ORIGINAL ARTICLE

Docetaxel and Estramustine Compared with Mitoxantrone and Prednisone for Advanced Refractory Prostate Cancer

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ABSTRACT

BACKGROUND

Mitoxantrone-based chemotherapy palliates pain without extending survival in men with progressive androgen-independent prostate cancer. We compared docetaxel plus estramustine with mitoxantrone plus prednisone in men with metastatic, hormone-independent prostate cancer.

METHODS

We randomly assigned 770 men to one of two treatments, each given in 21-day cycles: 280 mg of estramustine three times daily on days 1 through 5, 60 mg of docetaxel per square meter of body-surface area on day 2, and 60 mg of dexamethasone in three divided doses before docetaxel, or 12 mg of mitoxantrone per square meter on day 1 plus 5 mg of prednisone twice daily. The primary end point was overall survival; secondary end points were progression-free survival, objective response rates, and post-treatment declines of at least 50 percent in serum prostate-specific antigen (PSA) levels.

RESULTS

Of 674 eligible patients, 338 were assigned to receive docetaxel and estramustine and 336 to receive mitoxantrone and prednisone. In an intention-to-treat analysis, the median overall survival was longer in the group given docetaxel and estramustine than in the group given mitoxantrone and prednisone (17.5 months vs. 15.6 months, P=0.02 by the log-rank test), and the corresponding hazard ratio for death was 0.80 (95 percent confidence interval, 0.67 to 0.97). The median time to progression was 6.3 months in the group given docetaxel and estramustine and 3.2 months in the group given mitoxantrone and prednisone (P<0.001 by the log-rank test). PSA declines of at least 50 percent occurred in 50 percent and 27 percent of patients, respectively (P<0.001), and objective tumor responses were observed in 17 percent and 11 percent of patients with bidimensionally measurable disease, respectively (P=0.30). Grade 3 or 4 neutropenic fevers (P=0.01), nausea and vomiting (P<0.001), and cardiovascular events (P=0.001) were more common among patients receiving docetaxel and estramustine than among those receiving mitoxantrone and prednisone. Pain relief was similar in both groups.

CONCLUSIONS

The improvement in median survival of nearly two months with docetaxel and estramustine, as compared with mitoxantrone and prednisone, provides support for this approach in men with metastatic, androgen-independent prostate cancer.

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Men with newly diagnosed metastatic prostate cancer have a rapid response to surgical or medical castration, with improvement in bone pain, regression of soft-tissue metastases, and a decline in serum prostate-specific antigen (PSA) levels. [1] Nevertheless, in virtually all patients the tumor ultimately becomes androgen-independent a median of 18 to 24 months after castration.[1,2] During this terminal phase in the natural history of prostate cancer, approximately 29,900 affected men in the United States will die of the disease in 2004.[3] Patients with metastatic androgen-independent prostate cancer have a progressive and morbid disease with a median survival of 10 to 12 months; currently, no treatment offers a survival advantage. Chemotherapy for androgen-independent prostate cancer is ineffective[4]: mitoxantrone plus prednisone or hydrocortisone, the current standard of care, palliates bone pain in approximately 30 percent of patients but does not improve survival.[5,6]

Immunohistochemical studies have demonstrated that the antiapoptotic protein Bcl-2 is increased in metastatic cells from androgen-independent prostate tissue.[7] Docetaxel, a taxane used to treat a variety of solid tumors, phosphorylates Bcl-2 in vitro, leading to its inactivation and to eventual cell death by apoptosis.[8] Estramustine,[9] which disrupts microtubule-associated proteins in vitro, has synergistic activity with docetaxel against human prostate-cancer cell lines.[10,11] Phase 1 and 2 studies of docetaxel plus estramustine in men with androgen-independent prostate cancer demonstrated a decline in serum PSA levels of at least 50 percent in 68 to 84 percent of patients, a measurable disease response in 28 to 55 percent, and a median survival of up to 23 months.[11-14] These data provided the foundation for this prospective, randomized, phase 3 trial (Southwest Oncology Group [SWOG] Intergroup protocol 99-16), which we conducted to determine whether docetaxel plus estramustine improves survival over that afforded by mitoxantrone plus prednisone in men with androgen-independent prostate cancer.

METHODS

PATIENTS

Patients were enrolled by institutions affiliated with SWOG, Cancer and Leukemia Group B, the North Central Cancer Treatment Group, the Clinical Trials Support Unit, and the extended participation project program through the National Cancer Institute. Eligibility required pathologically confirmed adenocarcinoma of the prostate and progressive metastatic disease (stage D1 or D2) despite androgen-ablative therapy and cessation of antiandrogen treatment. Criteria for progressive disease were progression of a bidimensionally measurable lesion, as assessed within 28 days before study registration; progression of disease that could be evaluated but not measured (e.g., by bone scanning), as assessed within 42 days before registration; or an increase in the serum PSA level over the baseline level in at least two consecutive samples obtained at least 7 days apart.[15] Antiandrogen therapy was discontinued before registration, at least six weeks before in the case of nilutamide or bicalutamide and four weeks before in the case of flutamide or other secondary hormonal therapy. To ensure continued androgen ablation, patients continued taking luteinizing-hormone–releasing hormone agonists throughout study treatment. Patients were required to discontinue bisphosphonates at least 28 days before registration. Prior radiotherapy (to less than 30 percent of the bone marrow only) or one prior systemic therapy (except with estramustine, taxanes, anthracyclines, or mitoxantrone) was permitted if at least four weeks had elapsed since the completion of that therapy. Adequate renal, hepatic, and cardiac function and a SWOG performance-status score of 0 to 2 (a performance status of 3 was allowed if the score was due to bone pain) were also required. Patients were ineligible if they had received prior radioisotope or anticoagulant therapy (excluding aspirin), had active thrombophlebitis or hypercoagulability, had a history of pulmonary embolus, or pleural effusions or ascites.

STRATIFICATION

Patients were classified at registration according to the following factors: type of progression (i.e., progression of disease that could be measured or evaluated vs. increasing PSA level alone), grade of bone pain according to the Common Terminology Criteria of the National Cancer Institute (grade 1 [mild, not interfering with function] vs. grade 2 [moderate pain interfering with function but not interfering with the activities of daily life], grade 3 [severe pain, severely interfering with the activities of daily living], or grade 4 [disabling pain]), and SWOG performance-status score (0 or 1 vs. 2 or

3).[16] All patients provided written informed consent, and the study was approved by the institutional review board of each participating institution.

TREATMENT

Patients were randomly assigned to one of two treatments, each given in 21-day cycles: 280 mg of estramustine (Emcyt, Pfizer) three times daily one hour before or two hours after meals on days 1 through 5 plus 60 mg of docetaxel (Taxotere, Aventis) per square meter of body-surface area intravenously on day 2, preceded by 60 mg of dexamethasone orally in three divided doses, starting the night before docetaxel, or 12 mg of mitoxantrone (Novantrone, OSI) per square meter intravenously on day 1 plus 5 mg of prednisone twice daily. Doses of docetaxel and mitoxantrone were increased to 70 mg per square meter and 14 mg per square meter, respectively, if no grade 3 or 4 adverse events were observed during the first cycle. A report that prophylactic anticoagulation decreased estramustine-associated vascular effects prompted an amendment of the protocol on January 15, 2001, to include daily warfarin (2 mg) plus aspirin (325 mg) in the group assigned to receive estramustine.[16] Treatment continued until disease progression or unacceptable adverse effects occurred or until a maximum of 12 cycles of docetaxel and estramustine or 144 mg of mitoxantrone per square meter had been administered.

EVALUATION

The pretreatment evaluation included a history taking, a physical examination in which weight and performance status were recorded, computed tomography (CT) of the abdomen and pelvis, bone scanning, nuclear ventriculography (multiple gated acquisition [MUGA] scanning), a complete blood count, and measurement of serum PSA, serum creatinine, and serum testosterone. MUGA scans were repeated every four cycles among patients in the group given mitoxantrone and prednisone. At every cycle, the pretreatment evaluation was repeated (excluding MUGA scanning, measurement of serum testosterone, and baseline imaging studies). Adverse events were evaluated by means of the Common Toxicity Criteria of the National Cancer Institute, version 2.0. Imaging studies were repeated every six cycles; if positive, they were repeated every three cycles.

Objective responses were defined on the basis of the sum of bidimensional measurements of metastatic lesions. Confirmed objective responses required a follow-up scan (a minimum of four weeks later) that demonstrated a continued response. Progression was defined by one of the following: a 50 percent increase or an increase of 10 cm^2, whichever was smaller, in the sum of measurements of metastatic lesions over the sum at baseline; a clear worsening of nonmeasurable disease; reappearance of any lesion that had disappeared; appearance of any new lesion; or death.

A confirmed partial response of nonmeasurable disease was defined as a reduction by more than 50 percent over baseline in two or more PSA measurements obtained at least four weeks apart, with no evidence of disease progression on imaging. Progressive disease was defined as a 25 percent increase in the serum PSA level — to at least 5 ng per milliliter — over the last preregistration measurement, with confirmation of the increase at least four weeks later. For patients with a decrease in serum PSA levels during the trial, progressive disease was defined as a confirmed increase of 25 percent, to at least 5 ng per milliliter over the nadir.[14]

STATISTICAL ANALYSIS

The primary objective of the study was to compare overall survival in the two groups. Assuming an exponential distribution of survival times, 3.5 years for accrual, an additional year of follow-up, and a sample size of 310 patients per group, this study had a statistical power of 0.80 to detect an improvement of 33 percent in median survival in the group given docetaxel and estramustine, as compared with the group given mitoxantrone and prednisone, with the use of a one-sided log-rank test at a P value of 0.025. Interim analyses were to be conducted when half the patients had been enrolled and again when enrollment was complete. The null and alternative hypotheses were to be tested at a one-sided P level of 0.0025 at each analysis. The significance level for the final analysis, performed one year after study closure, was specified as a one-sided P value of 0.02. However, in accordance with the policy of the *Journal*, only two-sided P values are reported. Secondary end points included progression-free survival, the objective-response rate, the rate of PSA response (defined as a decline in the serum PSA level of at least 50 percent), and adverse events. The data set was locked and analyzed on March 9, 2004.

Kaplan–Meier curves were used to estimate rates

of overall survival and progression-free survival. Survival was defined from the date of randomization to the date of death from any cause or censored at the date of last contact. Progression-free survival was defined as the time from randomization to the first occurrence of objective or PSA progression or death from any cause. The general chi-square test was used to compare rates of response (objective and PSA) and adverse events between the two treatment groups. All analyses were performed with the use of SAS software, version 9.0.

The study was designed by the Genitourinary Committee of SWOG and was approved by the Cancer Treatment and Evaluation Program of the National Cancer Institute. The SWOG Statistical Center received funding from Aventis Pharmaceuticals for the additional cost of collecting data on the quality of life. Aventis was allowed to review the protocol and make comments before enrollment began. Aventis had no access to the data but received a semiannual summary of enrollment and adverse events.

Table 1. Baseline Characteristics of the Patients.

Characteristic	Docetaxel and Estramustine	Mitoxantrone and Prednisone
No. randomized	386	384
No. eligible	338	336
Age (yr)		
Median	70	70
Range	47–88	43–87
Race or ethnic group (%)*		
White	86	82
Black	12	15
Hispanic	7	6
Asian	1	1
Unknown	1	1
SWOG performance-status score (%)		
0 or 1	90	88
2 or 3	10	12
Type of progression (%)		
Measurable or able to be evaluated	81	82
Increased PSA only	19	18
PSA (ng/ml)		
Median	84	90
Range	0.1–10,820	0.1–8378
Sites of disease (%) *		
Bone	84	88
Soft tissue		
Lymph node	24	26
Liver	8	9
Lung	10	10
Bone pain (%)		
Grade <2	64	64
Grade ≥2	36	36

* Patients could be included in more than one category. Race or ethnic group was self-reported.

RESULTS

CHARACTERISTICS OF THE PATIENTS

A total of 770 patients were enrolled between October 1999 and January 2003. Ninety-six patients (12 percent) were found to be ineligible: 30 owing to the lack of adequate withdrawal of antiandrogen or other hormonal therapy, 11 because of missing documentation, 31 because of inadequate baseline laboratory studies, 17 because of rising PSA levels without evidence of metastatic disease, and 7 for miscellaneous reasons. The baseline characteristics of the 674 eligible patients in both treatment groups were similar (Table 1). The sole evidence of disease progression was a rising PSA level in 18 percent of patients.

TREATMENT

There were 11 major protocol deviations. Six patients in the group given docetaxel and estramustine and four patients in the group given mitoxantrone and prednisone did not receive the assigned treatment and were not included in the evaluation of adverse events. One patient in the latter group who received intermittent radiotherapy while receiving the assigned treatment, a major protocol deviation, was included in the evaluation of adverse events. Six patients who discontinued treatment within one week after starting mitoxantrone and prednisone (four men) or docetaxel and estramustine (two men) were not included in the evaluation of adverse events; however, in the case of all these men, the reported results and statistical analyses are based on the treatment group to which the patients were assigned.

RESPONSE AND SURVIVAL

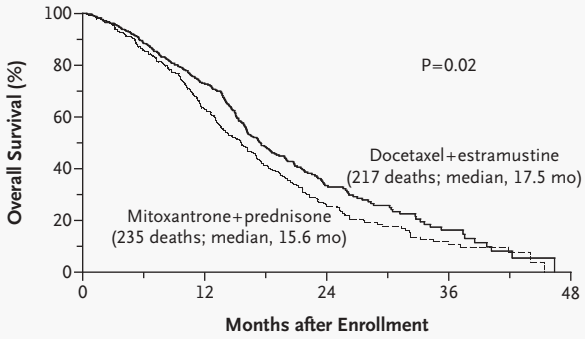
During a median follow-up of 32 months, 217 of the 338 patients in the group given docetaxel and estramustine died (64 percent), as did 235 of the 336 patients in the group given mitoxantrone and

prednisone (70 percent). According to the intention-to-treat analysis, the median survival was 17.5 months among the patients assigned to docetaxel and estramustine and 15.6 months among the patients assigned to mitoxantrone and prednisone (P=0.02) (Fig. 1); the corresponding hazard ratio for death was 0.80 (95 percent confidence interval, 0.67 to 0.97). The median time to progression was 6.3 months in the group given docetaxel and estramustine and 3.2 months in the group given mitoxantrone and prednisone (P<0.001) (Fig. 2).

Declines in serum PSA levels of at least 50 percent occurred more frequently after treatment with docetaxel and estramustine (155 of 309 patients, or 50 percent) than after treatment with mitoxantrone and prednisone (82 of 303 patients, or 27 percent; P<0.001). A partial response in measurable disease occurred in 17 percent of patients in the group given docetaxel and estramustine (17 of 103, 4 unconfirmed) and 11 percent of patients in the group given mitoxantrone and prednisone (10 of 93, 4 unconfirmed). This difference was not significant (P=0.30). Patients with an inadequate assessment were assumed to have had no response. There was no significant difference in pain relief, as reported by the patients, between the two groups (data not shown).

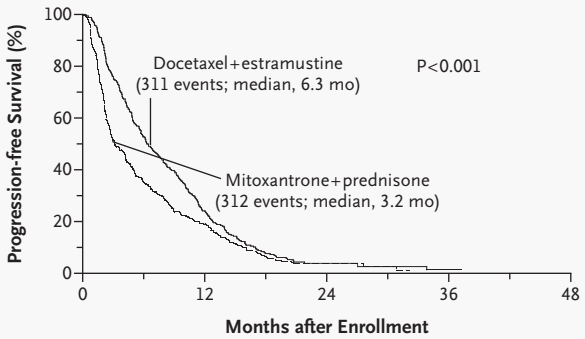
ADVERSE EVENTS

As of December 2003, all surviving patients had stopped the protocol treatment. Adverse events led to the withdrawal of 54 patients in the group assigned to docetaxel and estramustine (16 percent) and 32 patients in the group assigned to mitoxantrone and prednisone (10 percent). The rates of severe or life-threatening (grade 3 or 4) and fatal (grade 5) adverse events are summarized in Table 2. The rate of grade 3, 4, or 5 neutropenia in the group given mitoxantrone and prednisone did not differ significantly from that in the group given docetaxel and estramustine (12.5 percent vs. 16.1 percent, P=0.22). As compared with the group given mitoxantrone and prednisone, the group given docetaxel and estramustine had significantly higher rates of grade 3 or 4 neutropenic fevers (5 percent vs. 2 percent, P=0.01), cardiovascular events (15 percent vs. 7 percent, P=0.001), nausea and vomiting (20 percent vs. 5 percent, P<0.001), metabolic disturbances (6 percent vs. 1 percent, P<0.001), and neurologic events (7 percent vs. 2 percent, P=0.001). There were eight treatment-related deaths in the group given docetaxel and estramustine: three are still under review, a fourth was due to gastrointestinal bleeding thought to be due to aspirin, a fifth was caused by sepsis arising from necrotic prostate tissue, a sixth (due to liver and renal failure, atrial fibrillation, and pulmonary edema) occurred within a week after treatment was started, a seventh was associated with granulocytopenia and neutropenia, and the eighth was caused by a respiratory tract in-



No. at Risk				
Docetaxel+estramustine	338	218	60	13
Mitoxantrone+prednisone	336	185	50	10

Figure 1. Kaplan–Meier Estimates of Overall Survival among Men with Androgen-Independent Prostate Cancer Treated with Mitoxantrone and Prednisone or Docetaxel and Estramustine.



No. at Risk					
Docetaxel+estramustine	338	176	75	20	6
Mitoxantrone+prednisone	336	116	56	15	6

Figure 2. Kaplan–Meier Estimates of Progression-free Survival among Men with Androgen-Independent Prostate Cancer Treated with Mitoxantrone and Prednisone or Docetaxel and Estramustine.

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