

Phase II Study of Iproplatin (CHIP, JM-9) in Advanced Squamous Cell Carcinoma of the Head and Neck

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Abstract—A phase II study of iproplatin was conducted in advanced squamous cell carcinoma of the head and neck both in patients previously treated with chemotherapy or not. Iproplatin was given intravenously every 4 weeks at the dose of 240–300 mg/m² without hydration. A total of 101 4-week courses was given to 50 eligible patients. No antitumor activity was detected. Drug-induced toxicity consisted in moderate myelosuppression, frequent but mild nausea and vomiting, and occasionally diarrhea and stomatitis. This study demonstrates that iproplatin given in this dose and schedule is devoid of activity in advanced squamous cell carcinoma of the head and neck.

INTRODUCTION

IPROPLATIN (*cis*-dichloro-*trans*-hydroxy-bis-isopropylamine platinum (IV), CHIP, JM-9), a quadrivalent derivative of cisplatin, has a different spectrum of antitumor activity compared to cisplatin [1,2]. In clinical studies, thrombocytopenia was the major dose-limiting toxicity [3–6]. Using a single dose schedule, repeated every 4 weeks, a high response rate was reported in patients with ovarian carcinoma previously treated or not [6]. Based on this experience of a member of the EORTC Early Clinical Trials Group, we performed a phase II study with iproplatin in advanced squamous cell carcinoma of the head and neck.

MATERIALS AND METHODS

Patient selection

All eligible patients had histologically-proven progressive squamous cell carcinoma of the head

and neck, not amenable to surgery nor to radiation therapy, with measurable (in 2 dia.) or evaluable (in 1 dia.) lesions. Primary tumors originating in the nasal and paranasal cavities, as well as in the nasopharynx were excluded. Patients should have a performance status of 0–2, white blood cells (WBC) over $3.5 \times 10^9/l$, platelets over $130 \times 10^9/l$, serum creatinine less than 150 $\mu\text{mol/l}$ and bilirubin less than 25 $\mu\text{mol/l}$. In the 4 weeks prior to iproplatin administration, no chemotherapy nor radiation therapy was to be given.

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.

Iproplatin doses were 240 mg/m² for patients with previous chemotherapy or complete radiation therapy over the neck and 300 mg/m² in previously untreated patients. Courses were repeated every 4 weeks. Treatment was postponed for a maximum of 2 weeks in case of myelosuppression. Dose adjustments to 80 or 60% were made in case of World Health Organization (WHO) grade 3 and 4 myelosuppression.

Two iproplatin courses were to be given, unless there was clear evidence of progressive disease after

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Table 1. Eligible patient characteristics

	Previously treated with chemotherapy	Previously untreated with chemotherapy
Number	31	19
Median age in years (range)	55.3 (42-78)	55.3 (42-74)
Male/female	29/2	18/1
Performance index		
0 + 1	24	14
2	7	5
Prior radiation therapy	27 (87%)	19 (100%)

one course. These patients were considered as early progressions. In case of an increase of $\geq 25\%$ of the indicator lesions, or appearance of new lesions (defined as progressive disease), iproplatin administration was stopped. Otherwise, complete and partial response were defined with standard criteria [7]. No change indicated tumor shrinkage that was insufficient to qualify for a 50% partial response.

RESULTS

Fifty eligible patients were entered into the study, from 15 participating institutions. Table 1 shows the characteristics of all eligible patients, separated in 2 groups regarding prior exposure to chemotherapy. Both groups are comparable in their characteristics, most of the patients having received radiation therapy prior to entry into this study.

The higher starting dose of 300 mg/m² was given in 7/19 (37%) patients previously untreated with chemotherapy. Doses of 240 mg/m² were given to all the others because of prior extensive radiation therapy. All patients previously treated with chemotherapy were treated with the dose of 240 mg/m². In this group of patients, 25 (81%) had received prior treatment with cisplatin, the rest of the patients being treated with other drugs.

Antitumor response

Among 31 eligible patients previously treated with chemotherapy, 4 patients were considered as not evaluable for tumor response due to the absence of sufficiently documented tumor parameters. Three patients died during the first 4 weeks of treatment, and were considered as treatment failures. Six patients received only one cycle of iproplatin, and presented definite signs of early progressive disease. Three patients had no change after 2 courses of iproplatin, and thus were continued on treatment for 3, 4, and 5 cycles respectively,

without any evidence of tumor reduction. At least 15 patients were progressive after 2 full courses of iproplatin and were dropped out of the study at that time.

In the 19 eligible patients not previously treated with chemotherapy, 2 were inevaluable for tumor response, and one further patient died within 4 weeks of iproplatin administration. Two patients received only 1 course of iproplatin and were considered as early progression; 2 patients were no change and 12 had progressions after 2 courses.

Toxicity

Table 2 shows the lowest blood values for white blood cells (WBC) and thrombocytes. In patients previously untreated with chemotherapy, the nadir in the first course was on day 18 (range 5-38) for WBC and day 15 (7-31) for platelets. Median time to recovery above 4.0 and $100 \times 10^9/l$ was day 33 (range 31-38) and day 24 (15-33) for WBC and platelets, respectively.

For patients previously treated with chemotherapy, median number of days to nadir after the first course was 17 (range 7-28) and 16 (6-32) for WBC and platelets, respectively. Recovery was day 25 (range 20-30) and day 29 (14-50) for leukocytes and thrombocytes. WHO grades 3+4 toxicities were seen in 2/17 (12%) untreated patients for WBC and 4/17 (24%) for platelets, compared to 3/20 (15%) previously treated patients for WBC and 6/20 (30%) patients for platelets.

Non-hematological toxicities frequently observed are listed in Table 3. Universal nausea and vomiting were seen after iproplatin administration, usually being of mild intensity. Diarrhea and stomatitis were also seen in lower percentages of the patients. Other grade 1+2 toxicities included peripheral neuropathy (2 patients), alopecia (1) and drug fever (1).

Table 2. Hematological toxicity

	WBC $\times 10^9/l$ First/all courses	Lowest values Platelets $\times 10^9/l$ First/all courses
Patients previously treated with chemotherapy (range)	4.4/4.0 (0.6–10.9)	140/95 (6–388)
Patients previously untreated with chemotherapy (range)	4.6/4.1 (0.9–10.1)	128/80 (12–480)

Table 3. Non-hematological toxicities

Type	Total number of toxic patients	Number of patients with grade 3 + 4 toxicities	% total evaluable patients
Nausea and vomiting	36	5	88%
Diarrhea	7	1	18%
Stomatitis	4	1	10%

Serum creatinine elevation was observed in 2 patients. The first developed an increase from 118 to 212 $\mu\text{mol/l}$ on day 4 after the first course with 300 mg/m^2 , rapidly reversible after hydration and furosemide administration. The following iproplatin course was reduced to 240 mg/m^2 and no serum creatinine elevation was noted. The second patient was a 45-year-old male patient, heavily pretreated with radiation therapy and chemotherapy with cisplatin-containing regimens. He was considered as ineligible, and thus not included in the toxicity analysis, because he received his last chemotherapy treatment 26 days prior to iproplatin. He developed on day 21, after the first iproplatin

dose of 240 mg/m^2 , a septic shock secondary to grade 4 myelosuppression. He was treated with gentamycin and developed a fatal renal insufficiency.

DISCUSSION

No antitumor activity was detected in this phase II trial of iproplatin in advanced head and neck carcinoma conducted by the Early Clinical Trials Groups of EORTC. This contrasts with another report [8] in head and neck carcinoma. We conclude that iproplatin given at the dose of 240–300 mg/m^2 does not warrant further studies in this tumor type.

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