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CLINICAL TRIAL REPORT

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Phase II study of mitomycin, ifosfamide and cisplatin in adenocarcinoma of the oesophagus

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Abstract We evaluated the effect of brief neoadjuvant chemotherapy in patients with apparently operable adenocarcinoma of the oesophagus. Two courses of mitomycin (6 mg/m^2), ifosfamide (3 g/m^2) and cisplatin (50 mg/m^2; MIC) were given followed by evaluation of response by barium swallow and computed tomography scan. Of 20 patients, 17 completed both courses and 4 (20%) showed a partial response. Toxicity was generally mild and consisted principally of nausea and vomiting. Altogether, 15 patients were surgically explored; resection was completed in 12 patients, 3 of whom died in hospital (25%). Neoadjuvant therapy with MIC offers no advantage over surgery alone.

Key words Adenocarcinoma · Chemotherapy
Surgery · Oesophagus

Introduction

The prognosis for patients with adenocarcinoma of the oesophagus remains poor, with the overall 5-year survival being less than 1%. There is a strong rationale for using chemotherapy as the majority of patients have disseminated disease at the time of presentation. Mitomycin and cisplatin have been shown to be active single agents in carcinoma of the oesophagus [9], but the combination of the two drugs has not been tested in a phase II trial. The activity of ifosfamide as a single agent had not been reported when this study opened. However, cisplatin and ifosfamide have demonstrated synergism in experimental models [5], and our own experience with mitomycin, ifosfamide and cisplatin (MIC) has indicated this to be an effective and safe combination [2]. We therefore embarked on a phase II trial of MIC in adenocarcinoma of the oesophagus.

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Patients and methods

From January 1990 to March 1991 a series of 20 patients with previously untreated, evaluable and histologically proven adenocarcinoma of the oesophagus or gastroesophageal junction entered the study. All patients had apparently localised disease and were judged fit for operation. The clinical features of the patients are shown in Table 1. Prior to chemotherapy all patients were staged according to the criteria of the International Union Against Cancer (UICC) [7]. The chemotherapy regimen, delivered into a peripheral vein, consisted of mitomycin given at 6 mg/m^2 as a bolus, ifosfamide given at 3 g/m^2 by infusion over 3 h and cisplatin given at 50 mg/m^2 by infusion over 1 h. A combination of high-dose metoclopramide infusion with lorazepam and dexamethasone, or ondansetron was used as anti-emetic therapy, and mesna was used to counter the ifosfamide-related toxicity of cystitis. All patients underwent chemotherapy at 3-weekly intervals with an overnight stay in hospital for each course. Haematological and biochemical parameters and WHO performance status [13] were determined before the start of treatment and after each course. In patients who completed the treatment protocol the response was evaluated 3 weeks after the final course of chemotherapy using the general criteria of Miller et al. [13] by computed tomography (CT) scan and barium swallow.

Results

Of the 20 patients who entered the study, 17 completed 2 courses of chemotherapy followed by assessment of the response. Three patients had only one course of chemotherapy, because of increasing dysphagia in one case, renal toxicity in another and refusal of further chemotherapy in the third. They were assessed for toxicity only and were classified as having progressive disease. On post-chemotherapy assessment by CT and barium swallow, 4 patients (20%) showed a partial

Table 1 Patients' characteristics (*UICC* International Union Against Cancer)

Number	20
Sex	20M/0F
Mean age	61 (range, 38–70) years
Site:	
Lower third	13
Gastroesophageal junction	7
Performance status (WHO):	
Grade 0	8
Grade 1	9
Grade 2	3
Grade 3	0
Histology:	
Poorly differentiated	3
Moderately differentiated	11
Well differentiated	3
Differentiation not stated	3
Stage pre-chemotherapy (UICC):	
0	1
I	0
IIA	7
IIB	0
III	12
IV	0

response, 12 showed no change and 4 had progressive disease. Following assessment of the response, one patient was judged to have progressive disease that was inoperable and another was no longer considered fit for surgery. In all, 15 patients proceeded to surgical exploration and subtotal oesophagectomy was performed in 12 cases [12]. In three patients the tumour proved to be unresectable because of local disease in two cases and metastatic disease in one. In the first 30 days after resection there were three deaths (25%) due to anastomotic leakage, pulmonary embolism and septicaemia, respectively. The nine patients who underwent resection and were discharged from hospital died at a median of 17 (range, 6–42) months from the start of chemotherapy. The three patients who underwent exploration without resection made an uneventful recovery but died at 3, 9 and 18 months, respectively. The two patients who did not undergo exploration died at 4 and 6 months, respectively, from the start of chemotherapy. The three patients who completed only a single course of chemotherapy underwent resection, following which one patient died in hospital and the other two died at 10 and 13 months, respectively.

Toxicity was acceptable and principally consisted of nausea and vomiting, which was experienced by ten patients but was not severe or prolonged (over 48 h) in any case. All patients developed a varying degree of alopecia. Severe haematological toxicity (WHO grade 3) was seen in one patient. Nephrotoxicity was mild, with only one patient having an elevated serum creatinine value (WHO grade 2).

Discussion

Although there has been increasing interest in chemotherapy for oesophageal cancer in the past decade, most studies have involved only squamous-cell carcinomas or have used chemotherapy in combination with radiotherapy [10]. There have been relatively few studies reporting the results of chemotherapy for adenocarcinomas, despite evidence of an increasing incidence of this disease [14]. What is clear is that combinations of active agents have consistently yielded greater response rates than have single agents. [9]. In this study the overall response of 20% is within the range reported by other investigators (Table 2) but is lower than that achieved using combinations of cisplatin, vindesine and mitoguazone (37%) [4]; etoposide, fluorouracil and cisplatin (49%) [1]; or fluorouracil, doxorubicin and mitomycin (36%) [16] in adenocarcinoma of the oesophagus.

The MIC regimen is relatively simple and toxicity was acceptable. A major consideration in deciding upon this regimen was patient tolerance and in this respect it was satisfactory. Only one patient experienced severe toxicity (WHO grade 3 leukopenia) and there was no chemotherapy-related death. Although

Table 2 Results of chemotherapy in adenocarcinoma of the oesophagus

Authors	Year	Regimen	Number entered	Number evaluable	Response rate (%)	Operative mortality
Karlin et al. [8]	1982	FAMMe	10	8	1 (12)	–
Fein et al. [3]	1985	FAM	27	27	6 (22)	–
		N/S	19	19	4 (21)	–
Forastiere et al. [4]	1987	CVM	21	19	7 (37)	0/15 (0)
Kok et al. [11]	1988	EC	13	13	1 (8)	–
Steel et al. [15]	1988	Carboplatin	15	14	0 (0)	1/8 (12%)
Ajani et al. [1]	1990	EFC	35	35	17 (49)	0/31 (0)
Walker et al. [16]	1991	FAM	39	37	14 (36)	6/20 (30%)

(*FAM* 5-Fluorouracil/Adriamycin (doxorubicin)/Mitomycin, *FAMMe* FAM + semustine, *CVM* cisplatin/vindesine/mitoguazone, *EC* etoposide/cisplatin, *EFC* etoposide/fluorouracil/cisplatin, *N/S* not specified)

cisplatin and ifosfamide are associated with severe nausea and vomiting, the intensive anti-emetic schedule was largely effective.

In this series the operative mortality of 25% is greater than that previously reported for resected adenocarcinoma without chemotherapy in our unit (15%) [12]. We had a similar operative mortality (30%) in a previous study [16], and this raises the possibility that chemotherapy may have some detrimental effect. However, in another study of neoadjuvant chemotherapy [15] we did not experience a higher operative mortality, and other investigators have reported no death among cohorts of 15 [4] and 32 patients [1], suggesting that preoperative chemotherapy is generally safe in adenocarcinoma. In patients who responded, the changes identifiable at surgery were a reduction in tumour bulk and minor oesophageal fibrosis, neither of which adversely affected the technical aspects of surgery.

In summary, the results obtained in this study of neoadjuvant therapy with MIC in adenocarcinoma of the oesophagus are no better than those achieved in other studies. The identification of new active agents should be encouraged to improve on these response rates. Ultimately, the effectiveness of neoadjuvant chemotherapy as compared with surgery can be addressed only in large randomised trials employing a surgery-only control group. Such trials are now under way [6].

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