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ORIGINAL REPORT

Multicenter Randomized Phase II Study of Two Schedules of Docetaxel, Estramustine, and Prednisone Versus Mitoxantrone Plus Prednisone in Patients With Metastatic Hormone-Refractory Prostate Cancer

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Authors' disclosures of potential conflicts of interest are found at the end of this article.

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ABSTRACT

Purpose

Mitoxantrone-corticosteroid is currently the standard palliative treatment in hormone-refractory prostate cancer (HRPC) patients. Recent clinical trials documented the high activity of the docetaxel-estramustine combination. We conducted a randomized phase II study to evaluate prostate-specific antigen (PSA) response (primary end point) and safety of two docetaxel-estramustine-prednisone (DEP) regimens and mitoxantrone-prednisone (MP).

Patients and Methods

One hundred thirty metastatic HRPC patients were randomly assigned to receive docetaxel (70 mg/m^2 on day 2 or 35 mg/m^2 on days 2 and 9 of each 21-day cycle) and estramustine (280 mg PO tid on days 1 through 5 and 8 through 12) or mitoxantrone 12 mg/m^2 every 3 weeks; all patients received prednisone (10 mg daily).

Results

One hundred twenty-seven patients were assessable for PSA response and safety. A $\geq$ 50% PSA decline was found in a greater percentage of patients in the docetaxel arms (67% and 63%) compared with MP (18%; $P = .0001$). Median time to PSA progression was five times longer with DEP than with MP (8.8 and 9.3 *v* 1.7 months, respectively; $P = .000001$). Overall survival was better in the docetaxel arms (18.6 and 18.4 months) compared with the MP arm (13.4 months), but not significantly so ($P = .3$). Crossover rates differed significantly among treatment arms (16%, 10%, and 48% in arms A, B, and C, respectively; $P = .00001$). Treatment-related toxicities were mild and mainly hematologic.

Conclusion

The results of this randomized phase II study showed significantly higher PSA decline $\leq$ 50% and longer times to progression in HRPC patients receiving DEP-based chemotherapy than MP, and that DEP could be proposed in this setting.

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INTRODUCTION

Hormone-refractory prostate cancer remains (HRPC) the second leading cause of cancer death in men in Western countries.[1] Median survival of these patients is approximately 1 year, and new therapeutic options are needed.[2] Systemic chemotherapy, has been shown to improve quality of life but without providing a survival advantage. The combination of mitoxantrone and corticosteroid showed significant and substantial improvements in bone pain in three randomized trials in HRPC patients.[3-5] In the Canadian and Cancer and Leukemia Group B (CALGB) studies, mitoxantrone-prednisone

(MP) produced a 50% decrease in serum prostate-specific antigen (PSA) level in 29%, 33%, and 38% of patients.[3-5]

Estramustine phosphate is a nitrogen mustard derivative of estradiol-17-beta-phosphate; its mechanism of action in prostate cancer combines the hormonal effect of estrogen with cytotoxic action through microtubular inhibition and binding to nuclear matrix.[6] Although single-agent estramustine has limited activity in HRPC patients, combinations of estramustine with other antimicrotubule agents, such as vinblastine, paclitaxel, and docetaxel, have shown synergistic effects.[7]

Docetaxel, a semisynthetic taxoid, disrupts the cellular microtubular network, promoting assembly of stable microtubules and inhibiting disassembly. Results of phase I and II trials of docetaxel-estramustine combinations showed high activity in terms of both PSA and measurable disease response.[8-11] The recommended dose of docetaxel for phase II trials was 70 mg/m^2 in minimally pretreated patients.

In a preclinical study, we demonstrated the superiority of docetaxel compared with mitoxantrone in terms of growth inhibition on human hormone-dependent (PAC120) and -independent prostate cancer xenografts.[12] Estramustine alone had a modest effect but potentiated the activity of docetaxel in one of the hormone-independent tested tumors. Therefore, we designed a three-arm, prospective, randomized, phase II study to evaluate two different schedules of docetaxel-estramustine-prednisone (DEP) with MP in HRPC patients.

PATIENTS AND METHODS

Patient Selection

Eligibility criteria included histologically proven metastatic adenocarcinoma of the prostate with progressive disease, despite androgen deprivation and no prior chemotherapy (including estramustine), an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2, and at least 4 weeks since completion of radiation or the last dose of a therapeutic radionuclide. Antiandrogen withdrawal and subsequent documented disease progression was required before study entry (at least 4 weeks since prior flutamide or nilutamide and 6 weeks since prior bicalutamide). Patients were required to have a castrated level of testosterone ($<$ 50 ng/mL) achieved by bilateral orchidectomy or administration of luteinizing-hormone releasing-hormone agonist.

Patients had to meet the following biologic criteria: granulocyte count $\geq 1.5 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L, hemoglobin $\geq$ 10 g/dL, total serum bilirubin of $\leq 1.5 \times$ institutional upper limit of normal (ULN), transaminases $\leq 1.5 \times$ ULN, alkaline phosphatase less than $2 \times$ ULN, and creatinine $\leq 1.5 \times$ ULN.

Patients were excluded for uncontrolled diabetes and all comorbid conditions that may limit survival. The clinical investigation was based on radionuclide bone scan, computed tomography scan of the abdomen and pelvis, and chest x-ray. Laboratory studies included CBC, serum chemistry profile, testosterone, and PSA. Disease progression for HRPC patients was defined as appearance of new lesion(s), and/or an increase of $\geq$ 25% of measurable metastases, and/or the appearance of new foci on a radionuclide bone scan, and/or three consecutive increases in PSA concentration at least 1 week apart in the presence of testosterone castrate level of metastatic patients. A local ethics committee approved the protocol, and individual patient consent was obtained.

Design and Procedures

A total of 130 patients was randomly allocated to one of three treatment arms in this multicenter phase II trial conducted in 24 French centers from January 2000 to January 2002. Randomization was centralized at the Georges Pompidou Oncology Data Center. Patients were stratified by baseline PSA level ($\leq$ 150 *v* $\geq$ 150 ng/mL) and ECOG PS (0 *v* 1 to 2).

Treatment

Patients randomly assigned to group A received docetaxel (Taxotere; Laboratoire Aventis, Paris, France) at a dose of 70 mg/m^2 administered as a 1-hour intravenous (IV) infusion on day 2 every 21 days. Patients randomly assigned to the arm B regimen received docetaxel at a dose of 35 mg/m^2 administered as a 30-minute IV infusion on days 2 and 9 every 21 days. The planned dose-intensity of the two docetaxel regimens was the same (23.3 mg/m^2/wk). The dose was decreased in arms A and B to 60 and 30 mg/m^2, respectively, if significant toxicity occurred. Oral estramustine was administered 2 hours after meals in the docetaxel arms, at a total daily dose of 840 mg, in divided doses three times a day on days 1 to 5 and subsequently repeated from days 8 to 12. Premedication with oral prednisolone 300 mg total dose was administered in both DEP arms. Moreover, oral warfarin 2 mg/d was administered continuously in DEP arms to prevent thrombosis caused by estramustine.

Patients randomly assigned to arm C received mitoxantrone at a dose of 12 mg/m^2 administered as a 30-minute IV infusion on day 1 every 21 days. Daily low-dose prednisone (10 mg) was administered continuously in the three arms.

Patients were evaluated for response radiographically every two cycles and/or by a radionuclide bone scan every three cycles and then every 3 months while on study. Weekly CBCs and 3-week PSA levels were measured during treatments. Acute side effects of chemotherapy were scored according to the revised National Cancer Institute Common Toxicity Criteria, version 1.

Assessment of Outcome

The primary end point was antitumor response as determined by the effect of treatment on PSA concentration (decline $\geq$ 50%). PSA decrease ($\geq$ 50%) was documented in accordance with the consensus guidelines of the PSA Working Group.[13] The secondary end points were time to PSA progression, clinical benefit, safety, measurable disease, and overall survival.

The time to PSA progression was measured from the date of randomization to the date of PSA progression and was defined by a $\geq$ 25% increase in PSA level from baseline or a $\geq$ 50% increase in PSA level from the lowest value achieved, provided that the increase was at least 5 ng/mL, confirmed by three successive measurements at 3-week intervals. The duration of PSA response was the time interval between the date of the first 50% decline in PSA until PSA increased to 50% above the nadir.

The clinical benefit was assessed using the pain index defined by the modified McGill pain questionnaire and ECOG PS. The pain index was evaluated by using the pain control and analgesic consumption scores. These two parameters were recorded by the patients themselves using pain diaries and medication records.

The pain control was defined as follows: 0, no pain; 1, mild pain; 2, moderate pain; 3, severe pain; and 4, uncontrollable pain. The analgesic consumption was defined as follows: 0, no requirement for analgesics; 1, occasional nonnarcotic analgesic use; 2, regular nonnarcotic analgesic use; 3, occasional narcotic analgesic use; and 4, regular narcotic analgesic use. The clinical benefit improvement was defined as follows: positive response in one category (reduction of the pain index by at least one score and/or PS improved by at least one score).[14]

Measurable disease response was defined using standard bidimensional measurements in accordance with WHO guidelines for complete response (CR), partial response (PR), stable disease, and progressive disease. The date of progression was defined as the date of the first computed tomography scan that demonstrated either a new lesion(s) or a $\geq$ 25% increase in the bidimensional measurements of previously measurable disease. For patients with bone disease, new lesion(s) on radionuclide bone scan qualified as progressive disease.

Overall survival was defined as the time between study entry and death or date of last follow-up. Cross over from the docetaxel arms (A or B) to the mitoxantrone arm (C) and from arm C to arms A or B was allowed in patients who failed to respond to their primary treatment. In an exploratory manner, to calculate the time on primary treatment, patients receiving second-line chemotherapy were censored at the onset of the second-line treatment. Follow-up was calculated from date of last chemotherapy administration until death or date of last follow-up for living patients.

Statistical Analysis

A Simon design was used with accrual of 130 patients. With this sample size, a PSA response of 60% could be distinguished from a 30% response, with 80% power and a type I error (two-sided) of 0.05. The intent-to-treat (ITT) population included all randomly assigned patients. Patients who received at least one treatment cycle were assessable for response and toxicity (modified ITT).

Kaplan-Meier analysis was used to compare treatment arms with respect to survival duration and time to PSA progression. Cox hazards regression was used to study the relationship between any continuous covariate and survival. After the univariate analysis, a multivariate Cox regression analysis for multiple proportional hazards using a backward stepwise conditional approach was performed to explain which combination of the variables could predict the survival, after adjustment by treatment arm. Fisher's exact, Pearson's χ^2, and Kruskal-Wallis tests were used to compare demographic, clinical, and biologic variables, respectively. A Bonferroni multiple-comparison correction was used for two-by-two analyses.[15] The Bonferroni level of significance at $\alpha = .017$ was calculated to ensure an overall significance level of 0.05 or less for all three tests (A *v* B, B *v* C, and A *v* C). All the tests were two-sided. Statistical analysis was performed using SPSS 11 (SPSS Inc, Chicago, IL) and Epi Info 2000 v 1.1.1 (Center of Disease Control and Prevention, Atlanta, GA).

RESULTS

Patient Characteristics

Between January 2000 and January 2002, 130 patients entered onto this three-arm randomized study; 44, 44, and 42 patients were assigned to arms A, B, and C, respectively. There were no significant differences between the three treatment arms with respect to baseline clinical and biologic characteristics (Table 1). The ECOG PS showed a trend in favor of arm B, but this was not statistically significant ($P = .18$). Three patients who enrolled onto the study were never treated because one had a stroke before the first cycle and two withdrew their informed consent. Therefore, efficacy and safety analyses were performed on the 127 patients who comprised the modified ITT. The median age of patients was 68 years; the length of time since initial diagnosis was 3.2 years; and PSA level at study entry was 76 ng/mL. Ninety-three percent of patients had bone metastases, 35% had two or more organs involved, and 65% had tumor-related bone pain.

Exposure to Study Medication

Median relative dose-intensities were similar for all groups and were as follows: 1.0 for docetaxel arm A (range, 0.58 to 1.07), 0.98 for docetaxel arm B (range, 0.50 to 1.11), and 0.97 for mitoxantrone arm C (range, 0.33 to 1.17). The median cumulative dose was 414 mg/m^2 (range, 69 to 429 mg/m^2), 403 mg/m^2 (range, 66 to 423 mg/m^2), and 66 mg/m^2 (range, 10 to 76 mg/m^2) in arms A, B, and C, respectively. The estramustine cumulative dose was similar in the docetaxel arms.

Response to Therapy

The primary objective of this study was to evaluate the response as determined by PSA decrease in the docetaxel versus MP arms. Four patients had a baseline PSA level less than 4 ng/mL and were excluded from the biologic response evaluation. PSA declines of $\geq$ 50% and $\geq$ 75% were 67% and 51% in arm A, respectively, and 63% and 39% in arms B, respectively, compared with 18% or 8% in arm C, respectively (Table 2). Differences were significant for $\geq$ 50% and $\geq$ 75% PSA declines (both $P < .0001$). The two-by-two tests with Bonferroni correction were statistically significant between the DEP and MP arms ($P < .002$), but no difference was observed between the docetaxel arms. After treatment, PSA levels $\leq$ 4 ng/mL were achieved by 10 patients (23%) in arm A, seven patients (17%) in arm B, and one patient (2%) in arm C ($P = .02$). Two-by-two tests with Bonferroni correction were statistically significant between arms A and C ($P = .01$).

The median time to PSA progression (Fig 1) was at least five times longer with DEP compared with MP (8.8 months, 95% CI, 6.9 to 10.8 months; and 9.3 months, 95% CI, 7.5 to 11.1 month; *v* 1.7 months, 95% CI, 0.7 to 2.7 months, respectively; $P = .000001$). The median duration of PSA response was longer with DEP compared with MP (8 and 8.3 *v* 6.4 months, respectively).

Bidimensionally measurable metastases were present in 53 (42%) of the 127 assessable patients. The tumor response rate was higher with DEP than with MP, with nine objective responses in arm A (seven PRs and two CRs),

Table 1. Baseline Characteristics of Patients According to Random Assignment (N = 127)

Characteristic	Arm A* (n = 43)		Arm B† (n = 42)		Arm C‡ (n = 42)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Age, years						
Median	68		68		70	
Interquartile range	52-91		51-79		52-85	
ECOG performance status						
0	17	40	25	59	20	48
1	19	44	13	31	11	26
2	7	16	4	10	11	26
Gleason score						
2-4	2	5	0	0	1	2
5-6	10	23	5	12	10	24
7-10	30	70	37	88	28	67
Unknown	1	2	0	0	3	7
Time from diagnosis of prostate cancer to random assignment, months						
Median	33		33		47	
Interquartile range	3-219		5-151		6-150	
Time from start of hormonal treatment to random assignment, months						
Median	16		27		25	
Interquartile range	2-116		2-89		1-118	
Tumor-related symptoms						
Without bone pain	12	28	12	29	11	26
Bone pain	28	65	24	57	30	72
Unknown	3	7	6	14	1	2
Analgesic use at entry						
Analgesic treatment	24	56	21	50	25	60
No analgesic treatment	16	37	14	33	16	38
Unknown	3	7	7	17	1	2
Serum PSA, ng/mL						
Median	71		69.5		77.7	
Interquartile range	1.9-2818		0.01-2416		0.41-1840	
Hemoglobin level, mg/dL						
Median	12.9		12.4		12.9	
Interquartile range	9.9-17		8.2-15.7		8.7-15.6	
Number of organs involved						
One	27	63	28	67	27	64
Two	16	37	11	26	14	33
≥ Three	0	0	3	7	1	3
Sites of metastases						
Bone	38	88	39	93	41	98
Lymph nodes	16	37	11	26	13	31
Other sites	5	12	8	19	3	7
Type of previous hormonal regimen						
Total androgen blocade	36	84	36	86	35	83
Number of previous hormonal regimens						
One	30	70	26	62	32	76
Two	11	25	12	29	10	24
Three	2	5	4	9	0	0
Other previous anticancer therapy						
Surgery	6	14	10	24	8	19
Radiotherapy	10	23	9	21	7	17

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PSA, prostate-specific antigen.
*Docetaxel-estramustine-prednisone on day 2 every 21 days.
†Docetaxel-estramustine-prednisone on days 2 and 9 every 21 days.
‡Mitoxantrone-prednisone every 21 days.

three responses in arm B (two PRs and one CR), and one CR in arm C ($P = .01$). Two-by-two tests with Bonferroni correction were significant between arms A and C ($P = .016$), but no difference was observed between the docetaxel arms. Ten (77%) of 13 patients who had an objective response had at least a PSA decrease ≥ 50%, and the last three patients had a stable PSA level. The median time to disease progression was 11.5 months (95% CI, 6.9 to 16.9

Table 2. PSA Response Rates

PSA Response	Arm A* (n = 43) No. of Patients	Arm A* (n = 43) %	Arm B† (n = 42) No. of Patients	Arm B† (n = 42) %	Arm C‡ (n = 42) No. of Patients	Arm C‡ (n = 42) %
≥ 50%§	29	67	26	63	7	18
≥ 75%§	22	51	16	39	3	8
Normalisation, < 4 ng/mL	10	23	7	17	1	2

NOTE. One patient in arm B and three patients in arm C could not be evaluated for PSA response because of a baseline PSA level < 4 ng/mL.
Abbreviation: PSA, prostate-specific antigen.
*Docetaxel-estramustine-prednisone on day 2 every 21 days.
†Docetaxel-estramustine-prednisone on days 2 and 9 every 21 days.
‡Mitoxantrone-prednisone every 21 days.
§$P < .0001$.

months) for patients with measurable disease and 18.2 months (95% CI, 16.5 to 21.8 months) for patients with bone disease only.

Table 3 shows the clinical benefit for the three arms. The pain index was improved in the docetaxel arms compared with the MP arm (40% and 29% *v* 17%, respectively), but the differences were not statistically significant ($P = .06$). A significant difference was observed between the DEP and MP arms in terms of improved ECOG PS (60% and 48% *v* 28%, respectively; $P = .01$). Clinical benefit, as defined by pain index and ECOG PS, was not statistically different in the DEP arms compared with the MP arm (33% and 24% *v* 21%, respectively; $P = .06$). Two-by-two tests with Bonferroni correction were statistically significant between arms A and C only for improvement of ECOG PS ($P = .003$), and no differences were observed for all parameters between the docetaxel arms.

Safety

Docetaxel and mitoxantrone regimens were generally well tolerated and had manageable side effects (Table 4). The intensity of these events was usually mild to moderate.

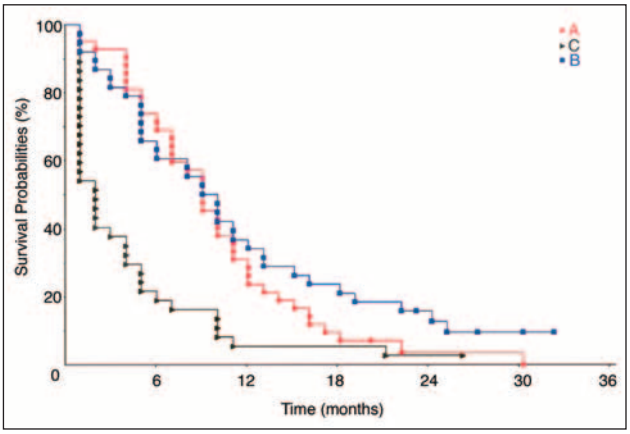

Fig 1. Kaplan-Meier plot of time to prostate-specific antigen progression in each treatment arm.

Most side effects were of short duration and resolved without incident. However, one death caused by diabetic coma (prior history of diabetes mellitus) was related to corticosteroid premedication for docetaxel arm A. Four patients were taken off therapy; three were taken off for nonhematologic toxicities (venous thrombosis, cutaneous reaction, and asthenia), and one was taken off for hematologic toxicity.

The primary treatment-related side effect observed in patients was granulocytopenia, which did not occur more significantly in arm C compared with arm A (48% *v* 37%, respectively; P = not significant). No patient in arm B developed granulocytopenia. Febrile neutropenia occurred in 7% of patients in the MP arm. Leucopenia was reported more frequently in patients who had received previous radiotherapy compared with patients who had not received previous radiotherapy (29% *v* 12%, respectively; $P = .016$). Dose reduction was required for 2.4% of the entire population (two patients in arm A and one patient in arm C). Asthenia was the prominent nonhematologic toxicity and was reported in 47%, 41%, and 26% of patients in arms A, B, and C, respectively ($P = .30$). Nail and skin toxicities occurred in approximately 14% of patients treated with docetaxel. Thrombotic complications caused by estramustine were observed in the docetaxel arms in three patients each (7%), despite warfarin prophylaxis. Four (10%) of 42 patients receiving mitoxantrone had a decrease in left ventricular ejection fraction (grade 1 to 2 according to National Cancer Institute Common Toxicity Criteria).

Survival

Survival analysis was performed at 12 months of median follow-up (95% CI, 10.1 to 13.8 months) when 99 patients (78%) had died. The 3-year survival rate for the entire cohort was actually 22%. Median overall survival was not significantly different between the arms and was 18.6 months (95% CI, 14.9 to 22.3 months), 18.4 months (95% CI, 14.1 to 22.8 months), and 13.4 months (95% CI, 9.4 to 17.5 months) in arms A, B, and C, respectively (Fig 2). No differences were found at two-by-two relative event rate

Table 3. Clinical Benefit Response

Characteristic	Arm A* (n = 43)		Arm B† (n = 42)		Arm C‡ (n = 42)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Pain control	10	23	9	21	7	17
Analgesic consumption	15	35	10	24	6	14
Improved pain index,§ 1 + 2	17	40	12	29	7	17
Improved ECOG PS	26	60	20	48	12	28‖
Improved clinical benefit,§ 3 + 4	14	33	10	24	9	21

Abbreviation: ECOG PS, Eastern Cooperative Group performance status.
*Docetaxel-estramustine-prednisone on day 2 every 21 days.
†Docetaxel-estramustine-prednisone on days 2 and 9 every 21 days.
‡Mitoxantrone-prednisone every 21 days.
§Evaluated according to the validated modified McGill pain questionnaire.
‖$P = .01$.

analysis, adjusted for multiplicity of tests by Bonferroni correction (Table 5). Level of cross over was 24% for the entire population (16% in arm A, 10% in arm B, and 48% in arm C, which was significantly different between treatment groups, $P = .00001$). The high level of cross over justified the date of censoring patients for time on primary treatment calculation. The median time on primary treatment was longer in the DEP arms compared with the MP arms (20.4 months, 95% CI, 17.5 to 23.3 months; and 19.2 months, 95% CI, 15.7 to 22.8 months; *v* 11.6 months, 95% CI, 7.1 to 16.2 months; $P = .003$). In an exploratory manner, the survival time of patients in the MP arm receiving salvage therapy with docetaxel was 31.7 months (95% CI, 26.4 to 36.9 months) compared with 7.5 months (95% CI, 4.9 to 10.1 month) for patients receiving either no further chemotherapy or a nondocetaxel chemotherapy.

Table 6 shows that the baseline characteristics associated with improvement in overall survival in univariate analysis were ECOG PS (0 *v* 1 *v* 2, 25.9 *v* 13.5 *v* 8.6 months, respectively; $P = .000001$, log-rank test), baseline hemoglobin level ($P = .0001$, Cox regression; cutoff ≥ 11 *v* < 11 g/dL, 19.9 *v* 9.2 months, respectively; $P = .02$, log-rank test), prior duration of hormone therapy ($P = .002$, Cox regression; cutoff ≥ 2 *v* < 2 years, 20.8 *v* 15 months, respectively; $P = .004$, log-rank test), and baseline bone pain ($P = .0001$). Overall survival was correlated with posttherapy PSA decline $\geq$ 50% (22 *v* 11.6 months; $P < .003$, log-rank test). Comparing DEP with MP, the relative risk of death reduction was 6% (95% confidence limits, −2%, 71%) between arms A and C and 14% (95% confidence limits, −8%, 32%) between arms B and C.

Multivariate analysis of prognostic variables (Table 6) adjusted by treatment arm demonstrated a significant association between overall survival and ECOG PS ($P = .0001$) and baseline hemoglobin level ($P = .006$). Poor ECOG PS and low hemoglobin level (< 11 g/dL) were associated with worsened prognosis.

DISCUSSION

This is the first multicenter randomized trial that shows that the DEP combination is superior to MP in HRPC patients. The rate of PSA decline $\geq$ 50% and time to PSA progression were at least three times higher and five times longer for

Table 4. Toxicity: Severe Adverse Events (grade 3 or 4)

Toxicity	Arm A* (n = 43)		Arm B† (n = 42)		Arm C‡ (n = 42)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Granulocytopenia	16	37	0	0	20	48
Granulocytopenic fever	0	0	0	0	3	7
Anemia	1	2	0	0	3	7
Thrombocytopenia	0	0	1	2	1	2
Nausea	1	2	0	0	0	0
Vomiting	1	2	0	0	0	0
Diarrhea	3	7	0	0	0	0
Thrombosis	3	7	3	7	0	0

*Docetaxel-estramustine-prednisone on day 2 every 21 days.
†Docetaxel-estramustine-prednisone on days 2 and 9 every 21 days.
‡Mitoxantrone-prednisone every 21 days.

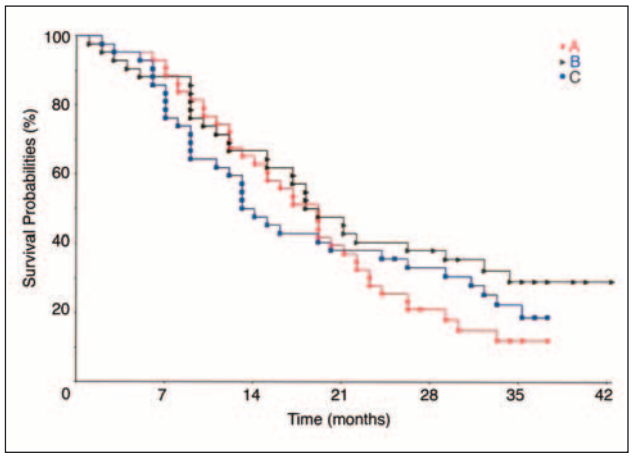

Fig 2. Kaplan-Meier plot of overall survival in each treatment arm.

DEP than for MP. For measurable disease, only arm A (docetaxel 70 mg/m^2 on day 2) was better than MP.

Our clinical data in both the MP and DEP arms are in accordance with those of previous published trials. Outcomes of patients treated with MP are in keeping with the Canadian and CALGB 9182 phase III trials.[3,4] Pain control in the Canadian study was 29% *v* 12% in the MP arm compared with prednisone alone, respectively. In our study, the MP arm improved the pain control by 17%. In the Canadian and CALGB studies,[3-5] MP produced a decrease in PSA of 29%, 33%, and 38% of patients, respectively, compared with 18% in our study. Overall survival ranged from 10 to 12 months in the three studies. For our patients treated with docetaxel-estramustine, overall 50% PSA response rate (63% to 67%) and objective tumor response (20% to 56%) were similar to that reported by published studies (45% to 74% for PSA response rate and 11% to 57% for measurable disease response).[10,11] The median survival of 20 months reported by Savarese et al,[11] is similar to our time on primary treatment of 20.4 and 19.2 months in the DEP arms.

The rationale for coadministration of estramustine and docetaxel for HRPC patients was based on their additive or synergistic modes of action.[12] Estramustine is relatively ineffective as a single agent for HRPC.[16] It interacts at the level of the nuclear matrix and microtubules, but its main activity may be a hormonal effect.

Corticosteroids are active in HRPC, resulting in PSA decreases greater than 50% in 22% to 61% of patients treated with daily continuous prednisone,[4,17,18] hydrocortisone,[3] or dexamethasone.[19] One study showed that the dexamethasone premedication regimen usually used for docetaxel administration by itself had no antitumor activity in HRPC patients,[20] but a potential antitumor mechanism has been described.[21] Therefore, docetaxel premedication is probably not responsible for the high PSA response rate found in our DEP arms.

Although pain control, analgesic consumption, and clinical benefit were better in the docetaxel arms, differences were not statistically significant. Nevertheless, patients in docetaxel arm A had an ECOG PS improvement under treatment.

Time to PSA progression was five times longer in the docetaxel arms. In our study, almost 50% of patients in the MP arm received docetaxel as second-line chemotherapy. Overall survival was not different in the three arms. According to our exploratory analysis, time on primary treatment was significantly higher in the DEP arms compared with the MP arm. This may be a result of docetaxel salvage therapy, which could mask the survival benefit of the DEP arms. This could be relevant because docetaxel administered as second-line therapy may increase overall survival in patients treated with MP in the first-line setting. This data should be taken with caution because our study was not designed and powered to demonstrate a survival advantage.

Consistent with previously published studies,[22,23] multivariate analysis of this study showed that baseline ECOG PS and hemoglobin were the main predictive factors of survival. Overall survival was correlated with posttherapy PSA decline ($\geq$ 50%), supporting other observations that this may be a clinically meaningful end point in patients with HRPC.[24-26]

Finally, the toxicity observed in the MP arm was similar to the Canadian and CALGB 9182 trials and was mainly hematologic, with almost a 50% incidence of grade 3 to 4 granulocytopenia. Febrile neutropenia was rarely observed. Granulocytopenia was reported in 37% of patients in arm A with no febrile neutropenia. In accordance with the

Table 5. Relative Event Rate

Parameter	A *v* B		A *v* C		B *v* C		
	RER	95% CI	RER	95% CI	RER	95% CI	*P*
Time to PSA progression	1.26	0.85 to 1.89	0.44	0.25 to 0.76	0.35	0.20 to 0.60	.00001
Overall survival	1.43	0.89 to 2.31	1.08	0.66 to 1.76	0.75	0.46 to 1.21	.13
Time on primary treatment	1.26	0.78 to 2.04	0.49	0.25 to 0.97	0.39	0.20 to 0.76	.0005

Abbreviations: RER, relative event rate; PSA, prostate-specific antigen.

Table 6. Association of Baseline Factors With Overall Survival Univariate and Multivariate Analysis

Factor	*P*
Univariate	
ECOG performance status	.0001
Hemoglobin	.0001
Prior duration of hormone therapy	.002
Bone pain at presentation	.0001
Multivariate	
ECOG performance status	.0001
Hemoglobin	.006

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

hematologic toxicity, one DEP schedule (docetaxel 35 mg/m^2 on days 2 and 9) can be recommended for elderly patients who exhibit poor ECOG PS or low hemoglobin level or who have received prior radiotherapy. The other DEP schedule (docetaxel 70 mg/m^2 on day 2) can be proposed to patients with good ECOG PS who prefer to come to the hospital once every 3 weeks. Grade 1 to 2 asthenia and nail changes were more frequent in the DEP arms. Similar to rates of published studies,[8,9,11] the rate of estramustine-induced vascular events was 7% in each of the docetaxel arms, despite warfarin prophylaxis. No conclusion can be drawn on the dose of warfarin to recommend.

Two phase III trials that compare taxane-based combination regimens with standard MP in men with HRPC are ongoing. Results of these trials may confirm the findings of our phase II randomized study, which emphasizes the superiority of the clinical and biologic response rate of DEP over MP. DEP seems to have a significant impact in the management of HRPC.

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Appendix

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Authors' Disclosures of Potential Conflicts of Interest

The following authors or their immediate family members have indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. Employment: Stephane Oudard, Aventis Laboratory. Consultant/Advisory Role: Stephane Oudard, Aventis Laboratory. Honoraria: Stephane Oudard, Aventis Laboratory; Philippe Beuzeboc, Aventis. For a detailed description of these categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section of Information for Contributors found in the front of every issue.

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