Original Article

Ixabepilone, Mitoxantrone, and Prednisone for Metastatic Castration-Resistant Prostate Cancer After Docetaxel-Based Therapy

A Phase 2 Study of the Department of Defense Prostate Cancer Clinical Trials Consortium

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BACKGROUND: Mitoxantrone plus prednisone and ixabepilone each have modest activity as monotherapy for second-line chemotherapy in patients with docetaxel-refractory castration-resistant prostate cancer. Clinical noncross-resistance was previously observed. Phase 1 testing determined the maximum tolerated dose and dose-limiting toxicities with the combination regimen; a phase 2 study was conducted to evaluate the activity of the combination. **METHODS:** Patients with metastatic progressive castration-resistant prostate cancer during or after 3 or more cycles of taxane-based chemotherapy enrolled in a phase 2 multicenter study of ixabepilone 35 mg/m^2 and mitoxantrone 12 mg/m^2 administered on Day 1 every 21 days with pegfilgrastim support, along with prednisone 5 mg twice daily. Patients were evaluated for disease response and toxicity. **RESULTS:** Results are reported for the 56 evaluable patients. Twenty-five (45%; 95% confidence interval [CI], 31%-59%) experienced confirmed ≥50% prostate-specific antigen (PSA) declines, 33 (59%; 95% CI, 45%-72%) experienced confirmed ≥30% PSA declines, and 8 of 36 patients (22%; 95% CI, 10%-39%) with measurable disease experienced objective responses. Median time to PSA or objective progression was 4.4 months (95% CI, 3.5-5.6), and median progression-free survival was also 4.4 months (95% CI, 3.0-6.0). Median overall survival was 12.5 months (95% CI, 10.2-15.9). Thirty-two percent of patients experienced grade 3 of 4 neutropenia, and 11% experienced grade 3 or higher neutropenic infections, including 1 treatment-related death. Grade 2 and 3 neuropathy occurred in 11% and 12.5% of patients, respectively. **CONCLUSIONS:** These results suggest that the combination of ixabepilone and mitoxantrone is both feasible and active in castration-resistant prostate cancer and requires dosing with pegfilgrastim. ***Cancer* 2011;117:2419–25.** *© 2010 American Cancer Society.*

KEYWORDS: prostate cancer, chemotherapy, metastatic, mitoxantrone, ixabepilone, docetaxel.

Mortality in prostate cancer is primarily related to the development of metastatic castration-resistant disease, and options after docetaxel, the first-line standard of care, remain limited.[1] Recent data have established cabazitaxel as the standard second-line therapy.[2] Mitoxantrone with prednisone, which has been demonstrated to improve quality of life as front-line therapy, has been used extensively, with 50% PSA declines reported in 20% of patients previously treated with docetaxel.[3-5] Ixabepilone, an epothilone analog, has similarly been demonstrated to have a 17% response rate in this setting. Of interest, objective responses to mitoxantrone/prednisone after second-line ixabepilone and conversely to ixabepilone after second-line mitoxantrone/prednisone were observed during a randomized phase 2 study, suggesting there is noncross-resistance with the 2 regimens.

On the basis of the nonoverlapping toxicity of these regimens and their apparent noncross-resistance, a phase 1 study combining these agents was undertaken in patients previously treated with docetaxel.[6] The combination was well

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Presented in part at the Annual Meeting of the American Society of Clinical Oncology, Orlando, Florida, May 29-June 2, 2009.

DOI: 10.1002/cncr.25810, **Received:** June 23, 2010; **Revised:** September 21, 2010; **Accepted:** October 18, 2010, **Published online** December 29, 2010 in Wiley Online Library (wileyonlinelibrary.com)

tolerated. Although hematologic toxicity required treatment with pegfilgrastim, other toxicity, including neurotoxicity, was modest. The regimen recommended for phase 2 testing was mitoxantrone 12 mg/m^2 and ixabepilone 35 mg/m^2, given with prednisone 5 mg twice daily, along with pegfilgrastim 6 mg on Day 2. Responses, as defined by a $\geq$50% PSA decline, were observed in 31% of patients, with objective responses in 2 of 36 patients in the phase 1 study. When limited to the 21 patients treated with 12 mg/m^2 of mitoxantrone plus ixabepilone at a dose of 30 mg/m^2 or higher, 43% of patients experienced prostate-specific antigen (PSA) declines of $\geq$50% (95% confidence interval [CI], 22% to 66%). When compared with the response proportions reported for monotherapy with either ixabepilone or mitoxantrone of approximately 20%, these results suggested at least additive effects of the 2 agents and were sufficiently promising to warrant a phase 2 study to determine the activity of this novel regimen.

MATERIALS AND METHODS

Study Design

This study was a multicenter, single-arm, phase 2 study of ixabepilone and mitoxantrone with prednisone in castration-resistant prostate cancer patients who developed progressive disease during or after docetaxel-based chemotherapy. This study was undertaken in the Department of Defense Prostate Cancer Clinical Trials Consortium, with accrual occurring at 6 academic centers. The primary endpoint of the study was the proportion of patients achieving $\geq$50% PSA declines. Secondary endpoints included overall safety, the frequency of objective responses, time to progression, progression-free survival, and overall survival. This study was approved by the Clinical Trial Evaluation Program of the National Cancer Institute, the Prostate Cancer Clinical Trials Consortium Review Committee, and the local institutional review boards of participating institutions. All patients provided written informed consent.

Eligibility

Patients were required to have histologically confirmed prostate cancer with metastatic spread and progressive disease despite castrate testosterone levels. Patients were required to have received at least 3 cycles of taxane-based chemotherapy, and only 1 prior chemotherapy regimen was permitted. For patients with measurable disease, progression was defined according to Response Evaluation Criteria in Solid Tumors (RECIST), and for patients without measurable disease, a PSA of $\geq$2 ng/mL and a bone scan consistent with metastasis were required. Patients without measurable disease were required to have either PSA progression or a bone scan demonstrating 1 or more new metastatic lesions. PSA progression was defined according to PSA Working Group 1 criteria.[7] Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 and $\leq$grade 1 peripheral neuropathy (National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0). Patients who had not undergone prior orchiectomy were required to remain on a luteinizing hormone-releasing hormone agonist. Other hormonal therapy, with the exception of prednisone 5 mg twice daily, as given with docetaxel, was not allowed within 4 weeks of study entry. Docetaxel was not allowed within 4 weeks of enrollment. No prior mitoxantrone or ixabepilone was allowed. Radiation or radiopharmaceutical therapy must have been completed at least 4 and 8 weeks, respectively, before enrollment. Cardiac ejection fraction was required to be above the lower limit of normal for the institution. Patients with clinically significant cardiovascular disease, including New York Heart Association class III or IV heart failure, active angina, or a history of myocardial infarction within 6 months, were excluded. Laboratory requirements included testosterone $<$50 ng/dL; creatinine $\leq 1.5 \times$ upper limit of normal (ULN) or calculated creatinine clearance $\geq$40 mL/min; alanine aminotransferase (ALT) and aspartate aminotransferase (AST) $<2.5 \times$ ULN; granulocytes $\geq$2000/mm^3; platelets $\geq$100,000/mm^3; and total bilirubin $\leq 1.5 \times$ ULN. Because ixabepilone is a CYP3A4 substrate, concurrent use of moderate to strong CYP3A4 inhibitors was prohibited.

Study Therapy

Patients were treated on day 1 of 21-day cycles. Premedication with oral H1- and H2-blockers was administered 1 hour before treatment to prevent hypersensitivity reactions. Patients received mitoxantrone 12 mg/m^2 intravenously over 30 minutes. Ixabepilone 35 mg/m^2 was subsequently administered as a continuous infusion over 3 hours. Patients were monitored for hypersensitivity reactions for 1 hour. If grade 2 to 4 hypersensitivity reactions developed despite antihistamine premedication, corticosteroid premedication was used for subsequent cycles. Prednisone was administered 5 mg twice daily continuously. Pegfilgrastim 6 mg was administered subcutaneously on Day 2. Patients were treated until disease

progression, unacceptable toxicity, or patient preference to discontinue therapy.

Assessment for Response and Toxicity

Patients were assessed with chest x-ray or chest computed tomography (CT), CT of the abdomen and pelvis, and bone scan every 3 cycles. PSA, complete blood count with differential and platelets, electrolytes, blood urea nitrogen, creatinine, magnesium, lactate dehydrogenase, albumin, AST, ALT, total bilirubin, and alkaline phosphatase were obtained every cycle. Physical examination and assessment of performance status were undertaken each cycle. Echocardiogram or MUGA (Multi Gated Acquisition) Scan was performed at baseline, every 3 cycles, and as clinically indicated.

Objective response was defined by RECIST, and both 50% and 30% PSA declines were determined, with a repeat PSA required 3 weeks later for confirmation.[7,8] Disease progression was defined as new metastases outside of the bone, $\geq$1 new bone lesions confirmed on repeat imaging, a need for radiation while on therapy, unequivocal progression of nontarget lesions, progression by RECIST, or PSA progression. PSA progression was defined according to PSA Working Group 1 criteria, with a PSA increase of 25% above the nadir value, occurring at least 9 weeks (3 cycles) after initiating the study.

Toxicity was monitored by history, physical examination, and laboratory assessment before each cycle. Adverse events were graded according to National Cancer Institute Common Toxicity Criteria version 3.0. For grade 3 or higher toxicities, both ixabepilone and mitoxantrone were held until resolution to $\leq$grade 1, then reinstituted at 5 mg/m^2 less of ixabepilone and 2 mg/m^2 less of mitoxantrone. The same process was required for recurrent toxicities, with a third recurrence resulting in removal from study therapy. For corticosteroid toxicity, prednisone doses could be modified without removing a patient from protocol therapy. For neurotoxicity secondary to ixabepilone, therapy was held for grade 2 or 3 toxicity but otherwise managed as above. Alopecia, lymphopenia, anemia, and toxicities related to androgen deprivation were excluded as dose-limiting or modifying criteria.

Statistical Considerations

The primary endpoint of this study was the proportion of patients responding to treatment defined as observing a PSA decline of $\geq$50% (PSA response) based on PSA Working Group 1 criteria. Treatment of 58 patients allowed for the detection of a PSA response proportion of 35%, compared with a null hypothesis of 20% with a power of 0.90 and a level of significance of 0.10. Simon's MiniMax 2-stage design was used for accrual, to allow for an interim analysis for efficacy after the first 33 patients had been accrued and had been followed for 3 cycles of treatment. Had 6 or fewer of the first 33 patients enrolled demonstrated a PSA decline of $\geq$50%, accrual would have been terminated, resulting in a probability of early termination if the null hypothesis were true of 50%. Objective responses were evaluated according to RECIST for patients with measurable disease. Descriptive statistics were calculated to characterize the patient cohort, baseline disease parameters, outcome, and toxicity. The time to progression, progression-free survival, and overall survival were measured from the start of protocol therapy and evaluated using the Kaplan-Meier product limit method.

RESULTS

Patient Characteristics

Between November 2007 and March 2009, 58 patients were enrolled at 6 member institutions of the Department of Defense Prostate Cancer Clinical Trials Consortium. Two patients were ineligible: 1 because of pre-existing spinal cord compression and 1 because of a secondary diagnosis of colon cancer diagnosed after 2 cycles of therapy; therefore, 56 evaluable patients were included in these analyses. Four patients did not complete the minimum 3 cycles of therapy defined by the protocol to be necessary for response assessment; 2 discontinued for progressive disease and 2 withdrew because of concerns over rising PSA. These 4 patients are included in both efficacy and toxicity analyses. Patient characteristics are summarized in Table 1. The median age of patients at the start of protocol therapy was 66.7 years. Sixty-nine percent of patients had a Gleason score of 8 to 10. Sixty-six percent had an ECOG performance status of 1 to 2, and 34% had an ECOG performance status of 0. The median PSA was 171.2 (range, 2.79-3717.1), and the median alkaline phosphatase was 134 (range, 42-1094). All patients had received prior docetaxel therapy once every 3 weeks. The median number of prior chemotherapy cycles was 8 (range, 3-33). The median prior treatment duration was 6.4 months (range, 2.2-29.1), and the median time between discontinuation of docetaxel and initiation of study therapy was 53 days (range, 5-413). Fifty percent of patients (28 of 56) had experienced a PSA response to prior taxane-based therapy by PSA Working Group 1

Table 1. Patient Characteristics (N=56)

Median age at entry (range)	66.7 (47-83)
ECOG PS at protocol entry, patients (%)	
0	19 (34)
1-2	37 (66)
Gleason score at diagnosis (n=54), patients (%)	
4-6	3 (5.5)
7	14 (26)
8-10	37 (68.5)
Median PSA, ng/mL (range)	171.2 (2.79-3717.1)
Baseline laboratory results at protocol entry	
Median LDH, IU/L (range)	290 (123-2333)
Median alkaline phosphatase, U/L (range)	134 (42-1094)
Median hemoglobin, g/dL (range)	11.7 (9.3-14.1)
Prior chemotherapy: best response, patients (%)	
PSA response/partial response	28 (50)
Stable disease for patients with objective disease	18 (32)
Progressive disease	10 (18)
Prior 3-week chemotherapy cycles, median No. (range)	8 (3-33)
Median duration, mo (range)	6.4 (2.2-29.1)
Median duration from end of taxane, d (range)	53 (5-413)
Study treatment	
Cycles received, median No. (range)	5+ (1-13)
Still on treatment, patients	1[a]

ECOG indicates Eastern Cooperative Oncology Group; PS, performance status; PSA, prostate-specific antigen; LDH, lactate dehydrogenase.
[a] Duration 10.4 months.

Table 2. Response Data

Response	No.	%
≥30% PSA decline	33	59
≥30% PSA decline by 12 weeks	31	55
≥50% PSA decline	25	45
≥50% PSA decline by 12 weeks	17	30
Objective responses	8/36	22

PSA indicates prostate-specific antigen.

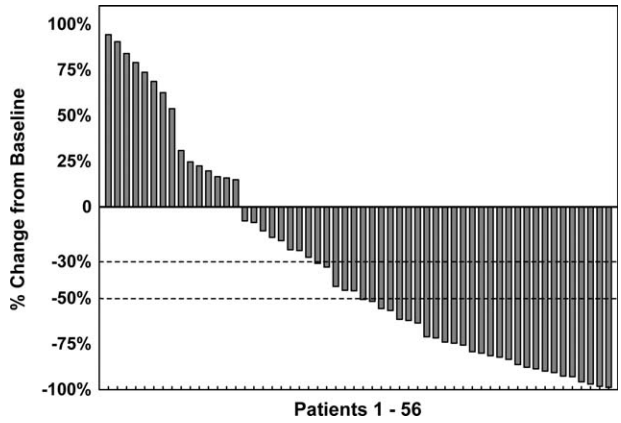

Figure 1. Maximum percentage change in prostate-specific antigen is shown.

criteria, whereas half of the enrolled patients never had a PSA response to docetaxel therapy. Fifty-nine percent of patients had subsequently progressed on docetaxel therapy by PSA criteria alone, 30% had radiographic progression, 9% stopped docetaxel therapy for toxicity, and 2% stopped with stable disease after completing a planned course of therapy. Thus, 89% of patients had developed docetaxel-resistant castration-resistant prostate cancer before enrolling on this trial. Twenty-five percent (14 patients) of patients received therapy after docetaxel but before beginning this study, including ketoconazole (n = 5), sunitinib (n = 3), bicalutamide (n = 2), palliative radiotherapy (N = 2), PSMA ADT (an antibody against prostate specific membrane antigen), and GVAX (a vaccine consisting of prostate cancer cells modified to secrete granulocyte-macrophage colony-stimulating factor), 1 each.

Clinical efficacy to ixabepilone and mitoxantrone with prednisone chemotherapy is reported for all 56 eligible patients (Table 2). Overall, 25 (45%) patients experienced confirmed PSA declines of ≥50% (Fig. 1; 95% CI, 31%-59%), and 33 (59%) had confirmed PSA declines of ≥30% (95% CI, 45%-72%). After 12 weeks of protocol therapy, 30% of the patients achieved PSA declines of at least 50%, indicating that the study null hypothesis of 20% can be rejected (1-sided binomial exact test: $P = .04$). Partial objective RECIST-defined responses were observed in 8 patients of 36 with measurable disease (22%; 95% CI, 10%-39%).

With a median follow-up of 9.9 months (range, 3.1-19.4) from the start of protocol therapy, the median time to progression was 4.4 months (95% CI, 3.5-5.6). The median PSA or objective progression-free survival was also 4.4 months (Fig. 2; 95% CI, 3.0-6.0), and the median overall survival was 12.5 months (Fig. 3; 95% CI, 10.2-15.9).

Patients with a prior response to docetaxel therapy were as likely to respond to ixabepilone and mitoxantrone with prednisone second-line therapy as patients with no prior response to docetaxel. Of the 28 patients who had a ≥50% PSA decline with docetaxel-based therapy, 39% had a ≥50% PSA decline with ixabepilone and mitoxantrone with prednisone. Of the 10 patients whose best

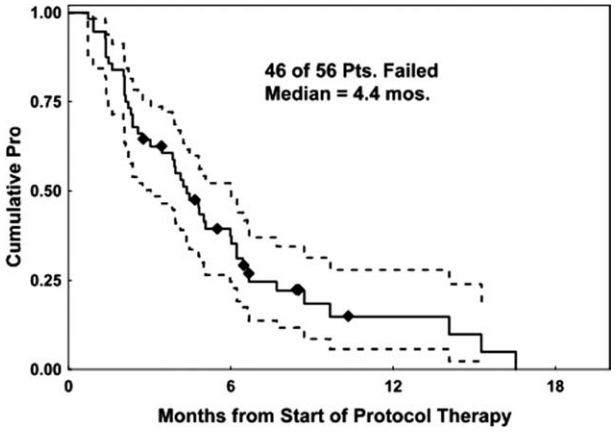

Figure 2. Progression-free survival with ixabepilone and mitoxantrone with prednisone is shown. Pro indicates progression; Pts., patients.

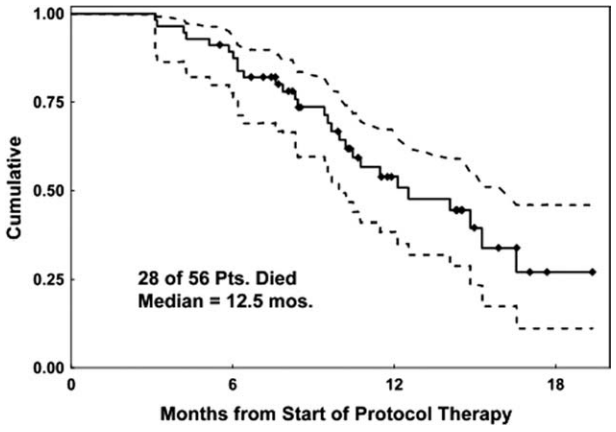

Figure 3. Overall survival with ixabepilone and mitoxantrone with prednisone is shown.

response to docetaxel-based therapy was progressive disease, 40% had a $\geq$50% PSA response to ixabepilone and mitoxantrone with prednisone ($P = .71$).

Toxicity

Toxicity data are reported for all 56 eligible patients and are summarized in Table 3. Thirty-two percent of patients experienced grade 3 or 4 neutropenia. Eleven percent of patients had neutropenia associated with infection. Five grade 3 infections occurred in 5 patients (2 pulmonary, 1 skin, 1 *Clostridium difficile* colitis, 1 septic arthritis of the elbow), and 1 grade 4 bacteremia occurred. One treatment-associated death occurred in the 1 patient on study on verapamil, a moderate CYP3A4 inhibitor. This patient experienced urosepsis in association with neutropenia. Grade 3 or higher thrombocytopenia and anemia were uncommon (18% and 7%, respectively). Cardiovascular toxicity included 1 grade 4 cardiac infarct, 1 grade 3 atrial fibrillation, and 1 grade 2 decrease in ejection fraction. Grade 2 and 3 sensory neuropathy was observed in 6 and 7 patients (11% and 13%), respectively. Other toxicities of note included grade 2 fatigue in 13 patients and grade 3 fatigue in 5 patients.

Table 3. Toxicity Related to Study Therapy

Adverse Event	Grade 3	Grade 4	Grade 5
Hematologic			
Leukopenia	9	11	
Lymphopenia	17	3	
Neutropenia	6	10	
Anemia	3	1	
Thrombocytopenia	7	3	
Nonhematologic			
Allergic reaction	1		
AST/ALT increased	1		
Dyspnea	2		
Fatigue	5		
Hyperbilirubinemia	1		
Hypoalbuminemia	1		
Infection	5[a]	1[a]	1[b]
Hypocalcemia	1		
Hypophosphatemia	1		
Mucositis	1		
Nausea/vomiting	1		
Neuropathy	7		
Vasovagal episode		1	

AST indicates aspartate aminotransferase; ALT, alanine aminotransferase.
[a] Sites of infection: skin (cellulitis), blood (methicillin-resistant *Staphylococcus aureus*, grade 4), pneumonia (2), colon (*Clostridium difficile* colitis), elbow (septic arthritis). All but septic arthritis associated with neutropenia. The *C. difficile* infection occurred in a patient with pneumonia treated with antibiotics.
[b] There was 1 treatment-related death in a patient with urosepsis and neutropenia who was on verapamil.

Treatment Administered

Patients were removed from study therapy primarily for progressive disease. Twenty-seven and 9 patients (48% and 16%) discontinued protocol treatment because of PSA and objective progression, respectively, and 4 (7%) others had both PSA and objective disease progression. Ten (18%) patients discontinued therapy for toxicity after a median of 7 cycles (range, 1-13). Two (4%) patients discontinued after completing 12 cycles, and 3 (5%) patients withdrew, 2 because of concerns over rising PSA, and 1 because of a combination of toxicity and concerns over rising PSA. One (2%) patient remains on therapy 10.6 months from the start of protocol therapy having received 8 cycles of therapy to date.

DISCUSSION

After progression on docetaxel-based chemotherapy, chemotherapy options for patients with metastatic castration-resistant prostate cancer remain poor. Recently reported data suggest that cabazitaxel may represent an important therapeutic option for patients with progressive disease after docetaxel.[2] Mitoxantrone with prednisone is often used as second-line therapy but is associated with a PSA response rate of only 20%.[5] Ixabepilone also has a disappointing PSA response rate of 17% after docetaxel. The objective response rates associated with ixabepilone monotherapy and mitoxantrone with prednisone after docetaxel are also low at 4% and 10%, respectively. On the basis of results from a randomized phase 2 study suggesting that ixabepilone and mitoxantrone with prednisone have noncross-resistance and a phase 1 trial of the ixabepilone and mitoxantrone with prednisone combination demonstrating surprisingly high activity, the present phase 2 trial was undertaken.[5]

The ixabepilone and mitoxantrone with prednisone regimen was found to have significant activity, with a PSA response proportion of 45%, and an equally promising objective response proportion of 22%. The overall survival in this group of patients was 12.5 months. Although direct comparisons are not possible across studies, and differences in patient populations may account for results observed, it is notable that the overall survival was 10.4 months on the ixabepilone arm (with mitoxantrone on progression) and 9.8 months on the mitoxantrone arm (with ixabepilone on progression) in the randomized phase 2 study of ixabepilone or mitoxantrone after docetaxel. The time to progression of 4.4 months also appears favorable in comparison to the 2.3-month time to progression on mitoxantrone monotherapy in the randomized phase 2 study.

Data from a randomized phase 3 study comparing cabazitaxel to mitoxantrone with prednisone in patients who had progressed after docetaxel-based therapy indicated that cabazitaxel was associated with a PSA response proportion of 39%, in comparison to 18% on the mitoxantrone/prednisone arm. Although these results cannot be directly compared with the results of the current study of ixabepilone with mitoxantrone and prednisone, the response proportion of 45% in the current study suggests further study may be warranted.

Of interest, response to ixabepilone and mitoxantrone with prednisone does not appear to be dependent on prior response to docetaxel. Although definitive conclusions cannot be drawn given the small numbers of patients, these data suggest that there is no significant cross-resistance between docetaxel and ixabepilone/mitoxantrone with prednisone, and that ixabepilone and mitoxantrone with prednisone therapy may be useful in patients with progressive disease after docetaxel, regardless of docetaxel sensitivity.

The combination of these 2 agents did not appear to result in a dramatic increase in toxicity. Although comparison across studies is fraught with difficulty, toxicity with the study regimen appears to be similar to that associated with mitoxantrone/prednisone use in the second-line alone. In the randomized phase 2 study of mitoxantrone/prednisone and ixabepilone monotherapy, 10% of the 41 patients on the mitoxantrone/prednisone second-line arm experienced febrile neutropenia, and 9% of the 56 patients on this study of the combination (with pegfilgrastim support) experienced febrile neutropenia. It is important to note, however, that this margin of safety can be achieved with the ixabepilone and mitoxantrone with prednisone regimen at the doses studied only with pegfilgrastim support.

Sixteen percent of patients discontinued therapy for toxicity in this phase 2 study of the combination, a number that appears to be similar to the number of patients discontinuing docetaxel as first-line treatment for toxicity. In the randomized phase 2 study of mitoxantrone or ixabepilone, 10% of the 41 patients on mitoxantrone discontinued therapy for toxicity.[1]

Nonhematologic toxicity was minimal. Despite substantial doses of mitoxantrone (66% of patients received >6 cycles), minimal cardiac toxicity was observed. Similarly, less neuropathy was observed than expected in this taxane-pretreated population, with 11% and 12.5% of patients developing grade 2 and 3 neurotoxicity, respectively. However, these results may reflect patient selection. As with the prior second-line ixabepilone prostate cancer studies, patients with grade 2 or higher neuropathy at baseline after docetaxel were excluded. This may have selected a patient population less likely to experience neuropathy. Nevertheless, neuropathy was comparable to that seen in breast cancer studies[9-13] in which 12% to 20% of patients develop grade 3 neurotoxicity.

One potential weakness of this study is that the eligibility criteria did not require a previous history of progression while receiving docetaxel-based therapy, but rather required disease progression during or after docetaxel therapy, possibly selecting for a more chemotherapy-sensitive population. However, 89% of the patients on study had, in fact, progressed while receiving docetaxel therapy, suggesting that this study enrolled patients with

docetaxel resistance. Furthermore, there did not appear to be a difference in response proportion as a function of prior response to docetaxel, although small numbers limit this analysis.

Another potential criticism of this study is that the primary endpoint, the proportion of patients achieving a $\geq$50% decline in PSA, per PSA Working Group Criteria, is of uncertain clinical significance. However, the PSA Working Group criteria were initially established to be used specifically in this setting, as a screen for the activity of cytotoxic agents in the phase 2 setting.[7] In addition, the objective response proportion, time to progression, and overall survival observed with ixabepilone and mitoxantrone with prednisone therapy all appeared to be favorable compared with that associated with mitoxantrone monotherapy, suggesting that the high proportion of patients with an observed PSA decline may be associated with improved survival outcomes. Definitive evidence of benefit can only be established by evaluating overall survival in a phase 3 study.

In summary, the combination of ixabepilone and mitoxantrone with prednisone appears to have greater activity than either mitoxantrone or ixabepilone alone in the second-line setting for castration-resistant prostate cancer, and suggests at least additive if not synergistic activity in a disease state where improvement in outcome is needed and long overdue. The combination is well tolerated, although some hematologic toxicity is present and dosing with pegfilgrastim is required. The results of this study suggest that it is appropriate to study further the ixabepilone and mitoxantrone with prednisone regimen in patients with docetaxel-resistant castration-resistant prostate cancer.

CONFLICT OF INTEREST DISCLOSURES

This study was supported in part by: Department of Defense Physicians Research Training Grant No. W81XWH-05-1-175 from the Cancer Therapy Evaluation Program of the National Cancer Institute, Department of Defense Prostate Cancer Clinical Trials Consortium Grant No. W81XWH-06-01-0256, and the Prostate Cancer Foundation.

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