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E.O.R.T.C. Phase II Study of Cisplatin in Cyvadic-Resistant Soft Tissue Sarcoma

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Abstract—Cis-*diamminodichloroplatinum* (II) (cis-*DDP*), 100 mg/m^2 *every* 3 weeks *was administered to* 24 *patients with advanced soft tissue sarcoma. All patients had received extensive prior chemotherapy and had measurable progressive disease and normal renal function on entry to the study. There were no objective responses in the* 17 *patients receiving an adequate trial of therapy. Nausea and vomiting were universal. Renal impairment was moderate in* 2 *patients and mild in* 4. *Serial audiometry detected hearing loss at high frequencies in* 3 *patients.*

INTRODUCTION

Cis-DIAMMINODICHLOROPLATINUM (II) (*cis*-DDP), an inorganic co-ordination complex of platinum has shown considerable activity in a number of human tumours, notably testicular [1], ovarian [2] and bladder cancers [3]. There is also evidence of activity in osteosarcoma and Ochs [4] has reported 1 complete remission of pulmonary metastases continuing at 18 months and 4 partial remissions in 8 patients, 7 of whom had relapse of disease following adjuvant therapy. Patients were given 20 mg/m^2/day × 5 or 120 mg/m^2 as a single dose, with forced osmotic diuresis. Baum [5], giving 3 mg/kg every 3 weeks to 17 patients who had had prior exposure to high dose methotrexate and adriamycin, obtained one complete remission lasting 8+ weeks and 2 partial remissions. The only data available on the effect of *cis*-DDP in soft tissue sarcoma comes from a recently completed South-West Oncology Group study [6], using *cis*-DDP 15 mg/m^2 × 5 every 4 weeks, which produced 3 partial remissions in 42 patients.

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This study by the Sarcoma Group of the European Organisation for Research on Treatment of Cancer (E.O.R.T.C.) has also evaluated *cis*-DDP in advanced soft tissue sarcoma. Early studies showed a high incidence of renal toxicity [7, 8] predicted by animal experiments [9]. Following the experiments of Cvitkovic [10] showing that massive hydration or mannitol infusion could prevent renal toxicity in dogs, Hayes [11] and Merrin [12] have demonstrated the value of similar measures in patients.

MATERIALS AND METHODS

Patients

Patients with histologically proven soft tissue sarcoma, above the age of 20 yr and with a Karnofsky performance status of at least 50 were considered eligible for this study. Other criteria for admission included the presence of measurable progressive disease, no chemotherapy within the previous 4 weeks and adequate renal (creatinine clearance >80 ml/min, or serum creatinine <120 μmole/l) and bone marrow function (WBC >3000, platelets >125,000).

Pretreatment investigations included clinical evaluation with measurement of lesions, Karnofsky grading, full blood-cell count, urea and electrolytes, liver function tests, chest X-ray, serum creatinine and creatinine clearance. These were repeated after 2 courses of treatment, 6 weeks after commencing therapy. Pre- and post-treatment pure tone audiograms were obtained in the majority of patients.

Drug administration

Cis-diamminodichloroplatinum II (*cis*-DDP), 100 mg/m^2 was dissolved in 1 litre of 5% dextrose or normal saline containing 37.5 g mannitol and infused over 3 hr. Adequate hydration was ensured by infusing 1 litre of normal saline in the 4 hr preceding drug administration and 3 litre of normal saline in the following 24 hr. A second course of treatment was administered after 3 weeks, the dose being escalated to 120 mg/m^2 if no toxicity resulted from the previous course.

Early in the study, *cis*-DDP was administered in 5% dextrose, but this was changed to normal saline following a report suggesting that the drug was unstable in 5% dextrose [13]. However, a recent study by Repta [14] suggests that in the presence of small amounts of chloride ion, little drug inactivation occurs within 3 hr.

RESULTS

Characteristics of the 24 evaluable patients are shown in Table 1. All had received extensive prior chemotherapy which, with one exception, was a drug combination which included adriamycin. All patients had received radiotherapy to the primary site and in three, lung metastases had also been irradiated. Three patients received 3 courses of *cis*-DDP, one received 4, and a further patient received 6 courses.

Seventeen patients received 2 courses of chemotherapy and are evaluable for response. In 8 patients, dose escalation for the second course was possible whereas 8 received the same dose and 1 patient had the dose reduced by 50%. The remaining 7 patients received one course of treatment and are evaluable for analysis of toxicity only. The second course was withheld in 3 patients because of rapidly progressive disease and, in 3, because of toxicity. One patient refused further treatment.

There were no remissions, 13 patients had progressive disease and 4 had stabilisation of disease or less than 50% reduction of measurable disease.

Table 1. Characteristics of evaluable patients

Total No.	24
Male	13
Female	11
Age (yr) (range)	23–72
(mean)	46.5
Sarcoma type	
Rhabdomyosarcoma	5
Fibrosarcoma	4
Synovial sarcoma	4
Leiomyosarcoma	3
Undifferentiated	3
Malignant fibrous histiocytoma	2
*Other	3
Site of disease	
Local recurrence/residual	12
Distant metastases	
Pulmonary	18
Lymph nodes	3
Bone	2
Liver	1
Skin	1

*Neurofibrosarcoma, liposarcoma, angiosarcoma.

Toxicity

Nausea and vomiting were moderate in 17 patients, mild in 6, one patient refusing further treatment. Irreversible renal toxicity occurred in one patient, serum creatinine rising from 102 to 245/μmole/l, 3 weeks later and remaining elevated at 258 μmole/l four days before death, which occurred from progressive malignant disease, 7 weeks after treatment. Autopsy showed a mild left hydronephrosis and hydro-ureter (which had been noted on an IVP prior to treatment) but the kidneys were histologically normal. One patient was taken off study when the creatinine clearance fell from 80 to 67 ml/min after the first course of treatment. Mild reversible elevation of serum creatinine occurred in 4 patients. The remaining 18 patients had no evidence of renal impairment. Serial audiograms were performed in 18 patients. Fifteen showed no change in hearing, but 3 showed significant hearing loss at high frequencies (>4000 Hz). There was no symptomatic impairment of hearing. Mild leucopaenia (WBC, 2000–3000 at 3 weeks) occurred in 5 patients and moderate leucopaenia (WBC, 1500 at 3 weeks) in one patient. Moderate thrombocytopaenia (platelets <50,000 at 3 weeks) occurred in one patient. There was no other toxicity.

DISCUSSION

As there were no major therapeutic responses in 17 patients receiving an adequate

trial of *cis*-DDP, it is unlikely that this drug has significant activity in soft tissue sarcoma, despite the fact that all patients had received extensive prior chemotherapy. This concurs with the findings of the South-West Oncology Group [6]. These results are particularly disappointing in view of the promising results in osteosarcoma [4, 5], although the majority of therapeutic responses in this tumour have been observed in children (age <20 yr), and experience in adults is not so favourable [6].

Nausea and vomiting were almost universal, although ameliorated in some cases by premedication with diazepam and metochlopramide. Adequate hydration and mannitol infusion seems to have prevented major renal toxicity. The only patient who developed irreversible renal impairment had a pre-existing abnormality of the urinary tract, which has been suggested by Hayes *et al.* [11] to predispose to renal toxicity of *cis*-DDP. Despite heavy prior chemotherapy, bone marrow depression (mainly leucopaenia) following *cis*-DDP was mild and rapidly reversible. Ototoxicity, only evident on serial audiometry, was present in 3/18 patients; a lower incidence than has been reported in earlier studies [11, 15].

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