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ORIGINAL ARTICLE

A randomized trial of 5-fluorouracil, leucovorin, cisplatin and epirubicin (PELF) versus 5-fluorouracil, leucovorin and etoposide (ELF) given as adjuvant chemotherapy to patients with resected advanced gastric adenocarcinomas

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Summary

Purpose: *To compare the efficacy and toxicity between 2 regimens [5 fluorouracil (5-FU), leucovorin and etoposide (ELF) and 5-FU, leucovorin, cisplatin and epirubicin (PELF)] administered as postoperative adjuvant chemotherapy to patients with completely resected advanced gastric cancer.*

Patients and methods: *Between 1998-2002, 78 patients with advanced gastric cancer were randomly assigned to receive 6 cycles of adjuvant ELF or PELF combination chemotherapy after complete surgical tumor resection. Endpoints were disease-free survival (DFS), overall survival and treatment toxicity.*

Results: *ELF was administered to 37 and PELF to 41 patients. Median overall survival was 12.3 months in the ELF group and 17.2 months in the PELF group (p=0.01), respectively. For the ELF group the median DFS was 17 weeks (range 7-160 weeks), while for the PELF group it was 35 weeks (range 12-172 weeks) (p=0.0004). Two-year overall survival was 8% (3 patients) in the ELF group and 24% (10 patients) in the PELF group (p=0.03). Grade 2 hematologic toxicity occurred in 21% (8 patients) in the ELF group and in 22% (9 patients) in the PELF group (p=0.5) and grade 3 in 29% (11 patients) in the ELF group and in 24% (10 patients) in the PELF group (p=0.2). Grade 2 non-hematologic toxicity was seen in 8% (3 patients) in the ELF group and in 17% (7 patients) in the PELF group (p=0.2). Grade 3 non-hematologic toxicity occurred in 29% (11 patients) in the ELF group and in 26.8% (11 patients in the PELF group) (p=0.2).*

Conclusion: *PELF combination chemotherapy resulted in DFS and overall survival advantage compared with ELF. No significant differences in hematologic or non-hematologic toxicities between the two groups were registered. PELF is superior to ELF and represents a valid option for the treatment of gastric cancer.*

Key words: adjuvant chemotherapy, cisplatin, epirubicin, etoposide, 5-fluorouracil, gastric cancer

Introduction

Postoperative adjuvant therapy of gastric cancer using systemic chemotherapy alone or as part of combined-modality therapy with curative intent has been widely used in the last 3 decades. Although the value of combination chemotherapy in advanced gastric cancer has been widely accepted as more effective compared to single-agent chemotherapy, the optimal regimen has not yet been established. In 1993, a meta-analysis by Hermans et al., which included 10 published randomized studies, showed no clear value for adjuvant chemotherapy [1]. Three randomized clinical trials have demonstrated superiority of chemotherapy over best supportive care alone [2]. In 1991-1992 the study by Wils et al. showed that the combination of 5-FU, doxorubicin and methotrexate (FAMTX) had to be considered standard therapy, with

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superior response and survival rates compared with previous regimens [3].

Long-term survival in advanced gastric cancer is very rare. Previous studies have reported a 10% 2-year survival rate for the FAMTX regimen [2,3]. Another reported multicenter randomized study comparing epirubicin, cisplatin, and 5-FU (ECF) with FAMTX showed that ECF was superior than FAMTX [4]. In 1994, in a randomized study Cocconi et al. showed that a combination of cisplatin, epirubicin, leucovorin and 5-FU (PELF) demonstrated impressive response rates [5].

In this paper we present the results of a randomized study conducted in our department, in which ELF or PELF were administered as postoperative adjuvant chemotherapy to patients with complete macroscopic resection of advanced gastric cancer.

Patients and methods

Between 1998-2002, patients with completely resected advanced gastric cancer were randomized to receive either ELF or PELF adjuvant combination chemotherapy. Patient inclusion criteria were as follows: histologically confirmed gastric adenocarcinoma; age 24-75 years; ECOG performance status ≤2; normal cardiac function confirmed by left ventricular ejection fraction; normal renal function with creatinine clearance >60 ml/min; normal liver function; no serious illness or medical condition; no previous malignancy other than nonmelanoma skin cancer and cervical carcinoma *in situ*. All patients had previously undergone subtotal or total gastrectomy before chemotherapy. Two patients in the ELF group were excluded from analysis because they refused to continue chemotherapy after 2 cycles and were lost to follow-up. In the ELF group, etoposide 120 mg/m^2/day in 500 cc normal saline was given as 45-min infusion; leucovorin 35 mg/m^2/day in 500 cc normal saline as 45-min infusion; and 5-FU 500 mg/m^2/day in 250 cc normal saline as 30-min infusion. All 3 drugs were administered on days 1, 2 and 3. Before chemotherapy, tropisetron or granisetron were given as antiemetic treatment along with i.v. dexamethasone 8 mg×2 /day. Courses were repeated every 3 weeks to a maximum of 6 cycles in patients without disease relapse. In patients with disease recurrence chemotherapy was stopped.

PELF chemotherapy comprised cisplatin 50 mg/m^2/day in 500 cc normal saline given as 2-h infusion, epirubicin 40 mg/m^2/day in 250 cc normal saline given as 15-min infusion, leucovorin 35 mg/m^2/day in 500 cc normal saline given as 45-min infusion and 5-FU 500 mg/m^2/day in 250 cc normal saline given as 30-min infusion. All drugs were administered on days 1 and 2. Prehydration with 2-h infusion of 1000 ml normal saline plus 20 mEq KCl, followed by 100 ml mannitol 20% in 15 min preceeded the cisplatin administration. Cycles were repeated every 28 days to a maximum 6 cycles in patients without disease relapse. Chemotherapy was stopped in case of disease recurrence.

Dose reduction (etoposide 100 mg/m^2 and 5-FU 500 mg/m^2 for ELF patients, and cisplatin 35 mg/m^2 for PELF patients) or treatment delay up to 2 weeks was planned for severe (grade 4) toxicity except anemia and alopecia where no dose reduction was planned.

Patients were followed up with clinical and laboratory examinations (white blood cell and platelet count, serum creatinine) before each cycle and with abdominal computerized tomography after the 3rd and 6th cycle of chemotherapy. The study endpoints were DFS, overall survival and toxicity of chemotherapy. Patient DFS and overall survival were assessed using the Kaplan-Meier method. Toxicity was recorded according to the ECOG criteria. Differences between groups were compared using the x^2 test.

Results

Seventy-eight patients with advanced gastric carcinoma were enrolled. Their characteristics are described in Table 1. Thirty-seven patients received ELF and 41 PELF combination chemotherapy. All 78 patients received 3 cycles of chemotherapy, while 62 received 6 cycles in both groups. Treatment toxicity is described in Table 2. There were no dose reductions because of toxicity, and no patient died because of toxicity.

DFS is presented in Figure 1. For the ELF group the median DFS was 17 weeks (range 7-160 weeks), while for the PELF group it was 35 weeks (range 12-172 weeks; p=0.0004).

The median overall survival was 12.3 months (range 6-48 months) in the ELF group, and 17.2 months (range 6-49 months) in the PELF group (p=0.01, Figure 2).

One-year overall survival was 37.5% (15 patients) in the ELF group, and 48% (24 patients) in the PELF group (p=0.03). Two-year overall survival was 8% (3 patients) in the ELF group, and 24% (10 patients) in the PELF group (p=0.03).

Table 1. Patient and disease characteristics

Characteristic	*Patients, n (%)*
Sex	
males	62 (79.5)
females	16 (20.5)
Age (yrs)	
median	56
range	24-74
WHO PS	
≤2	78 (100)
Histology	
adenocarcinoma	70 (89)
other (undifferentiated carcinoma)	8 (10.9)
Grade (in 58 patients)	
1	2 (2.5)
2	17 (21.7)
3	39 (50)
cTNM stage	
3	68 (87.1)
4 (M0)	10 (12.8)
Disease sites	
stomach	78 (100)
locoregional nodes	78 (100)
visceral peritoneum	46 (58.9)
abdominal wall	4 (5.1)
other [esophagus (4), duodenum(2)]	6 (7.6)

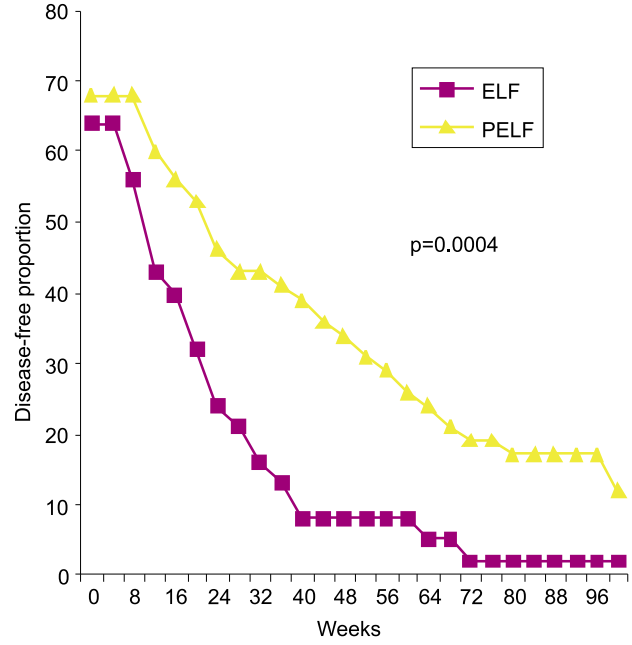

Figure 1. Disease-free survival.

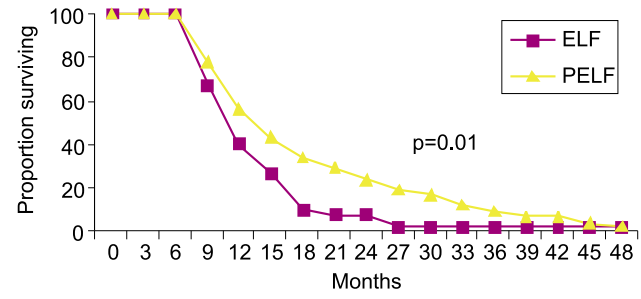

Figure 2. Overall survival.

Discussion

The only curative treatment of gastric adenocarcinoma is surgical resection [6,7]. In gastric cancer potentially resectable for cure, the surgical aim is to perform a tumor resection with at least partial gastrec-

Table 2. Toxicity of ELF and PELF chemotherapy (WHO/ECOG)

	ELF (201 cycles) Grade, n (%)					*PELF (219 cycles) Grade, n (%)*				
	0	*1*	*2*	*3*	*4*	*0*	*1*	*2*	*3*	*4*
Nausea*	72 (35.8)	93 (46.2)	6 (2.9)	30 (14.9)	–	123 (56.1)	54 (24.6)	18 (8.2)	24 (10.9)	–
Vomiting*	75 (37.3)	78 (38.8)	12 (5.9)	36 (17.9)	–	69 (31.5)	84 (38.3)	24 (10.9)	42 (19.1)	–
Neutropenia*	153 (76.17)	–	24 (11.9)	24 (11.9)	–	84 (38.3)	81 (36.9)	24 (10.9)	30 (13.6)	–
Thrombocytopenia*	201 (100)	–	–	–	–	219 (100)	–	–	–	–
Anemia*	63 (31.3)	72 (35.8)	24 (11.9)	42 (20.8)	–	75 (34.2)	84 (38.3)	30 (13.6)	30 (13.6)	–
Alopecia†	13 (35)	8 (21.6)	7 (18.9)	9 (24.3)		20 (48.7)	–	10 (24.3)	11 (26.8)	–

*number of cycles; †number of patients

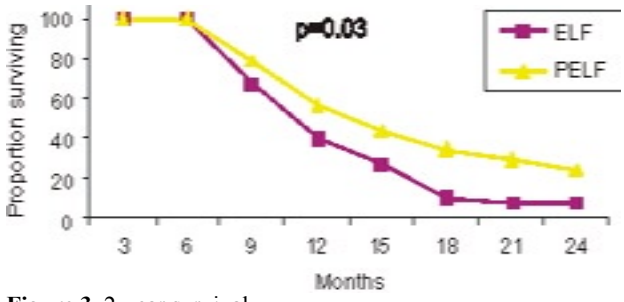

Figure 3. 2-year survival.

tomy and radical lymph node dissection. After surgical resection the survival of patients with node-positive gastric cancer is approximately 30% in the USA [1,8]. The cause of death is the development of metastatic disease arising from unresected microscopic metastases present at the time of surgical resection. Thus, these patients would be excellent candidates for post-gastric resection adjuvant therapy aimed at destroying metastatic cancer cells. Chemotherapy for advanced gastric cancer produces response rates greater than in other gastrointestinal adenocarcinomas. Single agents with response rates of 22% or greater include doxorubicin, 5-FU, cisplatin and mitomycin C [9,10]. Unfortunately, complete remisions are rare; remission duration is usually 3 to 5 months and survival is usually only 4 to 6 months for patients with advanced disease.A variety of combination chemotherapy regimens have been used widely in the palliative management of patients with gastric cancer [11,12]. None of these regimens result in cure when cancer is already disseminated. Combination chemotherapy regimens that have produced response rates of 30% to 45% include 5-FU , doxorubicin, and mitomycin C (FAM); 5-FU plus BCNU; 5-FU plus methyl CCNU; 5-FU plus mitomycin C; 5-FU,doxorubicin and methyl CCNU; 5-FU, doxorubicin, BCNU; 5-FU, doxorubicin and cisplatin [13-15].

Although response rates are somewhat greater for combined-modality therapy, this does not translate into improved survival [16].

Combination chemotherapy with FAM initially produced 42% partial responses; the median survival time was 12.5 months for responders and 3.5 months for nonresponders [17]. Antifolates added to combination chemotherapy achieved superior results in phase III studies. In comparing high dose FAMTX *versus* FAM, the therapeutic index, response and median survival advantages are unequivocal [3]. The antifolates are also effective in producing tumor regression in patients failing FAM [18].

Several combinations have been studied in advanced gastric cancer, including FAMTX (5-FU, doxorubicin, methotrexate) and ELF (etoposide, leucovorin, 5-FU). Adding etoposide to combination chemotherapy (ELF) produces results similar to those seen initially with FAMTX. ELF produces a median survival of 10 months and appears to be one of the safest of current regimens and perhaps the only one suitable for both elderly patients and those with impaired renal function.

Although response rates are higher for combination regimens (40% to 50%) than those with single agents (10% to 20%), the median survival for treated patients is the same, ranging from 6 to 8 months. Therefore, single-agent 5-FU is a reasonable and tolerable standard for palliation of these patients. The addition of cisplatin might be considered in patients for whom more aggressive treatment is desired.

Currently ECF (epirubicin, cisplatin, fluorouracil) has surplanted FAMTX, based on randomized trials. ECF was superior to FAMTX in a phase III trial, doubling the response rate to 45 *versus* 21%, reducing hematologic toxicity, and improving median survival to 8.9 *versus* 5.7 months [4,19].

A combination of cisplatin, epirubicin, leucovorin and 5-FU (PELF) has demonstrated impressive response rates in a randomized study in 1994 by Cocconi et al. [5].

In our study we have shown a definitive advantage of adjuvant PELF over ELF in terms of DFS and overall survival in patients with completely resected advanced gastric cancer.

For control of locally advanced disease, neoadjuvant chemotherapy, intraoperative radiotherapy, postoperative chemotherapy, and combined –modality therapy, all have shown promise. Neoadjuvant chemotherapy or neoadjuvant chemoradiotherapy is a new and promising area of clinical research.

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