ORIGINAL ARTICLE

Docetaxel plus Prednisone or Mitoxantrone plus Prednisone for Advanced Prostate Cancer

Ian F. Tannock, M.D., Ph.D., Ronald de Wit, M.D., William R. Berry, M.D., Jozsef Horti, M.D., Anna Pluzanska, M.D., Kim N. Chi, M.D., Stephane Oudard, M.D., Christine Théodore, M.D., Nicholas D. James, M.D., Ph.D., Ingela Turesson, M.D., Ph.D., Mark A. Rosenthal, M.D., Ph.D., and Mario A. Eisenberger, M.D., for the TAX 327 Investigators

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.

From the Department of Medical Oncology and Hematology, Princess Margaret Hospital and University of Toronto, Toronto (I.F.T.); the Department of Medical Oncology, Erasmus University Medical Centre, Rotterdam, the Netherlands (R.W.); Raleigh Hematology Oncology Associates, Cary, N.C. (W.R.B.); the Department of Chemotherapy and Clinical Pharmacology, National Institute of Oncology, Budapest, Hungary (J.H.); the Department of Chemotherapy, Medical University, Lodz, Poland (A.P.); BC Cancer Agency, Vancouver, B.C., Canada (K.N.C.); Hôpital Européen Georges Pompidou, Paris (S.O.); Institut Gustav Roussy, Villejuif, France (C.T.); Cancer Research UK Institute for Cancer Studies, Birmingham, United Kingdom (N.D.J.); the Section of Oncology, Uppsala University Hospital, Uppsala, Sweden (I.T.); Cancer Trials Australia, Victoria, Australia (M.A.R.); and the Sydney Kimmel Comprehensive Cancer Center, Johns Hopkins University, Baltimore (M.A.E.). Address reprint requests to Dr. Tannock at the Department of Medical Oncology and Hematology, Princess Margaret Hospital, 610 University Ave., Toronto, ON M5G 2M9, Canada, or at ian.tannock@uhn.on.ca.

N Engl J Med 2004;351:1502-12.

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.

tabase was locked on August 6, 2003, after the requisite number of deaths, specified in the statistical plan, had occurred.

The baseline characteristics of the patients were well balanced among the three treatment groups (Table 1). The median age was 68 years; about 20 percent of the patients were at least 75 years old. About 45 percent had pain, and about 40 percent had measurable soft-tissue lesions. The most common indicators of disease progression before study entry were an increasing serum PSA level and evidence of an increase in bone metastases on bone scanning.

Only nine patients (1 percent) did not receive chemotherapy and prednisone (Table 2). Patients tended to receive more cycles of the regimen in which docetaxel was given every three weeks than of the regimen in which mitoxantrone was given every three weeks. Most patients received the prescribed doses on schedule, with 8 to 12 percent requiring a dose reduction and 21 to 34 percent requiring at least one chemotherapy infusion to be delayed. Twenty percent of the patients who were randomly assigned to receive mitoxantrone subsequently received docetaxel, and 27 percent of those in the group given docetaxel every three weeks received subsequent mitoxantrone, as did 24 percent of those in the weekly-docetaxel group.

Table 2. Treatment.*

Variable	Docetaxel Every 3 Wk	Weekly Docetaxel	Mitoxantrone Every 3 Wk
No. randomized	335	334	337
No. treated with chemotherapy	332	330	335
No. treated with prednisone	332	330	335
No. of cycles			
Median	9.5	4	5
Range	1–11	1–6	1–11
≥1 Infusion delayed (%)	24	34	21
Dose reduction (%)	12	9	8
Major protocol violation (%)	7	8	7
Reasons for stopping treatment (%)			
Completed treatment	46	35	25
Progression of disease	38	35	56
Adverse event	11	16	10
Withdrawal of consent	1	6	3
Death	1	2	2
Other	4	6	5
Crossover to other drug (%)	27	24	20

* Percentages relate to the number of patients treated in each group. Because of rounding, not all percentages total 100.

EFFICACY

The median duration of follow-up was similar among the three groups: 20.8 months in the group given docetaxel every 3 weeks and 20.7 months in the other two groups. There were 166 deaths (50 percent; hazard ratio for death, 0.76; 95 percent confidence interval, 0.62 to 0.94) in the group given docetaxel every three weeks and 190 deaths (57 percent; hazard ratio, 0.91; 95 percent confidence interval, 0.75 to 1.11) in the group given weekly docetaxel, as compared with 201 deaths (60 percent) in the mitoxantrone group. When the two docetaxel groups were combined and compared with the mitoxantrone group, the hazard ratio for death was 0.83 (95 percent confidence interval, 0.70 to 0.99; P=0.04). As compared with the survival rate in the mitoxantrone group, the survival rate was significantly higher (P=0.009) in the group given docetaxel every three weeks but not in the group given weekly docetaxel (P=0.36). The median duration of survival was 18.9 months (95 percent confidence interval, 17.0 to 21.2) in the group given docetaxel every 3 weeks, 17.4 months (95 per-

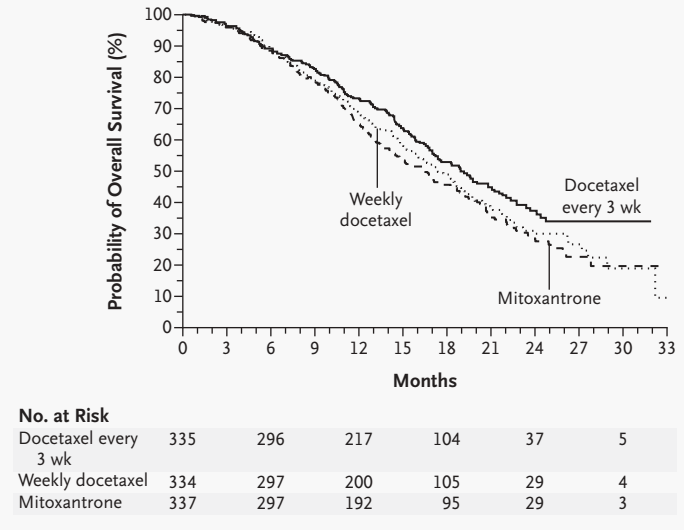

Figure 1. Kaplan–Meier Estimates of the Probability of Overall Survival in the Three Groups.

Table 3. Response to Treatment, as Measured by Decreases in Pain, PSA Level, and Tumor Burden and Improvements in the Quality of Life.*

Variable	Docetaxel Every 3 Wk	Weekly Docetaxel	Mitoxantrone Every 3 Wk
Pain†			
No. who could be evaluated	153	154	157
Response (%)			
Rate	35	31	22
95% CI	27–43	24–39	16–29
P value	0.01	0.08	
Duration (mo)‡			
Median	3.5	5.6	4.8
95% CI	2.4–8.1	2.8–6.8	4.4–indeterminate
≥50% Reduction in serum PSA			
No. who could be evaluated	291	282	300
Response (%)			
Rate	45	48	32
95% CI	40–51	42–54	26–37
P value	<0.001	<0.001	
Duration (mo)‡			
Median	7.7	8.2	7.8
95% CI	7.1–8.6	6.3–11.5	5.4–10.5
Tumor response			
No. who could be evaluated	141	134	137
Response (%)			
Rate	12	8	7
95% CI	7–19	4–14	3–12
P value	0.11	0.59	
Quality of life			
No. who could be evaluated	278	270	267
Response (%)§			
Rate	22	23	13
95% CI	17–27	18–28	9–18
P value	0.009	0.005	

* P values are for comparisons with the mitoxantrone group. CI denotes confidence interval.

† A pain response was defined as a two-point reduction in the Present Pain Intensity (PPI) score without an increase in the analgesic score or a reduction of at least 50 percent in the analgesic score without an increase in the PPI score, which was maintained for at least three weeks.

‡ Data on 54 percent and 63 percent of patients were censored in the Kaplan–Meier analysis of the median duration of pain and PSA response, respectively. The chief reason for data censoring was further antitumor therapy after progression of disease as defined by other criteria.

§ A response was defined by a 16-point improvement from baseline in the Functional Assessment of Cancer Therapy–Prostate (FACT-P) score on two measurements obtained at least three weeks apart.

cent confidence interval, 15.7 to 19.0) in the group given weekly docetaxel, and 16.5 months (95 percent confidence interval, 14.4 to 18.6) in the mitoxantrone group. Kaplan–Meier survival curves for the three groups are shown in Figure 1.

The result of the sensitivity analysis, in which survival was adjusted for possible imbalances in potential prognostic factors, was consistent with the primary result. The hazard ratio for death in the group given docetaxel every three weeks, as compared with the mitoxantrone group, was 0.76 without adjustment and 0.74 and 0.75 after adjustment in the full stratified and backward Cox proportional-hazards models, respectively. As expected, visceral involvement, a high baseline alkaline phosphatase level, and a low hemoglobin level were negative prognostic factors in the multivariate models, whereas a rising serum PSA as the sole indicator of progression was a favorable factor. Post hoc analysis indicated that a high Gleason score (8, 9, or 10) was an adverse prognostic factor for survival. The survival benefit of docetaxel given every three weeks was consistent across subgroups defined according to the presence or absence of pain at baseline, the Karnofsky performance-status score (70 percent or less vs. 80 percent or more), and age (younger than 65 years vs. 65 years or older) (data not shown).

A reduction in pain was more frequent among patients receiving docetaxel every three weeks than among those treated with mitoxantrone (35 percent vs. 22 percent, P=0.01) (Table 3), but the percentage of patients with reduced pain in the weekly docetaxel group (31 percent) did not differ significantly from that of the mitoxantrone group. The median duration of reduced pain was 3.5 to 5.6 months and did not differ significantly among the groups.

Rates of PSA response were significantly higher in the docetaxel groups (45 percent in the group given docetaxel every three weeks and 48 percent in the group given weekly docetaxel, P<0.001 for both comparisons) than in the mitoxantrone group (32 percent) (Table 3). The median duration of the PSA response ranged from 7.7 to 8.2 months and did not differ significantly among the three groups.

Although patients with measurable soft-tissue lesions who received docetaxel every three weeks had a somewhat higher rate of tumor response than such patients who received mitoxantrone every three weeks (12 percent vs. 7 percent, P=0.11), this difference was not significant (Table 3).

ADVERSE EVENTS

The incidence of grade 3 and 4 neutropenia was relatively low, and febrile neutropenia was rare (Table 4). Two patients died from sepsis during treatment, one in the docetaxel group and one in the mitoxantrone group. There was a higher incidence of cardiac events among patients who received mitoxantrone (Table 4). Most other types of adverse events were more frequent among patients receiving docetaxel, and there was no trend toward a lower frequency with weekly docetaxel than with docetaxel given every three weeks. Low-grade adverse events that occurred in at least 15 percent of patients in one of the groups included fatigue, nausea or vomiting or both, alopecia, diarrhea, nail changes, sensory neuropathy, anorexia, changes in taste, stomatitis, dyspnea, tearing, peripheral edema, and epistaxis (Table 4). More patients in the docetaxel groups than in the mitoxantrone group had at least one serious adverse event, with rates of 26 percent among those in the group given docetaxel every three weeks, 29 percent among those given weekly docetaxel, and 20 percent among those given mitoxantrone. Five deaths were probably related to treatment, three of them in the mitoxantrone group.

More patients in the mitoxantrone group stopped treatment because of disease progression than was the case in the docetaxel groups, and more stopped treatment because of completion of treatment or adverse events in the docetaxel groups (Table 2). Adverse events that led to the discontinuation of treatment included fatigue, musculoskeletal or nail changes, sensory neuropathy, and infection in the docetaxel groups and cardiac dysfunction in the mitoxantrone group.

Table 4. Adverse Events of Any Grade, or of Grade 3 or 4, That Occurred or Worsened during Treatment.

Adverse Event	Docetaxel Every 3 Wk (N=332)	Weekly Docetaxel (N=330)	Mitoxantrone Every 3 Wk (N=335)
		percent	
Grade 3 or 4 anemia	5	5	2
Grade 3 or 4 thrombocytopenia	1	0	1
Grade 3 or 4 neutropenia	32*	2†	22
Febrile neutropenia	3	0	2
Impaired LVEF‡	10†	8†	22
Major decrease	1†	2*	7
Fatigue	53†	49†	35
Grade 3 or 4	5	5	5
Alopecia	65†	50†	13
Nausea, vomiting, or both	42	41	38
Diarrhea	32†	34†	10
Nail changes	30†	37†	7
Sensory neuropathy	30†	24†	7
Anorexia	17	21*	14
Change in taste	18†	24†	7
Stomatitis	20†	17†	8
Myalgia	14	14	13
Dyspnea	15*	14*	9
Tearing	10†	21†	1
Peripheral edema	19†	12†	1
Epistaxis	6	17†	2
≥1 Serious adverse event	26	29	20
Treatment-related death	0.3	0.3	1

* P≤0.05 by Fisher's exact test for the comparison with the mitoxantrone group.
† P≤0.0015 by Fisher's exact test for the comparison with the mitoxantrone group. A Bonferroni adjustment for multiplicity was used to obtain the nominal significance level of 0.0015 (approximately 0.05÷34), on the basis of two tests being carried out on the 17 adverse events, with at least 20 events in at least one of the three treatment groups.
‡ A major decrease in the left ventricular ejection fraction (LVEF) was defined as a decrease of at least 10 percent in the absolute value to below the lower limit of the normal range.

QUALITY OF LIFE

The quality of life was evaluated in 815 patients, a group that made up the intention-to-treat population from countries in which a local translation of the FACT-P was available (Table 3). The percentage of patients who had an improvement in the quality of life was similar in the two docetaxel groups (22 percent in the group given docetaxel every three weeks and 23 percent in the group given weekly docetaxel) and significantly higher than that in the mitoxantrone group (13 percent; P=0.009 and P=0.005, respectively). Figure 2 shows the greatest changes in the scores and the median changes in the scores for individual domains of the FACT-P during treatment. The greatest benefit in the docetaxel groups was in the subscale representing prostate-specific concerns (including weight loss, appetite, pain, physical comfort, and bowel and genitourinary function).

DISCUSSION

In this phase 3 study, two schedules of docetaxel administered with prednisone were compared with mitoxantrone plus prednisone, the standard chemotherapy for hormone-refractory prostate cancer. The median overall survival was higher for the group that received docetaxel every three weeks

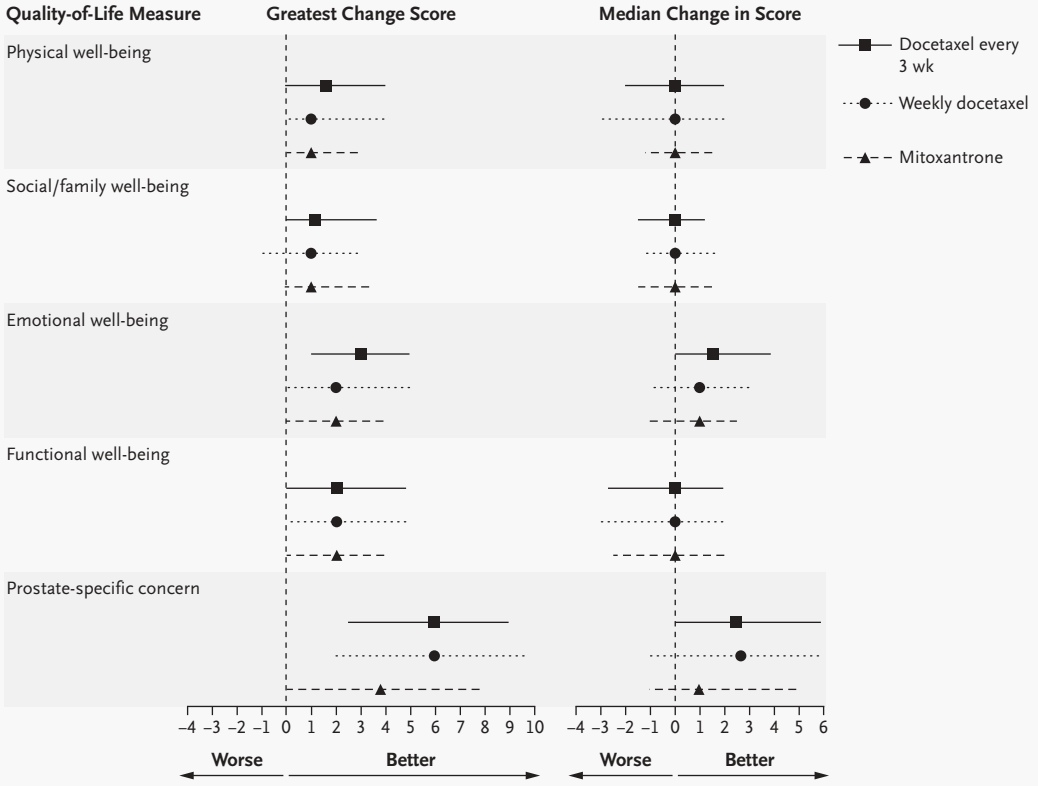

Figure 2. Greatest Change and Median Change from Baseline in Normalized Scores on the Functional Assessment of Cancer Therapy–Prostate Questionnaire for Individual Domains of the Quality of Life during Treatment.

than for the mitoxantrone group, but not for the group that received weekly docetaxel. These differences were not influenced by adjustment for potential prognostic factors, and there were consistent trends in survival in the intention-to-treat population and in various subgroups. Overall, as compared with the mitoxantrone group, the docetaxel groups had better pain control and quality of life and more frequent PSA responses, but at the cost of a higher incidence of adverse effects.

The characteristics of the patients in this study are typical of those seen in oncology practices. Most patients were elderly and had received at least two types of hormonal manipulation. Most had bone metastases and a high serum PSA level, and about half had substantial pain. All these patients had a short life expectancy. Four published phase 3 studies have evaluated mitoxantrone plus prednisone for hormone-refractory prostate cancer.[9-12] In our study, patients in the mitoxantrone group had a PSA response rate of 32 percent and a rate of predefined reduction in pain of 22 percent. In prior studies of symptomatic patients alone, mitoxantrone plus prednisone resulted in PSA response rates of 34 percent[9] and 29 percent,[12] whereas one study of asymptomatic patients reported a 48 percent response rate.[10] Rates of reduction in pain of 38 percent[9] and 39 percent[12] have been reported, but these studies used less strict response criteria than we did. The median survival among patients in the mitoxantrone group in our study was 16.5 months, as compared with 10 to 12.5 months in the Canadian and Cancer and Leukemia Group B studies[9,11,12] and 21 months in a study of asymptomatic patients.[10] Mitoxantrone plus prednisone remains an appropriate treatment for patients with hormone-refractory prostate cancer who might be susceptible to the toxic effects of docetaxel. However, treatment with mitoxantrone plus a corticosteroid has not improved survival over that afforded by a corticosteroid alone.[9-11]

Previous experience with docetaxel in the treat-

ment of hormone-refractory prostate cancer is limited to phase 2 studies. The PSA response ranged from 38 to 46 percent for docetaxel alone[13-16] and up to 80 percent for docetaxel combined with estramustine or calcitriol.[17-19] The rate of objective reduction in pain after treatment with docetaxel alone was 48 percent in the only study that evaluated pain.[13] In our study, the rates of PSA response were 45 percent in the group given docetaxel every three weeks and 48 percent in the group given weekly docetaxel, and the respective rates of predefined (and stringent) reductions in pain were 35 percent and 31 percent, all of which, except for the response of pain in the weekly-docetaxel group, were significantly higher than the rates in the mitoxantrone group. More important, we found a significant improvement in overall survival for docetaxel as compared with mitoxantrone. A similar improvement in survival for docetaxel plus estramustine in comparison with mitoxantrone plus prednisone was found in a phase 3 study by the Southwest Oncology Group that is reported in this issue of the *Journal*.[27]

Safe use of docetaxel requires premedication with dexamethasone. Since the docetaxel group received about twice the dose of corticosteroids that the mitoxantrone group received, the better results in the docetaxel group may have been due in part to the higher dose of corticosteroids.[5,6,9-11] This seems unlikely because with prednisone or hydrocortisone alone, the rate of PSA response in large phase 3 studies was in the range of 16 to 24 percent and was generally transient.[5,9-11,28] In symptomatic patients, prednisone or hydrocortisone treatment was inferior to chemotherapy plus corticosteroid in reducing pain and other symptoms.[9,10,28] Intensive treatment with dexamethasone was reported to have no effect on hormone-refractory prostate cancer in one small study.[29]

Serious adverse events occurred among 26 percent of patients in the group given docetaxel every three weeks and 29 percent of the group given weekly docetaxel, as compared with 20 percent in the mitoxantrone group. However, hematologic events were rare in all three groups, and most patients received the prescribed doses of the assigned drug on schedule. Although neutropenia was most common in the group given docetaxel every three weeks, infection was rare. There was a higher incidence of cardiotoxicity in the mitoxantrone group, but it was rarely of clinical importance. Most adverse events associated with docetaxel were of low grade and were bothersome rather than life-threatening; loss of sensation in the fingers and toes proved particularly annoying to some patients.

We designed this study to include a schedule with lower doses of docetaxel given weekly to assess whether a weekly regimen was better tolerated than treatment every three weeks. We found no evidence of a lower rate of adverse events or improved outcomes with the weekly schedule. Treatments given at intervals of three weeks are more convenient for most patients and we think should remain the standard with docetaxel.

Significantly more patients satisfied the stringent criterion of a 16-point improvement from baseline in the total FACT-P score in the docetaxel groups (22 percent in the group given docetaxel every three weeks and 23 percent in the weekly docetaxel group) than in the mitoxantrone group (13 percent). This result suggests that docetaxel has superior palliative effects despite the increase in toxicity. It is likely that the improvement in the quality of life would have been greater if our study had been restricted to symptomatic patients. Overall, the aspects of the quality of life that are assessed by the FACT-P questionnaire were maintained or improved during treatment, with the greatest benefit occurring for prostate-cancer–specific concerns.

Our findings provide evidence that cytotoxic chemotherapy can significantly prolong survival among men with hormone-refractory prostate cancer. Our data suggest that docetaxel plus prednisone is the preferred option for most patients with hormone-refractory prostate cancer.

Supported by Aventis.

We are indebted to the men who participated in this study; to the study contributors; to investigators who recruited patients, including D. Campos (Argentina); H. Gurney and M. Stockler (Australia); M. Rauchenwald (Austria); T. Gil, Y. Humblet, and A. van Oosterom (Belgium); D. Herchenhorn (Brazil); S. Ernst, L. Lacombe, M. Moore, F. Saad, D. Soulieres, P. Venner, and E. Winquist (Canada); M. Urban (Czech Republic) P. Kellokumpu-Lehtinen (Finland); G. Deplanque, B. Duclos, I. Krakowski, and L. Mignot (France); J. Breul and R. Paul (Germany); I. Bodrogi (Hungary); S. Bracarda (Italy); G. Chahine (Lebanon); J.L. Bruins and J.A. Witjes (the Netherlands); T. Demkow and K. Bar (Poland); O. Kariakine and M. Matveev (Russia); I. Andrasina (Slovak Republic); D. Vorobiof (South Africa); J. Bellmunt and J.-R. Germa (Spain); A. Widmark (Sweden); A. Horwich, T. Roberts, and J. Wylie (United Kingdom); and L. Baez, W. Dugan, and N. Tirumali (United States); to the members of the Data and Safety Monitoring Committee — D. Osoba (Canada), F. Boccardo (Italy), M. Parmar (United Kingdom), and N. Dawson and E. Klein (United States) — and to C. Beauchard (study manager), N. Yateman and S. Thompson (statisticians), M. Kopreski (safety), and E. Borghi, S. Yao, and A. Yver (clinical directors), who were key Aventis personnel.

Dr. Tannock reports having received grant support from Immunex; Drs. De Wit and Rosenthal consulting fees from Aventis; Drs. Berry, Oudard, and Turesson consulting fees and lecture fees from Aventis; and Drs. Chi, James, and Eisenberger consulting fees, lecture fees, and grant support from Aventis.

REFERENCES

1. American Cancer Society (ACS). Cancer facts & figures 2003. (Accessed September 13, 2004, at http://www.cancer.org/docroot/STT/stt_0_2003.asp?sitearea=STT&level=1.)
2. Oades GM, Coxon J, Colston KW. The potential role of bisphosphonates in prostate cancer. Prostate Cancer Prostatic Dis 2002;5:264-72.
3. Saad F, Gleason DM, Murray R, et al. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. J Natl Cancer Inst 2002;94:1458-68.
4. Dearnaley DP, Sydes MR, Mason MD, et al. A double-blind, placebo-controlled, randomized trial of oral sodium clodronate for metastatic prostate cancer (MRC PR05 Trial). J Natl Cancer Inst 2003;95:1300-11.
5. Fossa SD, Slee PH, Brausi M, et al. Flutamide versus prednisone in patients with prostate cancer symptomatically progressing after androgen-ablative therapy: a phase III study of the European Organization for Research and Treatment of Cancer genitourinary group. J Clin Oncol 2001;19:62-71.
6. Tannock I, Gospodarowicz M, Meakin W, Panzarella T, Stewart L, Rider W. Treatment of metastatic prostatic cancer with low-dose prednisone: evaluation of pain and quality of life as pragmatic indices of response. J Clin Oncol 1989;7:590-7.
7. Martel CL, Gumerlock PH, Meyers FJ, Lara PN Jr. Current strategies in the management of hormone refractory prostate cancer. Cancer Treat Rev 2003;29:171-87.
8. Osoba D, Tannock IF, Ernst DS, Neville AJ. Health-related quality of life in men with metastatic prostate cancer treated with prednisone alone or mitoxantrone and prednisone. J Clin Oncol 1999;17:1654-63.
9. Tannock IF, Osoba D, Stockler MR, et al. Chemotherapy with mitoxantrone plus prednisone or prednisone alone for symptomatic hormone-resistant prostate cancer: a Canadian randomized trial with palliative end points. J Clin Oncol 1996;14:1756-64.
10. Berry W, Dakhil S, Modiano M, Gregurich M, Asmar L. Phase III study of mitoxantrone plus low dose prednisone versus low dose prednisone alone in patients with asymptomatic hormone refractory prostate cancer. J Urol 2002;168:2439-43.
11. Kantoff PW, Halabi S, Conaway M, et al. Hydrocortisone with or without mitoxantrone in men with hormone-refractory prostate cancer: results of the Cancer and Leukemia Group B 9182 study. J Clin Oncol 1999;17:2506-13.
12. Ernst DS, Tannock IF, Winquist EW, et al. Randomized, double-blind, controlled trial of mitoxantrone/prednisone and clodronate versus mitoxantrone/prednisone and placebo in patients with hormone refractory prostate cancer and pain. J Clin Oncol 2003;21:3335-42.
13. Beer TM, Pierce WC, Lowe BA, Henner WD. Phase II study of weekly docetaxel in symptomatic androgen-independent prostate cancer. Ann Oncol 2001;12:1273-9.
14. Berry W, Dakhil S, Gregurich MA, Asmar L. Phase II trial of single-agent weekly docetaxel in hormone-refractory, symptomatic, metastatic carcinoma of the prostate. Semin Oncol 2001;28:Suppl 15:8-15.
15. 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 1999;26:Suppl 17:19-23.
16. Picus J, Schultz M. Docetaxel (Taxotere) as monotherapy in the treatment of hormone-refractory prostate cancer: preliminary results. Semin Oncol 1999;26:Suppl 17:14-8.
17. Savarese DM, Halabi S, Hars V, et al. Phase II study of docetaxel, estramustine, and low-dose hydrocortisone in men with hormone-refractory prostate cancer: a final report of CALGB 9780. J Clin Oncol 2001;19:2509-16.
18. Petrylak DP. Chemotherapy for androgen-independent prostate cancer. Semin Urol Oncol 2002;20:Suppl 1:31-5.
19. Beer TM, Eilers KM, Garzotto M, Egorin MJ, Lowe BA, Henner WD. Weekly high-dose calcitriol and docetaxel in metastatic androgen-independent prostate cancer. J Clin Oncol 2003;21:123-8.
20. Chen TT, Chute JP, Feigal E, Johnson BE, Simon R. A model to select chemotherapy regimens for phase III trials for extensive-stage small-cell lung cancer. J Natl Cancer Inst 2000;92:1601-7.
21. Kelly WK, Slovin S, Scher HI. Steroid hormone withdrawal syndromes: pathophysiology and clinical significance. Urol Clin North Am 1997;24:421-31.
22. Wirth MP, Froschermaier SE. The antiandrogen withdrawal syndrome. Urol Res 1997;25:Suppl 2:S67-S71.
23. Melzack R. The McGill Pain Questionnaire: major properties and scoring methods. Pain 1975;1:277-99.
24. Esper P, Mo F, Chodak G, Sinner M, Cella D, Pienta KJ. Measuring quality of life in men with prostate cancer using the Functional Assessment of Cancer Therapy–prostate instrument. Urology 1997;50:920-8.
25. Kornblith AB, Herndon JE II, Zuckerman E, Godley PA, Savarese D, Vogelzang NJ. The impact of docetaxel, estramustine, and low dose hydrocortisone on the quality of life of men with hormone refractory prostate cancer and their partners: a feasibility study. Ann Oncol 2001;12:633-41.
26. WHO criteria. In: WHO handbook for reporting results of cancer treatment. Geneva: World Health Organization, 1979. (Offset publication no. 48.)
27. 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 2004;351:1513-20.
28. Small EJ, Meyer M, Marshall ME, et al. Suramin therapy for patients with symptomatic hormone-refractory prostate cancer: results of a randomized phase III trial comparing suramin plus hydrocortisone to placebo plus hydrocortisone. J Clin Oncol 2000;18:1440-50.
29. Weitzman AL, Shelton G, Zuech N, et al. Dexamethasone does not significantly contribute to the response rate of docetaxel and estramustine in androgen independent prostate cancer. J Urol 2000;163:834-7.