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ORIGINAL ARTICLE

Docetaxel, low-dose estramustine, and doxifluridine in hormone-refractory metastatic prostate cancer

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Abstract
Purpose Advanced prostate cancer, which is one of the most common cancers, usually progresses to hormone-refractory prostate cancer (HRPC).

A recent randomized trial of treatment with docetaxel demonstrated improved survival for patients with HRPC. The combination of docetaxel and estramustine phosphate (estramustine) has been reported to be effective for HRPC. Low-dose estramustine suppresses the pituitary–gonadal axis. Docetaxel plus 5-fluoro-5′-deoxyuridine (5′-dFUrd) had supra-additive cytotoxic effects on HRPC cells consistent with the molecular mechanism. Therefore, we examined the efficacy of adding 5′-dFUrd on the chemotherapy regimen, which consist docetaxel and estramustine.

Methods All of the HRPC patients were treated with estramustine 140 mg orally twice 5′-dFUrd 200 mg orally four times daily on days 1–21, and docetaxel 60 mg/m^2 was administered on day 1.

We evaluated serum prostate-specific antigen (PSA) and measurable responses, the progression-free and overall survival, and the impact on adverse effects and the quality of life (QOL).

Results Of 34 patients with a median age of 72.3 years, 73% showed PSA responses and 70% showed measurable responses. The median progression-free survival was 18.0 and 5.8 months for PSA responders and non-responders and the overall survival was 19.4 months, respectively. There were few serious adverse effects. Grade 3/4 neutropenia occurred in 32.4% of the patients, and was easily managed with granulocyte colony-stimulating factor (G-CSF) injection. There was no significant change in the overall QOL scores serially.

Conclusions This study shows that the combined regimen is tolerable and effective in Japanese HRPC patients.

Keywords Hormone-refractory prostate cancer · Docetaxel · Estramustine phosphate · Doxifluridine

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Introduction

Prostate cancer is the most common cancer in men in the US.

In 2004, approximately 230,000 men were newly diagnosed and 30,000 men died of prostate cancer [1].

In Japan, prostate cancer was the seventh leading cause of cancer death in men in 2005, and 9,265 men died (15.0/100,000) of prostate cancer [2]. Although the incidence of prostate cancer in Japan is lower than in the US, it is the most rapidly increasing cancer in Japan [3].

Despite screening for serum prostate-specific antigen (PSA) and various treatment options for localized disease, which included surgical and radiation treatments, 22–48%

of patients develop recurrent disease after radical prostatectomy [4].

Although 80–90% of patients with advanced prostate cancer respond initially to surgical or medical androgen ablation, most advanced cases ultimately progress to hormone-refractory prostate cancer (HRPC) [2].

For patients with HRPC, treatment options include radiotherapy and chemotherapy. Current chemotherapy regimens include estramustine, vinka alkaloids, mitoxantrone, and taxanes as single agents and in combination [5]. Recent results of a randomized trial in patients with metastatic HRPC reveal improved overall survival, with improved time to progression, improved reductions in PSA levels, and improved objective tumor response rates in patients treated with estramustine plus docetaxel or docetaxel alone compared with patients treated with mitoxantrone plus prednisone therapy [6, 7].

Nevertheless, there are few reports on chemotherapy regimens that include docetaxel for Japanese patients with HRPC [8].

Recently, it has been reported that docetaxel plus 5′-deoxy-5 fluorocytidine, which is converted into 5-fluoro-5′ deoxyuridine (5′-dFUrd) by carboxylesterase, has supra additive cytotoxic effects on human HRPC cells, and the molecular mechanism revealed by gene expression profiling was consistent with these results [9, 10]. Furthermore, it has been reported that low-dose estramustine suppresses the pituitary-gonadal axis and is associated with fewer adverse effects than normal-dose estramustine [11]. Therefore, we examined the efficacy and safety of a chemotherapy regimen that comprised docetaxel, low-dose estramustine, and 5′-dFUrd in Japanese patients with HRPC on the following hypothesis; 5′-dFurd add some effects on the chemotherapy regimens of docetaxel plus estramustine compared with Petrylak report.

Materials and methods

Patients

The patients with metastatic HRPC were all refractory to hormonal therapy and anti-androgen withdrawal. To be eligible, each patient was required to meet the following criteria: (1) proven pathological evidence of adenocarcinoma of the prostate; (2) a new lesion on radionuclide bone scan, enlargement of a soft tissue mass, or an increasing PSA despite continued androgen ablation (serum testosterone level <50 ng/mL); (3) with respect to the increased PSA, at least two consecutive increases in PSA (PSA > 5.0 ng/mL); (4) documented metastatic disease (distant metastasis or positive bone scan); (5) adequate major organ function; and (6) no history of deep vein thrombus, myocardial infarction, or angina. Previous chemotherapy, except for taxane, was allowed. The patients had to have an eastern cooperative oncology group performance status of 0–3. Patients with abnormal hematological or biochemical parameters or brain metastases were excluded. This study obtained ethics committee approval from the institutional review board of the Graduate School of Medical Sciences, Kumamoto University. All patients in the study gave written informed consent before participating in the study.

Treatments

Treatment consisted of estramustine 140 mg orally twice and 5′-dFUrd 200 mg orally four times daily on days 1–21. Docetaxel was administered on day 1 at 60 mg/m^2 for 1 h. Premedication with 8 mg dexamethasone was administered intravenously 15 min before docetaxel administration, and 8 mg of oral dexamethasone was given 12, 24, and 36 h after docetaxel administration to prevent hypersensitivity reactions. The chemotherapy regimen was repeated every 3 weeks. Chemotherapy was continued for at least four cycles, unless disease progression, unacceptable toxicity, or patient refusal occurred. Oral ticlopidine HCl (200 mg/day) was added to reduce thromboembolic complications related to estramustine-containing regimens [12].

We modified the treatment plan as following in the event of toxicity.

The subsequent therapy was withheld until the grade 3–4 toxicity excluding anemia, neutropenia, alopecia or nausea and/or vomiting had recovered to at least grade 2, if grade 3–4 toxicity occurred. In addition, if neutropenic fever occuered, the subsequent therapy was withheld until recovery. The dose of estramustine was reduced by 50% in the case of persisitence of grade 3–4 nausea and/or vomiting. We resumed the subsequent therapy without dose reduction of any other drugs after recovery.

Outcomes

Physical examinations, complete blood cell counts, and serum blood chemistry tests were repeated at 3-week intervals. Imaging studies [whole-body computed tomography (CT), bone scan, and pelvic magnetic resonance imaging (MRI)] to determine the disease extent were performed at baseline, after the first two cycles of chemotherapeutic treatment, and subsequently after every fourth cycle of chemotherapeutic treatment.

Serum PSA was measured every 3 weeks. The prostate-specific antigen working group criteria were used to evaluate the PSA responses: a decrease in PSA level (baseline 5 ng/mL or more) of more than 50% from baseline with no objective progression was defined as a PSA response [13]. Two assessments at least 3 weeks apart were required to

document a PSA response. PSA progression was defined as the point at which the level returned to 50% of the baseline value for PSA responders, and as the point at which a 25% increase in PSA was achieved for PSA non-responders [13].

For patients with at least one lesion that was measurable in two dimensions, the response was evaluated using the World Health Organization criteria [14].

We grouped the patients into those treated with or without estramustine in their prior medication history, and compared the PSA and measurable responses between the groups.

The progression-free and overall survival times were determined using Kaplan–Meyer curves. The quality of life (QOL) was assessed using version 4 of the FACT-G (functional assessment of cancer therapy-general), and a prostate cancer specific subscale, the FACT-P (functional assessment of cancer therapy-prostate), at baseline, and before chemotherapy cycles 2 and 4 [15, 16]. All patients who completed the questionnaire at baseline were included in the evaluation, and the FACT-G and FACT-P scores were compared with the baseline value for each of these patients.

Adverse effects were classified according to the common toxicity criteria of the national cancer institute (version 2) [17]. Serious adverse events were defined as fatal or life-threatening, requiring or prolonging hospitalization, resulting in persistent or substantial disability or incapacity, and other important medical events.

Data analysis

Key null hypotheses were: No difference of the survival time with this chemotherapy regimen compared with Petrylak report. Comparison of the survival time was made by 95% confidential interval (95% CI). *P*-value of the independence test on contingency table was calculated by Fisher's exact test.

An independent radiologist reviewed key images to assess all of the responses in the imaging studies. All of the statistical analyses were performed using the Statcel software (OMS Publishing, Tokyo, Japan); SPSS and Mathematica. The overall and progression-free survival values were calculated from the date of the start of treatment to the date of death or last follow-up. The Kaplan–Meier method was used to estimate the probabilities of overall and progression-free survival. For the analysis of progression-free survival, we grouped the patients as PSA responders and non-responders. Repeated one-factor analysis of variance (ANOVA) was used to compare the FACT-G, FACT-P, FACT-T (sum of the FACT-G and FACT-P), and FACT-G subscale scores for each of these patients. Contingency table with Fisher's exact test was used to compare the PSA and measurable responses between the patients previously treated with or without estramustine. The patients were grouped as PSA responders or PSA non-responders for this analysis. *P* values of 0.05 or less were considered significant.

We had determined the α and β value as 0.05 and 0.20 with initial comparison with Sinibaldi report in 2001, the sample size was 61 HRPC patients under Freedman's method (null survival probability = 0.5 and alternative survival probability = 0.75 at 13.5 months) [18]. The power was calculated as 0.88 with final number of patients whom we had recruited were 34 comparing with Petrylak report in 2004, (null survival provability = 0.50 with $n = 338$, alternative survival provability = 0.65 with $n = 34$ at 17.5 months) [6].

Results

Patients

Between April 2003 and March 2006, 34 patients with a median age of 72.3 years (range 56–83 years) and a median PSA level of 69.1 (0–1,817 ng/mL) were enrolled in this study; 14 (41%) of the patients were at least 75 years old (Table 1). Ten (29%) of the patients had measurable lesions (lymph node, lung or liver metastases; Table 1). All of the patients had received at least two previous lines of hormonal therapy, and 19 (56%) patients had received chemo-hormonal therapy with estramustine. Four (12%) patients had received platinum-based chemotherapy (Table 1).

Efficacy

Of the 34 patients, one patient had a normal PSA level (0 ng/mL throughout the study from baseline) and had progressive multiple bone metastases despite hormone therapy. This patient was excluded from the analysis of PSA responses.

Of the 33 assessable patients, 24 (73%) patients had a PSA response (Tables 2, 3).

Of the ten patients with measurable disease, seven (70%) patients showed measurable responses; all of the responses were partial responses (Tables 2, 3).

The median duration of follow-up was 24.8 months (33 cycles). Nineteen (56%) patients died of prostate cancer and one patient died in a traffic accident. The progression-free survival values were 18.0/17.2 (median/mean) and 5.8/6.1 (median/mean) months in the PSA responder and non-responder subsets, respectively (Tables 2, 3, Fig. 1). The overall survival was 19.4/20.3 (median/mean) months (Tables 2, 3, Fig. 2). As survival time with this chemotherapy regimen, overall survival time was 19.4/20.3 (median/mean) months with 95% CI; 17.5-21.3 (median) and 17.1–23.6 (mean) months. The benchmark result 17.5 (median)

Table 1 Demographics of the enrolled patients

Baseline characteristics	Value
Number of patients	34
Average of age, (range), years	72.3 (56–83)
Average of PSA, (range), ng/mL	69.1 (0–1817)
ECOG PS (*n*)	
0	22
1	8
2	1
3	3
4	0
Metastatic sites (*n*)	
Bone	30
Lymph nodes	10
Lung	1
Liver	1
Prior treatment	
Radical prostatectomy	4
Radiotherapy	11
LH-RH analogue or orchiectomy plus anti-androgen	34
Estramustine	19
Platinum chemotherapy	4

PSA Prostate-specific antigen, *ECOG* eastern cooperative oncology group, *PS* performance status, *LH-RH* luteinizing hormone-releasing hormone

Table 2 Efficacy of treatment

Parameter	*N*	Value	95% CI
50% reduction in serum PSA (%)	33[b]	73	54–87[a]
Measurable responses (%)	10	70	35–93[a]
Progression-free survival (months)	33[b]	18.0 14.4	1.3–34.6 11.1–17.6
PSA responders median mean	24	18.0 17.2	n.d. 13.7–20.7
PSA non-responders median mean	9	5.8 6.1	4.4–7.1 4.4-7.7
Overall survival (months) median mean	34	19.4 20.3	17.5–21.3 17.1–23.6

PSA Prostate-specific antigen

[a] Calculated based on F-distribution

[b] There was a missing value

Survival time indicated by median unless otherwise indicated

months (Petrylak report) was included in the 95% CI therefore alternative hypothesis of improvement was rejected under 5% significance. However, 17.5 months was the border line of 95% CI and there was a positive possibility if tested under lager sample set.

As influence of the prior use of estramustine to the efficacy, there were no statistically significant differences in the PSA (68.4 vs. 78.6%; $P = 0.70$) and measurable (100.0 vs. 50.0%; $P = 0.20$) responses between the patients who previously received chemo-hormonal therapy with and without estramustine.

Table 3 Efficacy of treatment as classified by treatment history with or without estramustine

Medication history	Estramustine (with)	Estramustine (without)	*P*-value*
PSA response rate	19 (100)	14 (100)	0.70
Responder	13 (68, 43–87)	11 (78, 49–95)	
Non-responder	6 (32, 13–57)	3 (22, 5–51)	
Measurable response rate	4	6	0.20
Responder	4 (100, 47–100)	3 (50, 12–88)	
Non-responder	0 (0, 0–53)	3 (50, 12–88)	

PSA Prostate-specific antigen

* *P*-value was calculated by Fisher's exact test, 2-tails

Parentheses showed percentage with 95% CI (confidence interval). 95% CI was calculated based on F-distribution

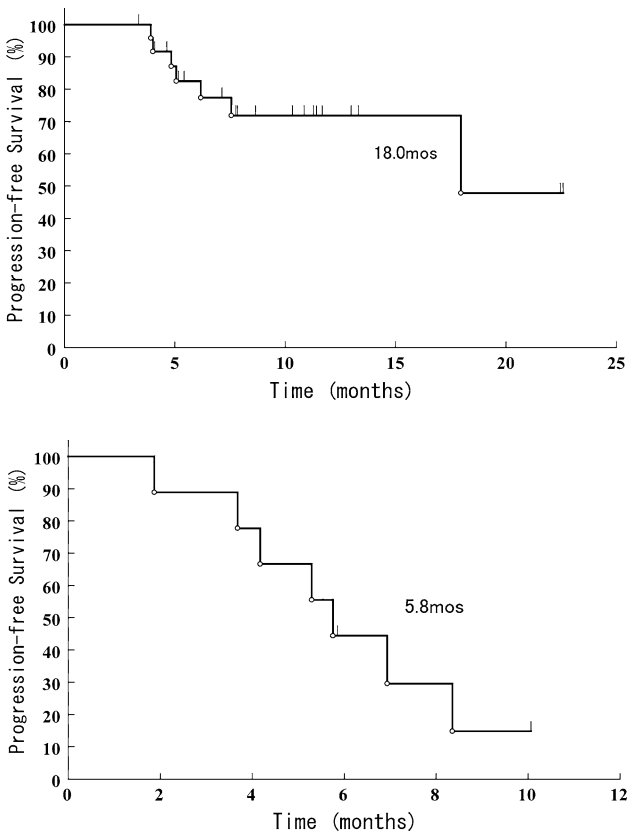

Fig. 1 Kaplan–Meier curves for progression-free survival. The Kaplan–Meier product-limit estimator was used to estimate the progression-free survival. The patients were grouped into PSA responders and non-responders for this analysis. The *upper* and *lower panels* show the Kaplan–Meier curves for the PSA responders and non-responders, respectively. Survival duration was defined as the time between the first docetaxel administration and the time of death or last follow-up

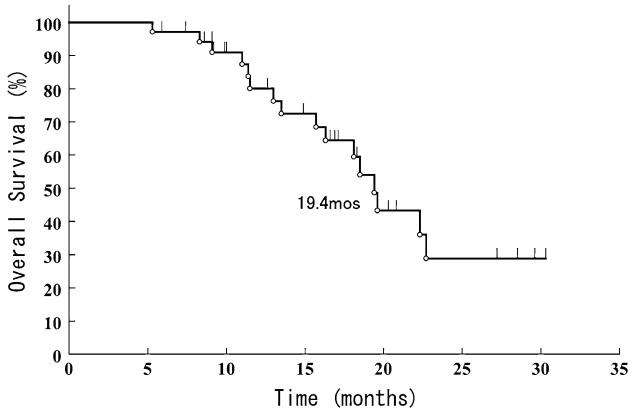

Fig. 2 Kaplan–Meier curves for the overall survival. The Kaplan–Meier product limit estimator was used to estimate the overall survival. Survival duration was defined as the time between the first docetaxel administration and the time of death or last follow-up

Adverse effects

The incidence of grade 3/4 neutropenia was relatively high (32%; Table 4), although most of the patients with grade 3/4 neutropenia were easily managed with granulocyte colony-stimulating factor (G-CSF) injection. One patient developed febrile neutropenia and required a short period of hospitalization. Only one patient had grade three nausea or vomiting and required drip infusion therapy (Table 4).

No patient had to discontinue treatment because of adverse effects. Low-grade adverse effects, which included general fatigue, anorexia, nausea or vomiting, diarrhea, alopecia, nail changes, sensory neuropathy, changes in taste or smell, stomatitis, tearing, and peripheral edema, were noted (Table 4).

Table 4 Drug-related adverse events

Toxicity	Grade			
	1	2	3	4
Anemia	10	11	4	0
Neutropenia	5	5	10	1
Thrombocytopenia	7	0	0	0
Renal	0	0	0	0
SAST/SALT	2	1	0	0
Anorexia	4	3	0	0
General fatigue	12	0	0	0
Nausea/vomiting	5	0	1	0
Alopecia	9	0	0	0
Sleeplessness	1	0	0	0
Headache	1	0	0	0
Edema	8	6	0	0
Diarrhea	5	2	0	0
Fever	2	0	0	0
Rash/desquamation	1	0	0	0
Gustatory dysfunction	1	0	0	0
Constipation	2	0	0	0
Neurotoxicity	2	1	0	0
Deep venous thrombosis	1	0	0	0
Pulmonary thrombosis	1	0	0	0
Neutropenic infection (pneumonia)	1	0	0	0

SAST Serum aspartate aminotransferase, *SALT* serum alanine aminotransferase

Quality of life

The quality of life was evaluated in 21 (62%) patients using the FACT-G and FACT-P questionnaires, which were translated locally. The FACT-G, FACT-P, and FACT-T (sum of the FACT-G and FACT-P) scores remained stable over the treatment course (Fig. 3). The only subscale that improved significantly was emotional well-being at cycle two in the separate FACT-G subscale (Fig. 3).

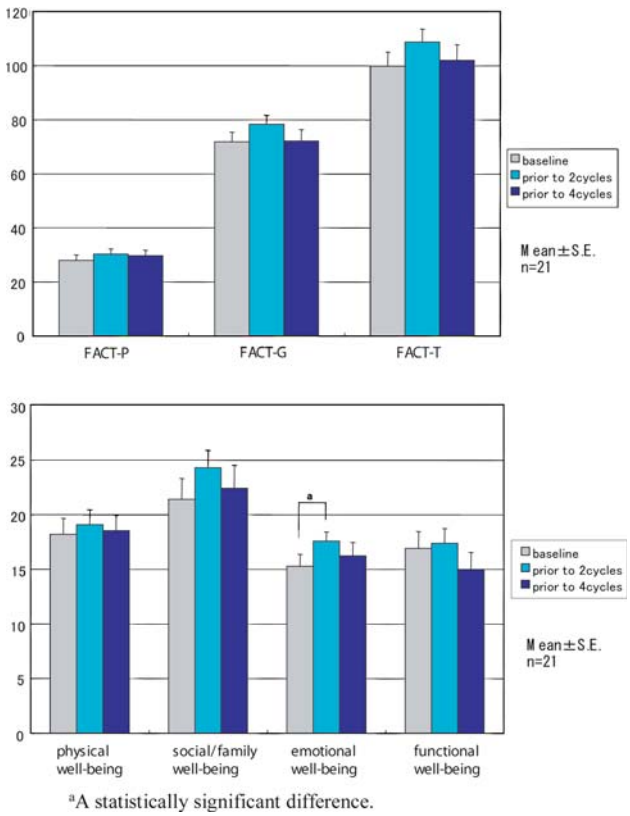

Fig. 3 Evaluation of the % quality of life (QOL) scales during treatment. QOL was assessed using version 4 of the FACT-G (functional assessment of cancer therapy—general), and a prostate cancer—specific subscale, the FACT-P (functional assessment of cancer therapy—prostate) and FACT-T (sum of the FACT-G and FACT-P) at baseline, and before chemotherapy cycles 2 and 4. The *upper panel* shows the QOL outcomes evaluated using the FACT-G, FACT-P, and FACT-T. The *lower panel* shows the separate QOL outcomes evaluated for the FACT-G subscales. An *asterisk* indicates a statistically significant difference

Discussion

In this study, we presented that 5′-dFUrd might added a significant clinical benefit on the combination of docetaxel and estramustine in the treatment of HRPC patients without increasing the frequency of severe adverse effects or diminishing patient QOL and there was not a statistically significant difference in the efficacy of this chemotherapy regimen between with and without medical prior history of estramustine.

In this study, the combination of docetaxel, low-dose estramustine, and 5′-dFUrd in 3-week cycles showed significant activity and an acceptable toxicity profile in the treatment of Japanese patients with HRPC. It has been reported that the combination of docetaxel and estramustine shows promise against HRPC, although some of those studies used different doses and schedules (Tables 5, 6) [19–24].

In previous studies using the combination of docetaxel and estramustine as a treatment option for HRPC, the PSA reduction rates and measurable response rates were reported to range from 26.7 to 100% and from 7.7 to 84% of patients which our results consist with (73 and 70%), respectively (Tables 5, 6).

In contrast, the reported median progression-free and overall survival values ranged from 4 to 14.25 months for which our results (18.0 months for PSA responders, 5.8 months for PSA non-responders) were somewhat better. The reported overall survival values ranged from 13.3 to 33 months in which our result (19.4 months) was included (Tables 5, 6). The benchmark result 17.5 months (Petrylak report) was the border line of 95% CI (17.5-21.3: median) of our results, our overall survival time might be somewhat better, as considering the background of patients between a Petrylak study and ours. Our patients likely to be advanced than the patients of Petrylak study, because Petrylak et al.

Table 5 Efficacy of chemotherapy with estramustine and docetaxel for HRPC in recent studies

Author	Year	Other agents	*N*	PSA decline >50%	Measurable response rate	Progression-free survival	Overall survival
Kreis [33]	1999	None	17	82	ND	ND	ND
Savarese [19]	2001	Hydrocortisone	46	68	50	8	20
Sinibaldi [18]	2001	None	40	45	20	4	13.5
Oh [34]	2003	Carboplatin	40	68	52	8.1	19
Petrylak [6]	2004	None	338	50	17	6.3	17.5
Oh [35]	2005	Carboplatin	30	63	29	ND	14.9
Safarinejad [36]	2005	Suramin	42	100	84	14.25	33
Oudard [37]	2005	Prednisone	85	63–67	ND	8.8–9.3	18.6
Font [38]	2005	Mitoxantrone	30	63	ND	10	18
Efstathiou [39]	2005	Zoledronic acid	54	45	38	4.4	13.3
Wilding [40]	2006	Gefitinib	30	26.7–33.3	7.7	ND	ND
This study	2006	5′-dFUrd	34	73	70	18.0[a]	19.4

PSA Prostate specific antigen
HRPC Hormone-refractory prostate cancer
G-CSF Granulocyte colony-stimulating factor 5′-dFUrd doxifluridine
[a] Median survival for all patients (PSA responder; 18 months and non-responder; 5.8 months)

Table 6 Blood toxicities in recent studies of chemotherapy including estramustine and docetaxel for HRPC

Author	Year	Dose of docetaxel	Dose of estramustine	Neutropenia	Anemia	Thrombo-cytopenia
Kreis [33]	1999	40–80 mg/m^2/3W	14 mg/kg/day	17.7	ND	ND
Savarese [19]	2001	70 mg/m^2/3W	10 mg/kg/day	61	13	18
Sinibaldi [18]	2001	60–70 mg/m^2/3W	1,120 mg/b/day	75	2.5	0
Oh [34]	2003	70 mg/m^2/3W	840 mg/b/day			
Petrylak [6]	2004	60–70 mg/m^2/3W	840 mg/b/day	19.7	ND	ND
Oh [35]	2005	43 mg/m^2/W	420 mg/b/day			
Safarinejad [36]	2005	70 mg/m^2/3W	10 mg/kg/day	33.3	50	21.4
Oudard [37]	2005	60–70 mg/m^2/3W	280 mg/b/day	53	3	0
Font [38]	2005	75 mg/m^2/3W	840 mg/b/day	20	0	3
Efstathiou [39]	2005	45 mg/m^2/W	420 mg/b/day	4	2	ND
Wilding [40]	2006	60 mg/m^2/3W	840 mg/b/day	26.7	0	ND
This study	2006	60 mg/m^2/3W	280 mg/b/day	32.4	11.8	0

HRPC Hormone-refractory prostate cancer

recruited HRPC patients not only with but also without metastases.

Capecitabine (N4-pentyloxycarbonyl-5′-deoxy-5-fluorocytidine; Xeloda) is a fluoropyrimidine carbamate. It is the prodrug of 5′-dFUrd, which is in clinical use in an oral formulation. It generates 5-fluorouracil (5-FUra) through the actions of three enzymes present in the liver and tumors, the overexpression of thymidine phosphorylase in tumor cells leads to preferential metabolism in the last step [25, 26]. This drug is first converted into 5′-deoxy-5 fluorocytidine by carboxylesterase in the liver, and then to 5′-dFUrd, which is prescribed in Japan, Korea, and China for the treatment of breast, colorectal, gastric, bladder, and cervical cancers in humans [27].

Recently, it has been reported that the combination of docetaxel and 5′-dFUrd exhibits sequence-dependent synergic cytotoxicity in human HRPC cells [10]. Moreover, clinical trials have shown that chemotherapeutic regimens of docetaxel and capecitabine provide improved objective response rates and overall survival without a significant increase in treatment-related adverse effects in advanced breast cancer and non-small cell lung cancer [28, 29]. Therefore, 5′-dFUrd, which is a 5-FUra agent that is activated relatively selectively in tumors, was used in this study.

The effectiveness of the combinatorial regimen of docetaxel, low-dose estramustine, and 5′-dFUrd was somewhat higher than expected, although the degree to which 5′-dFUrd enhances the clinical response and survival in HRPC patients treated with low-dose estramustine plus docetaxel is uncertain.

The most severe adverse effects were blood toxicities. The grade 3/4 neutropenia was easily managed by the administration of G-CSF. Indeed, docetaxel given every 3 weeks clearly causes neutropenia, which requires the administration of G-CSF, although estramustine may have a myeloprotective effect when combined with cytotoxic chemotherapeutic agents, such as vinblastine [30]. The blood toxicity profile was consistent with that of other regimens that include higher doses of estramustine [17]. In the first studies of docetaxel and estramustine against HRPC, docetaxel was used at a dose of 60–70 mg/m^2 every 3 weeks, with estramustine administration for 2.5–5 days at 280 mg every 6–8 h [31, 32]. These regimens have been associated with grade 3/4 neutropenia or fatigue in 20–70% of cases, which is consistent with our results (32 and 35%) (Tables 4, 5 and 6) [17, 32]. In addition, these regimens were associated with thromboembolic episodes in 10–20% of patients [17, 32]. Therefore, we administered estramustine at a lower than usual doses to reduce the probability of thromboembolic events. Moreover, we administered oral ticlopidine HCl (200 mg/day) to reduce thromboembolic complications related to estramustine-containing regimens [12, 33]. In our modified regimen, oral ticlopidine HCl may reduce adverse effects and improve the tolerance and compliance, although the contribution of our modifications to improvements in therapeutic outcome remains uncertain [12].

It has been suggested that low-dose estramustine is associated with fewer adverse effects except for blood toxicity, although it should suppress the pituitary-gonadal axis to the same extent as a high dose of estramustine, since the serum testosterone levels in all of the patients were at castration levels (data not shown; 0–9 ng/mL, median 0.81 ng/mL). Therefore, we did not use any LH–RH agonist in this study [11].

Recently, Miyoshi et al. [8] have reported the effect of docetaxel in Japanese patients with HRPC.

They reported a >50% reduction rate in serum PSA (%) in 75% of the patients, with a median progression-free survival time of 7.9 months, and a median overall survival time of 8.5 months for nine patients. Although our PSA response rate (73%) was similar to their result, our median survival time was somewhat better (18.0 months of progression-free survival for PSA responders, 5.8 months of progression-free survival for PSA non-responders, 19.4 months of overall survival), respectively.

This survival benefit may be due to the additive effects of estramustine and 5′-dFUrd on docetaxel in our regimen.

Concerning adverse effects, Miyoshi et al. [8] reported grade 3/4 neutropenia in three patients (33%), which is consistent with our result (31%), although our patients were considerably older (72.3 vs. 64 years). In our study, the well-described gastrointestinal adverse effects of estramustine were infrequent and mild, which could be attributed to the lower than usual estramustine dose. The superior tolerance and compliance characteristics of this regimen make it an attractive option for patients with HRPC.

This study shows that the combination of docetaxel, low-dose estramustine, and 5′-dFUrd is tolerable and effective against HRPC. These results are consistent with those from recent studies of docetaxel-based combination chemotherapy. Further studies are needed to discover novel and optimal treatment regimens for HRPC.

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