

Activity of Second-Line Chemotherapy in Docetaxel-Refractory Hormone-Refractory Prostate Cancer Patients

Randomized Phase 2 Study of Ixabepilone or Mitoxantrone and Prednisone

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BACKGROUND. This randomized, noncomparative, multicenter, clinical trial evaluated ixabepilone or mitoxantrone/prednisone (MP) as second-line chemotherapy for taxane-refractory, hormone-refractory, prostate cancer (HRPC).

METHODS. Patients with HRPC that progressed during or within 60 days of cessation of taxane chemotherapy were randomly selected with equal probability to ixabepilone 35 mg/m² intravenously every 3 weeks, or mitoxantrone 14 mg/m² intravenously every 3 weeks and prednisone 5 mg orally twice daily. Treatment continued until progression or toxicity; crossover was allowed.

RESULTS. Forty-one patients were accrued to each arm of the study. The median number of cycles administered for each arm was 3. Median survival from protocol entry was 10.4 months with ixabepilone and 9.8 months with MP. Prostate-specific antigen (PSA) declines of $\geq 50\%$ were observed in 17% of ixabepilone (95% CI, 7-32) and 20% of second-line MP patients (95% CI, 9-35). Partial responses were observed in 1 of 24 ixabepilone and in 2 of 21 MP patients with evaluable measurable disease. Median duration of second-line ixabepilone and MP treatment was 2.2 months and 2.3 months, respectively. For third-line crossover treatment, PSA declines of $\geq 50\%$ were observed in 3 of 27 ixabepilone-treated and 4 of 15 MP-treated patients. Prior taxane response was associated with an increased likelihood of second-line ixabepilone or MP response. Low baseline lactate dehydrogenase and absence of visceral metastases independently predicted improved survival. The most common grade 3/4 toxicity associated with second-line treatment was neutropenia (54% of ixabepilone patients and 63% of MP patients).

CONCLUSIONS. Ixabepilone and MP had modest activity as second-line chemotherapy for docetaxel-refractory HRPC. The median survival for the entire cohort treated in this study was 9.8 months. *Cancer* 2007;110:556–63. © 2007 American Cancer Society.

KEYWORDS: prostate cancer, taxane, hormone, refractory, ixabepilone, mitoxantrone, prednisone, second-line therapy.

Chemotherapy for taxane-refractory, hormone-refractory, prostate cancer (HRPC) is effective at prolonging survival and palliating symptoms. Two large phase 3 studies demonstrated that first-line docetaxel chemotherapy is associated with an improvement in median survival compared with mitoxantrone/prednisone (MP).^{1,2}

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Nearly all HRPC patients eventually progress during or after taxane-based treatment. Many patients have a good performance status and wish additional treatment. No standard chemotherapy exists for second-line treatment of patients with HRPC after progression on taxane-based therapies, although the community de facto standard has become MP.

The natural history of taxane-refractory (TR) HRPC has not been prospectively defined. Although second-line chemotherapy trials have been reported in HRPC, these trials are difficult to interpret because of heterogeneity of patient populations. Most importantly, those trials did not restrict enrollment to overtly TR-HRPC.

Resistance to taxanes appears mediated by tubulin mutation and multidrug resistant (MDR) gene overexpression. The epothilones are a new class of nontaxane tubulin polymerization agents whose cytotoxic activity has been linked to stabilization of microtubules, bypassing known taxane-resistant mechanisms.^{3,4} Ixabepilone (Bristol-Myers Squibb, New York, NY) is a semisynthetic analog of epothilone B that blocks the mitotic phase of the cell cycle. It is a highly potent cytotoxin, and preclinical data demonstrate noncross-resistance with taxanes. Ixabepilone has demonstrated antitumor activity as first-line chemotherapy in patients with metastatic HRPC.^{5,6}

The preclinical data indicating noncross-resistance of ixabepilone with taxanes, the front-line activity of ixabepilone in HRPC, and the lack of prospective data regarding MP as second-line chemotherapy provided the rationale for a randomized, non-comparative, phase 2 study in TR-HRPC. This study randomly assigned patients with TR-HRPC to either single-agent ixabepilone or the perceived community standard, MP.

MATERIALS AND METHODS

Study Design

This study was a multicenter, randomized, non-comparative phase 2 study. Patients were randomly assigned with equal probability to either MP or ixabepilone. The primary endpoint was the frequency of $\geq 50\%$ PSA declines with each second-line regimen. Secondary endpoints included safety, response duration, time to progressive disease, third-line (post-crossover) activity of each regimen, and overall survival.

Eligibility Criteria

All patients had histologically confirmed metastatic prostate cancer. Patients were required to have progressive disease despite castrate testosterone levels and at least 2 cycles of taxane-based chemotherapy,

with disease progression documented during or within 60 days of completing taxane-based chemotherapy. For patients with measurable disease, progression was defined by RECIST criteria.⁷ For patients without measurable disease, a positive bone scan and elevated PSA greater than 5 ng/mL were required. PSA evidence for progressive prostate cancer was defined by Consensus Criteria.⁸

All patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2 and \leq grade 1 neuropathy (Common Toxicity Criteria, version 2.0). Hormonal therapy other than luteinizing hormone-releasing hormone (LHRH) agonists was not allowed within 4 weeks of trial enrollment (6 weeks for bicalutamide or nilutamide). Treatment with a corticosteroid as part of first-line chemotherapy was discontinued over 10-14 days before enrollment. Any radiation therapy or radiopharmaceutical treatment must have been completed more than 4 weeks and 8 weeks before enrollment, respectively. All patients were required to have a cardiac ejection fraction greater than the institutional lower limit of normal. Patients were excluded for significant cardiovascular disease including congestive heart failure (New York Heart Association [NYHA] class III or IV), active angina pectoris, or myocardial infarction within 6 months before enrollment. Patients with known active brain metastases were excluded. Required laboratory values included testosterone < 50 ng/dL; creatinine $< 1.5 \times$ upper limits of normal (ULN) or calculated creatinine clearance > 40 mL/min; alanine aminotransferase (ALT) and aspartate transaminase (AST) $< 3 \times$ ULN; granulocytes $> 1500/\text{mm}^3$; platelets $\geq 100,000/\text{mm}^3$; total bilirubin $< 1.5 \times$ ULN; and, if no measurable disease, a PSA ≥ 5 ng/mL.

This clinical trial was sponsored by the Cancer Therapy Evaluation Program of the National Cancer Institute and approved by the review boards of each participating institution. All patients provided written informed consent.

Randomization and Treatment Plan

Eligible patients were randomly selected by the coordinating center statistician with equal probability to receive either ixabepilone or MP. Allocation to a treatment arm was concealed until the patient was enrolled. Patients were stratified by performance score (0 vs 1-2) and study site, and they were randomly assigned from within each stratum. Treatment assignment was balanced after every 4 patients within each stratum.

Ixabepilone 35 mg/m² was administered intravenously over 3 hours every 21 days. Patients were

premedicated with H1- and H2-blockers before ixabepilone infusion to prevent hypersensitivity reactions related to Cremophor EL diluent (BASF Group, Ludwigshafen, Germany) Corticosteroids were used with subsequent cycles for prior grade 2-4 hypersensitivity reactions to ixabepilone. Mitoxantrone 14 mg/m² was administered intravenously every 21 days with prednisone 5 mg orally twice daily. Treatment for all patients was continued until disease progression or unacceptable toxicity occurred. Myeloid growth factors were administered according to American Society for Clinical Oncology (ASCO) guidelines.⁹ Patients underwent imaging with chest s-ray, bone scan, and computed tomography (CT) or magnetic resonance imaging (MRI) of the abdomen and pelvis at baseline and after every 3 cycles. Electrocardiogram and multiple gated-acquisition (MUGA) scan or echocardiogram were obtained at baseline and repeated every 3 cycles for MP patients. Imaging studies were obtained at the time of crossover.

Dose Modifications

Dose modifications were made according to maximal toxicity. Doses were reduced for Day 1 neutrophil count <1500/m³ or platelet count <100,000/m³, ≥grade 3 nonhematologic toxicity, grade 4 neutropenia lasting for more than 7 days, grade 4 neutropenia and fever, and nadir platelet count <25,000. Ixabepilone dose was reduced by 5 mg/m², and mitoxantrone dose was reduced by 2 mg/m² for each dose reduction. Grade 2 neurotoxicity of any duration and grade 3 neurotoxicity lasting ≤7 days required dose reduction. Recurrent grade 3 neurotoxicity, grade 3 neurotoxicity of >7 days duration, or grade 4 neurotoxicity required discontinuation of treatment. Patients were removed from protocol therapy for a treatment delay greater than 3 weeks or recurrence of the same grade ≥3 toxicities despite 2 dose reductions.

Crossover Therapy

Patients who progressed after at least 2 cycles of protocol treatment or who stopped treatment for toxicity or other medical reasons were eligible to receive the alternate treatment. For patients initially treated with MP, prednisone was tapered over 10–14 days before starting ixabepilone.

Statistical Considerations

This was a noncomparative randomized phase 2 study to assess safety and efficacy of 2 treatment regimens, ixabepilone and MP, as second-line ther-

apy for metastatic TR-HRPC patients. The primary endpoint was the frequency of PSA declines ≥50% with second-line therapy, confirmed with 2 consecutive measurements. Response to therapy was determined for each patient by using PSA declines for nonmeasurable disease, and RECIST criteria for measurable disease, bone scans, and nontarget lesions.^{7,8} For each treatment arm, a ≥50% PSA decline in at least 25% of patients was considered promising and worthy of further investigation. Accrual of 40 patients to each treatment arm was sufficient to detect a 25% response proportion compared with a null hypothesis of ≤10%. A statistical level of significance of 0.04 for a directional test and power of 0.82 was assumed to test this hypothesis. Secondary endpoints included response duration, time to PSA progression, overall survival, frequency of toxicity, and frequency of response to third-line (crossover) treatment.

Comparability of the 2 treatment subsets was evaluated by using Fisher exact test for categorical variables (eg, Gleason score), Student *t* test for continuous variables (eg, lactate dehydrogenase [LDH]), and the Mann-Whitney test for distributions (eg, PSA). The effect of prior taxane response on second-line treatment response was analyzed by using the Mantel-Haenszel tests of association and homogeneity stratified by the second-line therapy.¹⁰ Duration of time to progression and overall survival were calculated from the start of second-line therapy with the Kaplan-Meier product-limit method.¹¹ Comparisons of a difference in distributions between subsets were performed by using the log-rank test.¹² Cox proportional hazard model was used to identify independent disease features of overall survival for the entire sample.¹³ Variables predictive of overall survival based on the log-rank test were considered in building a model. A forward stepwise approach was used with the likelihood ratio test to determine significant independent predictors of survival.

RESULTS

Patient Characteristics and Disposition

Between February 2003 and June 2005, 86 patients were entered at 6 participating centers. Four patients who never started protocol therapy were not included in the analysis, thus 82 patients were evaluable. Forty-one patients were randomly assigned to each treatment arm (Fig. 1). Patient baseline characteristics are detailed in Table 1. Both arms were balanced. All patients who received any protocol chemotherapy were included in evaluations of response and toxicity.

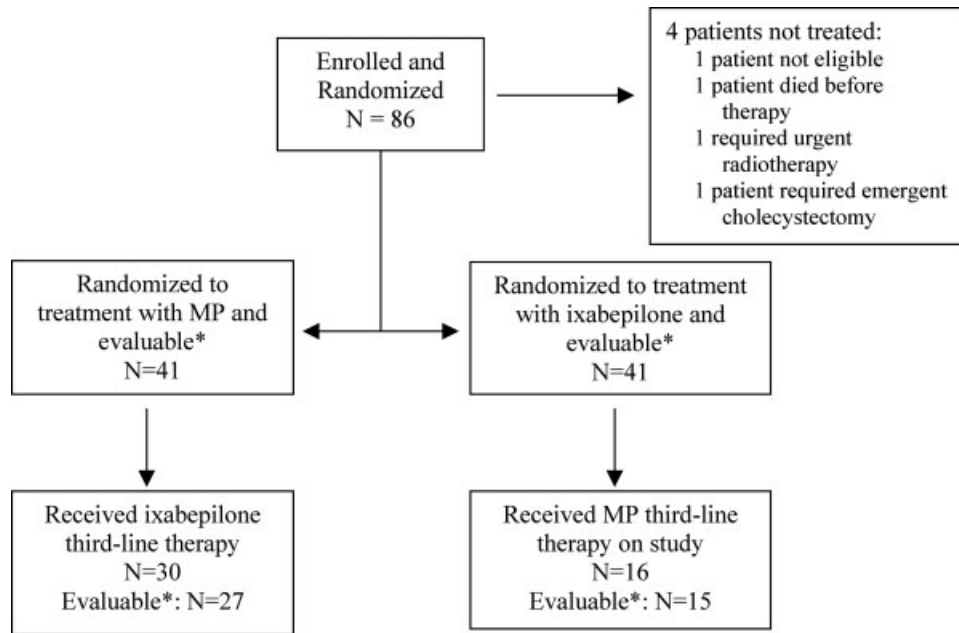


FIGURE 1. Patient Disposition. *Received at least 2 cycles of therapy.

TABLE 1
Baseline Patient Characteristics

2 nd Line treatment	Ixabepilone n = 41	MP n = 41
Median age, y (range)	66.5 (51-87)	69 (52-84)
ECOG PS		
0	15 (37%)	15 (37%)
1-2	26 (63%)	26 (63%)
Prior therapy		
Radiation (RT)	10 (24%)	7 (17%)
Prostatectomy (RP)	16 (39%)	15 (37%)
RP+RT	2 (5%)	5 (12%)
Other	13 (32%)	14 (34%)
Median PSA, ng/mL (range)	141 (4-17,995)	113 (7-1587)
Gleason score	n = 37	n = 38
Range	5-10	5-10
5-6	14%	11%
7	32%	18%
8-10	54%	71%
Median LDH, IU/L (range)	266 (103-2291)	273 (101-3065)
Median alkaline phosphatase, U/L (range)	126 (58-1432)	156 (45-664)
Median hemoglobin, g/dL (range)	11.7 (8.8-14.0)	12.2 (8.9-14.7)
Mean No. prior taxane chemotherapy cycles (range)	5.6 (2-25)	6.8 (2-17)
Prior chemotherapy		
Docetaxel-based	18 (45%)	18 (47%)
Docetaxel/estramustine-based	22 (55%)	20 (53%)

Second-Line Study Treatment

A median of 3 cycles of ixabepilone (range, 1 to 22 cycles) and 3 cycles of MP (range, 1 to 12 cycles) were administered as second-line treatment. Thirty-two percent of ixabepilone patients and 27% of MP patients received at least 5 cycles of therapy. Treat-

ment with ixabepilone was discontinued in 7 patients for toxicity, 1 for withdrawal of consent, and 33 patients for disease progression (23 for PSA progression, 6 for objective progression, 1 for both PSA and objective progression, and 4 for clinical and/or symptomatic progression that required additional

TABLE 2
Response to Second-line Therapy

	2 nd -Line Ixabepilone no. (%)	2 nd -Line MP no. (%)
Evaluable patients	41	41
Confirmed PSA decline $\geq 50\%$, 95% CI	7 (17, 7-32)	8 (20, 9-35)
Unconfirmed PSA decline $\geq 50\%$	1 (2)	—
Objective disease responses		
Measurable disease	30	23
Evaluable patients*	24	21
Partial response (RECIST)	1	2

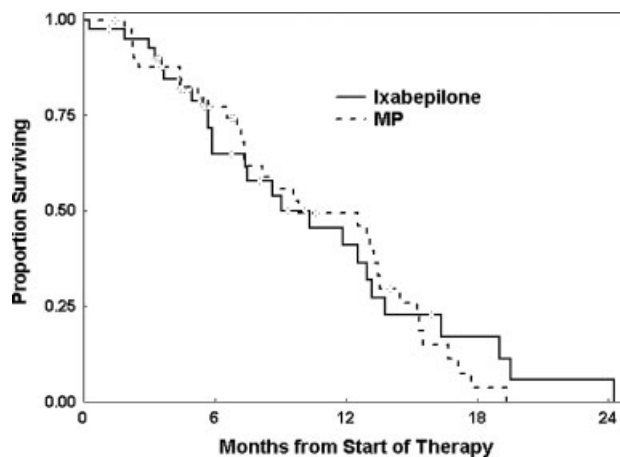
* Received at least 2 cycles.

therapy). Treatment with MP was discontinued in 4 patients for toxicity and in 36 patients for disease progression (28 for PSA progression, 6 for objective progression, 2 for both PSA and objective progression). One MP patient died on study of unrelated causes.

Response

Of 41 patients treated with second-line ixabepilone, 7 had a confirmed $\geq 50\%$ PSA decline (17%; 95% CI, 7-32; Table 2). One additional patient had an unconfirmed $\geq 50\%$ PSA decline. The median time to a $\geq 50\%$ PSA decline was 6 weeks (range, 3-14 weeks). Twenty-four patients treated with at least 2 cycles of second-line ixabepilone had measurable disease, and, of these, 1 (4%) patient had an objective partial response in addition to a PSA response. The median time to PSA progression on ixabepilone was 2.2 months, and the median duration of response was 3.8 months (range, 2.8-22.3 months). Three confirmed responders discontinued treatment for toxicity (motor neuropathy, atrial arrhythmia, and grade 2 infusion-site reaction), and 4 confirmed responders discontinued because of progressive disease.

Of the 41 patients treated with second-line MP, 8 had a confirmed $\geq 50\%$ PSA decline (20%; 95% CI, 9-35; Table 2). For responders, the median time to a $\geq 50\%$ PSA decline was 7 weeks (range, 3-19 weeks). Twenty-one patients treated with at least 2 cycles of second-line MP had measurable disease, and, of these, 2 (10%) patients had an objective partial response, 1 of whom also had a PSA response. The median time to PSA progression on MP was 2.3 months, and the median duration of PSA response for responders was 5.9 months (range, 2.7-8.2 months). Three responders discontinued treatment because of toxicity (minor decreases in cardiac ejection fraction did not meet criteria for an adverse event according to National Cancer Institute's Common Toxicity Crite-

**FIGURE 2.** Overall survival.

ria v2.0 in 2 patients; thrombocytopenia occurred in 1 patient), 4 discontinued for progressive disease, and 1 died without disease progression.

An exploratory analysis of the impact of initial response to front-line taxane-based therapy on response to second-line therapy was performed. Stratified by second-line treatment, there was a significantly greater response to second-line therapy among patients who previously responded to taxane therapy (Mantel-Haenszel test: $P = .0004$).¹⁰ The association was similar for both second-line treatment groups (test of homogeneity: $P = 0.87$). Among patients with a prior PSA response to taxane chemotherapy, 36% (5 of 14; 95% CI, 13-65) responded to ixabepilone and 35% (7 of 20; 95% CI, 5-59) responded to MP. In patients without prior PSA response to taxane-chemotherapy, 4% (1 of 26; 95% CI, 0-20) of patients responded to ixabepilone, and 5% (1 of 21; 95% CI, 0-24) responded to MP.

Survival

Evaluation of survival by treatment is complicated by the finding that 56% of patients received the alternate therapy on crossover. However, the median survival for each arm was 10.4 months for ixabepilone and 9.8 months for MP (Fig. 2). The median overall survival for the entire study was 9.8 months, and did not show differences based on prior taxane response.

Potential disease features predictive of survival from the start of second-line therapy were evaluated in patients enrolled on this study in an exploratory analysis. When the entire study sample was dichotomized at the median baseline value, a significantly prolonged survival was observed for decreased LDH (≤ 270 vs >270), decreased alkaline phosphatase (≤ 130 vs >130) and increased hemoglobin (≤ 12 vs >12) ($P = .007$, $.003$, and $.01$, respectively).

TABLE 3
Maximal Grade 3-4 Hematologic Toxicity

	Ixabepilone		MP	
	2 nd -Line, n = 41	3 rd -Line, n = 29	2 nd -Line, n = 41	3 rd -Line, n = 16
	No. (%)	No. (%)	No. (%)	No. (%)
Anemia	4 (10)	2 (7)	1 (2)	—
Neutropenia	22 (54)	10 (33)	26 (63)	10 (63)
Febrile neutropenia	2 (5)*	2 (7)	4 (10)	—
Thrombocytopenia	3 (7)	3 (10)	1 (2)	1 (6)

* 1 patient died of neutropenic sepsis.

The 3 laboratory parameters were highly correlated ($P < .002$ for all pairwise comparisons). Patients without visceral disease also achieved a significantly longer survival ($P = .02$). Categorized LDH (≤ 270 vs >270) was highly associated with visceral disease ($P = .005$). There was no difference in survival due to baseline performance score, PSA, or Gleason score. When the 4 individual parameters significant to predicting survival were considered simultaneously by using Cox proportional hazard model, a decreased LDH and absence of visceral metastases emerged as significant independent predictors of prolonged survival (likelihood ratio test, $P = .0003, .04$, respectively).

Toxicity

Grade 3 or 4 neutropenia occurred in 54% and 63% of patients treated with second-line ixabepilone and MP, respectively (Table 3). Febrile neutropenia and neutropenic infection occurred in 4 patients treated with second-line MP and 3 patients treated with second-line ixabepilone (including 1 patient who died from neutropenic sepsis). Treatment-related nonhematologic toxicities observed in $\geq 5\%$ of patients treated with second-line ixabepilone included anorexia, stomatitis, fatigue, muscle weakness, and prolonged prothrombin time (Table 4). Treatment-related nonhematologic toxicity observed in $\geq 5\%$ of patients treated with second-line MP included prolonged prothrombin times and liver function abnormalities. Dose reduction or delay were required in 20 of 41 (49%) patients treated with second-line ixabepilone and 10 of 41 (24%) patients treated with second-line MP.

Crossover Therapy

Sixteen of 41 (39%) patients on second-line ixabepilone crossed over to MP treatment. Of the 25 patients who did not cross over to MP, 8 withdrew consent, 2 died, and 14 experienced clinically signifi-

TABLE 4
Maximal Grade 3-4 Treatment-Related Non-Hematologic Toxicity

Grade	Ixabepilone				MP			
	2 nd -Line, n = 41		3 rd -Line, n = 30		2 nd -Line, n = 41		3 rd -Line, n = 16	
	3	4	3	4	3	4	3	4
GI								
Nausea/vomiting	2		1					2
Anorexia	2							
Stomatitis/pharyngitis	3		1					
Diarrhea			1					
Constipation						1		
Dehydration	1		3					
Hepatic	2		1			4		
Hypotension				3				
Fatigue	1	1		4				
Muscle weakness	2			2				
Renal		1						
Neurologic								
Motor neuropathy	1			2				
Sensory neuropathy				1				
CNS ischemia		1						
Syncope	1							
Lightheadedness	1			1				
Mood alteration	1							
Elevated PT	3		1			2		
Metabolic								
Hypophosphatemia	1			3				
Hypoglycemia						1		
Hyperuricemia		1						
Hypercalcemia		1	1					
Hypokalemia				1				
Hypersensitivity		1	1					

The following grade 3 toxicities occurred with second-line ixabepilone in 1 patient: thrombosis, atrial arrhythmia, urinary obstruction, and chest pain.

cant disease progression and/or treatment-related toxicity such that they did not cross over. Four of 15 evaluable patients who received third-line MP achieved a confirmed $\geq 50\%$ PSA decline (27%; 95% CI, 8-55; Table 5). One of 9 (11%) patients with measurable disease and at least 2 cycles of therapy demonstrated an objective response to third-line MP in addition to a PSA response.

Thirty of 41 (73%) patients on second-line MP crossed over to ixabepilone therapy. Of the 11 patients who did not cross over to ixabepilone, 2 withdrew consent, 1 died, 1 was not eligible to continue on study because of decreased clinical status, and 7 patients experienced clinically significant disease progression and/or treatment-related toxicity such that they did not cross over. Three of 27 (11%; 95% CI, 2-29) evaluable patients achieved a confirmed $\geq 50\%$ PSA decline to third-line ixabepilone. One of 14 (7%) patients with measurable disease and at least

TABLE 5
Response to Crossover Therapy

	3 rd -Line MP, n = 16	3 rd -Line ixabepilone, n = 30
PSA responses	No. (%)	No. (%)
Evaluable patients*	15	27
Confirmed PSA decline $\geq 50\%$, 95% CI	4 (27, 8-55)	3 (11, 2-29)
Unconfirmed PSA decline $\geq 50\%$	—	1 (4)
Objective disease responses		
Measurable disease	11	15
Evaluable patients*	9	14
Partial response (RECIST)	1	1

* Received at least 2 cycles.

2 cycles of therapy demonstrated both an objective and a PSA response.

None of the patients who achieved a PSA response to third-line therapy demonstrated a PSA response to second-line treatment. None of the patients who responded to third-line ixabepilone and only 1 patient who responded to third-line MP had achieved a previous response to front-line taxane chemotherapy.

DISCUSSION

This study evaluated second-line chemotherapy in TR-HRPC patients to address the question of clinical cross-resistance between taxanes, epothilones, and mitoxantrone, as well as to explore the natural history of chemotherapy-refractory HRPC. MP is the de facto community standard second-line chemotherapy for HRPC in the absence of prospective data in this setting. Therefore, determining the activity of second-line MP is important not only to understand the usefulness of this regimen as second-line chemotherapy but also to define its activity as a control arm for future second-line clinical trials. Encouraging preclinical activity in taxane-resistant model systems and substantial activity seen in front-line HRPC chemotherapy support the testing of ixabepilone in the second-line setting.

The median survival for patients with TR-HRPC has not been prospectively evaluated. In the present multicenter study, the median survival of all patients was 9.8 months from the initiation of second-line chemotherapy. As study treatments demonstrated only modest activity in this setting, this value provides a useful estimate of survival as a baseline for development of future clinical trials in this patient population.

Treatment of TR-HRPC with MP or ixabepilone demonstrated only modest activity. The PSA response proportions for MP and ixabepilone were 20% and

17%, respectively. Objective responses were infrequent ($\leq 10\%$ each arm). Although this study was not designed to compare the 2 regimens, the levels of activity in this study appear similar between the 2 arms. The anticancer activity of ixabepilone as measured by PSA declines and objective tumor responses contrasts with results of chemotherapy-naive HRPC trials with this drug. Although 17% of patients did experience PSA responses to ixabepilone in this study, this level of activity is not sufficient to justify further evaluation of ixabepilone in this dose and schedule as single-agent second-line HRPC chemotherapy.

Although patients were required to have progressive disease during or shortly after stopping taxane chemotherapy, 35% of ixabepilone and 49% of MP patients previously experienced a $\geq 50\%$ PSA decline to first-line taxane therapy. A retrospective analysis demonstrated that patients who experienced a PSA response to prior therapy were 7-fold to 8-fold more likely to respond to either second-line regimen. On the basis of these findings, future randomized studies should stratify patients for best response to prior therapy. In addition, patients who never responded to taxane-based therapy are unlikely to respond to ixabepilone or MP, and investigational therapy should be considered. In an exploratory analysis, elevated LDH and the presence of visceral metastases appear to be independent prognostic indicators of poor overall survival in the second-line setting. These indicators should be investigated further in future second-line chemotherapy studies.

The predominant toxicities seen were hematologic in nature. MP was well tolerated, with only 1 episode of neutropenic infection. Ixabepilone treatment resulted in 1 treatment-related death from neutropenic sepsis during Cycle 1. Although nonhematologic toxicities were seen with ixabepilone, none were observed with high frequency, and no single toxicity predominated. Low rates of neurotoxicity seen in this study compared with other trials of ixabepilone may in part be explained by the requirement that all patients enrolled were required to have grade ≤ 1 neuropathy after taxane chemotherapy. This requirement may have selected a population less susceptible to neuropathy.

Previously, the noncross-resistance of taxanes and ixabepilone was reported in a retrospective analysis of patients treated on a randomized phase 2 trial of first-line ixabepilone with or without estramustine.¹⁴ In that analysis of 49 patients, 51% of patients treated with second-line taxane achieved a $\geq 50\%$ PSA decline. The results of the current study suggest there may be a sequence-dependent effect of epothilone and that taxane therapy that may be responsible

for the lower level of activity seen with second-line ixabepilone.

In the present study, some patients who experienced disease progression on either MP or ixabepilone and crossed over to the third-line therapy achieved third-line PSA responses. In fact, none of the patients who responded to their third-line treatment responded to their second-line therapy. This implies some non-cross-resistance between the 2 regimens.

Although substantial progress in treating HRPC has been achieved with the introduction of effective first-line chemotherapy, the identification of new agents with high activity in front-line and TR-HRPC patients remains a priority. Median survival of patients with TR-prostate cancer from the start of second-line chemotherapy remains short. Both novel biologic agents as well as novel chemotherapies must continue to be investigated to improve survival in this patient population. Stratification by prior treatment response should be incorporated into future randomized clinical trials.

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