Weekly Docetaxel and Epirubicin in Treatment of Advanced Hormone-Refractory Prostate Cancer

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OBJECTIVES To evaluate the efficacy and safety of a new regimen that combines weekly docetaxel and weekly epirubicin for the treatment of advanced hormone-refractory prostate cancer.

METHODS Docetaxel 30 mg/m^2 and epirubicin 30 mg/m^2 were intravenously administered on a weekly basis, for a maximum of 24 cycles. The therapy was discontinued after the first 12 cycles in the patients who responded or had stable disease and was resumed as soon as any signs of progression were noted.

RESULTS Of the 38 evaluable patients, 26 achieved a confirmed greater than 50% decrease in prostate-specific antigen level (68.4%, 95% confidence interval [CI] 51.2% to 82.0%). The median response duration was 8.8 months (95% CI 6.2 to 11.8), and the median time to progression was 7.4 months (95% CI 5.6 to 9.6). Pain was rapidly reduced in 24 (72.7%, 95% CI 54.2 to 86.7) of the 33 patients who were symptomatic at baseline. Of the 38 patients, 21 resumed therapy after the planned interruption; of these, 3 had a prostate-specific antigen response (14.2%) and 12 had stable disease (57.1%). The regimen was well tolerated. Grade 3 neutropenia occurred in 15.7% of the patients, grade 3 anemia in 13.1%, and grade 3 thrombocytopenia in 7.8%.

CONCLUSIONS The results of this study have suggested the feasibility and tolerability of the combination of weekly docetaxel and weekly epirubicin, which led to a rapid and long-lasting decrease in prostate-specific antigen levels and a palliative response in patients with advanced hormone-refractory prostate cancer. UROLOGY 69: 142–146, 2007. © 2007 Elsevier Inc.

The results of two large randomized trials have recently provided substantial support in favor of the role of chemotherapy in the treatment of hormone-refractory prostate cancer (HRPC) by demonstrating that docetaxel and prednisone improve survival compared with older regimens and significantly improve patients' quality of life.[1,2]

Docetaxel is a semisynthetic taxoid that inhibits microtubule depolymerization and may independently promote apoptosis by inducing bcl-2 phosphorylation.[3] It is usually administered at a dose of 75 mg/m^2 every 3 weeks or on a weekly basis at a dose of 30 to 36 mg/m^2. It has been suggested that the efficacy of the weekly and every 3-week treatment is comparable, but their toxicity profiles are distinctly different.[4] The acute toxicity of weekly docetaxel (particularly myelosuppression) is mild and never dose limiting—the reason this schedule has been proposed for patients with poor performance status, decreased hematologic reserves, or multiple comorbidities and for elderly patients.[5,6] However, although docetaxel chemotherapy has become the first-line standard of care for advanced HRPC, prostate-specific antigen (PSA) responses have rarely exceeded 50% and the median survival has been less than 20 months. Therefore, the use of chemotherapy for HRPC remains the subject of active clinical investigation, and the mild toxicity of docetaxel makes it an attractive treatment option for the development of combination regimens.

Among other chemotherapeutic agents, doxorubicin has shown some activity against HRPC, and we have previously reported the satisfactory effectiveness of the doxorubicin analogue epirubicin, which, at equipotent doses, is associated with quantitatively less severe toxicity than its parent compound.[7,8] Our extended study of weekly epirubicin showed a 56% palliative response and 24% PSA response in 131 patients with HRPC.[9]

Given the specific activity and different toxicity profiles of the two agents, the primary aim of this study was to evaluate the efficacy and safety of a new regimen combining weekly docetaxel and weekly epirubicin in the treatment of advanced HRPC.

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MATERIAL AND METHODS

Eligibility Criteria

The study involved patients with histologically confirmed, measurable, or evaluable advanced HRPC. They were admitted to the chemotherapy protocol provided they had met at least one of the following criteria: a 50% or greater increase in PSA level compared with baseline on two successive occasions separated by at least 2 weeks; new metastatic lesions revealed by bone scan; and/or a 25% increase in a bidimensionally measurable tumor mass. The patients treated with luteinizing hormone-releasing hormone agonists continued their primary androgen ablation therapy and were required to have serum testosterone levels of less than 50 ng/mL before study entry. Antiandrogen agents had to be discontinued 4 to 6 weeks before the use of chemotherapy to allow the withdrawal to become effective. All the patients had to have an Eastern Cooperative Oncology Group performance status of 2 or less, and adequate hematologic (leukocytes 3000/mm^3 or more, hemoglobin 10 g/dL or more, and platelets 100,000/mm^3 or more), renal (serum creatinine 2.0 mg/dL or less), and hepatic (serum bilirubin 2.0 mg/dL or less) function. The exclusion criteria were previous chemotherapy, congestive heart failure, recent myocardial infarction, or any other previous malignant disease, except for basal cell carcinoma of the skin. All the patients provided written informed consent, and the Ethics Review Board of Siena University approved the protocol.

Treatment Plan

The treatment consisted of docetaxel 30 mg/m^2 as a 30-minute intravenous infusion, with a bolus of epirubicin 30 mg/m^2 diluted with 100 mL of saline solution, using a schedule of six consecutive weekly administrations followed by a 2-week rest interval. The cycles were administered if the serum white blood cell levels were greater than 3000/mm^3, granulocytes were greater than 1500/mm^3, and platelets were greater than 100,000/mm^3.

Premedication consisted of dexamethasone 8 mg orally 12 hours before, at the time of, and 12 hours after docetaxel administration. Ondansetron 8 mg was administered at the beginning of each treatment cycle as an antiemetic medication. The patients continued to take analgesic medication at doses adjusted to provide optimal pain control. Bisphosphonates were not used.

Chemotherapy was administered for a maximum of 24 cycles or until disease progression or dose-limiting toxicity. In the case of patients who responded or had stable disease after the first 12 cycles, chemotherapy was discontinued and then resumed as soon as evidence of progression was noted. The maximal planned cumulative dose of epirubicin was 720 mg/m^2.

Response Assessments

The tumor response in patients with measurable lesions was evaluated using the criteria of the World Health Organization.[10]

The serum PSA level was measured every 3 weeks. A PSA response was defined as a reduction from baseline of at least 50% for at least 3 weeks, and PSA progression was defined as an increase from nadir of at least 25% in the men with no PSA response or at least 50% for those with a response. A palliative response was defined as a 2-point reduction in the 6-point present pain intensity scale of the McGill-Melzack Pain Questionnaire (or the complete disappearance of pain if the initial score was 1+).[11] This criterion had to be maintained on two consecutive occasions separated by an interval of at least 3 weeks, without any increase in analgesic consumption. The pain scale uses verbal descriptors (0, no pain; 1, mild pain; 2, discomforting pain; 3, distressing pain; 4, horrible pain; and 5, excruciating pain), and the patients were asked to classify their average pain level during the previous 24 hours.

The time to response, duration of the PSA response, and duration of the palliative response were defined as the interval between starting chemotherapy and the last evaluation at which the response criteria were met. The time to progression (TTP) was defined as the interval from starting chemotherapy to the first occurrence of objective or PSA progression or death from any cause.

The laboratory studies (blood and platelet counts and comprehensive screening profile) were performed at baseline and every 3 weeks, and the patients underwent a weekly complete blood cell count before chemotherapy.

The imaging studies included abdominal and pelvic computed tomography or magnetic resonance imaging, bone scan, and chest radiography. All measurable disease was reevaluated at 8-week intervals. Radionuclide bone scans were repeated as clinically indicated. During the treatment holiday, the serum PSA level was measured every 4 weeks, and measurable disease was monitored by imaging every 8 weeks.

All the patients underwent baseline electrocardiography, and their left ventricular ejection fraction (LVEF) was measured using a multiple gated acquisition scan or echocardiography at baseline and every six treatment cycles. Additional cardiac examinations were performed as indicated. A major decrease in LVEF was defined as an absolute decrease to at least 10% less than the lower normal limit.

Treatment-Related Adverse Events

Toxicity was defined using the National Cancer Institute Common Toxicity Criteria, version 2.0. The treatment was delayed at the first occurrence of grade 2 hematologic toxicity, and administered at the same dose after it returned to grade 1 or better. In the case of grade 3 or 4 toxicity, the treatment was interrupted. A maximum of 3 weeks was allowed for recovery, after which the patients were withdrawn from the study. In the case of a second episode of grade 3 or 4 toxicity in the same patient, treatment was resumed after recovery and the subsequent administrations of each drug was reduced to 20 mg/m^2. Anemia was treated as clinically indicated; nausea and vomiting were treated symptomatically. Hematopoietic growth factors were only given when neutrophil counts decreased to less than 1000/mm^3 and were continued until complete hematologic recovery.

Statistical Analysis

In accordance with Simon's "minimax design," assuming that approximately 50% of the patients would achieve a PSA response with docetaxel alone, a sample size of 37 patients was required for a target level of interest of 70% in PSA response, with an alpha of 0.05 and beta of 0.80.

RESULTS

Patient Characteristics

From June 2003 to September 2005, the study enrolled 39 patients with advanced HRPC (median age 69 years,

Table 1. Main patient characteristics

Enrolled patients	39
Evaluable patients	38
Median age (yr)	69 (54–78)
ECOG performance status	
0	9
1	21
2	9
Sites of metastases	
Bone	31
Bone + prostate cancer	4
Lymph nodes	1
Bone + lymph nodes	2
Lymph nodes + prostate cancer	1
Median PSA (ng/mL)	126 (34–418)
Previous treatment	
Prostatectomy	34
Radiotherapy	5
Estramustine	9
Hormonal therapy	
1	4
2	29
>2	6
Baseline pain intensity	
0	6
1	11
2	16
3	5
4	1
5	0

ECOG = Eastern Cooperative Oncology Group; *PSA* = prostate-specific antigen.
Data in parentheses are ranges.

range 54 to 78). The initial Eastern Cooperative Oncology Group performance status was 0 to 1 in 30 patients and 2 in 9 patients. Of the 38 patients, 37 had bone metastases and 8 had measurable disease. Nine patients had been previously treated with estramustine phosphate (Table 1).

Treatment

A total of 618 weekly cycles (median number per patient 16 cycles, range 1 to 24) of docetaxel/epirubicin was administered. One patient received only one cycle before being lost to follow-up and was considered unevaluable for the response and toxicity analyses. Eleven patients (28.2%) received all 24 planned treatment cycles: two were lost to follow-up after the 10th and 16th cycles without showing any severe toxicity or signs of progressive disease.

Efficacy

Of the 38 evaluable patients, 26 achieved a confirmed greater than 50% decrease in PSA level (68.4%, 95% confidence interval [CI] 51.2% to 82.0%), including 14 whose PSA levels decreased by more than 75%. Of the 26 PSA responses, 22 (84.6%) were observed during the first six treatment cycles, with a 30.7% PSA response after cycle 3 and a 53.8% PSA response after cycle 6. Eleven patients (28.9%) had stable PSA levels for at least 12 cycles. Of the 8 patients with measurable disease, 3 had a partial response and 5 stable disease. The median duration of the PSA response was 8.8 months (95% CI 6.2 to 11.8), and the median TTP was 7.4 months (95% CI 5.6 to 9.6). Pain was reduced in 24 (72.7%, 95% CI 54.2% to 86.7%) of the 33 patients who were symptomatic at baseline. The median duration of the palliative response was 8.2 months (95% CI 5.8 to 10.4; Table 2).

Table 2. Responses to treatment

Evaluable patients (n)	38
PSA response (%)	68.4
Median duration of PSA response (mo)	8.8 (6.2–11.8)
Median TTP (mo)	7.4 (5.6–9.6)
Palliative response (%)	72.7
Median duration of palliative response (mo)	8.2 (5.8–10.4)

PSA = prostate-specific antigen; *TTP* = time to progression.
Data in parentheses are 95% confidence intervals.

Table 3. Number of patients experiencing the most frequent treatment-related adverse events

	Grade 1	Grade 2	Grade 3
Hematologic			
Neutropenia	17 (44.7)	15 (39.4)	6 (15.7)
Anemia	22 (57.8)	11 (28.9)	5 (13.1)
Thrombocytopenia	27 (71.0)	8 (21.0)	3 (7.8)
Nonhematologic			
Nausea/vomiting	30 (78.9)	7 (18.4)	1 (2.6)
Diarrhea	4 (10.5)	2 (5.2)	—
Constipation	5 (13.1)	4 (10.5)	—
Nail changes	14 (36.8)	6 (15.7)	—
Dry eye/tearing	11 (28.9)	3 (7.8)	—
Myalgia/arthralgia	12 (31.5)	5 (13.1)	—
Fatigue	15 (39.4)	18 (47.3)	1 (2.6)
Alopecia	17 (44.7)	18 (47.3)	3 (7.8)
Sensory neuropathy	9 (23.6)	4 (10.5)	—
Peripheral edema	6 (15.7)	3 (7.8)	—
Epistaxis	8 (21.0)	3 (7.8)	—
Dyspnea	11 (28.9)	5 (13.1)	—

Data in parentheses are percentages.

After the planned break following the first 12 cycles, weekly docetaxel/epirubicin was resumed in 21 patients, of whom 3 (14.2%) had a PSA response and 12 (57.1%) stable disease. The median duration of the treatment break was 4.2 months (95% CI 2.2 to 6.4). As of April 1, 2006, after a median follow-up of 16 months, 9 patients had died.

Toxicity

The regimen was generally well tolerated, and no unexpected toxic effects were observed (Table 3). The median cumulative dose received of docetaxel and epirubicin for the 38 evaluable patients was 420 mg/m^2 (range 90 to 720).

No grade 4 toxicity or congestive heart failure was observed, and 98% of the cycles were administered on an outpatient basis. The most frequent side effects were neutropenia, anemia, thrombocytopenia, and fatigue, which were grade 1 or 2 in most cases. Grade 3 neutro-

penia occurred in 15.7% of the patients, grade 3 anemia in 13.1%, and grade 3 thrombocytopenia in 7.8%. Grade 3 fatigue was observed in 1 patient after nine treatment cycles, and the treatment was resumed after a 2-week interval.

The administration of at least one treatment cycle was delayed by 1 week in 27 patients. The reasons for the delays were hematologic in 22 patients (57.8%) and nonhematologic in 5 (13.1%). The dose of docetaxel and epirubicin was reduced in 5 patients. Two patients had a greater than 10% decrease in LVEF after 16 and 21 cycles. Five patients (who received more than 18 treatment cycles) developed atrial fibrillation that was medically controlled without additional cardiac complications.

COMMENT

The results of this study suggest that the combination of weekly docetaxel/epirubicin is efficacious and tolerable in the treatment of advanced HRPC. The 68.4% PSA and 72.7% palliative response rates compare favorably with the results obtained in previous Phase II trials and randomized trials of docetaxel.[1,2,12,13]

Although a selection bias may occur in small Phase II trials, the characteristics of our study population were typical of the patients with HRPC observed in clinical practice. Most were elderly (43.5% older than 70 years) and had symptomatic bone metastases and high PSA levels, and 23.0% had also received estramustine phosphate after hormonal therapy. Better results in terms of PSA decreases (up to 80%) have been described with docetaxel plus high-dose calcitriol. A large randomized trial is currently being performed to verify the possible advantage of this combination.[14] Other promising findings have been recently reported with the addition of thalidomide to weekly docetaxel, with a 53% decrease in PSA level and 68% of the patients surviving at 18 months.[15]

The time to response was short in our population. The PSA level decreased by more than 50% during the first six weekly cycles in 84.6% of the responding patients. Palliative responses were also rapid. This may have resulted from the rapid-onset activity of the docetaxel/epirubicin combination, as has been previously observed in breast cancer, which is known to be sensitive to chemotherapy.[16]

We used a stop-and-go strategy, with a planned break after the first 12 treatment cycles. The median TTP was 7.4 months, and treatment resumption led to a 14.2% PSA response rate and 57.1% stable disease rate. These findings not only suggest that the TTP obtained with intermittent chemotherapy is similar to that observed when chemotherapy is administered until progression, but also that chemosensitivity to docetaxel/epirubicin may be at least partially restored after a treatment break. However, it was not the primary endpoint of our study. Moreover, the lack of randomization prevented us from drawing any definite conclusions concerning the contribution to efficacy of weekly epirubicin added to weekly docetaxel, or the use of intermittent chemotherapy, when treating advanced HRPC.

The weekly epirubicin schedule was chosen because our previous studies have shown that the drug can be administered weekly for long periods without giving rise to more than mild toxic effects.[7,9] The weekly docetaxel schedule was chosen because its efficacy is comparable to that with the standard 3-weekly schedule, and it is considered less toxic and particularly desirable for elderly patients.

As expected, the weekly docetaxel/epirubicin regimen was feasible and well tolerated, with no grade 4 toxic effects. Neutropenia was common (mainly related to the use of epirubicin) but reached grade 3 in only 15.7% of the patients and was only slightly more frequent than the rate observed with epirubicin alone.

The nonhematologic toxicities were also usually grade 1 to 2 (only 1 patient experienced grade 3 nausea), as previously reported for treatment with docetaxel or epirubicin alone.[1,9] The low incidence of acute toxicities was clearly related to the weekly schedule.[4] The use of weekly docetaxel/epirubicin was also associated with a low incidence of cardiotoxicity. The LVEF decreased by more than 10% in only 2 patients, and none experienced congestive heart failure. The median cumulative received dose of epirubicin was only 420 mg/m^2; however, in line with the results of our previous studies, the incidence of cardiotoxicity was also low in the patients who received all the planned cycles for a total cumulative dose of 720 mg/m^2.[7,9] Moreover, a very low incidence of cardiotoxicity has been decribed with the use of weekly or every 3 weeks docetaxel.[1] The characteristic and cumulative docetaxel toxicities of fatigue, excessive tearing, and nail disorders were mild in our population. Fatigue was the most frequent (grade 1 to 2 in 86.8% of patients), but only 1 subject required the transient discontinuation of therapy. Our stop-and-go strategy probably contributed to minimizing the occurrence of adverse events, as has been previously described in the case of other intermittent treatment schedules.[17,18]

CONCLUSIONS

The results of this study have suggested the feasibility and tolerability of the combination of weekly docetaxel and weekly epirubicin, which leads to a rapid and long-lasting decrease in PSA levels and palliative response in patients with advanced HRPC. It would be opportune to obtain the confirmation of these results in a wider case study and/or in a randomized study concerning the single use of weekly docetaxel.

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References

1. Tannock IF, de Wit R, Berry WR, *et al.* Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med **351:** 1502–1512, 2004.

2. Petrylak DP, Tangen CM, Hussain MHA, *et al.* Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. N Engl J Med **351:** 1513–1520, 2004.
3. Khan MA, Carducci MA, and Partin AW. The evolving role of docetaxel in the management of androgen independent prostate cancer. J Urol **170:** 1709–1716, 2003.
4. Engels FK, and Verweij J. Docetaxel administration schedule: from fever to tears? A review of randomised studies. Eur J Cancer **41:** 1117–1126, 2005.
5. Friedland D, Cohen J, Miller R Jr, *et al.* A phase II trial of docetaxel (Taxotere) in hormone-refractory prostate cancer: correlation of antitumor effect to phosphorylation of Bcl-2. Semin Oncol **26(**suppl 17): 19–23, 1999.
6. Petrioli R, Pozzessere D, Messinese S, *et al.* Weekly low-dose docetaxel in hormone-resistant advanced prostate cancer patients previously exposed to chemotherapy. Oncology **64:** 300–305, 2003.
7. Francini G, Petrioli R, Manganelli A, *et al.* Weekly chemotherapy in advanced prostatic cancer. Br J Cancer **67:** 1430–1436, 1993.
8. Brausi M, Jones WG, Fossa SD, *et al.* High-dose epirubicin is effective in measurable metastatic prostate cancer: a phase II study of the EORTC genitourinary group. Eur J Cancer **31A:** 1622–1626, 1995.
9. Petrioli R, Fiaschi AI, Pozzessere D, *et al.* Weekly epirubicin in patients with hormone-resistant prostate cancer. Br J Cancer **87:** 720–725, 2002.
10. World Health Organization: WHO criteria, in *WHO Handbook for Reporting Results of Cancer Treatment.* (Offset publication No. 48.) Geneva, World Health Organization, 1979.
11. Melzack R. The McGill Pain Questionnaire: major properties and scoring methods. Pain **1:** 277–299, 1975.
12. Beer TM, Pierce WC, Lowe BA, *et al.* Phase II study of weekly docetaxel in symptomatic androgen-independent prostate cancer. Ann Oncol **12:** 1273–1279, 2001.
13. Berry W, Dakhil S, Gregurich MA, *et al.* Phase II trial of single-agent weekly docetaxel in hormone-refractory, symptomatic, metastatic carcinoma of the prostate. Semin Oncol **28(**suppl 15): 8–15, 2001.
14. Beer TM, Eilers KM, Garzotto M, *et al.* Weekly high-dose calcitriol and docetaxel in metastatic androgen-independent prostate cancer. J Clin Oncol **21:** 123–128, 2003.
15. Dahut WL, Gulley JL, Arlen PM, *et al.* Randomized phase II trial of docetaxel plus thalidomide in androgen-independent prostate cancer. J Clin Oncol **22:** 2532–2539, 2004.
16. Pagani O, Sessa C, Nole F, *et al.* Epidoxorubicin and docetaxel as first-line chemotherapy in patients with advanced breast cancer: a multicentric phase I-II study. Ann Oncol **11:** 985–991, 2000.
17. Higano CS, Ellis W, Russell K, *et al.* Intermittent androgen suppression with leuprolide and flutamide for prostate cancer: a pilot study. Urology **48:** 800–804, 1996.
18. Beer TM, Garzotto M, Henner WD, *et al.* Intermittent chemotherapy in metastatic androgen-independent prostate cancer. Br J Cancer **89:** 968–970, 2003.