Eur J Cancer Clin Oncol, Vol. 24, No. 8, pp. 1345–1348, 1988.
Printed in Great Britain

0277-5379/88$3.00 + 0.00

Phase II Study of Iproplatin (CHIP, JM-9) in Advanced Testicular Cancers Progressing After Prior Chemotherapy

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Abstract—*Twenty-two patients with advanced testicular cancer received iproplatin at a dose of 180–240 mg/m² every 4 weeks. All the patients progressed or recurred after chemotherapy including cisplatin. The most severe toxicity was thrombocytopenia with two toxic deaths after a first cycle of 240 and 180 mg/m² respectively. Nausea and vomiting were almost universal but mild in intensity. One renal failure occurred 6 weeks after the first cycle while the tumor was progressing. No antitumor activity was observed in this heavily pretreated population of patients.*

INTRODUCTION

IPROPLATIN [*cis*-dichloro-*trans*-hydroxy-bis-isopropylamine platinum (IV), CHIP, JM-9] is a quadrivalent derivative of cisplatin, developed in the search for a better therapeutic index as compared to the parent cisplatin compound. The antitumor activity of iproplatin in animals is significant, although it was found to be cross-resistant with cisplatin in L 1210 leukemia [1].

Phase I studies conducted in the U.S.A. [2–4] and in Europe [5] used various schedules and doses ranging from 20 to 380 mg/m². In all the studies, dose limiting toxicity was thrombocytopenia, other toxicities consisting in cumulative myelosuppression, gastrointestinal toxicity, skin rashes and rarely renal toxicity.

Using a single dose schedule, repeated every 4 weeks, a high response rate was reported in patients with ovarian carcinoma including pretreated patients [5]. Based on this experience of a member of the EORTC Early Clinical Trials Group, we decided to embark on a large disease-oriented phase II program with iproplatin. This paper reports our conclusions in previously treated disseminated testicular cancer.

Accepted 5 April 1988.
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MATERIALS AND METHODS

Patient selection

All eligible patients had histologically proven progressive malignant teratocarcinoma with measurable (in 2 diameters) or evaluable (in 1 diameter) lesions. Patients in whom the only evidence of progressive disease was the presence of elevated levels of serum markers such as AFP and/or βHCG, were eligible for the study provided that the level was clearly rising within the 4 weeks prior to entry in the study. All of the patients had primary tumors which originated from the testis. Entry criteria included a performance status of 0–2, white blood cells (WBC) $\geq 3.5 \times 10^9$/l, platelets $\geq 130 \times 10^9$/l, serum creatinine ≤ 150 μmol/l and bilirubin ≤ 25 μmol/l. Patients had to be pretreated and resistant to or recurrent after a previous chemotherapy containing cisplatin. No previous chemotherapy or radiation therapy was allowed within the 4 weeks preceding the administration of iproplatin.

Drug and treatment

Vials containing 50 mg of iproplatin and mannitol were reconstituted with 50 ml of isotonic saline solution and then further diluted in 1000 ml of isotonic saline for intravenous administration over 60 min. No further hydration was administered.

At the start of the study, the dose of iproplatin given was 240 mg/m² but this was subsequently reduced to 180 mg/m² because of severe myelosuppression in the first 14 patients treated. Treat-

ment courses were repeated every 4 weeks. In the case of myelosuppression when retreatment was rescheduled treatment was postponed for a maximum of 2 weeks. Dose adjustments to 80% or 60% were performed when World Health Organization (WHO) grade 3 or 4 myelosuppression occurred. A minimum of two iproplatin courses were intended, unless clear evidence of progressive disease was apparent after one course. These patients were considered as early progressions. In the case of an increase of 25% of the indicator lesions or the appearance of new lesions (defined as progressive disease), iproplatin administration was stopped. Otherwise, complete and partial responses were defined with standard criteria. No change indicated a tumor shrinkage that was insufficient to qualify for a 50% partial response.

RESULTS

Twenty-two eligible patients were entered into the study from 11 institutions.

Table 1 shows the characteristics of all the eligible patients. One additional non-eligible patient (WHO PS 3) received iproplatin. All of the patients had progressive disease despite a prior regimen containing cisplatin. All had undergone prior surgery, 15 with a curative aim, seven with palliative intention. Seven patients received previous radiotherapy.

The majority of the patients (16) had predominantly embryonal carcinoma of the primary tumor, seven had a raised HCG + AFP, three a raised AFP alone, five a raised HCG alone. Fourteen patients received only one cycle of iproplatin, five received two cycles, and the remaining three patients received three cycles.

The first 14 patients received 240 mg/m^2 as a starting dose; because severe toxicity was observed, the next eight patients received a first dose of 180 mg/m^2.

Antitumor response

Among 22 eligible patients, four patients were considered as not being evaluable for tumor response due to early death within the first 4 weeks following treatment. In one case, this was considered to be a toxic death because of severe myelosuppresion in association with progressive disease.

- two patients were considered as no change after two courses of iproplatin and then received a third cycle without any evidence of tumor reduction.
- 10 patients with a definite progression during the first 4 weeks of treatment were considered as early progression and dropped out of the study.
- five patients progressed during the second 4 weeks interval, stopped the treatment and were considered as being in progression.
- one patient showed a clear definite progression after the third cycle was completed.

*Table 1. Characteristics of eligible patients**

Number	22
Median age in years	30
Range	(20–57)
Performance index	0: 10
	1: 7
	2: 5
Prior surgery	22
curative	15
palliative	7

*All patients were previously treated by chemotherapy including cisplatin [median number of drugs: 6 (4–9)].

Toxicity

Table 2 shows the lowest blood values for white blood cells and thrombocytes, together with the day of nadir.

In 14 patients receiving 240 mg/m^2 as a starting dose, six patients had no evidence of leucopenia while eight patients suffered a modest degree of leucopenia; five had a lowest WBC count between 3 and 3.9 × 10^9/l, 2 (2–2.9) and 1 (1–1.9). However, thrombocytopenia was much more severe. Among these 14 patients, only four patients had a platelet count higher than 100 × 10^9/l after the first course while four had the lowest value: between 50 × 10^9/l and 99 × 10^9/l, four between 20 and 49 × 10^9/l and two below 20 × 10^9/l.

One patient died. He was a 29-year-old patient, PS = 1, previously treated by a chemotherapy regimen containing six drugs. After the first iproplatin dose of 240 mg/m^2, he developed a grade 3 nausea–vomiting toxicity and delayed thrombocytopenia with a nadir platelet count of 9 × 10^9/l,3 weeks after the treatment. At that stage, he started gastro-intestinal bleeding and fatal bronchopneumonia. Leucopenia was not observed amongst *the eight patients who received a starting dose of* 180 mg/m^2. Thrombocytopenia, however, was still a significant problem.

A nadir platelet count between 50 and 99 was observed in two patients after the first cycle, while a life threatening thrombocytopenia occurred in another patient receiving 180 mg/m^2. He was a 48-year-old patient with a PS of 1, who had been previously treated with six different drugs. After 2 weeks of treatment with a dose of 180 mg/m^2 he developed thrombocytopenia with a nadir platelet count of 20, inducing a fatal upper gastro-intestinal bleeding despite intensive platelet transfusion.

The non-hematological toxicities which were observed are listed in Table 3. Nausea and vomiting occurred almost universally after iproplatin admin-

Table 2. Hematological toxicity

	Nadir values	
	WBC $\times 10^9$/l	Platelets $\times 10^9$/l
240 mg/m^2 starting dose		
1st course		
Median	4.2	87*
Range	(6.2–1.8)	(230–9)
Day of nadir	20 (5–34)	20 (7–31)
Overall		
Median	3.1	45*
Range	(5.1–1.8)	(218–9)
180 mg/m^2 starting dose		
1st course		
Median	3.9	72
Range	(2.4–9.5)	(31–175)
Day of nadir	13 (6–21)	13 (12–14)
Overall		
Median	3.9	54*
Range	(2.4–9.5)	(175–16)

*Two toxic deaths from thrombocytopenia.

Table 3. Non-hematological toxicities

Type	Number of patients	Number of patients with grade 3–4 toxicities	Percentage of total patients
Nausea–vomiting	20	7	90
Diarrhea	9	0	41
Mucositis	1		5
Drug fever	1		5
Renal failure	1	1	5

istration, of mild or moderate intensity. Diarrhea was observed in almost half of the patients but only mildly. Other grade 1 and 2 toxicities included drug fever and mucositis.

A severe renal toxicity occurred in a 30-year-old patient, previously treated with cisplatin, VP 16, Bleomycin and Ifosfamide. During treatment (240 mg/m^2), he developed a grade 3 nausea–vomiting toxicity; after 3 weeks, the platelets count was 2.7 $\times$ 10^9/l and he started bleeding. After recovering from hematological toxicity, he developed a fatal renal failure 6 weeks after the treatment. At that time tumor indicators showed a clear progression. Although it is not clear whether the fatal issue was drug-related, this case was considered as a WHO grade 4 renal toxicity.

DISCUSSION

Phase II trials of new drugs in testicular cancer are difficult to accomplish because of the extent of prior treatment in virtually all of the patients.

Initially the iproplatin starting dose was 240 mg/m^2 every 4 weeks given intravenously without hydration. Drug-induced myelosuppression was marked. Two patients developed thrombocytopenia graded 3 and 4, respectively, and in one case this persisted to the patient's death. Thus the initial dose was reduced to 180 mg/m^2. In spite of this reduction a second toxic death due to thrombocytopenia was noted. Nausea and vomiting were reported by the vast majority of patients but were of short duration and qualitatively less severe than with cisplatin.

With weekly creatinine we did not demonstrate any renal function impairment. The only fatal renal failure occurred 6 weeks after the treatment and was not proven to be drug-related. No antitumor activity was detected in this trial concerning patients pretreated with cisplatin.

We conclude that iproplatin given at a dose of 180–240 mg/m^2 is not active in this patient population.

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