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Phase II Trial of Pirarubicin in Epidermoid Carcinoma of the Head and Neck

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INTRODUCTION

ANTHRACYCLINES GENERALLY exhibit very low antitumour activity on epidermoid carcinomas of the head and neck [1]. Nonetheless, some doxorubicin analogues can be efficacious in these patients. Pirarubicin, synthesised in 1979 by Umezawa [2], shows high antitumour activity in animals, with less cardiotoxicity [3]. The first clinical studies of pirarubicin for treatment of epidermoid carcinomas of the head and neck, carried out in Japan, showed a response rate of 20% after intravenous injection and 52% [4] or 71% [5] after intra-arterial injection. The efficacy of pirarubicin has been suggested in one American trial [6] with one complete and four partial responses out of 16 patients. On the other hand three other studies [7–9] have not confirmed this result.

We have conducted a phase II clinical trial with the double aim of defining the antitumour efficacy of pirarubicin in patients presenting an advanced epidermoid carcinoma of the head or neck, and of determining its toxicity.

PATIENTS AND METHODS

From October 1986 to November 1988, 59 patients were enrolled in the trial. 5 patients were ineligible (absence of measurable lesion: 3, oesophageal localisation: 1, cylindroma: 1) and were excluded from analysis. The 54 eligible patients included 50 men and 4 women with a median age of 56 years (range: 36–70 years). According to WHO standards, 2 patients had a performance status grade 0, 28 grade 1 and 24 grade 2. All patients presented a histologically confirmed epidermoid carcinoma of the head or neck, undergoing recurrence and/or metastasis.

31 patients had been treated by surgery and 46 by radiation therapy. 36 patients had received one or several chemotherapy protocols, with the exception of anthracyclines. All patients had a normal initial haemogram, with a leucocyte count $> 4 \times 10^9$/l and a platelet count $> 120 \times 10^9$/l. None of the patients showed any major signs of hepatic insufficiency (bilirubin > 35 mol/l) or renal failure (creatinine > 135 mol/l). All patients presented at least one measurable tumour with progression of these lesions for at least 1 month.

The initial dose was 25 mg/m^2/day by slow intravenous injection in the tube of a rapid-flow isotonic glucose perfusion, for 3 consecutive days every 4 weeks.

Due to the haematological toxicity of this dose in the first patients, it was reduced to 20 mg/m^2/day for 3 days every 3 weeks.

During the treatment period, the dose was sometimes modified and/or the treatment delayed as a function of the haemogram, creatininaemia and bilirubinaemia. 42 patients received one to three cycles of chemotherapy, and the other 12 patients received four to 11 cycles. The median of the total pirarubicin dose was 159 mg/m^2 (20–546 mg/m^2). WHO response criteria were applied [10]. Response rates were calculated in relation to total eligible patients.

Table 1. Maximal haematological toxicity per patient (WHO grade) on day 15

	Grade					
	0	1	2	3	4	ND
Leucocytes	5	7	10	22	3	7
Neutrophils	7	4	8	17	11	7
Platelets	33	6	2	3	0	10

ND = not determined.

RESULTS

Response to treatment

One complete response was observed in a patient who had not been pretreated by chemotherapy, presenting an isolated pulmonary parenchymatous nodule, 15 × 10 mm, discovered after treatment of a piriform sinus carcinoma 1 year earlier. The response was obtained after five cycles, and it persisted for 14 weeks.

2 patients presented a partial response, for a loco-regional recurrence (nodal and cutaneous cervical) and a pulmonary metastasis. These responses persisted for 14 and 22 weeks.

The response rate for the entire group of eligible patients is therefore 6% (95% confidence intervals 1–15%). If only those patients not previously treated with chemotherapy are considered, the response rate is 11% (1–35%).

Stabilisation ($n=18$) or progression ($n=19$) was observed in 37 patients. Of the other 14 patients, 7 presented a rapid progression and 2 died from their tumours. 5 patients could not be evaluated in terms of response and were registered as treatment failures (1 death due to toxicity, 3 deaths unrelated to treatment, 1 undocumented evaluation).

Toxicity

At the doses used in this trial, pirarubicin had significant haematological toxicity (Table 1). 1 patient died from bone marrow failure 14 days after the first pirarubicin cycle.

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Table 2. Non-haematological toxicity

	WHO grade						
	0	1	2	3	4	ND	Pr.
Nausea/vomiting	32	15	5	1	0	1	0
Stomatitis	49	2	1	0	0	1	1
Hyperthermia	47	3	3	0	0	1	0
Alopecia	34	12	4	0	0	2	2
Infection	46	3	1	1	2	1	0
Cardiac	48	0	0	3	0	2	1

ND = not determined.
Pr. = preexisting toxicity.

The major non-haematological toxicity involved digestive symptoms in the form of nausea and vomiting, and alopecia occurred in 16 patients, including 4 with grade 2 symptoms (Table 2). 2 patients showed a decrease of the left ventricular ejection fraction (35% and 47% versus pretreatment levels of 80% and 60%, respectively), without clinical signs. The third patient showed signs of anterior ischaemia on the electrocardiogram during the second treatment cycle. The dose was decreased in 14 patients and at least one cycle was delayed in 17 others.

DISCUSSION

Pirarubicin at the dose of 20 mg/m^2/day for 3 consecutive days every 3 weeks showed no significant antitumour activity on advanced and/or metastatic epidermoid carcinomas of the head and neck. These results confirm those of Shin *et al.* [8] in which none of the 14 patients treated at the dose of 60 mg/m^2 every 3 or 4 weeks presented a response. In the Takeda series [4], only partial responses were obtained after doses of 5–20 mg 3 times per week, for a total dose of 40–100 mg. It should be emphasised that most of the treated patients presented one or several poor risk factors for a response to chemotherapy, including in particular a poor general condition, previous treatment and large tumour size [11]. In 10 of the patients, all the tumour targets were situated in previously irradiated areas.

Pirarubicin was myelotoxic at the doses used. The recommended dose is currently 50 mg/m^2 in pretreated patients and 60 mg/m^2 in patients not previously treated. One of the patients in our series died from aplasia after a single cycle of pirarubicin at 75 mg/m^2. In the Shin, *et al.* series [8], 8 of 14 patients had a grade 4 neutropenia. On the other hand, nausea, vomiting and alopaecia were less frequent and the cardiotoxic manifestations were rare and asymptomatic.

The therapeutic index might be improved with intra-arterial chemotherapy in previously untreated patients.

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