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Short Communication

Combination chemotherapy with weekly docetaxel and estramustine for hormone refractory prostate cancer in Japanese patients

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Abstract: The aim is to evaluate the efficacy and toxicity of weekly docetaxel and estramustine for Japanese men with hormone refractory prostate cancer who were treated at a single institution. Twenty eligible patients had histologically proven adenocarcinoma of the prostate with metastases that were progressing despite complete androgen blockade and antiandrogen withdrawal. All of the patients received docetaxel 30 mg/m^2 weekly (days 1, 8, 15, 22, 29, and 36). After a two week break, the treatment schedule was repeated. Patients were scheduled to receive daily oral estramustine 560 mg/day throughout the protocol. In the serum prostate specific antigen (PSA) response, three (15%) patients achieved a complete response, and 8 (40%) acheived a partial response. Overall survival and time to progression were 13.4 months and 6.4 months, respectively, however sixty-seven percent of the patients had to discontinue treatment because of toxicity. The high toxicity of this protocol suggests that the regimen and/or the timing should be altered for Japanese patients.

Key words: docetaxel, estramustine, hormone-refractory, prostate cancer, toxicity.

Introduction

Prostate cancer is the most commonly diagnosed cancer and the second leading cause of cancer-related deaths in men in the US.[1] Although the incidence is lower in Japan than in the US, it is the most rapidly increasing cancer in recent years.[2]

For patients with newly diagnosed metastatic prostate cancer, androgen deprivation therapy is initially effective in most patients. However, prostate cancer often becomes hormone independent (hormone refractory prostate cancer, HRPC) and progresses after the first or second round of endocrine therapy. Recently, the introduction of taxanes has led to the development of more effective treatments for HRPC. Docetaxel (DTX) has been reported to have activity as a single agent and a favorable toxicity profile when administered on a low-dose weekly schedule.[3] On the other hand, estramustine phosphate (EMP), which dysregulates normal microtubule assembly, is resulting in cell growth inhibition in human prostate cancer cell lines.[4] Thus, in an attempt, to improve outcome, many trials of combination therapy with taxanes and EMP have been performed.

This protocol combined weekly DTX and EMP for Japanese men with HRPC. The aims of this trial were to evaluate the efficacy and toxicity of this regimen for Japanese men with HRPC treated at a single institution.

Methods

Patient selection

From March 2003 to August 2006, 20 eligible patients had histologically proven adenocarcinoma of the prostate with metastases that were progressing despite complete androgen blockade therapy and antiandrogen withdrawal (Table 1).

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The median time from the first hormone therapy to the start of this protocol was 37.2 months (range: 8.1–174.3 months). All prior therapies had been discontinued for at least 1 month before the first cycle of treatment on this protocol. Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2.

Written informed consent was obtained from all patients as well as institutional review board approval.

Study design and treatment

All patients received DTX 30 mg/m^2 basically in the outpatient clinic by 90-minute intravenous infusion once a week (days 1, 8, 15, 22, 29, and 36). After a two week break, the treatment schedule was repeated every eight weeks. The median number of treatment courses received was 2 (range, 1–9 courses). Dexamethasone 24 mg, diphenhydramine 50 mg, and ranitidine 50 mg were administered before the DTX infusion to prevent a hypersensitivity reaction. Patients were scheduled to receive daily oral EMP 560 mg/day throughout the protocol. Aspirin 100 mg/day was administered to prevent thrombosis.

Toxicity was assessed using the National Cancer Institute – Common Toxicity Criteria (Version 2.0). The subsequent therapy was withheld until grade 3–4 toxicity had recovered to at least grade 2. EMP was reduced in the eight cases due to severe gastrointestinal toxicity.

Treatment was continued until disease progression, unacceptable adverse events or the patient's refusal occurred.

Outcome assessments

The serum PSA was measured every two weeks. PSA response criteria are defined below. A complete response (CR) required the normalization of the serum PSA (defined as a serum PSA < 4 ng/mL, for patients without prior radical prostatectomy, and <1 ng/mL, for those with prior radical prostatectomy). A partial response (PR) was defined as a 50% or greater reduction but without normalization. Patients were considered to have no change (NC) if the PSA levels decreased by <50% or increased by <25%. Patients with progressive disease (PD) had an

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Table 1 Patient characteristics

Total	20
Median cycle (Range)	2 (1–9)
Time (months) from first hormone therapy (Range)	37.2 (8.1–174.3)
Median age, Year (Range):	70.5 (59–80)
Median PSA (Range)	79.1 (4.1–1438)
Metastatic sites	
bone	19 (95%)
lymph node	5 (25%)
lung	1 (5%)
EOD	
0	1 (5%)
1	5 (25%)
2	7 (35%)
3	7 (35%)
4	0 (0%)
Prior treatment	
Hormone therapy	
LHRH-analog + antiandrogen	20 (100%)
Low dose steroid	9 (45%)
Estrogen	8 (40%)
Orchiectomy	5 (25%)
Chemotherapy	
EMP	17 (85%)
Cyclophosphamide	4 (20%)
Other	5 (25%)
Radiation	
Prostate	2 (10%)
Outside prostate	6 (30%)
Radical prostatectomy	
(+)	4 (20%)
(–)	16 (80%)

EMP, estramustine phosphate; EOD, extent of disease on bone scanning; LHRH, luteinizing hormone releasing hormone.

measurement. A therapeutic response in a lymph node or lung was defined as CR, PR, NC, and PD in the sum of the diameters of a bidimensionally measurable lesion by CT as well as PSA response.

Time to treatment failure (TTF), time to treatment progression (TTP) and over all survival (OS) were calculated. The TTF and TTP were measured from the start of chemotherapy to the date of the end and PD, respectively. OS was measured from the initiation of therapy to death or the last follow-up.

The correlation between each toxicity and patient's age, the number of the treatment, the prior chemotherapy, and the time from the first hormone therapy was examined.

Statistical analysis

The Kaplan-Meier product limit estimator was used to estimate the TTF, TTP and OS. Significant factors found to affect the toxicities were further analyzed using the Mann–Whitney test.

Results

PSA and objective response

Three (15%) patients achieved a CR, 8 (40%) achieved a PR, and 4 the PSA, and 5 (25%) had a 50–75% decrease. Overall, the PSA response rate was 55%. One of five patients with lymph node metastases achieved a PR, while a patient with lung metastases had

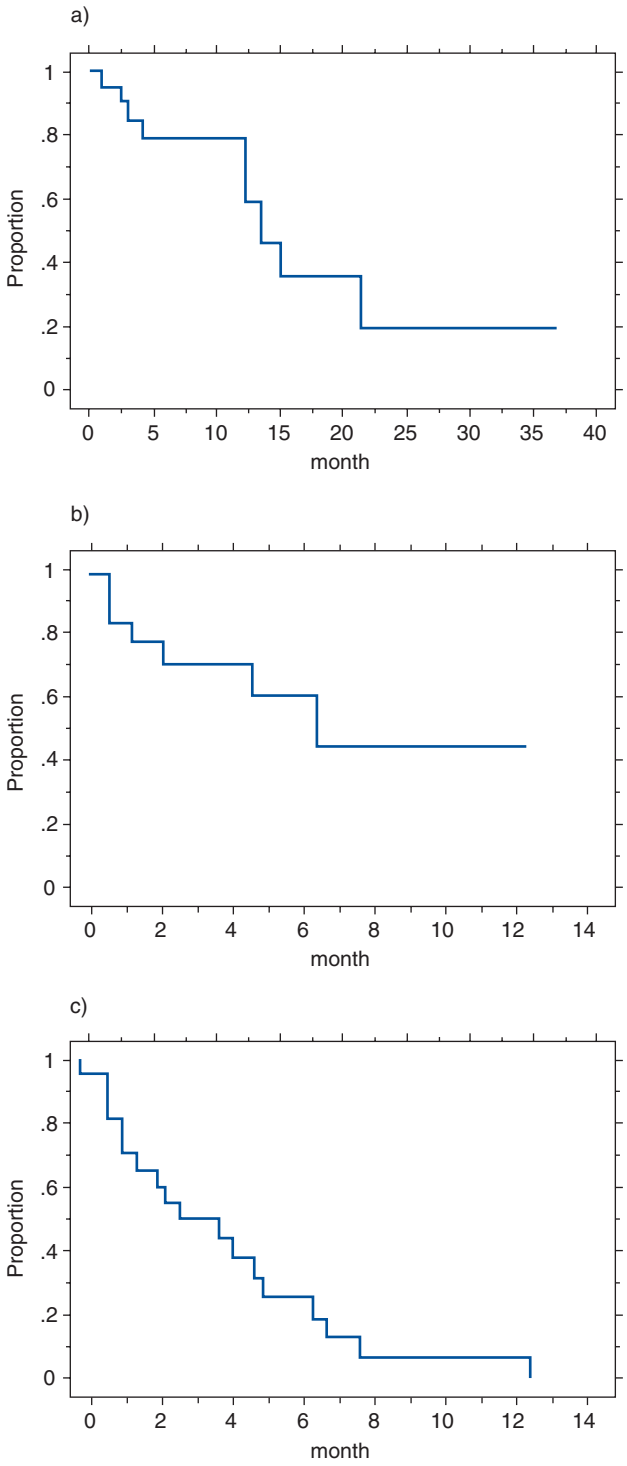

Fig. 1 Kaplan-Meier curves for overall survival (OS, A), time to treatment progression (TTP, B), and time to treatment failure (TTF, C). The median OS was 13.4 months, and the one and two year survival rates were 79.8% and 19.9%, respectively. The median TTP and TTF were 6.4 and 2.6 months, respectively.

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TTP, TTF and OS

The median follow-up at the time of analysis was 12.2 months. During the follow-up period, 10 patients died of prostate cancer, and one died of an adverse effect. The median OS was 13.4 months, and the one and two year survival rates were 79.8% and 19.9%, respectively Fig. 1A). The median TTP (Fig. 1B) and TTF (Fig. 1C) was 6.4 and 2.6 months, respectively.

Toxicity

Most events were moderate in intensity and were managed medically. On the other hand, grade 3–4 toxicities included leukocytopenia in 25% of patients, anemia in 20% and thrombocytopenia in 5%. There was one treatment-related death due to grade 4 febrile neutropenia. Other grade 3–4 toxicities included fatigue (10%), pneumonitis (10%), fluid collection, i.e. pleural effusion (10%) and edema of the limb (10%). Nail changes with grade 2 toxicity was observed in 10%, because grade 3–4 were not provided in the criteria. Overall, a fluid collection was observed in 11 (55%) patients, 7 with edema in the limbs and 4 with a pleural effusion. Figure 2 demonstrates the relationship between the proportion of those with a fluid collection and the cumulative dose of DTX. Edema increased in proportion to the cumulative chemotherapy dose. Pleural effusion occurred after the DTX exceeded about 1000 mg/m^2.

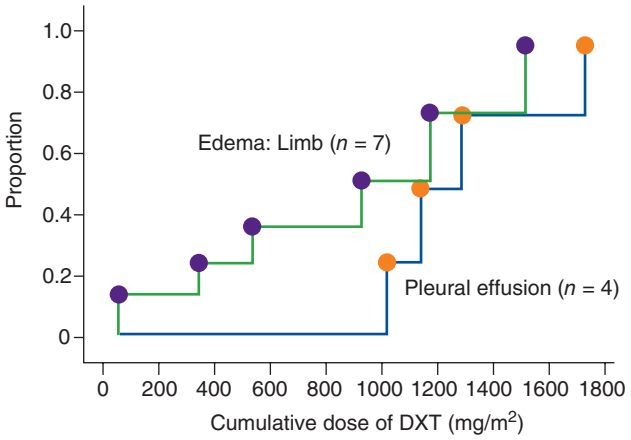

Fig. 2 Docetaxel-induced fluid collection. Edema increased in proportion to the cumulative dose. Pleural effusion occurred after the cumulative docetaxel dose exceeded about 1000 mg/m^2.

Two patients continue on the present protocol currently, and 12 out of the remaining 18 patients had to discontinue treatment because of toxicity including grade 1–2 fatigue and anorexia in three patients.

Discussion

We used combination therapy with DTX and EMP for Japanese outpatients with HRPC in order to assess both its efficacy and safety. The PSA response rate was 55%. In previous reports that used DTX and EMP as a treatment for HRPC, the PSA response rate ranged from 45% to 68%.[5–7] The OS and TTP were 13.4 months and 6.4 months, respectively. Previous studies found an OS from 13.3 to 33 months and a TTP from 4 to 18.0 months, respectively.[8] Consequently, our outcomes did not surpass the previous reports.

Although one patient died from grade 4 febrile neutropenia, overall myelotoxicity was moderate in intensity and hospitalization was not generally needed. Twelve out of 18 (67%) patients, however, had to discontinue treatment because of toxicity including unusual toxicities, i.e. nail changes, pneumonitis, and fluid collection, and even grade 1–2 fatigue and anorexia. Then, the TTF was only 2.6 months.

We have shown the only correlation between nail changes and the time from the first hormone therapy, and edema and the cycle of the present chemotherapy using univariate analysis (Table 2), but multivariate analysis couldn't prove these correlations, because this was a very small study. We couldn't demonstrate any other correlations except for the above two combinations.

The ultimate goal of a treatment for HRPC is a demonstration of a prolongation of disease-related survival without affecting a patient's quality of life, not a high response rate. This is a preliminary study and it might be hard to evaluate the efficacy of the regimen, however the short TTF suggests that the regimen and/or the timing of the chemotherapy should be altered for Japanese patients.

DTX-induced fluid collection is a peculiar but well-known adverse effect. Semb *et al*.[9] observed this in more than half of the patients who received a total DTX dose of at least 400 mg/m^2. The mechanism is due to endothelial inflammation followed by abnormal capillary permeability. In this study, fluid collection depended upon the cumulative dose of DTX, although two patients who received less than 400 mg/m^2 of DTX developed pretibial edema. Pleural effusion occurred after the cumulative dose exceeded about 1000 mg/m^2. Of course, EMP also might be concerned with fluid collection. Indeed, all four patients who met with grade 3–4 fluid collection, had taken EMP without dose reduction. Consequently, fluid collection might be one of the dose-limiting toxicities of this regimen for HRPC.

Table 2 Incidence of drug related toxicities of grade 3/4 and the predictors

Grade 3–4 toxicities	Anemia	Leukopenia†	Thrombocytopenia	Fatigue	Nail change‡	Pleural effusion	Edema	Pneumonitis
Incidence	4 (20%)	5 (25%)	1 (5%)	2 (10%)	2 (10%)	2 (10%)	2 (10%)	2 (10%)
Patient' age	0.1857	0.5703	0.34	0.8501	0.5286	0.2567	0.8997	0.5286
No. chemotherapy	0.3823	0.5307	NA	0.4007	0.4007	0.518	0.0386	0.4007
Time from first hormone therapy	0.2986	0.3594	0.3402	0.0588	0.0438	NA	0.6143	0.8997
Prior chemotherapy	0.5492	NA	NA	NA	NA	NA	0.1474	0.5211

†Including one treatment-related death by febrile neutropenia with grade 4. ‡Because grades 3/4 are not provided in the criteria, grade 2 cases are described.

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In conclusion, this study of combination chemotherapy with weekly docetaxel and estramustine revealed a PSA response rate of 55%, with an OS and TTP of 13.4 and 6.4 months, respectively. However, 67% had to discontinue treatment because of toxicity and TTF was only 2.6 months. Although it is a small study, this protocol might need to be modified including the regimen and the most appropriate time to start therapy for Japanese HRPC patients.

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