with HRPC and relieves pain in some patients, but tolerability is a concern, particularly since most patients are elderly and many have other medical problems[2]. However, newer regimens, particularly those that include docetaxel, are associated with higher rates both of objective and PSA response and improve quality of life (QOL). This regimen is tolerable for elderly patients with HRPC. Importantly, the median survival time approaches 2 years[3,4]. The Food and Drug Administration (FDA) has approved this regimen as a standard treatment for HRPC. In this study, we assessed the feasibility and efficacy for Japanese patients with HRPC.

MATERIALS AND METHODS

Between April 2004 and August 2005, we treated 14 patients with HRPC using docetaxel chemotherapy. Eligible patients had histologically confirmed adenocarcinoma of the prostate. All patients had both PSA and radiologic progression despite ADT. The antiandrogen withdrawal syndrome was confirmed if the patient had been prescribed antiandrogen. Pretreatment laboratory findings used as inclusion criteria were neutrophil count $>3{,}000/mm^3$, a platelet count $>100{,}000/mm^3$ and a hemoglobin level >8 g/dl. Prior chemotherapy and corticosteroid were allowed. The performance status (ECOG performance status scale) was 0 or 1. Table 1 shows patient characteristics. The median age was 70 (range : 50 to 78) years. The median pretreatment PSA was 135.5 ng/ml (range : 22.0 to 1,925.0). As a measurable soft tissue disease, 4 patients had nodal metastases and 1 patient had multiple liver metastases. As non-measurable lesions, all patients had osseous diseases. There were no patients with only tumor-marker elevation. Initial clinical stage was stage II in 1, stage III in 3 and stage IV in 10 patients. Initial treatments were radical prostatectomy in 4, radiotherapy in 4, hormonal therapy in 8 patients. Twelve patients had received antiandrogen drugs (flutamide or bicalutamide), 6 patients had received dexamethasone

Table 1. Patient characteristics

Case	Age	PS	Initial stage	Prior therapy	PSA (ng/ml)	Metastases
1	70	0	IV	RRP, RT, MAB, EST, VP-16	104.8	Bone
2	75	0	IV	RRP, RT, MAB	183.5	Bone
3	72	0	III	RRP, RT, MAB, DEX	1,567.0	Bone, liver
4	70	0	III	RT, MAB, EST, VP-16, DEX	153.7	Bone
5	75	1	IV	LHRHa, EST, FOS	117.1	Bone, LN
6	70	0	IV	MAB	37.2	Bone
7	73	0	IV	MAB, EST, VP-16, DEX	84.3	Bone
8	73	0	III	LHRHa, EST	22.0	Bone, LN
9	66	1	IV	MAB	1,925.0	Bone
10	70	0	II	RRP, RT, MAB, EST, VP-16, DEX	27.0	Bone
11	68	0	IV	MAB, EST, VP-16	200.9	Bone
12	66	0	IV	LHRHa, EST, FOS, DEX	687.6	Bone
13	50	0	IV	MAB, EST, DEX	1,411.9	Bone, LN
14	60	0	IV	MAB, EST	600.0	Bone, LN

PS: present status (ECOG), stage: AJCC stage groups, RRP: retropubic radical prostatectomy, RT: radiotherapy, FOS: fosfestrol, MAB: maximum androgen blockade, LHRHa: LHRH analogue, EST: estramustine phosphate, VP-16: etoposide, DEX: dexamethasone, LN: lymphnode.

and 2 patients had received fosfestrol. Ten patients had previously received chemotherapy. Five patients had received etoposide and 10 patients had received estramustine phosphate. Informed consent was obtained from all patients before entry into this study.

Treatment schedule

Docetaxel was administered at a dose of 70 mg/m^2 once every 21 days and oral prednisolone 5 mg was administered twice daily concurrently on days 1–21. The serum testosterone value of all patients was confirmed to be at castrate level and LHRH analogue administration continued. At first administration, hospitalization was needed in order to confirm toxicity. From the second administration, treatment was ambulatory in principle. The treatment was continued until disease progression or unacceptable adverse events occurred. If neutropenia with grade 4 or febrile neutropenia were observed, granulocyte-colony stimulating factor (G-CSF) was allowed. When febrile neutropenia was observed in spite of G-CSF administration, a dose of docetaxel was reduced by 10 mg/m^2.

PSA measurements

Kits were used (Abbott Laboratories, Abbott Park, IL, USA) for tumor marker assays. PSA was measured at least every 3 weeks.

Evaluation of response and toxicities

PSA response was defined as a reduction from baseline of at least 50% that was maintained for 4 weeks. PSA progression was defined as an increase from the nadir of either at least 25% for men with no PSA response or at least 50% for all others.

The response to metastatic lesions was evaluated by Response Evaluation Criteria in Solid Tumor (RECIST)[5]. Adverse events were graded using Common Terminology Criteria for Adverse Events version 3.0 (CTCAE). The first endpoint was feasibility of docetaxel and prednisolone. The second endpoints were PSA response and the time to progression (TTP).

RESULTS

The median follow-up was 8.4 (range: 3.7 to 16.5) months. During follow-up, 5 patients died. The median treatment cycle was 7 (range: 2 to 19) cycles.

Toxicities are shown in Table 2. For hematological toxicities (grade (G) 3 or more), anemia, neutropenia, thrombocytopenia and febrile neutropenia occurred in 2, 11, 1 and 1 patient, respectively. For non-hematological toxicities (grade 3 or more), nausea/vomiting, fatigue, oral mucositis, gastric hemorrhage and herpes zoster occurred in each 1 patient. The patients with grade 4 neutropenia were given G-CSF and were controlled safely as outpatients. The treatment was interrupted in 4 patients due to adverse events: oral mucositis (Pt. 1), gastric hemorrhage (Pt. 2), herpes zoster (Pt. 10) and febrile neutropenia (Pt. 8). Pt. 2 and Pt. 8 needed hospitalization. With the exception of the patient with oral mucositis, all other patients subsequently recovered from these events and treatment was resumed. The patient with oral mucositis also recovered, but died of disease progression. There were no treatment-related deaths. In 1 patient with febrile neutropenia the dose of docetaxel was reduced to 50 mg/m^2.

Table 2. Toxicities

CTCAE grade	0	1	2	3	4	G3/4
Hematological						
Anemia	0	6	6	1	1	14%
Neutropenia	1	1	1	3	8	78%
Thrombocytopenia	5	7	1	0	1	7%
Febrile neutropenia	13	—	—	1	0	7%
Non-hematological						
Nausea/vomiting	13	0	0	1	0	7%
Neurological	9	3	2	0	0	0%
Fatigue	12	0	2	0	0	0%
Alopecia	3	10	1	—	—	
Others						
Dermatitis G2, mucositis G3, gastric hemorrhage G4, herpes zoster G3						

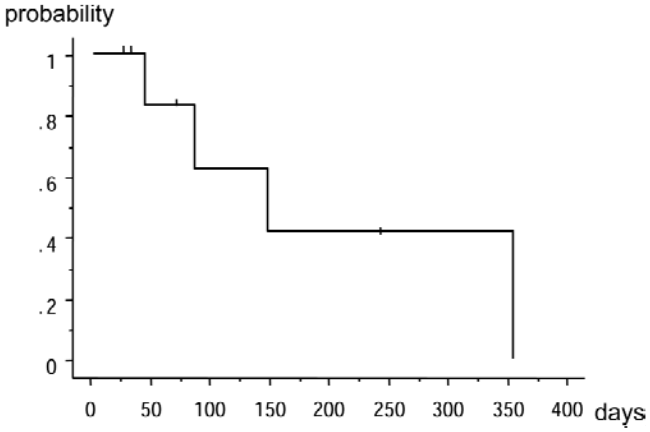

Fig. 1. The time to PSA progression.

Eight patients (57%) achieved a PSA reduction from baseline of at least 50% and 1 of these 9 patients achieved 75% reduction. Among patients with measurable soft tissue disease, 4 patients had partial response for 3 nodal metastases and 1 liver metastasis. In the non-measurable group, 1 had incomplete response for osseous disease and 1 lung metastasis. TTP is shown in Fig. 1. The median duration of PSA response was 147 days. The docetaxel regimen also improved subjective symptoms. Before administration, 7 patients took analgesic agents and subsequently four patients were able to stop or reduce them without palliative radiotherapy. The temperature of one patient with tumor-fever returned to normal.

DISCUSSION

For men with newly diagnosed metastatic prostate cancer, androgen deprivation therapy (ADT) is highly effective, providing disease control in over 80–90% for a median duration of 18–24 months. Although second-line hormone therapy may temporarily improve symptoms and diminish disease burden in some men, the vast majority eventually fail treatment[6–8]. The median survival of men with hormone-refractory prostate cancer (HRPC) is approximately 12 months and until recently this period has not been prolonged by any therapy[1].

Docetaxel binds to tubulin subunits and inhibits the disassembly of microtubules, which normally occurs during cell cycle progression, inactivating the anti-apoptotic protein bcl-2 by phosphorylation and promoting apoptosis. The drug has been used to treat a variety of solid tumors[9]. Two phase III studies were published in 2004[3,4]. Tannock et al reported on a comparison between docetaxel with prednisone and mitoxantrone with prednisone[3]. Petrylak et al reported on a comparison between docetaxel with estramustine and mitoxantrone and prednisone[4]. In these two studies, efficacy was similar. The median survival time was 18.9 and 17.5 months and was longer than the mitoxantrone arm. The PSA response rate was 45 and 50% and the response rate in measurable soft tissue disease was 12 and 17%. Severe toxicities were rare but neutropenia occurred. Grade 3 or 4 neutropenia occurred in 32 and 16.1% of patients. The most important difference between these two studies was the rate of cardiovascular events. In Petrylak's study, there were more cardiovascular events in the docetaxel arm than in the mitoxantrone arm because of estramustine. A response was defined as a reduction from baseline of at least 50% that was maintained for 4 weeks. In Tannock's study[3], comparing an infusion of 75 mg/m^2 every 3 weeks with a 30 mg/m^2 weekly infusion, PSA response and pain response were same but tumor response and overall survival were better in the 75 mg/m^2 group. Although neutropenia occurred more often, Tannock et al recommended a 75 mg/m^2 dose of docetaxel. In Oudard's study[10], comparing 70 mg/m^2 every 3 weeks with a 35 mg/m^2 weekly infusion, overall survival and PSA response were the same and tumor response was better in the 70 mg/m^2 group. Subsequently, the FDA approved a combination therapy of docetaxel every 3 weeks with prednisone.

Recently, two studies were published as part of a Japanese series[11,12]. In Kojima's study, 30 mg/m^2 docetaxel weekly was administered without combination drugs. In Miyoshi's study, 55 mg/m^2 docetaxel was administered with dexamethasone. The treatment schedule was different in each institution. In these two studies, PSA response rates were 56% and 75%. Fifty percent and 66.7% of patients could reduce analgesic agents. These results were similar to our results. Our PSA response rate was 56%, and 57% of patients gained pain relief. The only response that was different was that to measurable soft tissue disease. In our study, 80% of patients achieved partial response but in two other studies, 11%, 0%. In our study, neutropenia of grade 3 or more occurred in 81% of patients, which was much higher than in the other two studies. But the febrile neutropenia was occurred in only 1 patient. With concurrent G-CSF use, almost all patient were safely able to be controlled neutoropenia. In our study, the follow-up period is short and only TTP was evaluated. We believe that the subjective symptoms were improved, but a longer follow-up and larger studies

on more patients are needed to evaluate the overall survival.

Our study has two problems, one being accumulative toxicity. In our study, the maximum number of cycles was 19. It is unclear what prolonged administration may induce, including a second cancer. However, our patients who had undergone prolonged administration were not suffering adverse events and we continued the treatment. The second, is the time to administer docetaxel for patients with HRPC. Our study included patients with both first hormone-refractory disease and second, third or other chemotherapy-refractory diseases. These are problems that will have to be addressed in the future. In our institution, we recently use this therapy for the patients who are luteinizing hormone-releasing hormone analogue-refractory or maximum androgen blockade-refractory. Because FDA recommend the first hormone-refractory disease and in the situation the condition of patients is good for the chemothetrapy.

Combined docetaxel and prednisolone therapy for patients with HRPC has been shown to be feasible and effective in Japanese patients. However, a larger study is needed to clarify the level of efficacy for Japanese patients.

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和文抄録

ホルモン抵抗性前立腺癌に対するドセタキセル，プレドニゾロン併用療法

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【目的】ホルモン抵抗性前立腺癌に対しドセタキセル＋プレドニゾロン療法を行い，その有用性を検討した．

【対象・方法】対象は2004年4月以降に再燃前立腺癌と診断された14例．観察期間は8.4カ月，7コース（5.5コース）施行した．プレドニゾロン（10 mg/日）連日投与を併用しドセタキセル 70 mg/m^2 を21日毎に点滴投与を繰り返した．全例，転移巣を有しており，測定可能病変は4例がリンパ節，1例は肝臓であった．原則として外来通院治療とした．

【結果】14例中8例（57％）で腫瘍マーカーが50％以上減少した．測定可能病変とでは肝臓の1例とリンパ節の2例がPRとなった．鎮痛剤を使用していた7例中4例が減量・中止可能であった．貧血が2例で改善し，1例で発熱も改善した．血液有害事象では好中球減少ではgrade 3/4が11例であった．PDのため4例，高度の皮膚粘膜病変のため1例が中止し，ステロイドによる出血性胃潰瘍，帯状疱疹のため1例ずつが休薬となった．発熱性好中球減少のため1例が入院を要した．

【結語】好中球減少症を高頻度に認めるが外来治療が可能であり，また抗腫瘍効果，疼痛の改善においても有用と思われた．

（泌尿紀要 **53**：93-97，2007）