ORIGINAL ARTICLE

Docetaxel plus Prednisone or Mitoxantrone plus Prednisone for Advanced Prostate Cancer

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ABSTRACT

BACKGROUND

Mitoxantrone plus prednisone reduces pain and improves the quality of life in men with advanced, hormone-refractory prostate cancer, but it does not improve survival. We compared such treatment with docetaxel plus prednisone in men with this disease.

METHODS

From March 2000 through June 2002, 1006 men with metastatic hormone-refractory prostate cancer received 5 mg of prednisone twice daily and were randomly assigned to receive 12 mg of mitoxantrone per square meter of body-surface area every three weeks, 75 mg of docetaxel per square meter every three weeks, or 30 mg of docetaxel per square meter weekly for five of every six weeks. The primary end point was overall survival. Secondary end points were pain, prostate-specific antigen (PSA) levels, and the quality of life. All statistical comparisons were against mitoxantrone.

RESULTS

As compared with the men in the mitoxantrone group, men in the group given docetaxel every three weeks had a hazard ratio for death of 0.76 (95 percent confidence interval, 0.62 to 0.94; P=0.009 by the stratified log-rank test) and those given weekly docetaxel had a hazard ratio for death of 0.91 (95 percent confidence interval, 0.75 to 1.11; P=0.36). The median survival was 16.5 months in the mitoxantrone group, 18.9 months in the group given docetaxel every 3 weeks, and 17.4 months in the group given weekly docetaxel. Among these three groups, 32 percent, 45 percent, and 48 percent of men, respectively, had at least a 50 percent decrease in the serum PSA level (P<0.001 for both comparisons with mitoxantrone); 22 percent, 35 percent (P=0.01), and 31 percent (P=0.08) had predefined reductions in pain; and 13 percent, 22 percent (P=0.009), and 23 percent (P=0.005) had improvements in the quality of life. Adverse events were also more common in the groups that received docetaxel.

CONCLUSIONS

When given with prednisone, treatment with docetaxel every three weeks led to superior survival and improved rates of response in terms of pain, serum PSA level, and quality of life, as compared with mitoxantrone plus prednisone.

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Prostate cancer is the most common cancer among men, with approximately 220,000 cases and 29,000 deaths annually in the United States.[1] About 10 to 20 percent of men with prostate cancer present with metastatic disease, and in many others, metastases develop despite treatment with surgery or radiotherapy.

Treatment of metastatic prostate cancer is palliative. In about 80 percent of men, primary androgen ablation leads to symptomatic improvement and a reduction in serum levels of prostate-specific antigen (PSA), but in all patients the disease eventually becomes refractory to hormone treatment. The options then include symptomatic care with narcotic analgesics, radiotherapy to dominant sites of bone pain, treatment with bone-seeking isotopes such as strontium-89, and cytotoxic chemotherapy. Bisphosphonates may reduce skeletal complications,[2-4] and low-dose prednisone or hydrocortisone may be palliative in some patients.[5,6]

Chemotherapy can reduce serum PSA levels in patients with hormone-refractory prostate cancer and relieves pain in some patients, but tolerability is of concern, particularly since most patients are elderly and many have other medical problems.[7] A randomized trial showed that mitoxantrone plus low-dose prednisone relieved pain and improved the quality of life more frequently than did prednisone alone.[8,9] Consistent benefits of mitoxantrone plus a corticosteroid were observed in other randomized trials, but none found that this approach improved survival.[10-12] These trials established mitoxantrone plus a corticosteroid as the treatment of reference for hormone-refractory prostate cancer.

Phase 2 studies of the taxane docetaxel have reported PSA responses (defined as a reduction in serum PSA levels of at least 50 percent) in up to 50 percent of patients.[13-16] Studies of docetaxel plus either estramustine or calcitriol have shown PSA responses in up to 80 percent of patients.[17-19] However, outcomes of single-group studies are subject to bias.[20]

We conducted a phase 3 study, the TAX 327 Study, comparing docetaxel (given either every three weeks or weekly) plus daily prednisone with mitoxantrone plus prednisone. The docetaxel regimens were selected on the basis of their dose equivalence (a dose intensity of 25 mg per square meter of body-surface area per week and a maximal cumulative dose of 750 mg per square meter) and their activity and tolerability in phase 2 studies. The primary hypothesis was that treatment with docetaxel plus prednisone would improve overall survival as compared with mitoxantrone plus prednisone.

METHODS

PATIENTS

This randomized, nonblinded, phase 3 study involved centers in 24 countries. Eligible patients had histologically or cytologically confirmed adenocarcinoma of the prostate with clinical or radiologic evidence of metastatic disease, had had disease progression during hormonal therapy, and were receiving primary androgen-ablation therapy as maintenance therapy. At least four weeks had to have elapsed between the withdrawal of antiandrogens (six weeks in the case of bicalutamide) and enrollment, so as to avoid the possibility of confounding as a result of the response to antiandrogen withdrawal.[21,22] Another requirement was disease progression, as indicated by increasing serum levels of PSA on three consecutive measurements obtained at least one week apart or findings on physical examination or imaging studies.

Eligible patients had a Karnofsky performance-status score of at least 60 percent, no prior treatment with cytotoxic agents (except estramustine) or radioisotopes, no history of another cancer within the preceding five years (except basal or squamous-cell skin cancer), no brain or leptomeningeal metastases, no symptomatic peripheral neuropathy of grade 2 or higher, and no other serious medical condition. At least four weeks had to have elapsed between prior surgery or radiotherapy (limited to no more than 25 percent of the bone marrow) and enrollment. Prior treatment with corticosteroids was allowed. Normal cardiac function was required. Laboratory criteria for eligibility included a neutrophil count of at least 1500 per cubic millimeter, a hemoglobin level of at least 10.0 g per deciliter, a platelet count of at least 100,000 per cubic millimeter, a total bilirubin level below the upper limit of the normal range for each institution, and serum alanine aminotransferase, aspartate aminotransferase, and creatinine levels that were no more than 1.5 times the upper limit of the normal range.

A clinical history was obtained, and a physical examination, with radiographic imaging, computed tomography, and bone scanning, was performed within 14 days before randomization. Blood tests including measurement of serum PSA, electrocardiography, and an evaluation of the left ventricular ejection fraction by means of a multiple gated

acquisition scan or echocardiography were performed. Pain, analgesic intake, and the quality of life were assessed at baseline. Pain was assessed by means of the Present Pain Intensity (PPI) scale from the McGill–Melzack questionnaire, which uses verbal descriptors; scores can range from 0 to 5, with higher scores indicating greater pain.[23] Patients recorded their daily PPI score and analgesic use in a diary. A daily analgesic score was calculated by assigning a score of 4 for a standard dose of a narcotic analgesic (e.g., 10 mg of morphine) and a score of 1 for a standard dose of a nonnarcotic analgesic. Patients were required to have stable levels of pain for at least seven days before randomization, defined by a daily variation of no more than 1 in the PPI score or of no more than 25 percent in the analgesic score. The quality of life was assessed with the Functional Assessment of Cancer Therapy–Prostate (FACT-P) questionnaire; scores on this self-administered questionnaire can range from 0 to 156, with higher scores indicating a better quality of life.[24,25]

All patients provided written informed consent, and the study was approved by all institutional review boards in accordance with the international standards of good clinical practice. An independent data and safety monitoring committee was established.

RANDOMIZATION AND TREATMENT

Randomization was centralized with the use of a stratified, permuted-block allocation scheme according to the baseline pain level (pain was classified as present, as defined by a median PPI score of at least 2 or a mean analgesic score of at least 10, or as absent, as defined by a median PPI score of less than 2 and a mean analgesic score of less than 10) and the baseline Karnofsky performance-status score (70 percent or less vs. 80 percent or more). Patients who were randomly assigned to the docetaxel groups received either 75 mg of docetaxel (Taxotere, Aventis) per square meter as a 1-hour intravenous infusion on day 1 every 21 days or 30 mg of docetaxel per square meter as a 30-minute intravenous infusion on days 1, 8, 15, 22, and 29 of a 6-week cycle. Patients who were randomly assigned to the standard-therapy group received 12 mg of mitoxantrone (Novantrone, Immunex and Wyeth–Ayerst) per square meter as a 30-minute infusion on day 1 every 21 days. All patients received 5 mg of prednisone (or prednisolone, if prednisone was not available) orally twice daily starting on day 1. Premedication with dexamethasone was required in the docetaxel groups (8 mg given 12 hours, 3 hours, and 1 hour before the docetaxel infusion in the group treated every three weeks and 8 mg given 1 hour before docetaxel in the group treated weekly). Antiemetic medication was prescribed according to local practice.

Up to 10 cycles of treatment were planned for the group given docetaxel every three weeks and the mitoxantrone group and up to 5 cycles (of six weeks each) in the weekly-docetaxel group. Treatment delays of up to two weeks and up to two dose reductions were allowed. Dose reductions were specified for patients who had had grade 4 neutropenia for at least seven days, an infection, or grade 3 or 4 neutropenia with an oral temperature of at least 38.5°C. A dose reduction or treatment delay was also stipulated for patients who had an absolute neutrophil count of less than 1500 per cubic millimeter (for those on three-week schedules) or less than 1000 per cubic millimeter (for those receiving weekly docetaxel) on a treatment day and for those with grade 3 or 4 thrombocytopenia. Treatment with granulocyte colony-stimulating factor was allowed for patients with febrile neutropenia. Systemic corticosteroids (other than dexamethasone and prednisone) and bisphosphonates were not permitted.

FOLLOW-UP AND OUTCOMES

Physical examinations and baseline blood tests were repeated at three-week intervals. Imaging studies to determine the extent of disease were performed at intervals of six to nine weeks and repeated after four weeks to identify those with a response.

The primary end point was overall survival. Secondary end points were predefined reductions in pain, an improvement in the quality of life, a reduction in serum PSA levels of at least 50 percent, and objective tumor responses.

Patients with a PPI score of at least 2, an analgesic score of at least 10, or both (averaged over the previous week) at baseline were assessed for the pain response at three-week intervals. A pain response was defined as a two-point reduction in the PPI score from baseline without an increase in the analgesic score or as a reduction of at least 50 percent in the analgesic score without an increase in the PPI score, either of which was maintained for at least three weeks. Pain progression was defined as an increase in the PPI score of at least one point from the nadir, an increase from baseline of at least

25 percent in the analgesic score, or a requirement for palliative radiotherapy.

Serum PSA was measured every three weeks, and a response (for patients with a baseline PSA level of at least 20 ng per milliliter) was defined as a reduction from baseline of at least 50 percent that was maintained for at least three weeks, whereas PSA progression was defined as an increase from the nadir of either at least 25 percent for men with no PSA response or at least 50 percent for all others. The duration of the PSA response and the pain response was defined as the time between the first and last evaluations at which the response criteria were met. For patients with at least one bidimensionally measurable lesion, tumor response was evaluated with the use of World Health Organization criteria.[26]

The quality of life was assessed with the FACT-P questionnaire at baseline, every three weeks during therapy, and every month after the completion of therapy. All patients who answered the questionnaire at baseline were included in the evaluation, and the FACT-P score was compared with the baseline value for each of these patients. Patients were defined as having a quality-of-life response if they had a 16-point improvement in their FACT-P score, as compared with baseline, on two measurements obtained at least three weeks apart.

Adverse events were classified according to the Common Toxicity Criteria of the National Cancer Institute (version 2). Serious adverse events were fatal or life-threatening, required or prolonged hospitalization, resulted in persistent or substantial disability or incapacity, or were considered important medical events. Treatment was stopped for any of the following reasons: completion of planned treatment, progression of disease, severe adverse events, or withdrawal of consent.

STATISTICAL ANALYSIS

There were three comparisons of interest between the docetaxel and mitoxantrone groups: docetaxel given every three weeks was compared with mitoxantrone, weekly docetaxel was compared with mitoxantrone, and the combined docetaxel groups were compared with mitoxantrone. The study was designed to detect with 90 percent power a hazard ratio of 0.75 for death in the docetaxel groups as compared with the mitoxantrone group, with a two-sided type I error of 0.05 and with the data analyzed according to the intention to treat. The sample size was established as 1002 patients, and analysis was planned after 535 deaths had occurred. To allow for multiple comparisons, a P value of 0.04 was considered to indicate statistical significance for the comparison of the combined docetaxel groups with the mitoxantrone group, and a P value of 0.0175 was considered to indicate statistical significance for the comparison of each docetaxel group with the mitoxantrone group (all P values were two-sided), thus ensuring an overall significance level of 0.05.

In the primary analysis, overall survival was analyzed by means of the Kaplan–Meier method, with log-rank comparisons stratified according to the level of pain and the Karnofsky performance-status score. Pain, PSA, tumor, and quality-of-life responses were compared by means of the Cochran–Mantel–Haenszel test. All randomized patients were included in the analysis of survival, and all treated patients were included in the evaluation of adverse effects.

Hazard ratios for death were calculated after adjustment for any chance imbalance in potential prognostic factors between the groups. The following factors were entered into a full stratified Cox proportional-hazards model and a backward selection model in which nonsignificant factors were eliminated sequentially at a P level of 0.10: age (less than 65 years vs. 65 years or older); visceral involvement (yes vs. no); liver involvement (yes vs. no); number of prior hormonal therapies (two or fewer vs. more than two); prior estramustine (yes vs. no); presence of rising serum PSA levels alone, as compared with the presence of other indications of progression; baseline hemoglobin level; and baseline serum level of alkaline phosphatase. One planned interim analysis of safety was conducted after the recruitment of 120 patients. No interim analysis for efficacy was performed.

The study was designed by Dr. Tannock in collaboration with Aventis personnel, and the protocol was finalized after being reviewed by the other study cochairs, Drs. de Wit and Eisenberger. The data were collected and maintained by Aventis, but the cochairs handled all questions regarding the management of the study. Only the data and safety monitoring committee saw the results of the interim safety analysis; no analysis was undertaken nor were the results seen by Aventis, the study cochairs, or any other investigator until the predefined number of events had occurred. The protocol contained a plan for analysis and publication at that time. All data were provided to the cochairs at the comple-

tion of the study. Aventis personnel undertook the statistical analysis. The article was drafted by Dr. Tannock and modified after being reviewed by the cochairs and other coauthors. Aventis reviewed the manuscript, but its final content was entirely determined by the investigators.

RESULTS

CHARACTERISTICS OF THE PATIENTS AND TREATMENT

A total of 1006 patients underwent randomization from March 2000 through June 2002. The da-

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Docetaxel Every 3 Wk	Weekly Docetaxel	Mitoxantrone Every 3 Wk
No. randomized	335	334	337
Ineligible (%)	12	12	12
Age			
Median (yr)	68	69	68
Range (yr)	42–92	36–92	43–86
≥75 Yr (%)	20	21	20
Gleason score (%)			
≤7	42	40	42
8–10	31	31	28
Not available	26	29	30
Prior treatment (%)			
Prostatectomy	19	24	21
Radiotherapy	52	44	51
Estramustine	19	18	20
Hormonal manipulations (%)†			
1	9	8	6
2	68	72	69
>2	23	21	25
Karnofsky performance-status score ≤70% (%)	13	12	14
Pain (%)‡	45	45	46
Serum PSA			
Median (ng/ml)	114	108	123
≥20 ng/ml (%)	87	84	89
Extent of disease (%)			
Bone metastases	90	91	92
Visceral disease	22	24	22
Measurable lesions	40	39	40
Evidence of progression at entry (%)§			
Bone scan	71	69	69
Increase in measurable lesions	28	30	28
Increase in nonmeasurable lesions	13	16	15
Increased PSA	72	66	68

* All patients were included in the intention-to-treat analysis. Because of rounding, not all percentages total 100.
† Hormonal manipulation was defined as bilateral orchiectomy or hormone therapy.
‡ Pain was defined by a score of 2 or more on the Present Pain Intensity scale or an analgesic score of at least 10.
§ Patients may have more than one indication for progression of disease.

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