Cancer Chemother Pharmacol (1993) 31: 340–342

Cancer Chemotherapy and Pharmacology

Short communication

Ifosfamide in advanced epidermoid head and neck cancer

M. Martín, E. Diaz-Rubio, J. L. González Larriba, A. Casado, J. Sastre, J. M. López-Vega, J. Almenarez, S. Dominguez

Servicio de Oncología Médica, Hospital Universitario San Carlos, Madrid, Spain

Received 26 May 1992/Accepted 11 August 1992

Summary. A total of 37 men with epidermoid head and neck cancer whose disease had recurred following primary treatment (surgery and/or radiotherapy) received first-line chemotherapy with ifosfamide at i. v. doses of 3 g/m^2 given daily on 3 consecutive days in combination with mesna (600 mg/m^2 × 3 oral daily doses on days 1–3) every 3 weeks. In all, 7 patients showed a partial response and 2 patients achieved a complete response, for an overall objective response rate of 26% (9 of 35 eligible patients; 95% confidence interval, 12.5%–43%). Excluding the 5 early nontoxic deaths observed during the first 3 weeks of therapy, the objective response rate was 30% (9 of 30 patients; 95% confidence interval, 15%–49.5%). Responses were seen in lung metastases (2 patients), lymph nodes (2 patients), skin (3 patients), and cases of local recurrence (5 patients). The median duration of responses was 3 months (range, 2–5 months). The main side effects of ifosfamide were alopecia (83% of patients), emesis (80%), granulocytopenia (23%), and mild mucositis (20%). Two poor-risk patients suffered severe CNS complications that were probably related to treatment. Three patients died due to chemotherapy-related complications (2 patients with CNS toxicity and 1 patient with granulocytopenic sepsis). In conclusion, ifosfamide appears to be an active drug in epidermoid head and neck cancer and merits further evaluation in this disease.

Introduction

Chemotherapy is frequently given as palliative treatment to patients with epidermoid head and neck cancer who present with recurrent disease after undergoing primary therapy with surgery and/or radiotherapy. Although several drugs and combinations have shown their capacity to induce antitumoral responses in this disease, the duration of tumor regression is brief and a survival advantage for patients treated with chemotherapy has not yet been proved [1]. The identification of new, active drugs in these tumors is therefore necessary. This report presents the results of a phase II study of first-line ifosfamide chemotherapy in recurrent epidermoid head and neck cancer.

Correspondence to: M. Martin, Servicio de Oncología Médica, Hospital Universitario San Carlos, Ciudad Universitaria, 28040 Madrid, Spain

Patients and methods

Patients with epidermoid head and neck cancer who presented with histologically proven recurrent disease after undergoing primary treatment (surgery and/or radiotherapy) were eligible for the present study. Other eligibility criteria included (1) no previous chemotherapy, (2) measurable disease in at least one site, (3) a leukocyte count of greater than 4,000/mm^3, (4) a platelet count of greater than 100,000/mm^3, (5) adequate renal function (a serum creatinine level of less than 1.2 mg/dl), (6) a Karnofsky performance status of 60 or better, and (7) written informed consent.

Ifosfamide was given by 1-h i. v. infusion at doses of 3 g/m^2 daily on days 1–3 in an outpatient setting. Prior to and after ifosfamide therapy, patients were hydrated i. v. with 1 l normal saline solution. Patients also received mesna orally at doses of 600 mg/m^2 prior to and at 4 and 8 h after the ifosfamide infusions on days 1–3. Patients were given oral phenothiazines (thiethylperazine or levomepromazine) in some cases together with i. v. methylprednisolone (250 mg before ifosfamide) as antiemetic therapy on days 1–3. Chemotherapy was repeated every 3 weeks until progression of the disease.

Prior to the initial chemotherapy and to each subsequent course, patients underwent a complete medical examination and routine determination of hematological, urinary and chemical parameters. Chest X-rays were performed prior to treatment and after every two courses of ifosfamide. Response and toxicity were coded according to WHO criteria [8]. The duration of response was calculated in months from the start of chemotherapy (partial responses) or from the first date of assessment of complete responses.

Results

A total of 37 patients entered the trial; 2 patients were ineligible because of the absence of measurable disease. The characteristics of the remaining 35 patients are shown in Table 1. In all, 7 patients received only 1 course of ifosfamide due to early nontoxic death (5 cases) or to death

Table 1. Patients' characteristics

Number of eligible patients	35
Number of men	35
Age (years)	
Median	55
Range	35–75
Karnofsky index:	
60	4
70	10
80	14
90	7
Primary tumor:	
Larynx	18
Oral cavity	9
Pharynx	8
Sites of measurable disease[a]:	
Local recurrence	20 (14)
Lymph nodes	10 (5)
Skin	5 (2)
Lung	7 (0)

[a] Number of lesions arising in previously irradiated areas are shown in parentheses

Table 2. Response by site

Lung	2/7
Skin	3/5
Lymph nodes	2/10
Local recurrence	5/20

probably related to ifosfamide toxicity (2 patients). Overall, 10 patients received 2 courses of ifosfamide, 8 patients received 3 courses, and the remaining 10 patients received 4 or more courses of chemotherapy.

Altogether, 7 patients showed a partial response and 2 patients achieved a complete response. The overall response rate in all eligible patients was 26% (9/35; 95% confidence interval, 12.5%–43%), and in the 30 evaluable patients (excluding the 5 early nontoxic deaths) it was 30% (9/30; 95% confidence interval, 15%–49.5%). The response rate by site is shown in Table 2; 4 responses were seen in lesions in previously irradiated areas. The median duration of responses was 3 months (range, 2–5 months).

Table 3 shows the toxicity encountered (maximal WHO grade). Despite the administration of antiemetics, most patients experienced emesis after ifosfamide treatment. The majority of patients also had some degree of alopecia. Granulocytopenia occurred in 8 patients, although this figure was probably underestimated, since weekly leukocyte counts were not systematically taken. Neither renal nor urothelial toxicity was observed. In all, 3 patients died due to chemotherapy-related complications: 1 patient developed granulocytopenic sepsis and died despite antibiotic therapy; 2 additional poor-risk patients (Karnofsky index of 60, low serum albumin levels) presented with progressive stupor and coma, probably due to ifosfamide, and died immediately after the administration of the first course of treatment.

Table 3. Toxicity of treatment: maximal WHO grade

	Number of patients
Alopecia:	
Grade 1	2/35 (6%)
Grade 2	12/35 (34%)
Grade 3	15/35 (43%)
Emesis:	
Grade 1	2/35 (6%)
Grade 2–3	26/35 (74%)
Granulocytopenia:	
Grade 1	2/35 (6%)
Grade 2	1/35 (3%)
Grade 3	1/35 (3%)
Grade 4	4/35 (11%)
Mucositis:	
Grade 1	3/35 (9%)
Grade 2	4/35 (11%)
CNS toxicity:	
Grade 4	2/35 (6%)

Discussion

The antitumor activity of ifosfamide in epidermoid head and neck cancer has thus far been tested in only a few trials. Ifosfamide has not shown important antitumor activity as second-line chemotherapy in recurrent head and neck cancer, although some sporadic responses have been observed [2, 5, 6, 10]. However, as investigators at the National Cancer Institute have pointed out [7], the study of new drugs in second-line chemotherapy leads to frequent false-negative conclusions and can cause the erroneous rejection of active drugs in disease-specific phase II trials.

In contrast with the above-mentioned lack of activity as second-line chemotherapy, ifosfamide has shown interesting antitumor activity in three trials carried out in chemotherapy-naive patients with head and neck cancer [3, 4, 9]. Buesa et al. [3] obtained a response rate of 28% (complete plus partial responses) among 32 patients treated at doses of 5–6.25 g/m^2 every 3 weeks. Cervellino et al. [4] reported 4 complete and 8 partial responses among 28 patients (overall response rate, 42.7%); the total dose of ifosfamide in this trial was relatively high (3.5 g/m^2 daily $\times$ 5). Pai et al. [9] obtained 13 objective responses among 26 patients (50%) using an ifosfamide schedule of 1.5 g/m^2 daily for 5 consecutive days every 3 weeks.

The response rate obtained in the present study also supports the idea that ifosfamide is an active drug in epidermoid head and neck cancer and merits further evaluation in this disease. The toxicity of ifosfamide on the schedule used in our study (3 g/m^2 daily $\times$ 3) was mild except in poor-risk patients, who should not be included in further trials of the drug. Additional studies using ifosfamide either alone or in combination with other active drugs such as cisplatin are warranted to define the precise role that this drug may play in the management of patients with epidermoid head and neck cancer.

References

1. Al-Sarraf M (1988) Head and neck cancer: chemotherapy concepts. Semin Oncol 15: 70–85
2. Buesa JM, Fernandez R, Esteban E, et al (1987) Phase II clinical trial with ifosfamide (IFX) in advanced squamous cell carcinoma of the head and neck (SCCHN) (abstract). Proceedings, ECCO-4 (4th European Conference on Clinical Oncology), Madrid, November 1–4, p 255
3. Buesa JM, Fernandez R, Esteban E, et al (1991) Phase II trial of ifosfamide in recurrent and metastatic head and neck cancer. Ann Oncol 2: 151–152
4. Cervellino JC, Araujo CE, Pirisi C, Francia A, Cerruti R (1991) Ifosfamide and mesna for the treatment of advanced squamous cell head and neck cancer. Oncology 48: 89–92
5. Kish JA, Tapazoglou E, Ensley J, Al-Sarraf M (1990) Activity of ifosfamide (NSC-109724) in recurrent head and neck cancer patients (abstract). Proc Am Assoc Cancer Res 31: 190
6. Lucas P, Coninx P, Nasca S, Lebrun-Jezekova D (1986) Ifosfamide in relapsing head and neck cancer (abstract). Cancer Chemother Pharmacol 18 [Suppl 1]: A46
7. Marsoni S, Holth D, Simon R, Leyland-Jones B, De Rosa M, Wittes RE (1987) Clinical drug development: an analysis of phase II trials, 1970–1985. Cancer Treat Rep 71: 71–80
8. Miller AB, Hoogstraten B, Staquet M, Winkler A (1981) Reporting results of cancer treatment. Cancer 47: 207–214
9. Pai VR, Advani SH, Mazumdar AT (1990) Phase II study of high dose ifosfamide as a simple agent or in combination chemotherapy in the treatment of advanced and/or recurrent squamous cell carcinoma of the head and neck (abstract). J Cancer Res Clin Oncol 116 [Suppl 1]: 701
10. Verweij J, Alexieva-Figusch J, De Boer MF, Reichgelt B, Stoter G (1988) Ifosfamide in advanced head and neck cancer. A phase II study of the Rotterdam Cooperative Head and Neck Cancer Study Group. Eur J Cancer Clin Oncol 24: 795–796