Cancer Chemother Pharmacol (1994) 33: 438–440

Cancer Chemotherapy and Pharmacology

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Short communication

A phase II study of pirarubicin in patients with advanced recurrent head and neck squamous cell carcinoma

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Received 24 August 1993/Accepted 15 September 1993

Abstract. Background: Head and neck squamous carcinoma (HNSCC) is a chemotherapy-sensitive tumour, but this sensitivity is not reflected in an impact on survival. The study of new drugs is therefore indicated. Pirarubicin (4′-*O*-tetrahydropyranyl-doxorubicin) has a higher preclinical index than doxorubicin, with low cardiotoxicity in animal models. Patients and methods: Twenty-six patients with squamous cell carcinoma of the head and neck and documented progression after or during previous chemotherapy were entered into the study. Two patients were ineligible for evaluation. Pirarubicin was given at a dose of 70 mg/m^2 every 3 weeks. Results: Partial remission was seen in 1 of the 24 evaluable patients. The predominant toxicity was bone marrow depression, with leucopenia in 62% of the patients. One patient died due to a gastrointestinal haemorrhage during a period with WHO grade IV thrombocytopenia. Conclusion: On the basis of these results, pirarubicin cannot be recommended as second-line treatment in patients with recurrent and metastatic HNSCC. Its possible relevance for first-line treatment cannot be judged from these data.

Introduction

Squamous cell carcinomas of the head and neck region are considered sensitive to chemotherapy, on the grounds of the high response observed when chemotherapy is given as primary treatment for such tumours [1]. Despite this observation, metastatic or recurrent disease is the only accepted standard indication for chemotherapy at present. The four most active drugs in this disease are methotrexate, cisplatin, bleomycin and 5-fluorouracil [2]. The prognosis for patients with locally recurrent or metastatic disease is poor, with a median survival of 6 months. The role of chemotherapy in these cases, whether single-agent or combination chemotherapy, is marginal. This is partly explained by the extensive prior treatment, a decreased vascularity in the local area and a declining performance and nutritional status [1]. Combination chemotherapy results in a higher response rate, but has no significant impact on survival [3].

Obviously the study of new drugs is indicated. Pirarubicin (4′-*O*-tetrahydropyranyl doxorubicin) has a higher preclinical index than doxorubicin [4], with low cardiotoxicity in various animal models. Phase I studies showed granulocytopenia as the dose-limiting toxicity with doses ranging from 45–75 mg/m^2 every 3 weeks. Several regimens have been explored in phase II, and promising responses in patients with head and neck squamous cell carcinoma have been observed [5, 6].

We evaluated the antitumour activity or pirarubicin when given as second-line treatment in patients with recurrent or metastastic squamous cell carcinoma of the head and neck.

Patients and methods

Patients were eligible for the study if they had measurable or evaluable, histologically or cytologically proven, squamous cell carcinoma of the head and neck. Prior chemotherapy except for anthracyclins was allowed and progression after first-line chemotherapy should be documented. Patients had to be under the age of 75; to have a WHO performance status of WHO 0, 1, or 2; to have serum creatinine of <133 μmol/l and normal haematological, liver and cardiac function; and to be free of acute illness or overt infectious disease and of any second primary tumour. Criteria for measurable and evaluable disease, for the assessment of response and toxicity were the standard WHO/UICC criteria [7].

Pirarubicin was given in a dose of 70 mg/m^2 as a short i. v. infusion (within 15–30 min once every 3 weeks. Dose modifications were made according to the nadir values of white blood cell (WBC) and platelet counts observed during weekly measurements. The dose was reduced with 25% in case of grade III toxicity in WBC and/or grade II

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Table 1. Patient characteristics

Sex (M/F)	23/3
Age median (range)	55 (36–75)
WHO Performance status	
0	4
1	18
2	4
Prior surgery	
Curative	7
Palliative	1
Prior radiotherapy	
Responders	14
Non-responders	9
Adjuvant	1
Prior chemotherapy	
Responders	13
Non-responders	12
Adjuvant	1
Primary site	
Oral cavity	12
Hypopharynx	5
Larynx	3
Oropharynx	3
Pharynx	1
Other	2
Extent of disease	
Locoregional recurrence	9
Recurrent	8
Metastatic	9

in platelet counts, and with 50% in case of grade IV toxicity for WBC and grade III for platelets. At the time of retreatment WBC had to be greater or equal to 3×10^9/l and platelets greater or equal to 100×10^9/l. After a delay of more than 2 weeks patients went off study.

Furthermore, treatment was withold in case of hepatotoxicity (bilirubin >25 μmol/l), nephrotoxicity (serum creatinine >132 μmol/l) or cardiotoxicity (drop in left ventricular ejection fraction of 15% or more or when the left ventricular ejection fraction dropped below 50%). A total of at least two courses had to be given unless this was clearly not in the best interest of the patient. In case of a complete response (CR) or partial response (PR) or when stabilization was observed treatment was continued until disease progression or until unacceptable toxicity occurred, whichever came first. All eligible patients were included in the response analysis.

Performance status, haematological parameters and serum creatinine were evaluated weekly; a physical examination was performed before each cycle and side effects were recorded. After every second course the response was assessed. The left ventricular function was measured after cumulative dosages of 210, 420, 630 mg/m^2.

Results

Initially 26 patients were entered in the study, 23 men and 3 women, of whom 24 were eligible and 23 fully evaluable. Two patients were considered ineligible because they had no evaluable lesions prior to entry in the study. One patient refused further treatment after one course. The patient characteristics are summarized in Table 1. In 35% of the patients metastatic disease was present. The median number of courses administered was three (range one to six). Table 2 summarizes the observed toxicities. The most

Table 2. Side effects

	Percentage of patients affected
Leucopenia	100 (62)[a]
Thrombocytopenia	31 (8)[a]
Anaemia	65 (15)[a]
Alopoecia	46
Nausea	42 (4)[a]
Vomiting	23 (4)[a]
Oral	23
Infection	15 (8)[a]
Fever	12
Haemorrhage	8 (8)[a]
Local	8
Diarrhoea	8
Consciousness	4
Cutaneous	4
Neuropathy	4
Other	15 (8)[a]

[a] Percentage of grade III–IV (WHO)

prominent toxicity was leucopenia, which was severe (grade III–IV) in 62% of the patients and led to serious infectious complications in 8%. In 1 patient a *Pseudomonas* sepsis was diagnosed in the presence of a grade III leucopenia after the fourth course. The dose was reduced in 8 of the 22 patients who received a second course, and in 7 there was a delay due to inadequate recovery. In 5 patients doses were both reduced and delayed. Thrombocytopenia was seen in 31% of the patients, and grade IV thrombocytopenia was seen in 2 of these, leading to severe gastrointestinal haemorhage and death in 1. Furthermore, alopoecia was seen in 46% of the patients. Other grade III toxicity consisted in constipation and weakness probably not related to the drug studied. No cardiac toxicity was observed, but high cumulative doses were not achieved in this study.

Partial remission was seen in 1 of the 23 evaluable patients, no change in 8, and progression in 12. In 2 patients early progression was seen. The partial remission was observed in the lungs; the same patient had concomitant local disease, which was not, however, measurable or evaluable. The response lasted 3 months, at the end of which new lesions were observed in the neck while the remission in the lungs was still ongoing. The patient died 3 weeks later of malignant disease.

Discussion

In this open-label phase II study, pirarubicin in a dose of 70 mg/m^2 was ineffective in patients with squamous cell carcinoma in the head and neck region who had failed to achieve remission or had or showed a relapsed after previous chemotherapy. Pirarubicin is a semisynthetic derivative of doxorubicin. The major differences between the new compound and the parent compound are the larger distribution volume of pirarubicin and the more rapid uptake in the cell; in addition, the accumulation in the heart muscle and bile is lower [8]. It is therefore potentially less

toxic to the myocardium, and this was confirmed in animal experiments.

Experience with anthracyclines in head and neck squamous cell carcinoma (HNSCC) is limited. In one phase II study a response rate of 44% (8/18) was found in previously untreated patients [9]. Initial studies with pirarubicin in HNSCC suggested relevant activity. In pooled phase II data [10, 11] a response rate of 18.8% was observed when 20 mg pirarubicin was given weekly. In a multicentre phase II study 49 patients were treated with variable doses and regimens. A PR was seen in 11 patients (22.4%) [5]. When it was given as second-line treatment at a dose of 70 mg/m^2 every 3 weeks, 7 out of 16 patients who each received at least two cycles achieved response: CR in 2 (13%) and PR in 5 (31%) [5]. The total group consisted of 23 patients, so that the true response rate is 30%. Nonetheless, this result is in sharp contrast with our observation of 1 PR among 24 eligible patients treated with the same dose and regimen.

The value of evaluating new drugs in patients who have received prior chemotherapy can be questioned. In a recent analysis of prognostic factors related to the probability of response to cisplatin-based chemotherapy in recurrent and or metastatic HNSCC, the relevance of PS, age, previous therapy, absence of local relapse, metastatic disease, long disease-free interval and the measurability of disease was shown [12]. The recognition of these factors may explain the broad variation in response frequently encountered. Those relapsing and failing on prior chemotherapy certainly represent a negatively selected population.

The toxicity, as might be expected from published experience, was mainly related to the bone marrow suppressive properties of pirarubicin. Leucocytopenia in particular was considerable, with WHO grades III and IV toxicity in 62% of patients, leading to serious infectious complications in 2 patients. Another patient died of a fatal haemorrhage while suffering grade IV thrombocytopenia.

In conclusion, pirarubicin cannot be recommended as second-line medication for patients with HNSCC. Conclusions on its possible value for first-line treatment cannot be drawn from these observations.

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