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5-Fluorouracil, Folinic Acid, Etoposide and Cisplatin Chemotherapy for Locally Advanced or Metastatic Carcinoma of the Oesophagus

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38 patients with advanced oesophageal carcinoma were treated with intravenous (iv) folinic acid (300 mg/m²), 5-fluorouracil (500 mg/m²), etoposide (100 mg/m²), and cisplatin (30 mg/m²) (FLEP), on days 1, 2 and 3, every 22–28 days. 26 patients had locally advanced disease (LAD) and 12 had metastatic disease (M1). Oesophagectomy was planned for patients with LAD in case of tumour regression after chemotherapy, while patients with M1 disease received chemotherapy only. The overall remission rate was 45% (17/38) including four clinical and two pathologically confirmed complete remissions. 16 patients underwent oesophagectomy, 12 after response to FLEP, and 4 after FLEP and subsequent irradiation ± 5-fluorouracil/mitomycin. Toxicity was mainly haematological, with WHO grade 3 and 4 leucocytopenia in 50% and thrombocytopenia in 31% of the patients. Two treatment-related deaths were observed; one due to chemotherapy and one postoperatively. Median survival time of LAD patients was 13 months, and actuarial 2-year survival was 31%. Patients with complete tumour resection after FLEP had a median survival time of 18 months and a 2-year survival rate of 42%. Median survival of M1 patients was 6 months. FLEP is an active combination for oesophageal cancer, especially when used pre-operatively in LAD.
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INTRODUCTION

THE PROGNOSIS of patients with locally advanced oesophageal cancer has only been slightly improved during the past 10 years, due to improved surgical techniques and reduction of peri-operative mortality. The 2- and 5-year survival rates are still less than 20 and 10%, respectively [1]. This is due to the fact that currently available, local treatment modalities, such as surgery and/or radiotherapy, are unlikely to achieve sufficient local tumour control and furthermore, the majority of patients will develop distant metastases [2]. From this, it appears that the ultimate limitation to present therapy is distant disease. Thus, effective chemotherapy will probably be an essential part of any successful program.

To date, active chemotherapy programs are usually cisplatin/bleomycin- or cisplatin/5-fluorouracil (5FU)-based. In locoregional disease, these regimen induce approximately 50–60% of objective remissions (major responses) but usually less than 40% in extensive disease [3].

In this disease-orientated phase II trial, we investigated the activity and toxicity of a new drug combination consisting of folinic acid, 5FU, etoposide and cisplatin (FLEP) in patients with far advanced oesophageal cancer. The rationale for FLEP is based on the demonstrated single agent activity of cisplatin, 5FU and etoposide [4, 5], the synergistic interactions between all three drugs [6, 7], the well known enhancement of 5FU cytotoxicity by the biochemical modulator folinic acid, and the results of a pilot study with FLEP in gastric and oesophageal cancer [8].

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PATIENTS AND METHODS

From January 1989 to February 1991, 38 consecutive chemo- and radiotherapy naive patients with biopsy-proven squamous cell or adenocarcinoma of the oesophagus were entered into this trial. Eligibility criteria included histologically proven oesophageal cancer, measurable or evaluable disease, locally advanced tumours unlikely to undergo curative resection or metastatic disease [except central nervous system (CNS) metastases], World Health Organisation (WHO) performance status ≤ 2, age ≤ 65 years, adequate liver function (bilirubin < 1.5 mg/dl), renal function (creatinine clearance > 60 ml/min), cardiac function and bone marrow [white blood cell (WBC) count $> 4 \times 10^9/l$, platelet count $> 100 \times 10^9/l$] function, and informed consent.

Staging included physical examination, upper intestinal endoscopy, bronchoscopy, barium swallow, thoracic X-ray, computerised tomography (CT) of thorax, abdomen, and CNS if indicated, abdominal ultrasound and bone scan.

Response and toxicity were classified according to WHO criteria [9]. The disease-free interval was calculated from the

first disease-free day until time of relapse, and survival time was recorded from the first day of treatment (Kaplan–Meyer method).

For patients with locally advanced disease (LAD), a complete response was defined as normal barium swallow, no visible tumour by endoscopy with negative biopsies, and normal CT. Partial response was defined as a greater than 50% tumour regression evaluated by CT and a greater than 50% reduction of intra-oesophageal tumour extension assessed by barium enema and endoscopy. No change was defined as a less than 50% regression of measurable/evaluable tumour parameters or no evidence of tumour progression assessed by CT, barium swallow and endoscopy.

Chemotherapy consisted of folinic acid (300 mg/m^2, 10 min intravenously, iv) followed by etoposide (100 mg/m^2, 50 min iv) followed by 5FU (500 mg/m^2, 10 min iv) followed by cisplatin (30 mg/m^2, 60 min iv), days 1–3, every 3 to 4 weeks. The dose of etoposide was reduced by 20% in cases of leucopenia/thrombocytopenia of WHO grade 4 or severe infection, and 5FU was reduced by 10% if stomatitis or diarrhoea > grade 2 occurred.

In patients with metastatic disease, up to six cycles of FLEP were administered. Patients with LAD received four cycles of FLEP. In the case of an objective remission they were then referred to surgery. LAD patients with no change or tumour progression after FLEP, but still without distant disease, were allowed to undergo either one cycle of simultaneous chemoradiotherapy (mitomycin/5FU + 40 Gy within 4 weeks) and surgery thereafter if feasible, or irradiation alone to a dose of 60 Gy. Surgery was performed as transthoracic en bloc oesophagectomy, with the stomach used as oesophageal replacement.

RESULTS

Overall results

Table 1 outlines patients' characteristics. 26 patients had LAD defined as stage IIB (T2 N1 M0) or stage III (T3/4 Nx M0). The tumours were found to be irresectable by explorative laparotomy/thoracotomy in 6 patients, or were judged to be unlikely to undergo curative resection after clinical staging (CT scans showing broad infiltration of surrounding structures or gross lymph node involvement) in 20 patients. 12 patients had metastatic disease (M1) (lymph node only 5, other distant sites 7). One hundred and forty one chemotherapy courses (median 3; range 1–6) have been administered. The overall remission rate was 45% (17/38) including four (11%) clinically complete remissions (cCR) and two (5%) pathologically complete remissions (pCR). No change (NC) was observed in 11 (29%), progressive disease (PD) in 9 (24%), and treatment-related death in 1 (3%) of the patients.

The main toxicity of FLEP was myelosuppression with leucopenia of WHO grades 3 and 4 in 37% and 13% of the patients, respectively. Thrombocytopenia of WHO grades 3/4 occurred in 31% of the patients. Median leucocyte nadir was 1900 (range 700–3600) and median thrombocyte nadir was 74000 (range 12000–170000) occurring on days 11–20. Peripheral blood counts normalised on days 18–26 (median day 21). Severe infections occurred in 4 patients including one lethal septicaemia. Nausea/vomiting of WHO grades 1/2 were observed in 61% of the patients. Mucositis/stomatitis and diarrhoea were mild to moderate, with WHO grade 3 in only 1 patient each. The worst toxicity scores per patient are listed in Table 2.

Table 1. Patients' characteristics

Patients entered/evaluable	40/38
Median age	53 years (range 25–65)
Male/female	35/3
Karnofsky performance status	
90–100%	20
70–80%	18
Histology	
Squamous cell carcinoma	31
Adenocarcinoma	5
Undifferentiated carcinoma	2
Tumour stage	
IIB	4
III	22
IV	12
Tumour length in locally advanced disease	
≥ 5 cm	20
< 5 cm	6
Tumour location in oesophagus	
Upper	3
Middle	14
Lower	18
Local recurrence	3

Table 2. Toxicity (maximum WHO grade, % of all patients)

	WHO grade				
	0	1	2	3	4
Leucopenia	3	23	23	37	13
Thrombopenia	23	23	23	23	8
Infection	53	8	23	13	3
Anaemia	81	13	3	3	0
Nausea/vomiting	37	53	8	3	0
Mucositis	74	23	0	3	0
Diarrhoea	63	32	3	3	0
Alopecia	0	8	37	53	0
Neurotoxicity	84	8	8	0	0
Nephrotoxicity	100	0	0	0	0

Results in M1 patients

In 12 patients with metastatic disease, 3 partial remissions (PR) and two complete remissions (CR/PR rate 42%) were achieved. The median remission duration was 12 months (range 6–24). None of these 12 patients remained disease-free and all have already died. The median survival time was 6 months (range 2–28) for all patients, and 15 months (range 9–28) for responding patients.

Results in LAD patients

In 26 LAD patients, clinical tumour response was as follows: cCR 2, pCR 2 (cCR/pCR 15%), PR 8 (31%), CR/PR rate 46%, NC 8 (31%), PD 5 (19%), toxic death 1. All 12 patients with an objective response after FLEP chemotherapy underwent oesophagectomy. All patients had complete tumour resection (R0 resection) with a resection rate of 46% in 26 patients with

Table 3. Preoperative chemotherapy for locally advanced oesphageal carcinoma

Study	Chemotherapy Protocol	Number of patients	CR/PR (%)	R0 resection* (%)	pCR* (%)	Perioperative mortality (%)	Median survival (months) All patients	Median survival (months) Resected patients
Miller [15]	CDDP (VBL/5FU)	20	55	n.a	n.a.	5	n.a.	n.a.
Preusser [11]	CDDP/5FU/VP	27	52	37	30	20	11	17
Larroche [16]	CDDP/BLM/5FU	23	44	26	n.a.	20	n.a.	n.a.
DeBesi [17]	CDDP/5FU	152	44	33	6	10	n.a.	n.a.
Ajani [18]	CDDP/5FU	25	72	n.a.	17	8	21	n.a.
Resbeut [19]	CDDP/MTX/VDS	73	44	n.a.	n.a.	20	n.a.	n.a.
Feliu [20]	CDDP/5FU/FA	28	52	61	4	14	n.a.	11
Own results	CDDP/5FU/FA/VP	26	46	46	8	6	13	18

R0 resection, complete tumour resection; pCR, rate of complete histopathological response in those undergoing resection; CDDP, cisplatin; 5FU, 5-fluorouracil; VP, etoposide; VBL, vinblastine; BLM, bleomycine; MTX, methotrexate; VDS, vindesine; FA, folinic acid; n.a., not available.
* Based on all patients enrolled for preoperative chemotherapy.

LAD. One cCR was pathologically confirmed and in 1 case with a clinically partial remission the pathohistological work-up of the resected specimen revealed no viable tumour cells (pCR). 9 of the 13 patients not responding to FLEP (NC/PD) received either chemoradiotherapy ($n = 6$) or irradiation ($n = 3$) alone. 4 patients underwent surgery (3 after chemoradiotherapy and 1 after irradiation) thereafter. Three R1 resections and one R2 resection were performed. Postoperative morbidity consisted of pneumonia in 5 patients, paralysis of the nervus recurrence in 2, and chylothorax in 1 patient. 1 patient with pCR died on day 13 after surgery due to pancreatitis and septicaemia, resulting in a mortality rate of 6%.

After R0 resection, 5/12 patients remain continuously disease-free after 29–43 months follow up. 2 patients died 6 and 10 months after surgery due to concurrent cardiac disease, without evidence of tumour. 4 patients had recurrences, with distant failures as first site of relapse in 3 and local plus distant metastases in 1. After a median observation time of 33 months for surviving patients (29–47 months), the median survival time of all LAD patients was 13 months (range 0.5–47), and their 2-year survival rate 31% (Fig. 1). Patients with R0 resection had a median survival time of 18 months (range 5–47) and 2-year and 3-year survival rates of 42 and 31%, respectively (Fig. 2).

DISCUSSION

Locally advanced disease represents more than two thirds of all newly diagnosed locoregionally confined oesophageal cancers. Whether a standard treatment can be defined in these stages is still a matter of debate, although surgery and/or radiotherapy are often used as primary treatment. However, results with local treatment alone are disappointing. Even after complete tumour resection, the 2-year survival rate of patients with stages IIB or III is usually less than 20% [1]. The pattern of failures after local treatment are locoregional recurrences and distant metastases, which demonstrate disease dissemination beyond the borders that can be reached by surgery/radiotherapy. Thus, an improvement of the prognosis of patients with LAD oesophageal cancer may most likely be expected by chemotherapy within combined modality programs.

For these reasons, we used pre-operative (neoadjuvant) chemotherapy in patients with stage IIB and III oesophageal cancer. The reported results of neoadjuvant chemotherapy in LAD are very limited. In contrast to potentially resectable tumours, there are no prospective randomised trials. To date, no more than seven studies with pre-operative chemotherapy have been published (Table 3). Five of these seven trials were reported as abstracts, mostly lacking definition of LAD, remission criteria, pattern of tumour recurrence, and treatment of the patients who went off study. Only one of the reports comprised long-term follow-up data. Currently, the reported data suggest that pre-operative chemotherapy is feasible in LAD oesophageal cancer, but do not indicate whether neoadjuvant

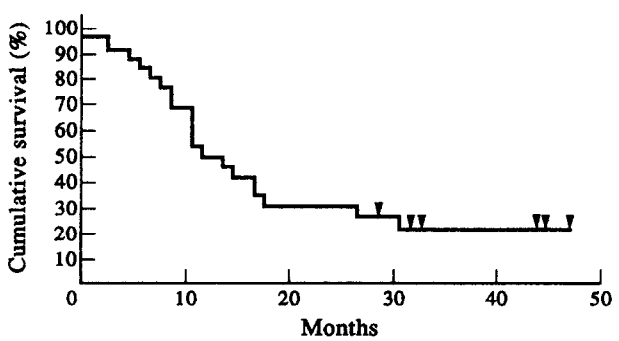

Fig. 1. Overall survival of 26 patients with locally advanced disease. Arrows represent patients who were alive at the date of the last valuation.

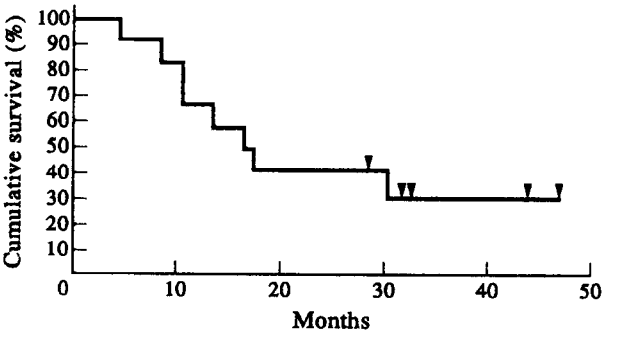

Fig. 2. Overall survival of 12 patients with locally advanced disease, who had complete tumour resection after pre-operative treatment. Arrows represent patients who were alive at the date of the last valuation.

chemotherapy can improve local tumour control or even prognosis of the patients.

We investigated the efficacy and toxicity of the new combination FLEP. Besides cisplatin and 5FU, etoposide was added because of its single-agent activity in oesophageal cancer as demonstrated in a recently published phase II trial [5], and because the results of etoposide-containing combinations are amongst the best being reported in the literature [10–14]. Moreover, all three drugs act synergistically in preclinical models [6, 7], and do not induce overlapping, dose-limiting non-haematological toxicities. The time and dose schedule was established in a pilot study, which also indicated efficacy of this regimen. 5 out of 10 patients with metastatic oesophageal cancer achieved an objective remission [8].

Our results in 26 patients with LAD compare favourable with the data of the literature, with regard to response and resection rate, rate of pCR and peri-operative mortality (Table 3). Of course, to determine whether FLEP is superior to cisplatin/5FU, the most frequently used combination in oesophageal cancer, would require a prospective randomised study. Nevertheless, the long-term results of this trial are promising. 12 out of 26 patients showed tumour remission after FLEP, and could be rendered disease-free by subsequent surgery. After a median observation time of 33 months, only 4 of these 12 patients had tumour recurrence. 1 patient died postoperatively and 2 died due to concurrent cardiac disease without evidence of tumour, resulting in a 2-year survival rate of 42% for patients with R0 resection. This compares very favourably with the results of surgery alone, where the probability of surviving 2 years after complete tumour resection is usually less than 20% in patients with LAD oesophageal cancer [1]. Although based on only a small number of patients, our study suggests that intensive pre-operative treatment may provide a definite improvement in the prognosis of patients with LAD, when compared to surgery alone. However, this apparently positive impact of pre-operative chemotherapy remains to be proven by randomised trials.

In 12 patients with distant metastases, chemotherapy with FLEP induced 5 objective remissions (42%), but a median survival time of only 6 months. Therefore, FLEP may not be recommended for patients with metastatic disease. Of note, however, is the remarkable long median remission duration of 12 months and the median survival time of 15 months for responding patients. This indicates that individual patients, even with metastatic disease, may benefit from intensive chemotherapy.

The predominant toxicity of FLEP was haematological. Approximately 50% of the patients experienced severe but short-lasting leuco- or thrombocytopenia, which rarely led to delay of treatment. Twenty-three per cent of the patients had infectious complications requiring antibiotic treatment. Non-haematological side-effects were usually only mild to moderate, and never life-threatening.

In conclusion, FLEP is an active combination for oesophageal cancer. Moreover, the concept of intensive pre-operative chemotherapy in patients with locally advanced tumours looks promising, with a 2-year survival rate of 42% for patients with secondary R0 resection. Because combined chemoradiotherapy has proven to increase local tumour control in oesophageal cancer compared to chemotherapy alone, it may be useful to include chemoradiotherapy in pre-operative treatment modalities.

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