Biweekly Docetaxel Is Better Tolerated than Conventional Three-weekly Dosing for Advanced Hormone-refractory Prostate Cancer

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Abstract. *Background: Docetaxel administered every three weeks is the standard treatment for advanced hormone-refractory prostate cancer (HRPC). However, biweekly administration might be better tolerated due to the reduced peak drug concentrations. Therefore, we compared biweekly to triweekly docetaxel as first- or second-line chemotherapy for advanced HRPC in this prospective randomized multicenter trial. Patients and Methods: In this study, 360 patients were randomly allocated to receive docetaxel 75 mg/m^2 i.v. d1 q3 weeks (tT) or 50 mg/m^2 i.v. d1 and d 14, q4 weeks (bT) from March 2004 to May 2009. Oral prednisolone (10 mg/day) was administered in both groups. The groups were well balanced according to the WHO performance status in terms of mean age (70 vs. 68, range 45-87 years) and median serum PSA level at the time of study entry (109 vs. 98 μg/l, range 11-1490 μg/l). The primary endpoint was time to treatment failure (TTF). Clinical Trials.gov study identifier: NCT00255606. Results: Ultimately, 158 patients (tT=79; bT=79) were included in this preplanned interim safety analysis; 567 and 487 cycles (equivalent to 1701 and 1948 weeks of treatment) were administered in the tT and bT groups, respectively. The most common grade 3-4 adverse events (expressed as %/cycles) in tT /bT were neutropenia 20%/14%; infection with/without neutropenia 8%/3%; fatigue 3%/3%; febrile neutropenia 2%/1%; and bone pain 2%/1%. Serious adverse events occurred more frequently in the group tT (n=60, 10.6% of cycles) than in the group bT (n=29, 6.0%, p=0.012). One patient died due to coronary infarction, and another was diagnosed with acute lymphocytic leukemia (both in the bT group). Thirty patients (38%) in the bT group and 22 patients (28%) in the tT group were still receiving treatment at 6 months (p=0.176). Conclusion: Biweekly docetaxel was tolerated better than conventional triweekly with fewer serious adverse events and more patients were still on the therapy at 6 months. Biweekly docetaxel therapy might be considered as an option for elderly patients exhibiting a compromised general condition.*

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Prostate cancer is the most common type of cancer among men in Western countries. While there are many options for the treatment of localized prostate cancer, the optimal treatment of hormone-refractory prostate cancer (HRPC) warrants further investigation (1).

Docetaxel-based chemotherapy is considered the standard treatment for HRPC due to its ability to achieve progression-free survival and provide an overall survival benefit as well as a significant improvement in bone pain palliation and quality of life as compared to mitoxantrone plus prednisone in two randomized phase III studies (2, 3). Docetaxel-based

Table I. *Patient characteristics*.

Baseline characteristics	Group bT: docetaxel 50 mg/m^2	Group tT: docetaxel 75 mg/m^2
Mean Age (years)	68 (46-84)	70 (44-86)
Mean PSA (ng/ml)	98 (11-1490)	109 (10-964)
WHO performance status		
0	25%	25%
1	65%	65%
Site of metastasis: Bone (n)	72	73
Liver metastasis (n)	6	6
Lung metastasis (n)	3	6
Lymph node metastasis (n)	26	26
Other metastasis (n)	6	4
Mean Alkaline phosphatase AFOS (range)	251 (42-1489)	263 (33-1487)

chemotherapy has been investigated in combination with estramustine phosphate, which resulted in only modest efficacy at the expense of increased gastrointestinal and thromboembolic complications (4). However, with this therapy, the median survival does not exceed 20 months, and treatment with docetaxel is associated with many toxicities, which should be taken into account when treating an elderly patient population. Patients with lower performance status and pain have been shown to have shorter survival when treated with docetaxel.

Docetaxel administration with a standard three-weekly schedule and dosing of 75 mg/m^2 is associated with grade 3 or 4 neutropenia in up to one third of patients. Other common adverse events include fatigue (53%), nausea and vomiting (42%) and diarrhea (32%)(5). The majority of patients with advanced prostate cancer are treated with long-term anti-androgen therapy and, typically, with maximal androgen blockade prior to chemotherapy, which often results in osteopenia, anemia, lowered performance status and fatigue at baseline. Treatment-related side-effects, co-morbidities common in elderly patients and disease-related symptoms such as pain and fatigue play major roles in determining the optimal approach to palliative chemotherapy for HRPC for a given individual (6, 7).

The addition of antiangiogenic treatments such as bevacizumab or sunitinib to docetaxel chemotherapy has not proven beneficial (8-10). Recently, abiraterone and cabazitaxel were approved for the second-line treatment of docetaxel-resistant HRPC. Cabazitaxel seems to be beneficial and well-tolerated even after docetaxel treatment in a carefully selected study patient population. However, while grade >3 neutropenia occurred in 82% of patients, only 8% of patients exhibited febrile neutropenia. However, cabazitaxel-treated patients had a higher risk of death within 30 days of the last dose than those treated with mitoxantrone (11). Dose reduction was three times more common in cabazitaxel-treated patients.

Even today the optimal scheduling of an efficacious and safe first-line docetaxel-based chemotherapy regimen remains investigational. Better-tolerated treatments should be evaluated for the treatment of patients with advanced HRPC in common clinical practice (11, 12).

The purpose of the study was to develop an effective and well-tolerated treatment for this elderly patient population. We compared the safety and efficacy of a standard three-weekly schedule of docetaxel plus prednisone to an investigational arm of biweekly docetaxel plus prednisone as first-line chemotherapy of advanced HRPC. The preplanned interim safety results are reported here.

Materials and Methods

Patient selection. From March 2004 to May 2009, 360 patients with advanced HRPC were randomized to receive docetaxel-based chemotherapy in nine collaborating study centers in Finland, Sweden and Ireland; 158 patients were included in this preplanned interim safety analysis.

Eligible patients had confirmed adenocarcinoma of the prostate with metastasis and exhibited elevated serum PSA >10 μg/l during treatment with hormonal therapy, good performance status (<2 WHO), adequate renal and hepatic function and laboratory values including hemoglobin >11.0 g/dl, creatinine <1.5 times the upper limit and aminotransferase <2.5 times the upper limit. All patients had castrate levels of testosterone prior to treatment. The patient characteristics at baseline are presented in Table I.

All patients provided their written informed consent, and the study was approved by the Ethics Committee. The primary endpoint was the time to treatment failure (TTF), which was defined as the time interval from the date of randomization to the date of progression of the disease, unacceptable toxicity, the patient´s refusal to continue treatment, or death.

The secondary endpoints were quality of life, response rates, safety and overall survival. Overall survival was calculated from the date of randomization to the date of death.

Patients were centrally randomly assigned to receive docetaxel at 75 mg/m^2 intravenously on day 1 every 3 weeks group or docetaxel 50 mg/m^2 intravenously on days 1 and 14 every 4 weeks group;

therefore, the cumulative dose (*i.e.*, 12 weeks) was identical. Continuous oral prednisolone (10 mg) daily and premedication with oral dexamethasone (7.5) mg twice daily for 3 days, starting 12 h before docetaxel, was also administered in both treatment groups. The prophylactic administration of G-CSF was not routinely performed.

All patients were evaluated for myelosuppression, renal and hepatic dysfunction and adverse events before the start of each treatment cycle and when clinically indicated. There was no predetermined maximal number of chemotherapy cycles. Each patient's medical history was recorded at baseline, and physical examinations and laboratory measurements were performed. Pretreatment evaluation of disease staging was performed using computed tomography and bone scanning.

Tumor response was assessed according to Response Evaluation Criteria In Solid Tumors (RECIST) every 12 weeks using computed tomography for lesions determined to be measurable at baseline, and the responses were confirmed within 4 weeks. Toxicities for every treatment cycle in both arms were evaluated according to the National Cancer Institute- Common Terminology Criteria of Adverse Events (NCI-CTCAE) statistical analysis software, version 3.0.

Interim hematological toxicity analysis was performed when 50 patients had participated in the trial for at least 3 months. The toxicity and tolerability of the two treatment arms were analyzed based on a reduction in the frequency of grade 3-4 side-effects from 40% to 20% using α=0.05 and β=0.20. Seventy-nine patients were required in each arm for a total of 158 patients. The results of this pre-planned interim analysis are published separately from the final efficacy analysis.

Results

One hundred and fifty-eight patients were included in this preplanned safety analysis. The patient characteristics were well balanced between the treatment groups at baseline. The baseline PSA, age and type of metastasis are presented in Table I. The duration of the treatment is often associated with cumulative side effects. Seventy-nine patients in the tT group received a total of 567 cycles every three weeks, and 79 patients in the bT group received a total of 487 cycles every four weeks. Therefore, the overall length of treatment was 1701 and 1948 weeks, respectively, suggesting that therapy in the pT group was tolerated as least as well as in the tT group.

The most common (≥10% of cycles) grade 1-2 non-hematological adverse events were quite evenly distributed (biweekly *vs*. triweekly, expressed as % of the cycles): fatigue, 62/49; alopecia, 75/81; nail changes, 12/10; anorexia, 10/10; diarrhea, 13/12; stomatitis, 15/16; neuromotor, 29/19; tearing, 42/41; arthralgia, 14/14; bone pain, 33/31; myalgia, 13/15; and pain, 32/33.

There were significantly more patients receiving the study treatment for at least 6 months in the bT group (38%) than in the tT group (28). The most common grade 3-4 adverse events are presented in Table II. Serious adverse events were reported more frequently in the tT group (60 reports, 10.6 % of cycles) than in the bT group (29 reports, 6.0% cycles).

Table II. *Grade 3-4 adverse events.*

Grade 3-4 adverse events	bT Group % of cycle given	tT Group % of cycles given
Neutropenia	14	20
Infection with/without neutropenia	3	8
Leukopenia	3	8
Febrile neutropenia	1	2
Fatigue	3	3
Bone pain	1	2
Pain	2	1

One patient died of coronary infarction, and another patient was diagnosed with acute myelocytic leukemia after two cycles of treatment. Both patients were in the bT group.

Discussion

Docetaxel chemotherapy remains the standard treatment option for metastatic HRPC, although several new treatment options are currently being approved for the second-line treatment of docetaxel-resistant prostate cancer (13). Docetaxel chemotherapy is often associated with dose-limiting toxicity, mainly neutropenia, neuropathy and treatment-related fatigue, especially in elderly patients.

Biweekly docetaxel chemotherapy seems to be a well-tolerated and safe chemotherapy regimen for the treatment of HRPC. Grade 3-4 neutropenia occurred in only 14% of patients and was very rarely associated with an infection that required hospitalization. In the TAX 327 study (5), there was less febrile neutropenia than was observed in our tT group, which could be explained by the presence of more advanced disease in our study population, or by factors related to genetic variants in different populations.

In addition to the number of hospitalizations due to febrile neutropenia or infection, the patients in the biweekly arm reported fewer serious adverse events that extended the duration of treatment. The bT regimen could represent an option for the active treatment of elderly patients that present with co-morbidities and compromised performance status.

Historically, the combination of other agents with docetaxel has yielded disappointment, even in large randomized trials. Therefore, novel approaches to reverse drug resistance in castration-resistant prostate cancer should be explored (14, 15).

Conclusion

As patients present with different characteristics at the time of HRPC diagnosis, the treatment options and optimal chemotherapy regimen should be versatile and adapted to each

individual patient. The biweekly docetaxel chemotherapy regimen offers a safe and well-tolerated option for the administration of chemotherapy to our prostate-cancer patients. It will be important to study whether efficacy is sustained in the bT arm in comparison to the arm involving treatment with the standard tT regimen.

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