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The Use of Cisplatin Plus 5-Fluorouracil Chemotherapy in an Unselected Group of Patients with Recurrent Squamous Cell Carcinoma of the Head and Neck

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Cisplatin and infusional 5-fluorouracil (5-FU) has become regarded as the standard chemotherapy for squamous cell carcinoma (SCC) of the head and neck. Results of phase II studies vary widely and do not always reflect the activity of regimen in general clinical practice. We have treated 20 consecutive patients with cisplatin 100 mg/m^2 and 5-FU given as a 4-day infusion at 1 g/m^2 for 24 h. In order to reflect more accurately the activity of this regimen in everyday practice we have followed as many patients as possible to relapse and death and measured the duration of remissions from the end of treatment. 6 patients responded (30%, 95% CI: 10–48%) with 1 patient achieving a complete remission. Partial remission lasted for 3–18 months and the complete remission lasted for 7 months. Median survival of patients from the date of first treatment was 7 months (range 1 week–20.5 months). The regimen was well tolerated but required hospitalisation. We conclude that this regimen is well tolerated, active and a good choice for treating recurrent SCC of the head and neck in an unselected population of patients with recurrent disease in the context of everyday oncological practice.
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INTRODUCTION

SCC IS THE most common histological type of tumour occurring in the head and neck region and the principal sites of involvement in the U.K. are oral cavity and larynx [1]. The treatment of choice is surgical excision, radiotherapy or both depending on the site and size of the local disease. Chemothrapy has no clear role in the treatment of early disease [2] but it is often used to palliate patients with recurrent or metastatic disease. In this setting, cisplatin in combination with 5-FU is thought to be the most active regimen but reported response rates vary widely between 11 and 79% [3]. There are a number of reasons for this inconsistency, including drug scheduling; for instance, 5-FU is more effective when given as a continuous infusion rather than a bolus injection [4]. In addition, it is known that patients treated in the neoadjuvant setting have a higher response rate than those with recurrent or metastatic disease [2, 5, 6]. We wished to study the activity of this regimen in the context of everyday clinical practice. Much of the data on the use of cisplatin plus infusional 5-FU in patients with recurrent disease is derived from phase II studies. The precisely defined patient entry criteria in such trials do not always reflect the heterogeneity of the patient population encountered and therefore their results do not always reflect those obtained in everyday clinical practice. Furthermore, long-term follow-up is not usually part of phase II study methodology. We therefore report a series of 20 unselected consecutive patients with recurrent SCC of the head and neck region who were all treated with cisplatin an infusional 5-FU and were all followed to relapse.

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MATERIALS AND METHODS

20 consecutive patients who required treatment for recurrent SCC of the head and neck region were treated with cisplatin and infusional 5-FU. All patients had clinical evidence of recurrent disease after initial treatment (surgery ± radiotherapy) had not received any prior cytotoxic chemotherapy, had adequate renal function (glomerular filtration rate greater than 60 ml/min) and had an ECOG performance status of 0–3 inclusive.

Cisplatin was given at a dose of 75–100 mg/m^2 over 1 h, following hydration with 2 l of normal saline over 12 h and 200 ml of 20% mannitol which was administered over 30 min just prior to the cisplatin. This was followed by a 96-h continuous intravenous infusion of 5-FU at a dose of 1 g/m^2/24 h. Standard antiemetic therapy (dexamethasone and high-dose metoclopramide or ondansetron) was given. The regimen was repeated every 3 weeks.

Tumour size was assessed clinically and by computerised tomography (CT scan) before the first course and subsequently after alternate treatment cycles. Standard criteria for

Table 1. Previous treatments and sites of disease

	No. of patients
Primary treatment	
Radiotherapy alone	11
Surgery + radiotherapy	9
Biological therapy	2
Sites of recurrent disease	
Local only	14
Local + metastases (lung × 2, bone × 1)	3
Local + regional nodes	2
Local + hypercalcaemia	1

Table 2. Toxicity of treatment assessment according to WHO grade

	WHO grades				
	0	1	2	3	4
Anaemia	7	6	7	0	0
Neutropenia	12	2	5	1	0
Thrombocytopenia	20	0	0	0	0
Infection	18	2	0	0	0
Nausea and vomiting	18	1	1	0	0
Phlebitis	18	2	0	0	0
Neuropathy	19	1	0	0	0
Mucositis	18	0	2	0	0
Alopecia	16	1	2	1	0
Renal impairment	18	2	0	0	0
Hearing loss	19	0	1	0	0

assessing response were used [8] except that the duration of response was measured from the end of treatment. Patients responding after two courses of treatment received a further two courses and those who continued to respond received a maximum of six courses. Treatment was discontinued at any time if there was clinical or radiographical evidence of tumour progression. Toxicity of treatment cycles was assessed prior to each subsequent course and classified according to WHO criteria [8].

The median age of the patients was 60.5 years (range 34–71 years); 13 males and 17 females were treated. Sites of initial disease were oral cavity (floor of mouth, tongue, buccal cavity, 7 patients), larynx (3 patients), hypopharynx (2 patients), oropharynx (2 patients) and parotid, submandibular gland, auditory meatus, frontal sinus and piriform fossa (1 patient each). The median time from original diagnosis to relapse was 9 months (range 0–132 months). The performance status of patients was ECOG 0, 3 patients; ECOG 1, 7 patients; ECOG 2, 8 patients; ECOG 3, 2 patients. Details of previous treatments and sites of recurrence are shown in Table 1.

RESULTS

The overall response rate was 30% (95% CI; 10–48%) with one complete remission and five partial remissions out of the 20 patients treated. 3 patients had stable disease; the remainder developed progressive disease or died early with disease. The patient who achieved a complete remission had been treated for a local recurrence in the piriform fossa. The five partial remissions were in patients with local recurrence in floor of mouth (2 patients), hypopharynx (2 patients) and tongue (1 patient). Neither histology nor performance status predicted for response. The patient with a complete remission had an initial performance status of 2; partial responders had performance statuses of 1 (3 patients) and 0 (2 patients). The durations of the partial remissions were 5, 6, 7, 7 and 12 months. The complete response lasted for 7 months. Median survival from date of first treatment was 7 months (range 1 week–20.5 months).

The median number of treatment cycles given was two (range one to five): 6 patients received only one course, 5 patients received two courses, 3 patients received three courses, 5 patients received four courses and 1 patient received five courses. Reasons for stopping treatment in the patients who received only 1 course were progressive disease (5 patients) and early death (1 patient, cerebrovascular accident). In the other 14 cases treatment was stopped because of maximum response (6 patients), stable disease (3 patients) and progressive disease (5 patients). Treatment was well tolerated and haematological and other toxicities are shown in Table 2. Anaemia (12 patients) and neutropenia (8 patients) were the most common side-effects.

DISCUSSION

Patients with SCC of the head and neck frequently have a history of heavy smoking and excessive alcohol intake. The disease occurs in an older age group being most common after the fifth decade of life and patients tend to have poor nutritional status. This means that intensive chemotherapy programmes are not feasible for this condition. Recurrent SCC of the head and neck has a very poor prognosis with a median survival of 6–10 months [2] but patients frequently require palliation which is often attempted by using chemotherapy. Data from phase II studies suggest that the most active combination is cisplatin with infusional 5-FU. However, such studies have strict entry criteria and this means that results are often difficult to translate into the unselected patient population that is encountered in everyday clinical practice. This report specifically presents an unselected consecutive group of patients who were treated with this regimen and followed up to relapse. It therefore perhaps better reflects the results that can be expected in a general head and neck cancer clinic. Furthermore, although WHO guidelines state that response duration should be measured from the start of treatment [8], in this study we measured response duration from the end of treatment. We feel that with a regimen that is potentially toxic and requires hospitalisation for 5–6 days, this method of calculating response duration may be a more accurate guide to the true benefit to patients of undergoing palliative chemotherapy. We have found an overall response rate of 30% with the duration of these reponses being 5–7 months in most patients although 1 patient had a prolonged duration of response of 12 months.

In the situation where cure or even prolonged remission is an unrealistic expectation, the toxicity of any treatment is all important. The toxicity encountered in our patient group was mild and transient. We paid strict attention to antiemetic cover and this may have contributed to the regimen being well tolerated. Unfortunately, despite the fact that cisplatin and 5-FU only rarely cause alopecia when these two drugs are given together, alopecia did occur (4/20 patients). Although it is reversible, this is an unavoidable negative aspect of this regimen.

In conclusion, we have shown that in an unselected group of patients with incurable recurrent SCC of the head and neck 30% of patients respond to a combination of cisplatin and infusional 5-FU and the duration of these responses can be considered useful.

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