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Original Paper

Squamous Oesophageal Cancer can be Downstaged Using Protracted Venous Infusion of 5-Fluorouracil with Epirubicin and Cisplatin (ECF)

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21 patients with squamous oesophageal carcinoma were treated with a new regimen designed in our unit and effective in treating gastric adenocarcinoma, consisting of continuous venous infusion of 5-fluorouracil for up to 24 weeks (200 mg/m²/day) with epirubicin (50 mg/m²) and cisplatin (60 mg/m²) every 3 weeks. 12 patients (57%) had an objective response. The median relapse free period was 7 months, median survival from start of chemotherapy 8.4 months, and median survival from diagnosis, 14 months. Symptomatic improvements were reported by 10/11 patients with pain (91%), 8/9 with anorexia (89%), 8/10 with reflux (80%) and 10/14 with dysphagia (71%). Grade 3 or 4 toxicity was reported by 11 patients: 5 had haematological toxicity, 3 vomiting, 2 infection and 1 diarrhoea. One patient developed peripheral neuropathy, 1 renal impairment and another peripheral vascular disease. Following chemotherapy, surgery was attempted in 5 patients. One remains well 3 years on, 2 had macroscopic clearance of tumour but died of postoperative complications. In 2, disease was irresectable. This regimen of moderate toxicity is effective at improving symptoms in the majority of patients. In some patients, tumours are briefly downstaged so that inoperable tumours may become operable.

Key words: squamous oesophageal cancer, infusional chemotherapy, 5-fluorouracil, cisplatin, epirubicin, ECF
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INTRODUCTION

SQUAMOUS OESOPHAGEAL carcinoma has a dismal prognosis. In a review of the published outcome of more than 83,000 patients with squamous oesophageal cancer referred to surgeons in the two decades before 1980, for every 100 patients, only 58 were clinically suitable for surgery and of the 39 who subsequently had their tumour resected, 13 died in hospital, 18 survived 1 year, 9 survived 2 years and only 4 survived for more than 5 years [1]. More recent data suggest that patients have not fared any better with surgery in the 10 years since then [2]. The conclusion reached in 1980 still seems valid for most patients, namely "would the patient being properly informed, consent to surgical exploration with a 29% operative mortality rate and an 18% chance of surviving 1 year or would he ask whether there was any other available treatment?" [1]

A symptomatic response to radiotherapy alone in squamous oesophageal cancer is of the order of 60–85% [3]. However, median and 5 year survival following irradiation therapy are akin to those achieved by surgery. The poor survival seen with either surgery or radiotherapy is inevitable because systemic spread of this tumour occurs early. Thus, there is a compelling rationale for offering effective chemotherapy either alone or combined with surgery or radiotherapy.

Individual chemotherapeutic agents have antitumour activity in this condition. Cisplatin has a dose responsive effect [4–8]. Anthracyclin antibiotics [9] and 5-fluorouracil either given as bolus injections [10], or protracted venous infusion (given over 6 weeks) [11] can induce response in the tumour. However, the cumulative response rates for single agent regimens are low, with no survival benefit and minimal symptomatic relief.

Published series using a combination of drugs have included relatively small numbers of patients. However, in general, three-drug combinations result in higher response rates (26–55%), although duration of response and survival are not improved [12]. One phase II study has been reported using a combination of bolus 5-fluorouracil, doxorubicin and cisplatin and achieved a response rate of 33% [13].

In colorectal cancer, a randomised trial using protracted infusional 5-fluorouracil at 300 mg/m²/day yielded a higher

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tumour response (30% versus 7%) with less toxicity than an intermittent bolus schedule of 5-fluorouracil given for 5 days each month [14]. In adenocarcinoma of the stomach, our unit has reported the results of a phase II study using infusional 5-fluorouracil in combination with epirubicin and cisplatin (ECF), and have shown that this regimen has high antitumour activity with only moderate toxicity [15].

These results reflect the fact that 5-fluorouracil has its major chemotherapeutic effect during the S phase of the tumour cell cycle but its plasma half-life is short. So, when a bolus of 5-fluorouracil is given, only a small proportion of tumour cells will be susceptible to its effects, limiting its efficacy. Prolonged infusion schedules allow higher cumulative doses to be given and greater dose intensity to be reached. The dose intensity of 5-fluorouracil is related to clinical efficacy [16].

Our group has also shown that quality of life is maintained with no observed reduction in functioning compared to baseline values in patients receiving infusional chemotherapy through indwelling central venous catheters. This is a despite a minor complication rate with the catheters of approximately 30%, necessitating their replacement in 11% of patients. Overall toxicity with protracted venous infusions of 5-fluorouracil also appears to be reduced and median survival increased by 50% compared to bolus schedules of the same drug [17].

In view of the particular need for adequate palliation of symptoms with minimal toxicity in patients whose response is likely to be of limited duration, we combined epirubicin and cisplatin with prolonged continuous infusion of 5-fluorouracil to treat squamous oesophageal cancer. We report the results of treatment with this regimen here.

PATIENTS AND METHODS

A prospective study was undertaken on patients referred to the Gastrointestinal Unit at the Royal Marsden Hospital, Sutton, U.K. since 1991 with irresectable, locally advanced or metastatic squamous oesophageal carcinomas as determined by clinical, radiological (CT) and endoscopic criteria. Patients gave their informed consent to treatment which was approved by the Royal Marsden Hospital ethical committee.

Pretreatment assessment

All histology was reviewed at the Royal Marsden Hospital, Sutton, U.K. Pretreatment assessment included a full blood count, measurement of serum electrolytes and liver function. Initial estimation of renal function was calculated by EDTA clearance. Blood measurements were repeated every 3 weeks. A chest X-ray and CT scan were performed before treatment and were repeated after three cycles and at the end of chemotherapy. A single radiologist reviewed all X-rays. TNM staging was used [18]. Patients' general well-being was assessed in terms of their performance status according to published criteria [19].

Assessment of response

Response was evaluated clinically, endoscopically and radiologically. Endoscopy was performed by the referring surgeon. At endoscopy, the size of the tumour was not routinely measured, but complete disappearance of the oesophageal tumour was classified as a complete endoscopic reponse and when change in evaluable disease following chemotherapy was considered to be (subjectively) at least a 50% reduction in tumour size, it was deemed to be an endoscopic partial response. A radiological complete response was said to have occurred when disease previously seen disappeared. A partial response was defined as a 50% or greater reduction in the product of the longest perpendicular diameters of specified marker lesions for at least 4 weeks, in the absence of new lesions or progression of existing lesions. Stable disease was defined as a reduction in tumour size of less than 50%, or an increase in tumour size or marker measurement of less than 25%. Progressive disease was defined as an increase in tumour mass of greater than 25% or the development of new metastases.

Symptomatic response was evaluated by direct questioning. Toxicity was graded according to common toxicity criteria (CTC) by physical examination, direct questioning and measurement of haematological and biochemical parameters [19].

Treatment and dose modifications

5-fluorouracil was given as a continuous infusion of 200 mg/m^2/day through the central line using a small, portable battery powered pump. The infusion was continued for up to 6 months allowing six to eight courses of cisplatin and epirubicin.

Patients developing diarrhoea or mucositis had treatment interrupted until these symptoms resolved and were restarted with a 50 mg/m^2 dose reduction. A dose reduction of 100 mg/m^2 was used for patients with grade 3 or 4 toxicity. If patients developed Planter–Palmer syndrome, 50 mg pyridoxine, three times a day was prescribed. If symptoms did not improve, 5-fluorouracil was discontinued for a week and was restarted at a dose of 150 mg/m^2/day.

Cisplatin 60 mg/mg^2 was given once every 3 weeks with standard hydration. Dose modification was based on the glomerular filtration rate which was estimated using [^{51}Cr]EDTA clearance. If the glomerular filtration rate was greater or equal to 60 ml/min, the full dose of cisplatin was given. If the glomerular filtration rate was reduced to below 40–60 ml/min, the dose of cisplatin in milligrams per metre equalled the glomerular filtration rate value in millilitres per minute. If the glomerular filtration rate fell below 40 ml/min, cisplatin would be discontinued.

Any patient with a history of ischaemic heart disease or abnormal electrocardiogram (ECG) underwent a MUGA scan to evaluate cardiac function. If the ejection fraction was less than 50%, epirubicin was omitted. If epirubicin was omitted from the start of treatment, it was planned to increase the dose of 5-fluorouracil to 300 mg/m^2.

Epirubicin was given as a bolus intravenous injection every 3 weeks. If, on the day of treatment, the white cell count was less than 2.0×10^9/l or the platelet count was less than 100×10^9/l, epirubicin and cisplatin were delayed for a week or until myelosuppression resolved. A second episode of treatment delay due to myelosuppression or neutropenic sepsis required a 25% dose reduction of epirubicin on subsequent cycles. With repeated episodes of grade 3 or 4 toxicity despite dose reductions, treatment was stopped.

Patients were admitted to hospital for insertion of their central venous catheter under local anaesthesia with antibiotic cover on the first day of treatment. Routinely, they were prescribed 1 mg of warfarin to reduce the risk of subclavian vein thrombosis [20].

Statistical methods

Patient survival and failure free survival (time to progression or death) were examined using the Kaplan–Meier product limit method.

RESULTS

Patient details (*Table* 1)

21 patients were recruited for this study with a median age of 61 years (range 41–78 years). Of these, 11 were men and 10 women. They were followed up for a median duration of 11.5 months (range 7–36 months). At the start of treatment, 2 had a performance status of 0, 15 a performance status of 1 and 4 a performance status of 2.

Two tumours were in the middle third and 12 in the lower third of the oesophagus. Seven were at the gastrooesophageal junction. The tumours were TNM stage II in 2 patients, stage III in 5 patients and stage IV in 14 patients. They were well differentiated in 1, moderately differentiated in 14 and poorly differentiated in 6 patients.

18 patients were started on full doses of epirubicin, cisplatin and 5-fluorouracil. 3 patients did not receive any epirubicin, 2 for poor cardiac function and 1 in breach of protocol.

Prechemotherapy treatment

2 patients underwent surgery before chemotherapy but were found to have irresectable tumours. 2 patients had an oesophagogastrectomy performed but with incomplete macroscopic clearance of tumour. A fifth patient had undergone radiotherapy 21 months earlier and was referred when liver metastases developed. A sixth patient had an oesophageal stent inserted. Another patient had previously undergone two cycles of selection therapy.

Endoscopic response

6 patients (29%) were not re-evaluated endoscopically after chemotherapy because 3 had clearly progressive disease, 2 liver metastases but no oesophageal disease and 1 died suddenly. In 4 of the 21 (19%) patients, endoscopy showed complete disappearance of the oesophageal tumour, a partial response in 6 (29%) and no improvement in 5 (24%) patients. In the 10 patients with an endoscopic response, 7 also had a radiological response while 3 had radiologically stable disease.

Radiological response

An objective response rate of 43% (95% confidence intervals 22–66%) was seen radiologically. A complete response was seen in 1 (5%) patient, a partial response in 8 (38%) patients and no radiological response in 12 (57%) patients. All patients who had a radiological response also had an endoscopic response, except for 2 patients whose oesophageal disease had been resected and were being treated for liver metastases. They did not undergo repeat endoscopy.

Response by site

Of 18 patients with evaluable primary tumours, 3 (17%) had a complete response, 5 (28%) a partial response and 10 (56%) showed no response to treatment. Of 4 patients with local disease, 1 (25%) had a complete response and 3 (75%) showed no response. Of 6 patients with liver metastases, 5 (83%) had a partial response in the liver and 1 (17%) did not respond. 4 of 11 (36%) patients with lymph node metastases had a complete response, 1 (9%) a partial response and 6 (55%) did not respond. Neither of the 2 patients with lung metastases responded to chemotherapy. In patients who had a response to treatment both in the oesophageal tumour and lymph node masses, there was frequently a greater response in the lymph nodes than in the primary tumour.

Symptomatic response

In patients with pain before treatment, there was an improvement in pain in 10 of the 11 (91%) patients. Ten of the 14 (71%) patients with dysphagia found benefit as did 8 of the 10 (80%) patients with reflux. Symptomatic response was reported by

Table 1. *The characteristics of the* 21 *patients with oesophageal squamous carcinomas*

Patient number	Age	Gender	Site	Histology (differentiation)	Stage	No. of courses given	Response Endoscopic	Response Radiological	Survival (months)
1	41	F	OGJ	Moderate	IV	ECF × 3	–	SD	2
2	75	M	Md	Moderate	IV	ECF × 5	CR	SD	2.5
3	58	F	L	Moderate	III	CF × 8	PR	PR	4+
4	66	M	L	Moderate	IV	ECF × 6	–	SD	4
5	60	M	OGJ	Moderate	IV	ECF × 4	PR	PR	4
6	54	F	L	Moderate	IV	ECF × 3	NR	SD	5
7	72	M	L	Moderate	IV	CF × 4	–	SD	6+
8	67	F	L	Well	IV	ECF × 4	–	PR	6.5
9	65	F	L	Poor	II	CF × 2	NR	SD	7.5
10	65	F	Md	Moderate	III	ECF × 5	PR	SD	7.5+
11	63	M	OGJ	Poor	IV	ECF × 8	CR	PR	8
12	48	F	L	Moderate	IV	ECF × 8	PR	PR	8
13	54	M	OGJ	Poor	IV	ECF × 8	CR	PR	8
14	53	M	L	Poor	IV	ECF × 8	NR	SD	9.5
15	62	F	L	Poor	IV	ECF × 3	–	PR	12
16	47	M	L	Moderate	IV	ECF × 8	PR	PR	13+
17	61	M	OGJ	Moderate	II	ECF × 6	–	SD	17+
18	52	M	L	Moderate	III	ECF × 2	NR	SD	17.5
19	63	F	L	Moderate	III	ECF × 5	PR	SD	18
20	78	F	OGJ	Poor	IV	ECF × 2	NR	SD	20
21	45	M	OGJ	Moderate	III	ECF × 10	CR	CR	36+

CF, cisplatin and 5-fluorouracil; CR, complete response; ECF, epirubicin, cisplatin and 5-fluorouracil; F, female; L = lower third of oesophagus; M, male; Md, middle third of oesophagus; NR, no response; OGJ, oesophago-gastric junction; PD, progressive disease; PR, partial response; SD, stable disease; +, patients still alive.

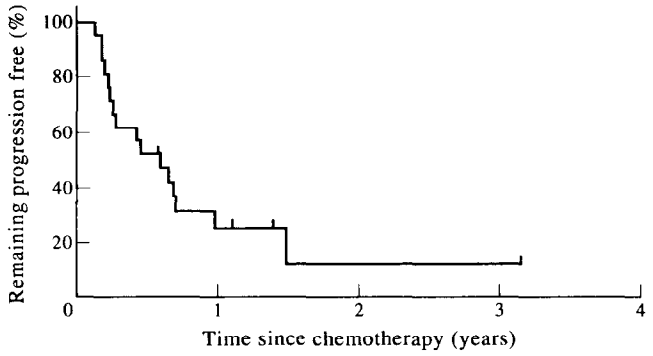

Figure 1. Failure free survival in 21 patients receiving ECF chemotherapy for squamous oesophageal tumours.

all 14 (100%) patients who complained of weight loss before treatment. 8 of the 9 (89%) patients with anorexia also noted an improvement.

Outcome

Time to relapse and survival. The median time to failure (relapse or death) following chemotherapy was 7 months. 4 patients remained failure free beyond 1 year. One year failure free survival (Figure 1) was 25% (95% confidence intervals 8.8–45.7%). One patient was still in remission more than 3 years after chemotherapy. The median survival was 8.4 months (Figure 2), 5 patients surviving beyond 1 year. One year survival was thus 33% (95% confidence intervals 13–54%).

The median time from diagnosis to the start of chemotherapy was 51 days (range 10–703 days). Survival calculated from diagnosis at 1 year was 55.3% (95% confidence intervals 31–74%) and median survival was 14 months.

Toxicity

Dose reductions. 10 patients required dose reduction from the intended 200 mg/m^2 5-fluorouracil because of toxicity. 4 patients finally received 50% of their intended dose, 1 patient received 72% and the other 5 received between 80 and 90% of their intended dose. 2 patients had a reduction in their doses of cisplatin and 1 patient, in their dose of epirubicin. Reasons for discontinuing chemotherapy prematurely are given in Table 2.

Complications of treatment. Details of the toxicities which commonly arose following treatment are given in Table 3. Much toxicity was minor in nature and included limited nausea, vomiting, diarrhoea, stomatitis, Planter–Palmer syndrome and loss of taste. Minor infections, epistaxis and alopecia were also reported, although 2 patients developed grade 3 alopecia.

Potentially more severe toxicity was experienced by 11 patients. 5 developed potentially serious haematological toxicity, (3 with grade 3 neutropenia, 1 with grade 3 thrombocytopenia, 1 with both grade 3 neutropenia and thromobocytopenia). When haematological toxicity was present, it tended to develop with the later courses of chemotherapy. Significant neutropenic sepsis occurred in 1 patient. 3 patients developed grade 3 or 4 nausea and vomiting. 2 patients had grade 3 infections, 1 patient developed grade 4 diarrhoea, another patient renal toxicity and 1 patient peripheral neuropathy. This patient was switched to carboplatin but needed further dose reductions because of haematological toxicity. Hypercalcaemia required discontinuation of treatment in 1 patient, but hypercalcaemia improved on treatment in a second patient. One patient who had known peripheral vascular disease, developed a critically ischaemic leg while on treatment which was dealt with surgically, and later developed repeated visual disturbances which resolved after chemotherapy was stopped.

Hickman line. 17 (81%) patients experienced no problems with their Hickman lines. Three had to be replaced during treatment; one for infection, one became dislodged and another clotted. One patient developed an entry site infection which resolved with antibiotics.

Surgical intervention after chemotherapy. 5 patients underwent surgery after chemotherapy. 3 had completed eight cycles of chemotherapy with good apparent responses. 2 patients were found to have inoperable disease. The third patient underwent apparently curative surgery but died from postoperative complications.

One patient underwent surgery before chemotherapy but had irresectable disease. After seven cycles, he underwent a second operation where complete macroscopic clearance of the tumour was performed. Postoperatively, he received a further three cycles of ECF and is the longest survivor of this group.

One patient failed to receive any relief of severe dysphagia after two cycles of chemotherapy and underwent dilatation of his stricture which led to oesophageal rupture. This was managed conservatively but following radiotherapy, he developed an oesophago-tracheal fistula. Surgery resulted in complete resection of the tumour, but he died of aspiration pneumonia 6 months later.

DISCUSSION

Our unit has developed a regimen combining 5-fluorouracil, cisplatin and epirubicin for the treatment of upper gastrointestinal adenocarcinoma, against which it has proved to have valuable activity. In our hospital, this regimen has subsequently been successfully extended to treat patients with breast cancer [21], and there are early reports of its' benefits in patients with relapsed ovarian tumours [22].

In a previous study of 21 patients, combining bolus 5-fluorouracil (600 mg/m^2 days 1 and 8), cisplatin (75 mg/m^2) and doxorubicin (30 mg/m^2), a 33% objective response rate with 8 month median survival was obtained [13]. Serious toxicity was limited in this series, 1 patient developed leucopenia and 1 patient heart failure. However, there was a high incidence of vomiting and alopecia.

Our study using cisplatin 60 mg/m^2, epirubicin 50 mg/m^2 and protracted venous infusion of 5-fluorouracil (200 mg/m^2)

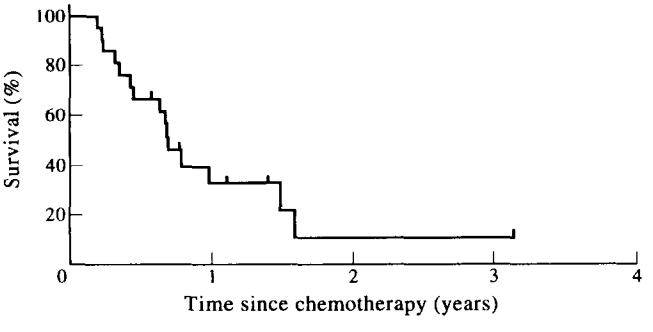

Figure 2. Survival curve of 21 patients receiving ECF chemotherapy for squamous oesophageal cancer.

Table 2. The reasons for discontinuing chemotherapy in all 21 patients and the stage of treatment at which it was stopped

No. of cycles of chemotherapy given	Number of patients	Reasons for stopping chemotherapy (*n*)
10	1*	Good response (1)
8	6	Good response (6)
6	2	Progressive disease (1), toxicity (1)
5	3	Good response (1), sudden death (1), local complications (1)
4	3	Progressive disease (2), hypercalcaemia (1)
3	3	Progressive disease (2), toxicity (1)
2	3	Progressive disease (3)

*This patient received seven cycles pre-operatively and three further cycles postoperatively.

Table 3. The number of patients reporting common toxicities according to grade after treatment with this chemotherapy regimen

	Nausea and vomiting	Alopecia	Infection	Diarrhoea	Stomatitis	Planter–Palmer Syndrome	WBC	Platelets
	(Grades 0–4)	(Grades 0–3)	(Grades 0–4)	(Grades 0–4)	(Grades 0–4)	(Grades 0–4)	(Grades 0–4)	(Grades 0–4)
Grade 0	3	4	11	13	8	16	8	16
Grade 1	11	6	2	6	5	4	4	3
Grade 2	4	9	6	1	8	1	5	–
Grade 3	2	2	2	–	–	–	4	2
Grade 4	1	–	–	1	–	–	–	–

appears to give a substantially better combined endoscopic and radiological objective response rate of 57%, which is comparable to the best rates achieved by other regimens. Our study also reports a 55% 1 year survival figure from diagnosis which is in marked contrast to Earlam's 18% 1 year survival in the surgical cohorts [1].

In our patients, symptomatic response to treatment was good and usually rapid, while a failure to respond would be observed early in treatment, enabling other palliative measures to be used. In particular, the symptoms of anorexia, weight loss and dysphagia, which may be very distressing for patients and may not be corrected by stenting alone, responded particularly well.

This regimen appeared particularly useful in inducing response in the primary tumour and in liver and lymph node metastases, although a differential response was seen in some patients. This brief period of response may allow, for some patients, a window for re-assessment with view to surgery. It may be that the use of this regimen before surgery would reduce operative mortality. Although surgery was attempted in 5 patients, only 1 is a long-term survivor. Advances in imaging, particularly the use of endoscopic ultrasound, may be helpful in determining which previously inoperable patients become operable. This is particularly important, since lymph node masses may respond more than the primary oesophageal tumours. In other patients, whose disease remains inoperable, it has been demonstrated that chemotherapy, together with radical radiotherapy, may cure some patients with squamous oesophageal cancer [23]. It would, therefore, be appropriate to combine this chemotherapy regimen with radiotherapy in future studies of this condition.

In conclusion, this relatively well tolerated regimen with moderate toxicity provides good palliation in patients with oesophageal squamous carcinomas and may sufficiently downstage the tumour so the subsequent use of other therapeutic modalities may lead to cure. It would seem worthwhile to explore the benefits of this regimen further.

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