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PHASE III STUDY OF MITOXANTRONE PLUS LOW DOSE PREDNISONE VERSUS LOW DOSE PREDNISONE ALONE IN PATIENTS WITH ASYMPTOMATIC HORMONE REFRACTORY PROSTATE CANCER

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ABSTRACT

Purpose: We compared median time to treatment failure of men with asymptomatic, hormone refractory, progressive prostate cancer treated with mitoxantrone plus prednisone versus prednisone alone.

Materials and Methods: In a multicenter phase III trial 120 men with asymptomatic, progressive, hormone refractory prostate cancer were randomly assigned to treatment with mitoxantrone and prednisone or prednisone alone. Patients received 12 mg./m.^{2} mitoxantrone intravenously once every 3 weeks for 6 cycles and 5 mg. prednisone twice daily with or without mitoxantrone. Time to treatment failure was assessed as an aggregate end point comprised of time to disease progression, time to toxicity or death, or time to initiation of alternate therapy.

Results: Median followup was 21.8 months. Median time to treatment failure and median time to progression were the same: time to treatment failure and time to progression in the mitoxantrone and prednisone group was 8.1 months compared to 4.1 months in the prednisone alone group ($p = 0.017$ versus $p = 0.018$). More patients (27 or 48%) treated with mitoxantrone and prednisone achieved a 50% or greater reduction in prostate specific antigen levels than those who received only prednisone (15 or 24%, $p = 0.007$). There was no significant difference in median survival between the 2 groups, which was 23 and 19 months, respectively. Death was mainly attributable to disease progression.

Conclusions: Patients with hormone refractory prostate cancer who are asymptomatic but had progressive disease had a significantly higher response rate when treated with mitoxantrone and prednisone as demonstrated by the 50% or greater decrease in prostate specific antigen compared to treatment with prednisone alone. Time to treatment failure was significantly prolonged in the chemotherapy treated group but survival rates were not different.

KEY WORDS: prostatic neoplasms; antineoplastic agents; comparative study; mitoxantrone; treatment outcome

Treatment for hormone refractory prostate cancer is typically palliative and expected survival is 6 to 12 months.[1,2] As no single agent treatment has been found to extend this survival estimate,[3–5] efforts have focused on drug combinations that may improve palliative response and work synergistically to improve survival.[6–12] One such promising combination, mitoxantrone[13] and prednisone, has been evaluated for the treatment of symptomatic advanced cancers. In an early study Moore et al monitored changes in analgesic intake and quality of life in 27 patients treated with mitoxantrone and prednisone.[12] Pain scores improved and were maintained in 36% of the patients treated. Likewise, mitoxantrone and prednisone also provided a palliative effect in 29% of 161 patients enrolled in a multicenter Canadian study.[14] In a recent report from the Cancer and Leukemia Group B 9182 Study patients randomized to receive mitoxantrone and hydrocortisone had delays in the interval to disease progression and improved palliation of symptoms as a result of combined therapy.[8] Findings from each of these studies supported early safety data that found mitoxantrone to be well tolerated. The main toxicity in this patient population was mild to moderate myelosuppression.[15,16]

In this study we extend the investigations of Tannock et al[14] and the Cancer and Leukemia Group B[8] by evaluating mitoxantrone and prednisone in asymptomatic patients with progressive hormone refractory prostate cancer. The primary objective was to compare time to treatment failure in each patient group. Secondary objectives included comparison of objective response rate, prostate specific antigen (PSA) decrease, duration of response and survival.

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PATIENTS AND METHODS

The study population for this open label, randomized, phase III trial consisted of 120 patients diagnosed with adenocarcinoma of the prostate. The U. S. Oncology Institutional Review Board approved the study protocol and informed consent was obtained from all trial participants. Recruitment took place from March 1997 to January 1999 and patients were randomly assigned to treatment with mitoxantrone and prednisone or prednisone alone. Surviving patients were followed for 4 years.

All study participants exhibited asymptomatic, hormone refractory carcinoma of the prostate that had progressed on at least 1 hormonal regimen (orchiectomy or therapy with a luteinizing hormone releasing hormone analogue or diethylstilbestrol). Pretreatment disease progression was defined as increasing PSA (2-fold or greater increase over 2 determinations), 25% increase in number of bone scan lesions or 25% increase in size of soft tissue lesions.

Patients were eligible for enrollment if at least 4 weeks had elapsed since antiandrogen treatment, systemic corticoste-

roid therapy or radiotherapy, or at least 3 weeks had elapsed since major surgery. Requirements for pretreatment hematopoietic status included an absolute neutrophil count of 1,500 cells per μl. or greater (normal 1,500 to 7,500), platelet count 150,000 cells per μl. or greater (normal 140 to 450,000) and hemoglobin 9 gm./dl. or greater (normal 12 to 18). Registered patients were also required to have adequate pretreatment liver and cardiac function, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2. Patients were excluded from study if they had a history of other malignancy within the last 5 years, parenchymal brain metastases, prior immunotherapy, prior chemotherapy or concurrent use of exogenous corticosteroids.

Pre-study evaluation included complete medical history and physical examination. Laboratory assessments included a complete blood count with differential and platelet counts, PSA (normal less than 4.0 ng./ml.), serum glucose (normal 65 to 110 mg./dl.) and liver chemistry screen. Additionally, each case was assessed clinically. Objective assessments of indicator lesions (computerized tomography, magnetic resonance imaging, bone scan, liver scan, ultrasound and/or x-rays) were performed within 6 weeks of study entry. Cardiac function was evaluated before starting mitoxantrone. Patients randomized to mitoxantrone and prednisone received 12 mg./m.^{2} mitoxantrone by intravenous infusion for 15 to 30 minutes once every 3 weeks for 6 cycles. A dose of 5 mg. prednisone was administered orally twice daily to all patients and was continued even after mitoxantrone therapy was stopped.

All patients who had not undergone orchiectomy continued androgen suppressive therapy for the duration of the study. All other forms of hormone therapy were disallowed. Supportive care was administered at the discretion of the investigator. Patients were closely monitored for evidence of cardiac or hepatic toxicity that would require discontinuation or delay of treatment. Hematopoietic growth factors were administered according to American Society of Clinical Oncology guidelines as needed, and a maximum of 2, 25% dose reductions for mitoxantrone were allowed per patient. No dose reductions were made for prednisone. Treatment was delayed no more than 2 weeks to allow for recovery from acute toxicity. Patients were removed from the study for significant intercurrent illness, unacceptable toxicity, progressive disease or patient request to withdraw.

During treatment complete blood count with differential, platelet counts and liver function tests were assessed weekly in cycle 1 and before each succeeding cycle. PSA assessments were performed every other cycle through cycle 6, every 3 months after cycle 6 and again at study termination. Radiological assessments were performed at the end of cycle 6, every 3 months if PSA values were more than 50% over baseline and at study termination. Physical examination, complete tumor assessment and ECOG evaluation were performed at the end of every cycle. Patients who completed treatment were followed every 3 months for progression and survival. However, patients with disease progression or who withdrew from the study were followed forward only for survival. Patients who had progressive disease were then treated at the discretion of the attending physician. The study did not allow for crossover.

The primary end point was time to treatment failure, an aggregate end point, defined by the interval between the start date of treatment and occurrence of progressive disease, removal from study or initiation of other antitumor therapy. Progressive disease was defined as a greater than 25% increase in sum of products of bidimensionally measurable masses, new soft tissue lesions or increasing bone lesions. Increasing PSA alone was not a criterion of progressive disease but was considered to be indicative of progression if present with 1 of the aforementioned signs. Secondary efficacy end points were achievement of a 50% or greater decrease in PSA with stable or improved performance status, time to 50% decrease in PSA, number of patients with objective response, duration of response, time to development of symptoms of progressive disease and survival.

Tumor response was judged by PSA and performance status and objective response by patients with measurable tumors. Treatment safety was evaluated by incidence of adverse experiences, changes from baseline in physical examination findings, changes from baseline in laboratory values, and changes in performance status and preexisting conditions. In this study toxicity referred to grade 3 and 4 side effects (National Cancer Institute toxicity criteria) which occurred after exposure to the study drug. The treating physician assessed the relationship of each event to treatment.

The study was designed to detect a difference in median time to treatment failure, which was 10 months for patients randomized to receive mitoxantrone and prednisone versus 4 months for patients randomized to prednisone alone. Assuming a 2-year accrual period with a 1-year followup, 45 evaluable patients per group were needed to detect this difference using a 2-sided significance level of 0.05 and a power of 85%. In addition, it was assumed that there would be a dropout rate of 15 patients per group in year 1 resulting in 60 patients per group, for a total of 120 patients.

Efficacy analysis included 119 patients, and all patients who received at least 1 dose of study drug were analyzed for safety. Survival curves and time to progression were generated using the Kaplan-Meier method,[17] and the log-rank test[18] was used to measure differences between the curves. Statistica '99 Edition (StatSoft, Inc., Tulsa, Oklahoma) and SPSS for Windows, Release 10.0.5 (SPSS, Inc., Chicago, Illinois) were used for analysis.

RESULTS

A total of 120 eligible patients with asymptomatic, progressive hormone refractory prostate cancer were registered for the study. Data were unavailable for 1 patient. Of the 119 patients analyzed 56 were randomized to receive mitoxantrone and prednisone and 63 were randomized to receive prednisone alone. Median followup was 21.8 months (range 2.4 to 50).

Patient characteristics, including age, performance status and extent of disease involvement, were well balanced between the 2 groups and no statistically significant differences were detected (table 1). Median serum PSA at study entry ranged from 3.7 to 2,375.0 ng./ml. (median 56.7) in the mitoxantrone and prednisone group and 1.1 to 1,233.0 ng./ml. (median 71.0) in the prednisone group. A total of 71 patients (60%) had received prior radiation therapy and 65 (55%) had undergone prior surgery. The ECOG performance status was 0, 1 and 2, respectively, in 42, 13 and 1 patients in the mitoxantrone and prednisone group and 47, 16 and 0 in the prednisone group.

Tumor characteristics at baseline are given in table 2. Measurable tumors were present in 8 of the mitoxantrone and prednisone and 9 of the prednisone cases. Nonmeasurable tumors and increased PSA levels were present in 46 (82%) of the mitoxantrone and prednisone and 49 (78%) of the prednisone cases. An increasing PSA was the only sign of disease in 7 patients. Of the patients 98 (82%) had bone as the metastatic site, 21 (18%) had metastasis in the lymph nodes and 7 (6%) had metastasis in the liver or lung.

By treatment arm time to treatment failure and time to progression were found to be equivalent. Estimated median time to treatment failure/time to progression from treatment start was 8.1 months (range 1 to 50) for the mitoxantrone and prednisone group and 4.1 months (range 1 to 37) for the prednisone group ($p = 0.017$ versus $p = 0.018$). For simplicity the remaining results will be presented as time to progression. The percentage of progression-free survival in the mi-

TABLE 1. *Pretreatment patient characteristics by randomized group*

	Mitoxantrone and Prednisone	Prednisone Alone	Total
No. race (%):			
White	52 (93)	53 (84)	105 (89)
Black	4 (7)	6 (10)	10 (8)
Hispanic	0 (0)	4 (6)	4 (3)
Age:			
Median	70	74	71
Range	49–87	51–90	49–90
No. performance status (%):			
0	42 (75)	47 (75)	89 (75)
1	13 (23)	16 (25)	29 (24)
2	1 (2)	0 (0)	1 (1)
No. diagnosis stage (%):			
A	2 (4)	5 (8)	7 (6)
B1	4 (7)	2 (3)	6 (5)
B2	10 (18)	9 (14)	19 (16)
C1	3 (5)	9 (14)	12 (10)
C2	5 (9)	2 (3)	7 (6)
D1	9 (16)	13 (21)	22 (18)
D2	19 (33)	21 (34)	40 (34)
D3	1 (2)	0 (0)	1 (1)
Unknown	3 (5)	2 (3)	5 (4)
No. radical prostatectomy (%):			
Yes	27 (48)	38 (60)	65 (55)
No	29 (52)	25 (40)	54 (45)
No. definitive local radiotherapy (%):			
Yes	36 (64)	35 (56)	71 (60)
No	20 (36)	27 (43)	47 (39)
Unknown	0 (0)	1 (1)	1 (1)

TABLE 2. *Pretreatment tumor characteristics by randomized group*

	No. Mitoxantrone and Prednisone (%)	No. Prednisone Alone (%)	Total No. (%)
Tumor:			
Measurable	8 (14)	9 (14)	17 (14)
PSA only	2 (4)	5 (8)	7 (6)
Nonmeasurable	46 (82)	49 (78)	95 (80)
Metastatic sites:*			
Bone	48 (86)	50 (79)	98 (82)
Lymph nodes	10 (18)	11 (18)	21 (18)
Lung	1 (2)	4 (6)	5 (4)
Liver	2 (4)	0 (0)	2 (2)

* Some patients had more than 1 metastatic site.

toxantrone and prednisone group at 12 and 24 months after treatment start compared to the prednisone group was 36% and 13% versus 15% and 10%, respectively (fig. 1).

Patients were evaluated according to serum PSA changes, performance status and, when possible, by objective response. A 50% or greater decrease in serum PSA from baseline lasting 2 or more months with stabilization or improvement of performance status for at least 2 weeks occurred in 27 (48%) patients who received mitoxantrone and prednisone and 15 (24%) who received P alone ($p = 0.007$). As shown in table 3 median time to achieve a serum PSA decrease of 50% or greater was 2.2 months for both groups.

Table 4 presents a comparison of time to progression for PSA responders and nonresponders. There was no statistically significant difference in estimated median time to progression for patients with a PSA response, which was 13.5 months (range 3.5 to 46.5) in the mitoxantrone and prednisone group and 11.7 months (range 6.5 to 46) in the prednisone group. However, estimated median time to progression for patients who did not have a PSA response was 6.9 months (range 1.1 to 35) in the mitoxantrone and prednisone group ($p = 0.007$) versus 3.2 months (range 0.9 to 34.5) in the prednisone group. Of the patients with measurable tumors 2 (25%) in the mitoxantrone and prednisone group and 2 (22%) in the prednisone group had partial responses. No patient experienced a complete response.

Among the 119 patients analyzed 91 (76%) died within 4 years of the start of the study, including 43 (77%) in the mitoxantrone and prednisone group and 48 (76%) in the prednisone group, and death was mainly attributable to progressive disease. As shown in figure 2 estimated median survival from treatment start for the mitoxantrone and prednisone group was 23 months (range 3 to 49) compared to 19 months (range 2 to 50) for the prednisone group ($p = 0.48$). Percent survival at 12 and 24 months in the mitoxantrone and prednisone group compared to the prednisone group was 82% and 45% versus 76% and 44%, respectively. Median survival times for patients who responded in the mitoxantrone and prednisone and prednisone alone groups were 32 and 33 months, respectively (ranges 11.2 to 46.5 and 9.5 to 50). A summary of toxicities occurring at any time during treatment is presented in table 5. There were no treatment-related deaths.

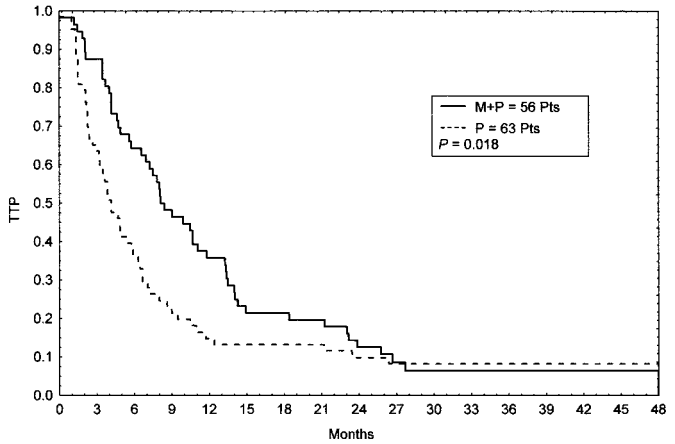

FIG. 1. Estimated time to progression (*TTP*) for patients who received mitoxantrone and prednisone (*M + P*) versus prednisone (*P*) alone.

DISCUSSION

Recent large, randomized studies have confirmed a role for systemic therapy with mitoxantrone and corticosteroids for hormone refractory prostate cancer.[8,14] Our results extend the earlier findings by indicating a benefit of mitoxantrone and prednisone in a subgroup of patients with asymptomatic hormone refractory prostate cancer. Time to treatment failure was improved for patients who received mitoxantrone and prednisone versus those who were treated with prednisone alone. However, as noted in other efficacy trials of mitoxantrone, survival benefit could not be demonstrated for mitoxantrone and prednisone in this study population. This finding may, in part, be explained by study design. Patients whose disease progressed on prednisone alone and who were taken off the study likely received mitoxantrone and prednisone or another systemic chemotherapy regimen at the

TABLE 3. *Median time to 50% or greater serum PSA responses by treatment arm*

	PSA Reduction	Nadir	Increase After Nadir
Mitoxantrone and prednisone (56):			
No.	27	27	15
Av. mos.	2.2	5.0	7.2
Range	0.6–4.6	1.6–18.5	3.0–22.2
P alone (63):			
No.	15	15	9
Av. mos.	2.2	4.2	8.0
Range	0.2–7.1	1.6–16.5	4.6–10.6
Total (19):			
No.	42	42	24
Av. mos.	2.2	4.7	7.3
Range	0.2–7.1	1.6–18.5	3.0–22.2

TABLE 4. *Median survival and time to progression by serum PSA reduction*

	PSA Reduction	
	50% or Greater	Less Than 50%
Mitoxantrone and prednisone (56):		
No. (%)	27 (48)	29 (52)
Av. survival (mos.)	31.8	18.3
Av. time to progression (mos.)	13.5	6.9
P alone (63):		
No. (%)	15 (24)	48 (76)
Av. survival (mos.)	32.9	18.3
Av. time to progression (mos.)	11.7	3.2

Patients who experienced an increase in PSA from baseline were included in the analysis of patients with less than 50% PSA reduction.

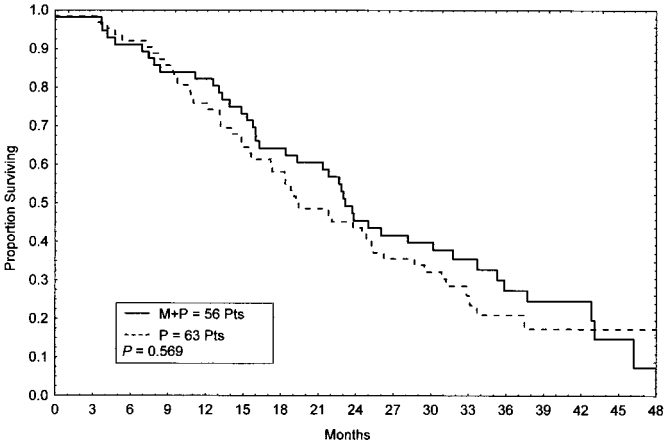

FIG. 2. Estimated survival for patients who received mitoxantrone and prednisone ($M + P$) versus prednisone (P) alone.

TABLE 5. *Incidence of drug related toxicities (grade greater than 3)*

	No. Mitoxantrone and Prednisone (%)	No. Prednisone Alone (%)	Total No. (%)
Neutropenia	27 (48)	6 (10)	33 (28)
Leukopenia	11 (20)	5 (8)	16 (13)
Pulmonary complications	4 (7)	4 (6)	8 (7)
Asthenia	3 (5)	3 (5)	6 (5)
Renal complications	1 (2)	3 (5)	4 (3)
Gastrointestinal complications	3 (5)	1 (2)	3 (3)
Sepsis	2 (4)	0 (0)	2 (2)
Melanoma	1 (2)	0 (0)	1 (1)

Some patients had more than 1 toxic reaction.

time of progression, and some of those patients would likely have responded to subsequent treatment. As a result it was anticipated that survival curves for the 2 arms of the trial were likely to be similar.

This study reaffirmed the value of PSA as a reasonably good surrogate marker of disease response.[19] As noted in other studies, a PSA response of 50% or more in either treatment arm correlated with improvement in time to treatment failure and survival.[6,8,20] PSA response in the present study was higher (48%) than in either the Canadian[14] (33%) or Cancer and Leukemia Group B[8] studies (33%). Median overall survival for all patients in our study was estimated to be 23 months, as opposed to 12 months in the Canadian and Cancer and Leukemia Group B studies. Better survival time is not unexpected given that patients who were enrolled in our study were asymptomatic and had lower median baseline PSA than those in the Cancer and Leukemia Group B and Canadian trials. Nevertheless, the observation that PSA response was higher in this progressing but asymptomatic group of patients than in either of the studies of symptomatic patients is noteworthy.

This study also confirmed the value of prednisone as a single agent for the treatment of hormone refractory prostate cancer. In the prednisone group 24% were PSA responders, and the time to progression and survival were similar to those of PSA responders in the mitoxantrone and prednisone group. Although a greater percentage (48% versus 24%) of the mitoxantrone and prednisone group were PSA responders, prednisone alone is a potentially beneficial therapy for selected patients with hormone refractory prostate cancer.

CONCLUSIONS

This study reaffirms the efficacy of mitoxantrone and prednisone for the treatment of hormone refractory prostate cancer and suggests that potential benefit exists in treating asymptomatic men with this disease. In this patient group mitoxantrone and prednisone using a regimen of reasonably low toxicity delayed the onset of progressive disease. Survival benefit has not been demonstrated and, thus, future studies of treatment of patients with varying stages of advancing prostate cancer are warranted. The Southwest Oncology Group (SWOG) is pursuing 2 such studies. SWOG 9916/ Cancer and Leukemia Group B is an intergroup trial that will compare the effectiveness of mitoxantrone and prednisone to docetaxel and estramustine for the treatment of androgen independent metastatic carcinoma of the prostate.[7] SWOG 9921 will compare the effectiveness of mitoxantrone and prednisone combined with androgen ablation in patients presenting with high risk local disease.

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