Eur J Cancer, Vol. 28, No. 2/3, pp. 477–478, 1992.
Printed in Great Britain

0964–1947/92 $5.00 + 0.00

Phase II Study of Platinum and Mitoxantrone in Metastatic Prostate Cancer: a Southwest Oncology Group Study

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44 eligible patients with measurable or evaluable metastatic prostate cancer were treated with monthly cycles of cisplatin and mitoxantrone. Good-risk patients received cisplatin 60 mg/m² intravenously and mitoxantrone 10 mg/m² intravenously every 4 weeks. The dose in poor-risk patients (elderly or white blood cell count < 4000/μl, 4 × 10⁹/l, or extensive prior radiation) was reduced to 8 mg/m². Toxicity was manageable and consisted primarily of myelosuppression. There were no complete responses and the partial response rate was only 12%. Median progression-free survival was 2.7 months for measurable and 4.1 months for evaluable disease patients. Median survivals were 4.9 and 8.7 months, respectively. This combination has minimal activity in hormone refractory metastatic prostate cancer.
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INTRODUCTION

METASTATIC PROSTATE cancer is a major cause of morbidity and mortality in the elderly male population. Although endocrine therapy offers effective palliation for many patients, benefit is temporary and alternative therapy becomes necessary. Chemotherapy has been of limited value in this disease, and more effective drugs or drug combinations are needed. A variety of chemotherapeutic agents have modest activity in hormone-refractory prostate cancer [1]. Among them is cisplatin which has response rates reported to be in the range of 20–40% [2–4]. Mitoxantrone is a new anthraquinone derivative that also demonstrated modest activity in prostate cancer in a previous phase II trial [5]. Moreover, the drug was well tolerated in older patients making it well suited for incorporation into combination regimens for this disease. Synergism with these agents was observed in murine tumour models [6]. We now report the results of a phase II trial of the combination of cisplatin plus mitoxantrone in metastatic prostate cancer.

PATIENTS AND METHODS

Patients

Patients with recurrent or metastatic adenocarcinoma of the prostate with bidimensionally measurable or evaluable disease were eligible for study. Patients with blastic bone disease or those with a positive bone scan as the only indication of disease were eligible only if they had an elevated acid phosphatase. All patients must have demonstrated progressive disease on endocrine therapy. Patients must not have had prior cytotoxic chemotherapy. Other eligibility criteria included a total white blood cell (WBC) count > 4000/μl (4 × 10⁹/l) and platelets > 100 000/μl (100 × 10⁹/l) unless low counts were due to bone marrow infiltration by tumour, serum creatinine ≤ 1.5 mg% (133 μmol/l) and a total bilirubin < 2.0 mg% (35 μmol/l). Patients with a SWOG Performance Status > 3 (bedridden) and those with a history of congestive heart failure were excluded.

Treatment

At the time of registration, patients were defined as 'good risk': ≤ 65 years of age, total WBC count ≥ 4000/μl (4 × 10⁹/l), and prior radiation therapy to not more than 10% of bone marrow-containing sites; or 'poor risk': patients > 65 years old, or total WBC < 4000/μl (4 × 10⁹/l), prior radiation to more than 10% of bone marrow, or those with large pleural effusions or ascites. Good-risk patients received cisplatin 60 mg/m² intravenously and mitoxantrone 10 mg/m² intravenously repeated every 4 weeks until disease progression. Poor-risk patients were treated with the same dose of cisplatin, but a reduced dose of mitoxantrone of 8 mg/m² intravenously. Doses of mitoxantrone for subsequent cycles were based on nadir WBC and platelet counts: 30% dose reduction for WBC between 1000 and 1999/μl (1 and 1.9 × 10⁹/l) or platelet count between 50 000 and 99 999/μl (50 and 99.9 × 10⁹/l), and 50% for WBC < 1000/μl (1 × 10⁹/l) or platelets < 50 000/μl (50 × 10⁹/l). Platinum was not given if the serum creatinine was > 1.5 mg% (133 μmol/l).

Data analysis and statistical considerations

Response criteria were different for measurable compared with evaluable disease patients. Complete remission in both groups required complete resolution of all signs of disease. Partial remission in measurable disease required a ≥ 50% reduction in the sum of the perpendicular diameters of measurable lesions without deterioration in pain, weight loss (> 10% from baseline) or performance status. In evaluable disease, partial remission required improvement or no change in evaluable disease together with any three of the following: normalisation of acid phosphatase, > 50% reduction in alkaline phosphatase, and improvement in

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Recieved 18 Sep. 1991; accepted 11 Oct. 1991.

Table 1. Tumour response

	Measurable disease (n=17)	Evaluable disease (n=26)
Complete response	0 (0%)	0 (0%)
Partial response	2 (12%)	3 (12%)
Stable disease	0 (0%)	3 (12%)
Progressive disease	15 (88%)	20 (76%)

performance status or pain index. Disease progression was defined as the appearance of new lesions, a > 50% increase in the size of measurable lesions or deterioration in the pain index, performance status, or weight. In evaluable disease patients, progression was also defined by any three of the following: ≥ 100% increase in acid or alkaline phosphatase, or deterioration in pain index, performance status, or weight (> 10% from baseline). Stable disease included patients not fitting the definition of response or progression. The trial was designed using the method of Fleming [7] and was based on the assumption that a complete and partial response rate of 30% would be sufficient evidence that this regimen is worth further study.

RESULTS

Patients' characteristics

45 patients, 17 with measurable disease and 28 with evaluable disease, were registered. 9 patients were considered good-risk and 36 patients poor-risk. 1 patient with evaluable disease was ineligible. 1 eligible patient who never received protocol therapy was considered not evaluable. The median age of the patients was 68.

Toxicity

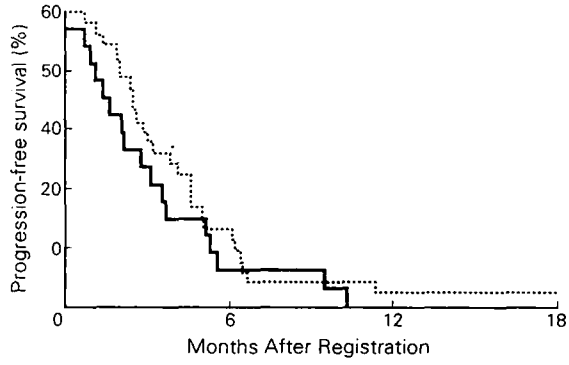
There was one treatment-related death due to congestive heart failure. The most common toxicity was myelosuppression. One patient had Grade 4 (WBC < 1000/μl) leukopenia and another had Grade 4 thrombocytopenia (platelets < 25 000/μl). Thrombocytopenia was not observed in other patients, but the majority had Grade 2 (< 3000/μl) or 3 (< 2000/μl) leukopenia. The only other commonly observed toxicity was nausea and vomiting which were moderate or severe in 15 patients. One patient had renal toxicity with a fall in creatinine clearance to 25 ml/min. Alopecia was not observed.

Tumour response

43 patients were evaluable for response (Table 1). The response rate was 12% in measurable disease patients and 12% in patients with evaluable disease. No complete responses were seen. Overall 5 of 43 patients had a partial response for an overall response rate of 11.6% [95% confidence interval (CI) 3.8–25.1%]. Kaplan–Meier plots of progression-free survival are shown in Fig. 1. The estimates of median progression-free survival were 2.7 months in measurable disease patients and 4.1 months in those with evaluable disease. Estimated median survivals were 4.9 and 8.7 months, respectively.

DISCUSSION

Cytotoxic chemotherapy is of limited benefit in patients with prostatic cancer, and there is no evidence that it causes worthwhile prolongation of survival [8]. In an effort to improve the treatment of this disease, we studied a combination of two agents that had reported activity in this disease and that had shown synergistic antitumour effects in animal models. Cisplatin



	At risk	Relapse or death	Median (mo)
Measurable disease	17	17	2.7
Evaluable disease	27	27	3.9

Fig. 1. Progression-free survival in measurable (———) and evaluable disease (.....) patients.

in doses similar to those used in the present trial was reported to have response rates ranging up to 43% [2–4]. However, many of these 'responses' in fact represented disease stabilisation or could not be called responses by more rigidly defined response criteria. Mitoxantrone also was reported to have activity in metastatic prostate cancer with 20% of patients achieving partial remission or disease stabilisation [5].

Unfortunately, the results of the present trial show that the combination of cisplatin and mitoxantrone, although reasonably well-tolerated by patients, has little activity in metastatic prostate cancer. The overall response rate of only 12% with a 95% confidence interval ranging from 3.8% to 25.1% failed to provide evidence for a 30% or greater response rate, the criterion established at trial design for further study of this combination. Furthermore, the progression-free and overall survivals are brief, suggesting that these agents are of no significant value in this disease. Identification of new active drugs for cancer of the prostate is urgently needed.

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Acknowledgements—This investigation was supported in part by the following PHS Cooperative Agreement grant numbers awarded by the National Cancer Institute, DHHS: CA-22433, CA-37429, CA-42777, CA-04919,CA-35261, CA-04915, CA-35192, CA-27057, CA-35438, CA-35431, CA-35090, CA-03096, CA-12213, CA-35283, CA-32102.