Docetaxel Plus Prednisolone for the Treatment of Metastatic Hormone-refractory Prostate Cancer: A Multicenter Phase II Trial in Japan

S. Naito1, T. Tsukamoto2, H. Koga1, T. Harabayashi3, Y. Sumiyoshi4, S. Hoshi5 and H. Akaza6

1Department of Urology, Faculty of Medicine, Kyushu University, Fukuoka, 2Sapporo Medical University School of Medicine, Sapporo, 3Graduate School of Medicine Hokkaido University, Sapporo, 4Shikoku Cancer Center, Matsuyama, 5Yamagata Prefectural Central Hospital, Yamagata and 6University of Tsukuba, Tsukuba, Japan

Received February 1, 2008; accepted March 18, 2008; published online April 15, 2008

Background: Docetaxel-based chemotherapy has been shown to be effective and well tolerated by Western patients with metastatic hormone-refractory prostate cancer (HRPC). This study was undertaken to assess the feasibility of docetaxel in combination with prednisolone in Japanese patients with HRPC.

Methods: Patients aged 50–74 years with measurable metastatic HRPC were included in this non-comparative Phase II study. Treatment consisted of docetaxel 70 mg/m2 once every 3 weeks plus prednisolone 5 mg twice daily, for a maximum of 10 cycles. The primary endpoint was overall tumor response rate, assessed by Response Evaluation Criteria in Solid Tumors; secondary endpoints included prostate-specific antigen (PSA) response and toxicity.

Results: A total of 43 patients were evaluable for efficacy and toxicity. The response rate was 44.2% (90% CI, 31.2–57.8%), with partial responses in 19/43 patients. The median duration of response was 19.3 weeks. PSA responses were recorded in 44.4% of patients (95% CI, 27.9–61.9%). The most common non-hematological adverse events (of any grade) possibly related to treatment were alopecia (88.4%), anorexia (65.1%) and fatigue (53.5%). Grade 3/4 leukopenia and neutropenia occurred in 81.4 and 93.0% of patients, respectively; however, the grade 3/4 rates of febrile neutropenia (16.3%) and infection without fever (14.0%) were lower.

Conclusion: The combination of docetaxel and prednisolone was feasible and active in Japanese patients with HRPC, with a manageable adverse-event profile similar to that observed in Western patients.

Key words: prostate cancer – docetaxel – prednisolone – phase II – chemotherapy

INTRODUCTION

Prostate cancer is the most common cancer type in men, with approximately 218,890 new cases and 27,050 deaths occurring annually in the USA alone (1). In Japan, as dietary habits change, detection methods improve, and the size of the elderly population increases, cases are increasing. Indeed, the estimated number of new cases in 2005 was 37,060, representing a 61% increase in the rate of new cases since 2000 (2). Mortality from prostate cancer in Japan has also shown a marked 23% increase over recent years, rising from 7,514 deaths in 2000 to 9,265 deaths in 2005 (2,3). It is estimated that the incidence and mortality cases for prostate cancer will increase 3-fold by 2020 compared with 2000 (2).

As prostate cancer initially grows in an androgen-dependent manner, it has been observed that androgen deprivation therapy is effective in approximately 80% of patients with metastatic disease (4). However, under prolonged androgen deprivation, prostate cancer generally becomes hormone-refractory, and while symptomatic relief may be afforded by analgesics, radiotherapy to dominant sites of bone pain, and chemotherapy, treatment has until recently remained largely palliative.

© The Author (2008). Published by Oxford University Press. All rights reserved.
Systemic chemotherapy for hormone-refractory prostate cancer (HRPC) has been evaluated for many years, with disappointing results. In a review of 26 Phase II trials of chemotherapy in advanced prostate cancer, only six agents had an objective response rate greater than 10% and the median survival was 10–12 months (5). Two trials in the late 1990s demonstrated that the combination of mitoxantrone and corticosteroids could provide pain relief and prostate-specific antigen (PSA) decreases, with improved quality of life compared with corticosteroids alone, but there was no improvement in survival (4,6). Mitoxantrone combined with corticosteroids was approved for patients with symptomatic HRPC.

More recently, studies with newer agents, including docetaxel, have shown encouraging results and a need has arisen to re-explore the value of chemotherapy in this disease setting (7). Docetaxel is the first chemotherapeutic agent to demonstrate a survival benefit in patients with advanced or metastatic HRPC, as shown in two landmark trials—TAX 327 (4) and the Southwest Oncology Group (SWOG) Intergroup protocol 99–16 (8). In the multinational, TAX 327 Phase III randomized trial, 1006 men with HRPC received either docetaxel (75 mg/m² every 3 weeks or 30 mg/m² weekly for 5 out of every 6 weeks) or mitoxantrone 12 mg/m² every 3 weeks, each combined with prednisone 5 mg twice daily (4). Median overall survival with 3-weekly docetaxel was statistically superior to that with mitoxantrone (18.9 versus 16.5 months, respectively; \( P = 0.009 \)) and 3-weekly docetaxel was associated with a 24% reduction in the risk of death compared with mitoxantrone (166 versus 201 deaths; hazard ratio 0.76; 95% confidence interval [CI], 0.62–0.94). Results from the TAX 327 study led to the approval of docetaxel 75 mg/m² every 3 weeks in combination with prednisone for front-line therapy of HRPC in the USA, Canada and the European Union.

In the SWOG 99–16 trial, 770 men were randomized to receive either estramustine 280 mg orally three-times daily on Days 1–5 of a 3-week cycle, docetaxel 60 mg/m² on Day 2 or mitoxantrone 12 mg/m² on Day 1 plus prednisone 5 mg daily (8). Median overall survival was significantly longer among patients treated with docetaxel–estramustine compared with those receiving mitoxantrone–prednisone (17.5 versus 15.6 months, respectively; \( P = 0.02 \)), with a corresponding hazard ratio for death of 0.80 (95% CI, 0.67–0.97). The median time to progression was 6.3 months for docetaxel–estramustine and 3.2 months in the mitoxantrone–prednisone group.

As a result of these and other studies, docetaxel-based chemotherapy is now considered the standard of care in the treatment of metastatic HRPC in the USA, Canada, and Europe (9,10). However, until now, there has been no equivalent standard for Japanese patients with HRPC. We therefore conducted this Phase II study to evaluate the efficacy and tolerability of the combination of docetaxel and prednisolone in Japanese patients with metastatic HRPC. The present report focuses on the efficacy of treatment with regards to overall tumor response rate. Survival and time to progression will be reported in a subsequent publication.

**MATERIALS AND METHODS**

**STUDY DESIGN AND PATIENTS**

This was a multicenter, open-label, Phase II study in patients with metastatic HRPC. Eligible patients had histologically or cytologically proven prostate adenocarcinoma and at least one measurable visceral or soft-tissue metastatic lesion ≥10 mm in diameter (≥20 mm in chest X-ray for lung lesions). Patients also must have had documented progression of prostate cancer regardless of all prior hormonal therapy (including corticosteroids) defined by one or more of the following criteria: at least two consecutive increases in PSA from the reference level (≥5 ng/ml) measured prior to study entry; progression of measurable visceral and/or soft-tissue lesions; or appearance of new lesions. Patients were required to have undergone prior castration by orchidectomy and/or luteinizing hormone-releasing hormone agonist; to have testosterone levels <50 ng/dl; and to have received no prior cytotoxic therapy and/or molecularly targeted therapy, with the exception of estramustine monotherapy. Chlormadinone acetate or flutamide must have been stopped at least 4 weeks before the last PSA evaluation while bicalutamide had to have been stopped at least 6 weeks beforehand. Adequate hepatic, renal and hematological function, a life expectancy of ≥2 months and Eastern Cooperative Oncology Group performance status of 0–2 were also required.

Patients were ineligible if they had received prior radiotherapy to ≥25% of the bone marrow (including whole pelvis irradiation); had a second active malignancy, including prior malignancies from which they had been free for ≤5 years (but excluding adequately treated basal cell skin cancer); or had brain or leptomeningeal involvement. Other ineligibility criteria included peripheral sensory neuropathy assessed to be National Cancer Institute Common Toxicity Criteria (NCI-CTC) grade ≥2; edema NCI-CTC grade ≥2; hypersensitivity to the study drugs or their formulation components; interstitial pneumonitis (including previous history) or pulmonary fibrosis; or other serious medical conditions.

The study protocol was approved by the institutional review board at each participating center, and all patients provided written informed consent.

**TREATMENT**

Patients received docetaxel 70 mg/m² administered as ≥1-h intravenous infusion on Day 1, every 3 weeks plus oral prednisolone 5 mg twice daily starting on Day 1 and continuing throughout treatment. The docetaxel dose was selected on the basis of experience in other cancer indications in which doses of up to 70 mg/m² are approved in Japan and have been in clinical use since 1997. Treatment was planned for
10 cycles; for those patients who had a continued clinical benefit beyond 10 cycles, entry into a separate clinical study of extended therapy was permitted. Patients continued to receive prednisolone in the event of withdrawal from the study and after completion. In the event of prednisolone discontinuation, the dose was tapered to avoid withdrawal syndrome. Premedication with corticosteroids for the prevention of fluid retention was not allowed; however, once sign(s) were observed, premedication by corticosteroids was allowed beginning at the first cycle.

Patients were required to meet the following criteria prior to commencement of each treatment cycle: neutrophil count \( \geq 2000 \times 10^6/l \); platelet count \( \geq 100 \times 10^6/l \); total bilirubin \( \leq \) upper limit of normal (ULN); aspartate and alanine aminotransferase levels \( \leq 1.5 \times \) ULN; creatinine levels \( \leq 1.5 \times \) ULN; non-hematological toxicity possibly related to docetaxel (excluding hyperglycemia and hypertension) of grade \( \leq 2 \).

The dose of docetaxel was reduced by 10 mg/m\(^2\) in subsequent treatment cycles if any of the following criteria were met: hematological toxicity, defined as hemorrhage with grade 3/4 thrombocytopenia; grade 3/4 non-hematological toxicity (excluding hyperglycemia, hypertension, vomiting, nausea, anorexia, fatigue or allergic reaction); or any other toxicities that required dose reduction according to the investigator’s judgment. There was no dose adjustment for neutropenia or anemia. Patients were withdrawn from the study if toxicities persisted after two dose reductions; doses could not be increased after initial reduction. The dose of prednisolone could be adjusted upwards or downwards at the discretion of the investigator. Dose reduction or cessation of prednisolone administration was considered in cases of peptic ulcer, posterior subcapsular cataract, glaucoma, infection, or for any other toxicities judged by the investigator to mitigate treatment.

Prophylactic administration of granulocyte colony-stimulating factor (G-CSF) was prohibited during the first treatment cycle. However, G-CSF could be administered during any cycle in which the neutrophil count was \(<1000 \times 10^6\) cells/l in the presence of fever (\(\geq 38^\circ\)C) or \(<500 \times 10^6\) cells/l in the absence of fever; in such cases, prophylactic administration of G-CSF was allowed in subsequent cycles. G-CSF was suspended when the neutrophil count rose to \(\geq 5000 \times 10^6\) cells/l after reaching the nadir. Prophylactic anti-emetics, antihistamines and corticosteroids were prohibited during the first treatment cycle, but could be administered in subsequent cycles if required.

**ASSESSMENTS**

The primary endpoint was the overall tumor response rate, assessed using the Response Evaluation Criteria in Solid Tumors (RECIST), in the full analysis population. Secondary endpoints were overall tumor response rate assessed using RECIST in the per-protocol population; overall tumor response rate assessed by the Japanese Urological Association (JUA) response criteria, which is a modification of World Health Organization (WHO) criteria (11,12); PSA response rates; and toxicity. For the purposes of the current study, patients were followed for a maximum of 10 treatment cycles. The extended protocol beyond 10 cycles was designed as a secondary study including the endpoints of time to progression and overall survival; mature results from this study will be presented in a subsequent report.

Patient baseline assessment (including demographics, physical assessment and laboratory tests) took place \(\leq30\) days before study entry for tumor assessment and \(\leq14\) days before study entry for laboratory assessments. Overall tumor response (measured by visceral and/or soft-tissue assessment, primary prostate lesion assessment, and bone scan) was assessed at Cycles 3, 6 and 10, and to confirm response. Primary measurement of tumor lesions and evaluation of best overall tumor response were conducted by the investigator or sub-investigator and were confirmed by an extramural evaluation review committee. RECIST responses were independently measured by the central reviewer. PSA response (defined as a PSA decline of \(\geq 50\%\), confirmed at least 3 weeks later) was assessed once per treatment cycle from Cycle 2 onward.

The patient population was analysed in two groups. The full analysis population (the primary population used for efficacy analysis) consisted of all subjects who received study medication at least once, while the per-protocol population consisted of all patients in the full analysis population other than those with major protocol deviations. PSA response was calculated only for patients with baseline PSA \(\geq 20\) ng/ml; therefore, the full analysis population for PSA response excluded those patients with baseline PSA \(<20\) ng/ml.

Treatment-emergent adverse-event (TEAE) data were collected from the first administration of docetaxel through to either 6 weeks from the last administration of docetaxel, the start of other anti-cancer therapy for HRPC (except corticosteroids), the first dose of docetaxel as part of an extension study, or the documented date of loss to follow-up. The observation period for TEAEs started with first cycle of docetaxel and continued until the earliest of the following: 6 weeks (Day 43) from the last administration of docetaxel; the start of another anti-cancer therapy for HRPC (other than corticosteroid therapy); the start of the Cycle 11 if patients were treated for more than 10 cycles for ethical reasons; or the documented date when patients were lost to follow-up.

**STATISTICAL ANALYSIS**

For an expected tumor response rate of 15% and assuming a threshold response rate of 5% according to clinical evaluation guidelines for anti-tumor agents, a total of 40 patients were required for the study to have 70% power with a one-sided alpha error of 5%. Assuming 5% of enrolled patients would be excluded from the full analysis population, a sample size of 42 patients was required.
For the primary efficacy analysis, summary statistics were calculated for the overall tumor response rate by RECIST, as assessed by an independent evaluation committee, and the response rate with 90% exact binominal CIs provided the full analysis set. For secondary efficacy variables, response rates and corresponding 95% CIs were calculated for the full analysis population using the exact method.

RESULTS

PATIENTS

A total of 44 patients were enrolled between August 26, 2004 and January 27, 2006, in 24 centers in Japan. One patient developed pyelonephritis after registration and was not treated; thus, 43 patients comprised the full analysis set and were evaluable for efficacy and toxicity. Two patients had major protocol violations (1 had less than the protocol-specified 4-week washout period after radiotherapy, while the other had his PSA assessment 6 weeks after bicalutamide discontinuation) and were therefore not included in the per-protocol population, which comprised 41 patients. The full analysis population for PSA evaluation included 36 patients. Patient baseline characteristics are summarized in Table 1. All patients had at least one measurable lesion in soft-tissues or viscera, with lymph nodes (98%) and prostate (86%) being the most commonly involved sites. A total of 24 patients (56%) discontinued the study treatment prior to receiving 10 cycles, 11 (26%) as a result of progressive disease and 13 (30%) because of TEAEs.

TREATMENT

A total of 295 cycles of treatment were administered to 43 patients (median 7 cycles [range 1–10] per patient). The median docetaxel dose was 20.5 mg/m²/week and the median daily dose of prednisolone was 9.9 mg. Median relative dose intensities were 0.88 for docetaxel and 0.99 for prednisolone. Docetaxel dose reduction was required during 28 cycles in 23 of the 41 patients who received at least two cycles of treatment (56.1%), with five patients (12.2%) requiring dose reduction by two levels to 50 mg/m². Non-hematological toxicities, considered treatment-related, led to dose reductions in 17 cycles; hematological toxicities were responsible for dose reductions in seven cycles and the remaining four dose reductions were a result of both hematological and non-hematological toxicities.

EFFICACY

Response to the treatment is shown in Table 2. In the full analysis population, the overall tumor response rate according to RECIST was 44.2% (19/43 patients, 90% CI: 31.2–57.8%); all responses were partial responses (PR). In these patients, the median number of cycles to PR was two. Stable disease was observed in 14 patients (32.6%). With a median follow-up of 5.8 months, the median duration of response was 19.3 weeks, with a maximum duration of response of 27.7 weeks (censored at the end of Cycle 10).

The docetaxel dose was reduced in 13 of the 19 patients who had a PR, five of whom achieved response after

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Docetaxel + prednisolone (n = 43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>65</td>
</tr>
<tr>
<td>Range</td>
<td>50–74</td>
</tr>
<tr>
<td>ECOG performance status, n (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>32 (74.4)</td>
</tr>
<tr>
<td>1</td>
<td>8 (18.6)</td>
</tr>
<tr>
<td>2</td>
<td>3 (7.0)</td>
</tr>
<tr>
<td>Prostate-specific antigen, ng/ml</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>61</td>
</tr>
<tr>
<td>Range</td>
<td>1–2,800</td>
</tr>
<tr>
<td>Gleason score at initial diagnosis, n (%)</td>
<td></td>
</tr>
<tr>
<td>2–4</td>
<td>0 (0)</td>
</tr>
<tr>
<td>5–7</td>
<td>6 (14.0)</td>
</tr>
<tr>
<td>8–10</td>
<td>23 (53.5)</td>
</tr>
<tr>
<td>Unknown</td>
<td>14 (32.6)</td>
</tr>
<tr>
<td>Time since diagnosis, n (%)</td>
<td></td>
</tr>
<tr>
<td>&lt;1 year</td>
<td>4 (9.3)</td>
</tr>
<tr>
<td>1–5 years</td>
<td>28 (65.1)</td>
</tr>
<tr>
<td>&gt;5 years</td>
<td>10 (23.2)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (2.3)</td>
</tr>
<tr>
<td>Prior treatment, n (%)</td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>13 (30.2)</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>22 (51.2)</td>
</tr>
<tr>
<td>Estramustine</td>
<td>27 (62.8)</td>
</tr>
<tr>
<td>None excluding hormonal therapy</td>
<td>9 (20.9)</td>
</tr>
<tr>
<td>Number of metastatic sites involved, n (%)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2 (4.7)</td>
</tr>
<tr>
<td>2</td>
<td>10 (23.3)</td>
</tr>
<tr>
<td>3</td>
<td>23 (53.5)</td>
</tr>
<tr>
<td>4</td>
<td>6 (14.0)</td>
</tr>
<tr>
<td>≥ 5</td>
<td>2 (4.7)</td>
</tr>
<tr>
<td>Metastatic site involved, n (%)</td>
<td></td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>42 (97.7)</td>
</tr>
<tr>
<td>Prostate</td>
<td>37 (86.0)</td>
</tr>
<tr>
<td>Bone</td>
<td>31 (72.1)</td>
</tr>
<tr>
<td>Lung</td>
<td>8 (18.6)</td>
</tr>
<tr>
<td>Liver</td>
<td>3 (7.0)</td>
</tr>
<tr>
<td>Other</td>
<td>4 (9.3)</td>
</tr>
</tbody>
</table>

ECOG, Eastern Cooperative Oncology Group.
The reduction of the docetaxel dose to 60 mg/m², and two after dose reduction to 50 mg/m². Both older and younger patients benefited from treatment with docetaxel and prednisolone, with a response rate of 50.0% (10/20 patients) in those aged <65 years and a response rate of 39.1% (9/23 patients) in patients aged ≥65 years. A higher response rate was seen in patients who had only received prior hormone therapy compared with those who had received prior chemotherapy in addition to hormone therapy (66.7 versus 38.2%, respectively). Responses were seen in patients with good and poor performance status: the response rate was 46.9, 37.5 and 33.3% in patients with a performance status of 0, 1 or 2, respectively. Similar results were seen when patients were stratified according to tumor Gleason score: those with Gleason scores of 5–7 had a response rate of 50.0% and those with Gleason scores of 8–10 had a response rate of 43.5%. The response rate was 62.5% (5/8 patients) in lung lesions, 50.0% (21/42 patients) in lymph nodes, 25.0% (8/32 patients) in bone lesions, and 13.5% (5/37) in the prostate bed.

According to JUA response criteria, the overall tumor response rate was 39.5% (95% CI, 25.0–55.6%), consisting of 17 patients with a PR. Eleven patients (25.6%) had stable disease.

A PSA response was seen in 16 of 36 evaluable patients, for a PSA response rate of 44.4% (95% CI, 27.9–61.9%). The median duration of PSA response was 19.8 weeks and the median time to PSA progression was 24 weeks.

**TOXICITY**

Both non-hematological and hematological TEAEs were reported for all 43 patients (100%), regardless of relationship to study drug. Grade 3/4 events that may have been related to treatment with docetaxel or prednisolone are summarized in Table 3. Among TEAEs possibly related to study drug, the most common grade 3/4 non-hematological event was infection without neutropenia (14.0%), and the most common grade 3/4 hematological event was neutropenia (93.0%); seven patients (16.3%) developed febrile neutropenia. Only one patient (2.3%) developed grade 3/4 anemia; grade 3/4 thrombocytopenia was not observed. Edema occurred in 9/43 (20.9%) patients.

A total of 22 serious adverse events were reported in 14 patients; 10 patients had a total of 12 serious adverse events that were assessed by the investigator to be related to study treatment, including infection with grade 3/4 neutropenia (three events), febrile neutropenia (three events), pneumonitis/pulmonary infiltrates (two events), influenza (one event), infection without neutropenia (one event), neutrophil/granulocyte abnormality (one event) and hypotension (one event).

No treatment-related deaths were observed during the observation period.
DISCUSSION

To our knowledge, this study is the largest prospective interventional investigation conducted in Japanese men with HRPC. We have shown that combination docetaxel and prednisolone is highly effective treatment for this patient population, with an overall objective response rate of 44.2% (90% CI, 31.2–57.8), which exceeds the pre-study hypothesis. Response to treatment was independent of performance status or Gleason score at initial diagnosis. Furthermore, the response to treatment with docetaxel–prednisolone was durable, with a median response duration of 19.3 weeks. No patients died during the 10-cycle observation period. Reported side effects were acceptable and were as previously described with docetaxel-based therapy. An extended protocol is currently underway to confirm time to progression and assess overall survival.

It is noteworthy that in our study all patients were required to have measurable disease. Among 31 patients with bone metastases, all had lymph-node involvement, 28 (90.3%) had additional prostate lesions, and eight (25.8%) had metastases to other soft-tissues. These patients represent those least likely to respond to treatment in the metastatic HRPC setting. The primary endpoint in this Phase II feasibility study was overall tumor response rate assessed by RECIST, with PSA response as the secondary endpoint. The objective tumor response rate of 44.2% and PSA response rate of 44.4% in the present study compares favorably with previous Phase II and III studies of docetaxel in HRPC. Single-agent treatment with docetaxel 75 mg/m² for every 3 weeks was associated with tumor response rates of 38 and 28% in two Phase II studies, with 38 and 46% of a patients in each study, respectively, achieving a PSA response of ≥50% (13,14). Similar PSA response rates were seen with weekly docetaxel, typically administered at doses of 35–36 mg/m², in a series of Phase II trials (15–17). In the randomized Phase III TAX 327 study, the PSA response rate was 45% in patients receiving 3-weekly docetaxel 75 mg/m² plus prednisone 5 mg twice daily, and 48% in patients receiving weekly docetaxel plus prednisone, compared with 32% for patients receiving mitoxantrone 12 mg/m² every 3 weeks plus prednisone (P < 0.001 for both docetaxel groups versus mitoxantrone) (4). The respective tumor response rates in the three treatment groups were 12, 8 and 7%; however, the number of patients with measurable soft-tissue lesions was relatively low. Therefore, the results of our study in Japanese patients were comparable with results from studies conducted in Western patients with HRPC.

Most of the adverse events observed in our study were predictable and manageable. For example, asymptomatic neutropenia is a common side effect of chemotherapy. Although the incidences of grade 3/4 neutropenia and leukopenia were 93.0 and 81.4%, respectively, only 7 of 43 patients (16.3%) had febrile neutropenia. Adverse events required dose reduction in only 11 of 295 cycles (3.7%). The usage of G-CSF occurred in 145 of 295 cycles (49.2%). There were no deaths during the study or within 30 days of the last dose of study medication. Weekly administration of docetaxel has been reported to result in lower rates of myelosuppression than the 3-weekly schedule; however, weekly dosing may also compromise treatment efficacy. Kojima et al. enrolled nine patients in a pilot phase II study (18), in which only one patient had reported grade 3 neutropenia. A PSA response of ≥50% was observed in five patients, for a response rate of 56%, and the estimated median survival time was 6 months.

In the TAX 327 study, the weekly docetaxel regimen was associated with grade 3/4 neutropenia in 2% of patients, compared with 32% of patients for the 3-weekly regimen (4). However, the 3-weekly regimen demonstrated a survival advantage and improved rates of response in terms of pain, serum PSA level and quality of life which led to the approval by the USA FDA in 2004 and by the European EMEA in 2005. The 3-weekly docetaxel regimen is preferred by most clinicians outside Japan.

As interstitial pneumonia has been reported in patients treated with docetaxel in Japan, baseline patient assessment in this study included a diffusing capacity of lung for carbon monoxide (DLCO) test to eliminate those at high risk of this complication. Nonetheless, interstitial pneumonia occurred in two patients, one of whom had fibrous lesions noted in both lungs at baseline but a normal DLCO test. In both, patients’ recovery or alleviation of symptoms was confirmed after discontinuation of treatment. Care must therefore be taken to ensure that Japanese patients treated with docetaxel are not at risk of developing pneumonia.

Higher PSA response rates have been observed for docetaxel-based combination chemotherapy compared with monotherapy, with PSA response rates of 75% in patients treated with docetaxel plus estramustine every 3 weeks (19,20). The randomized Phase III SWOG 99-16 trial showed a significantly higher PSA response rate after treatment with docetaxel plus estramustine than with mitoxantrone plus prednisone (50 versus 27%, respectively; P < 0.001) (8). In contrast, the combination of docetaxel 60 mg/m² plus mitoxantrone 8 mg/m² every 3 weeks produced PSA responses in only 26% of patients (21). A lower response rate of 45% was seen in patients treated with docetaxel plus estramustine every 3 weeks plus dexamethasone (22). The addition of estramustine to docetaxel therapy was associated with additional toxicities, including vascular events (such as deep vein thrombosis) and gastrointestinal toxicity (8). The incidence of these additional toxicities was reduced in a study by Eymard et al. (23), in which a lower estramustine dose was used and anticoagulant prophylaxis was provided.

The demographics of the Japanese patients enrolled in this study are typical of those seen for patients with prostate cancer, with a median age of 65 years (range 50–74). Most patients had bone and lymph node involvement. Notably, however, 53.5% of patients in this study had tumors with a Gleason score at baseline of eight or more. This is slightly
higher than the Gleason scores observed in patients in the TAX 327 study (4), which may be due to the fact that our study required all patients to have measurable lesions, and HRPC that has metastasized to sites other than the bone tends to be a more aggressive disease.

Several studies have investigated the treatment of HRPC in Japanese populations with docetaxel. Single-agent docetaxel has been investigated in Japan in a number of small studies. A study performed in nine patients demonstrated a PSA decline >50% in six patients and >75% in four patients after treatment with docetaxel 55 mg/m² every 3 weeks (24). In a second study, 14 Japanese patients with HRPC received docetaxel 70 mg/m² on Day 1 of a 3-week cycle plus prednisone 5 mg twice daily on Days 1–21 (25). A total of eight patients (57%) achieved a PSA reduction ≥50% from baseline. The median time to PSA progression ranged from 4.5 to 7.9 months in these studies, comparable with the median TTP of 24.7 weeks (5.7 months) shown in our exploratory analysis of the present study, which only enrolled patients with measurable disease.

The effect of adding 5-fluoro-5'-deoxyuridine (5'-dFUrd; 200 mg on Days 1–21) to the combination of docetaxel (60 mg/m² on Day 1) and estramustine (140 mg four-times daily on Days 1–21) in HRPC patients was evaluated in 34 Japanese patients with a median age of 72.3 years (26). PSA response was observed in 73%, and 70% showed measurable responses. The median progression-free survival was 18.0 and 5.8 months for PSA responders and non-responders, respectively, and the overall survival was 19.4 months. Grade 3/4 neutropenia occurred in 32.4% of the patients and was managed effectively with G-CSF prophylaxis.

In a second study, estramustine was administered twice daily (total daily dose 560 mg) with etoposide 50 mg/kg/day on Days 1–21 in 42 patients with HRPC (27). Treatment was continued until confirmed disease progression or a ≥25% increase in PSA level from baseline. After a median follow-up period of 77.4 months, 19 patients (43%) achieved a PSA decrease ≥50%. The median survival time of PSA responders and non-responders was 29.3 and 14.1 months, respectively (P = 0.01). However, excluding patients with only PSA elevation, the survival time was 14.9 months with no significant difference between PSA responders and non-responders. Grade 3/4 adverse events included leukocytopenia (5%), thrombocytopenia (2%), cardiovascular events (2%) and gastrointestinal (14%) and hepatic disorders (2%).

A preliminary study evaluated the use of docetaxel (70 mg/m² every 21 days) in combination with prednisolone (5 mg twice daily on Days 1–21) to treat 14 Japanese patients with HRPC (28). Only five patients in this study had measurable soft-tissue lesions. The median follow-up was 8.4 months, during which five patients died. With a median of seven treatment cycles delivered, eight patients (57%) achieved a ≥50% reduction in PSA level from baseline. Among the patients with measurable lesions, three with nodal metastases and one with liver metastasis achieved a partial response. Grade 3/4 neutropenia occurred in 11 patients (78%) and there was one case of febrile neutropenia.

Patient ethnicity may have an impact on both appropriate treatment dosage and response. In the present study, the treatment schedule was based on that used in the TAX 327 study, but with a reduced docetaxel dose of 70 mg/m². The reduced dose was considered appropriate in Japanese patients based on previous studies of maximum tolerated dose of docetaxel in Japanese patients (29,30). Among Japanese patients with ovarian cancer, an initial dose of 70 mg/m² showed greater efficacy than 60 mg/m² (30). Compared with the 60 mg/m² dose, the incidences of some TEAEs (including allergic reaction, leukopenia, neutropenia and anemia) are slightly higher with docetaxel 70 mg/m² but are still tolerable. Further studies to determine the most appropriate dose of docetaxel in different subgroups of patients with HRPC may be needed.

In conclusion, the combination of docetaxel 70 mg/m² every 3 weeks and daily prednisolone 10 mg is feasible and active in Japanese patients with metastatic HRPC. On the basis of the promising efficacy results and relatively low toxicity profile, and in consideration of global evidence for improved survival with docetaxel-based regimens, the combination of docetaxel and prednisolone may be considered standard treatment for Japanese patients with HRPC. Further investigation of this chemotherapy combination is warranted.

Acknowledgments

We thank the investigators at the following participating institutions. Participating Institutions (Japan): Hokkaido University Hospital, Sapporo Medical University Hospital, Tohoku University Hospital, Yamagata Prefectural Central Hospital, Tsukuba University Hospital, University of Tokyo Hospital, National Cancer Center, Keio University Hospital, Yokohama City University Hospital, Kanagawa Cancer Center, Hamamatsu University School of Medicine University Hospital, Kanazawa University Hospital, Nagoya University Hospital, Kyoto University Hospital, University Hospital Kyoto Prefectural University of Medicine, Osaka University Hospital, Osaka Medical Center for Cancer and Cardiovascular Diseases, Nara Medical University Hospital, Okayama University Hospital, Yamaguchi University Hospital, National Hospital Organization Iwakuni Clinical Center, Kagawa University Hospital, Tokushima University Hospital, Shikoku Cancer Center, Kyusyu University Hospital, Harasanshin Hospital, Nagasaki University Hospital of Medicine and Dentistry, Kagoshima University Faculty of Medicine.

Funding

This study was sponsored by sanofi-aventis KK.
Conflict of interest statement
None declared.

References