Original article

Annals of Oncology 14: 1258–1263, 2003
DOI: 10.1093/annonc/mdg329

Cisplatin, epirubicin, leucovorin and 5-fluorouracil (PELF) is more active than 5-fluorouracil, doxorubicin and methotrexate (FAMTX) in advanced gastric carcinoma

G. Cocconi[1]*, P. Carlini[2], A. Gamboni[1], S. Gasperoni[3], C. Rodinò[4], S. Zironi[5], G. Bisagni[6], S. Porrozzi[7], F. Cognetti[2], F. Di Costanzo[3], R. Canaletti[4], E.M. Ruggeri[2], R. Camisa[1] & F. Pucci[1]
On behalf of the Italian Oncology Group for Clinical Research

[1]*Medical Oncology Division, Azienda Ospedaliera Universitaria, Parma;* [2]*Regina Elena Institute, Rome;* [3]*Medical Oncology Service, Azienda Sanitaria Locale, Terni;* [4]*Medical Oncology Service, Azienda Sanitaria Locale, Piacenza;* [5]*Medical Oncology Division, Azienda Osperdaliera Universitaria, Modena;* [6]*Medical Oncology Service, Azienda Osperdaliera, Reggio Emilia;* [7]*Medical Oncology Division, Azienda Osperdaliera Universitaria, Perugia, Italy*

Received 11 October 2002, revised 9 January 2003, accepted 8 April 2003

Background: 5-Fluorouracil (5-FU), doxorubicin and methotrexate (FAMTX) and cisplatin, epirubicin, leucovorin and 5-FU (PELF) have both been reported to be superior to the combination 5-FU, doxorubicin and mitomycin C (FAM) in advanced gastric carcinoma. On the basis of the presence and dose intensity of the included agents, we hypothesised that PELF would be superior to FAMTX.

Patients and methods: Two hundred patients with untreated advanced gastric carcinoma were randomised to receive PELF or FAMTX for a maximum of six cycles or until disease progression.

Results: The complete response (CR) rates to PELF and FAMTX were, respectively, 13% [95% confidence intervals (CI) 6% to 20%] and 2% (95% CI 0% to 5%; $P = 0.003$), and the objective response rates [CR plus partial response (PR) rates] 39% (95% CI 29% to 49%) and 22% (95% CI 13% to 30%; $P = 0.009$), thus significantly favouring the PELF combination. The survival rates after 12 months (30.8% versus 22.4%) and 24 months (15.7% versus 9.5%) were also higher among patients receiving PELF, but these differences were not statistically significant. The toxicities were qualitatively different but quantitatively similar. Both regimens seem to be feasible provided that careful patient monitoring is assured.

Conclusions: PELF is significantly more active than FAMTX and deserves further research in the adjuvant setting.

Key words: advanced gastric carcinoma, chemotherapy, FAMTX combination, PELF combination

Introduction

During the 1980s, the reference treatment for advanced gastric carcinoma was the combination 5-fluorouracil (5-FU), doxorubicin and mitomycin C (FAM). In 1991, a randomised European Organisation for Research and Treatment of Cancer (EORTC) clinical trial found that the 5-FU, doxorubicin and methotrexate combination (FAMTX) was superior to FAM [1]. In 1994, a similar randomised clinical trial [2] found that the same was true of PELF regimen (cisplatin, epirubicin, leucovorin, 5-FU) designed by the Italian Oncology Group for Clinical Research (GOIRC).

There was indirect evidence that both the response rates (41% and 43%) and median survival (9.8 and 8.1 months) that could be achieved using two combinations were similar and that both could be defined as 'new-generation regimens' in the 1990s. However, there were substantial differences between them in terms of drugs, dose intensities and schedules. PELF was a three-drug regimen (cisplatin, epirubicin and 5-FU modulated by leucovorin), and FAMTX a two-drug regimen (doxorubicin and 5-FU modulated by methotrexate). The dose intensity of 5-FU was slightly higher in the PELF than in the FAMTX regimen, that of anthracycline was reasonable in PELF but very low in FAMTX, and that of the cisplatin component in PELF was adequate.

For these reasons, the members of the GOIRC Group hypothesised that PELF may be more active than FAMTX, and decided to perform a multicentre, prospective, randomised trial in order to compare the two combinations.

Patients and methods

Patients were required to have the following: a histological diagnosis of gastric carcinoma with an unresectable primary tumour and/or metastases that were measurable or assessable by means of clinical examination, X-ray, computed tomography (CT) or ultrasound; age ≤75 years; a Karnofsky performance status of ≥60%; and a life expectancy of >2 months. The exclusion criteria included any different prior or concomitant malignant tumours, heart failure with New York Heart Association class ≥3, or any previous chemotherapy for advanced disease.

The laboratory requirements at the start of treatment were as follows: white blood cell (WBC) count of >3500/ml; a platelet count of >100 000/ml; bilirubin <1.5 mg/dl; creatinine ≤1.5 mg/ml; and creatinine clearance >50 ml/min.

Correspondence to: Dr G. Cocconi, Via Archimede 11, 43100 Parma, Italy. Tel: +39-521-460474; Fax: +39-521-467829;
E-mail: giorgio.cocconi@tin.it

Eligible patients were centrally randomised by the operational office of GOIRC (Parma, Italy) to the PELF or FAMTX combination. The stratification and balancing factors included: institution; age (≤60, >60 years); sex; performance status (100–90, 80–60); prior gastric resection (yes, no); and type of disease presentation (locoregional, primary exceeded-metastatic, primary not exceeded-metastatic, locoregionally recurrent, and metastatic). The protocol was approved by the ethics committee of each participating institution, and all of the patients gave their informed consent.

The PELF combination consisted of cisplatin (40 mg/m^2 in a 30-min i.v. infusion) on days 1 and 5; epirubicin (a short i.v. infusion of 30 mg/m^2) on days 1 and 5; and L-leucovorin (100 mg/m^2 i.v. bolus) followed by 5-FU (300 mg/m^2 i.v. bolus) on days 1–4. A single oral dose of allopurinol 900 mg was administered 12 h after 5-FU on days 1–4. The same cycle was repeated every 3 weeks. Before and after receiving cisplatin, the patients were hydrated with 3 l of 5% dextrose and 0.9% saline containing potassium chloride 20 mEq/l and magnesium sulfate 16 mEq/l. Antiemetic therapy was routinely given.

The FAMTX combination consisted of methotrexate (a short i.v. infusion of 1500 mg/m^2) and, 1 h after the end of the methotrexate infusion, 5-FU 1500 mg/m^2 i.v. bolus on day 1; oral L-leucovorin 7.5 mg/m^2 was administered every 6 h for 72 h as rescue treatment; and a doxorubicin 30 mg/m^2 i.v. bolus on day 15. The same cycle was repeated every 4 weeks.

Laboratory measurements were made before each cycle. Haemoglobin levels, and WBC and platelet counts were determined before each administration of chemotherapy except on days 2–4 of the PELF regimen.

The PELF drug doses were reduced by 50% when the WBC count was <3500/ml and/or the platelet count <100 000/ml, and by 100% (treatment discontinued) when the WBC count was <2500/ml and/or the platelet count <75 000/ml. The beginning of a new cycle was delayed by 1 week whenever the WBC or platelet count required a dose reduction, whenever plasma creatinine levels were >25% above the upper baseline value, or in the case of any persistent gastrointestinal toxicities (vomiting, stomatitis, diarrhoea) of any grade. The 4-day administration of leucovorin and 5-FU was interrupted whenever early gastrointestinal toxicities (stomatitis or diarrhoea) appeared during this period. The patients had to be examined between day 7 and 10 of each cycle, when any subjective toxicities were recorded, and blood counts as well as serum creatinine, sodium, potassium, calcium and magnesium levels were determined. Creatinine clearance had to be measured between day 15 and 18 of each cycle.

The FAMTX drug doses were reduced by 50% when the WBC count was <3000 and/or the platelet count was <70 000/ml, and by 100% when the WBC count was <2000/ml and/or the platelet count was <50 000/ml. The beginning of a new cycle and the administration of doxorubicin on day 15 was delayed by a maximum of 2 weeks whenever the WBC or platelet count required a dose reduction, whenever plasma creatinine levels were >25% above the upper baseline value, or in the case of any persistent gastrointestinal toxicities (vomiting, stomatitis, diarrhoea) of any grade. The drug doses of both regimens were reduced by 25% whenever grade 4 haematological toxicity or grade 3 stomatitis or diarrhoea had been reported during the previous cycle.

Response was defined on the basis of the World Health Organization (WHO) criteria [3]. Briefly, a complete response (CR) required the complete disappearance of all clinical evidence of disease, and a partial response (PR) a >50% reduction in the sum of the products of the two longest perpendicular diameters of bidimensionally measurable lesions. In the case of assessable but non-measurable lesions, a PR was recorded if a definite reduction (estimated as >50%) was documented by photography, X-ray, ultrasound or CT scan. Endoscopic disease monitoring was not allowed.

Response was evaluated after the first two cycles, and then every 2 months. In the absence of progression or intolerable toxicity, the treatment was continued for six cycles, after which the patients were followed up until progression. After six PELF or FAMTX cycles, local treatment (second-look surgery and gastric resection, if feasible) was allowed if required in individual patients. Response was assessed by the clinical investigators at each participating unit, and centrally reviewed in the case of CR, PR, no change for more than 6 months, or in the case of patients who underwent gastric resection at the end of the chemotherapy programme.

The χ^2 test and Fisher's exact test were used to compare the types of response and toxicities in the two treatment groups. The time to failure and time to progression, as well as the duration of response and survival, were all measured from the date of randomisation using the method of Kaplan and Meier [4]. The time to failure and time to progression were evaluated in all eligible patients, the duration of response in the eligible patients achieving a CR or PR and the duration of survival in all of the randomised patients, even if they were not eligible. The events considered when evaluating time to failure were progression, death due to any cause, a failure to start chemotherapy, the discontinuation of chemotherapy because of refusal, intolerable toxicities or non-neoplastic medical events, protocol violations and loss to follow-up. The events considered when evaluating time to progression were progression or death due to neoplastic disease. The event used to evaluate survival was death due to any cause. Unless otherwise stated, values of P <0.05 were considered significant; all P values are two-sided. Toxicity was evaluated in all of the patients receiving at least one dose of chemotherapy whether they were eligible or not, and was graded according to WHO criteria [3].

With an estimated objective response rate of 40% for either treatment, the trial was originally designed to demonstrate a significant 20% higher or lower objective response rate in one of the two treatment arms. With an α error of 0.05 and a β error of 0.2 (two-sided test), ~105 patients per arm were required; however, it was decided to stop accrual after reaching 100 patients per arm because the rate of enrolment substantially declined towards the end.

Results

From May 1993 to November 1999, 200 patients from 11 medical oncology institutions belonging to GOIRC were equally randomised to PELF or FAMTX. Five patients were not eligible because they had baseline bilirubin levels >2 mg/ml (two patients in the FAMTX arm), a performance status of <60 (one in each arm) or no relapse of resected disease (one in the PELF arm).

The characteristics of the eligible patients are shown in Table 1: 68% were men, 54% had an optimal performance status, 51% had been previously resected, and 35% had primary resected and metastatic disease. None of the between-group differences were statistically significant.

Toxicity

Thirteen of the 200 randomised patients (six in the PELF and seven in the FAMTX group) did not begin the assigned chemotherapy and were not evaluated for toxicity. Ninety-four patients treated with PELF received a total of 423 cycles [a median of five per patient (range 1–6)]; the 93 patients treated with FAMTX received a total of 319 cycles [a median of three per patient (range 1–8)].

Table 2 shows that there were no significant differences in haematological toxicities between the PELF and the FAMTX group (grade 4 WBC toxicity occurred in 14% and 20% of cases, respectively), and the platelet and haemoglobin toxicities were generally mild in both arms. Among the non-haematological toxicities, nausea/vomiting (P = 0.004) and diarrhoea (P = 0.002) were significantly more frequent and severe in the PELF arm, whereas mucositis (P = 0.04) was significantly more frequent and severe in the FAMTX arm; renal, hearing and neurological toxic-

Table 1. Characteristics of eligible patients

Characteristics	PELF no. (%)	FAMTX no. (%)
Total	98 (100)	97 (100)
Median age, years (range)	62 (26–74)	62 (27–75)
Gender		
Male	67 (68)	66 (68)
Female	31 (32)	31 (32)
Karnofsky performance status		
100–90	50 (51)	55 (57)
80–60	48 (49)	42 (43)
Previous resection		
Yes	49 (50)	50 (52)
No	49 (50)	47 (48)
Disease presentation		
Locoregional	16 (16)	14 (15)
Primary excised, metastatic	34 (35)	35 (36)
Primary not excised, metastatic	42 (43)	43 (44)
Locoregionally recurrent and metastatic	6 (6)	5 (5)

FAMTX, 5-fluorouracil, doxorubicin and methotrexate; PELF, cisplatin, epirubicin, leucovorin and 5-fluorouracil.

ities were not relevant in either arm. Four patients on PELF (4.2%) and three on FAMTX (3.2%) died as a result of toxicity. Three of the four deaths in the PELF arm occurred in a single institution, which admitted to having suboptimal facilities for directly admitting patients complaining of severe toxicities.

Response

The response rates are shown in Table 3. The response of 15 patients in the PELF group and 14 in the FAMTX group were unevaluable or not evaluated for the following reasons: the treatment was never started (five versus five), protocol violations (zero versus one), insufficient treatment due to early death (five versus three), refusal (four versus two), early discontinuation due to toxicity (zero versus three) or severe medical events (one versus zero). All of these patients were included as non-responders in the denominator of the response evaluation.

The rates of progression (22% versus 33%) and no change (24% versus 31%) were not significantly different between the PELF and FAMTX arms, but the CR rate was significantly higher ($P = 0.003$) in the PELF arm [13% (95% CI 6% to 20%) versus 2% (95% CI 0% to 5%)], which also had a significantly ($P = 0.009$) higher overall objective response rate (CR plus PR) [39% (95% CI 29% to 49%) versus 22% (95% CI 13% to 30%)].

The number of patients with assessable but non-measurable bidimensional lesions was very low: seven of 98 eligible patients in the PELF arm and six of 97 in the FAMTX arm. The overall

Table 2. Toxicities

Type of toxicity	PELF ($n = 94$)					FAMTX ($n = 93$)				
	Grade					Grade				
	0	1	2	3	4	0	1	2	3	4
Haematological										
WBC	14	13	27	27	13	18	11	26	19	19
Platelets	63	10	11	8	2	75	4	5	5	4
Haemoglobin	22	33	27	11	1	28	31	21	11	2
Non-haematological										
Nausea/vomiting	21	26	28	13	6	41	29	14	5	4
Mucositis	64	10	14	5	1	43	14	25	7	4
Diarrhoea	50	9	18	12	5	72	6	13	2	0
Renal	87	3	4	0	0	85	4	3	1	0
Hearing	90	2	2	0	0	93	0	0	0	0
Skin	93	0	1	0	0	89	4	0	0	0
Neurological	87	3	3	1	0	89	5	1	0	1
Cardiac	92	0	0	2	0	90	0	1	0	2
Hepatic	93	0	1	0	0	92	0	0	0	1
Conjunctivitis	91	1	2	0	0	85	4	4	0	0
Cystitis	93	0	1	0	0	92	1	0	0	0
Others	60	12	17	5	0	57	16	17	3	0

FAMTX, 5-fluorouracil, doxorubicin and methotrexate; PELF, cisplatin, epirubicin, leucovorin and 5-fluorouracil; WBC, white blood cells.

Table 3. Types of response

Types of response	PELF no. (%)	FAMTX no. (%)	*P* value
Total	98 (100)	97 (100)	
Insufficient treatment	15 (15)	14 (14)	
Progression	21 (22)	32 (33)	
No change	24 (24)	30 (31)	
Partial response (PR)	25 (26)	19 (20)	
Complete response (CR)	13 (13)	2 (2)	0.003
95% CI	6–20	0–5	
CR plus PR	38 (39)	21 (22)	0.009
95% CI	29–49	13–30	

CI, confidence interval; FAMTX, 5-fluorouracil, doxorubicin and methotrexate; PELF, cisplatin, epirubicin, leucovorin and 5-fluorouracil.

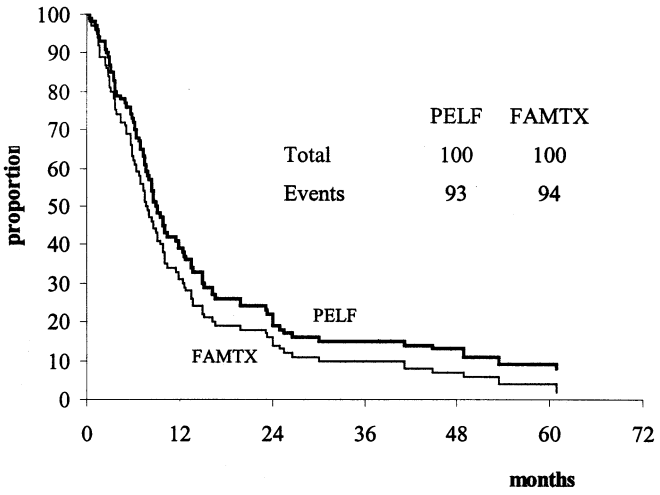

Figure 1. Survival by treatment: all randomised patients.

Table 4. Objective responses by patient characteristics

Characteristics	Objective response[a] [*n* (%)]	
	PELF	FAMTX
Age		
<60 years	21/46 (46)	12/45 (27)
>60 years	17/52 (33)	9/52 (17)
Gender		
Male	26/67 (39)	17/66 (26)
Female	12/31 (39)	4/31 (13)
Karnofsky performance status		
100–90	22/50 (44)	15/55 (27)
80–60	16/48 (33)	6/42 (14)
Previous gastric resection		
Yes	22/49 (45)	13/50 (26)
No	16/49 (33)	8/47 (17)
Disease presentation		
Locoregional	7/16 (44)	3/14 (21)
Primary excised, metastatic	14/34 (41)	8/35 (23)
Primary not excised, metastatic	15/42 (36)	8/43 (19)
Locoregionally recurrent and metastatic	2/6 (33)	2/5 (40)

[a]Objective response rate = CR + PR/total number of patients.
CR, complete response; FAMTX, 5-fluorouracil, doxorubicin and methotrexate; PELF, cisplatin, epirubicin, leucovorin and 5-fluorouracil; PR, partial response.

objective response rates among the patients with measurable lesions was still significantly ($P = 0.006$) higher in the PELF arm [40% (95% CI 30% to 50%) versus 21% (95% CI 13% to 29%)].

Table 4 shows the responses by patient characteristics. The differences between treatments in most of the patient subgroups were similar to the overall difference shown in Table 3, but this analysis may be limited by the small patient numbers in some groups. As expected, the response rate in both arms was lowest in the patients with a lower performance status and in those who had not undergone previous resection. The difference between the PELF and FAMTX groups remained statistically significant in the subgroup of females (39% versus 13%; $P = 0.02$) and that of the patients with a performance status of 80–60 (33% versus 14%; $P = 0.036$).

The median time to failure was 4.1 months (range 0–72+) on PELF and 3.2 months (range 0–63+) on FAMTX ($P = 0.29$); the median time to progression was 5.9 months (range 0.5–72+) and 3.5 months (range 0.5–63+), respectively ($P = 0.34$); and the median duration of response was 7.9 months (range 1.5–72+) and 8.1 months (range 2.7–63+) ($P = 0.90$). Survival is shown in Figure 1: the median values were 7.7 months (range 0.4–72+) on PELF and 6.9 months (range 0.4–63+) on FAMTX ($P = 0.19$). The 12- and 24-month survival rates were higher in the PELF arm (30.8% versus 22.4% and 15.7% versus 9.5%), but these differences were not statistically significant.

Discussion

The PELF response and survival results of this study substantially confirm those of our previous comparative study versus FAM (objective response rates, 39% and 43%; median survival 7.7 and 8.1 months), and demonstrate that PELF is significantly more active than FAMTX in terms of response.

The significantly higher CR rate in the PELF arm clearly sustained the significantly higher objective response rates, although (particularly in advanced gastric carcinoma patients) a complete clinical response hardly ever reflects a complete pathological response. Nevertheless, the fact that some of the objective responses were classified as complete at least indicates that the PELF regimen led to some very good objective remissions. Survival was not significantly prolonged, but the higher proportion of patients surviving after 12 months and 24 months in the PELF arm suggests that the statistical power of the study (which was planned on the basis of response rates) was perhaps too low to demonstrate any superiority in survival.

The non-haematological toxicities of the two regimens seem to be equally relevant, qualitatively different and quantitatively

similar. PELF was associated with frequent and severe nausea/vomiting and diarrhoea (as in our previous study), whereas FAMTX was associated with frequent and severe mucositis.

The similar proportion of toxic deaths in the two groups was not negligible, but this is not unusual in the case of chemotherapy trials in advanced gastric carcinoma. The disease is often diagnosed in older patients (possibly with non-neoplastic comorbidity problems), and its natural history may be aggressive and life-threatening in the short term. The clinical severity of the disease at the time of entering the study was confirmed by the relatively high proportion of patients in both groups classified as non-responders because of insufficient treatment for clinical reasons.

The achievement of an objective remission is usually associated with a subjective and objective clinical improvement in symptoms, even in advanced gastric carcinoma patients. However, insufficient compliance in completing the forms aimed at assessing symptomatic improvement and the quality of life prevented any direct comparative assessment.

With reference to the FAMTX regimen, our results do not confirm those of the previous EORTC study comparing it with FAM: the response rate was lower (22% versus 41%), the median duration of survival shorter (6.9 versus 9.8 months) and the proportion of toxic deaths was higher (3.2% versus 1%). Furthermore, since then, a number of other studies of FAMTX have indicated that it has a low level of activity and relevant toxicity: a Dutch study in which patients were randomised to FAMTX as neo-adjuvant chemotherapy or immediate surgery showed no increase in resectability, and the chemotherapy was discontinued early in 44% of the FAMTX patients due to progression or toxicities [5]. Another randomised study carried out by a European cooperative group in order to compare FAMTX with ELF (etoposide, leucovorin, bolus 5-FU) and FUP (infusional 5-FU, cisplatin) reported a response rate of only 12% in the FAMTX arm [6].

Furthermore, a number of other studies of PELF or similar combinations have found that they are more active and have other advantages over FAMTX: a weekly PELF schedule designed by Cascinu et al. [7] led to high rates of complete (18%) and objective responses (62%) in a phase II study of 105 patients; a randomised study of a similar FLEP regimen designed by a Hispanic cooperative group [8] revealed a significantly higher response rate than that observed in the FAMTX arm (23% versus 7%) [9]; and a randomised phase III trial comparing FAMTX with a similar ECF schedule, which was designed by investigators from London's Royal Marsden Hospital (cisplatin and epirubicin administered together with 5-FU, and not modulated by leucovorin but by means of prolonged i.v. infusion) and very favourably tested in phase II studies [10, 11], showed that the latter led to a significantly higher response rate (45% versus 21%) and longer survival (median, 8.9 versus 5.7 months) [12, 13].

In summary, our results show that PELF is significantly more active than FAMTX in terms of complete and objective response rates; that the 12- and 24-month survival rates are not significantly higher; that the toxicities are quantitatively comparable but qualitatively different; and that both regimens are feasible provided that the patients are carefully monitored. The PELF regimen deserves further research in the adjuvant setting, and the results of a randomised trial already carried out by the GOIRC group will soon be available.

Furthermore, our results (together with those of other studies) indicate that combinations of cisplatin, epirubicin and 5-FU, modulated by leucovorin or by means of prolonged i.v. infusion (i.e. PELF, FLEP, ECF and possibly even MCF [14]), are currently the most active in advanced gastric carcinoma, and that FAMTX should no longer be included among the most active regimens.

Since the start of this study, a number of new agents (particularly the taxanes, irinotecan and oxaliplatin) have also been found to have significant activity in advanced gastric carcinoma [15]. As a consequence, a number of phase II and a few phase III trials have been conducted combining paclitaxel, docetaxel or irinotecan with 5-FU (plus or minus leucovorin), cisplatin or both [16–18], and other phase II studies have combined oxaliplatin with 5-FU and leucovorin [19]. These combinations have generally contained only one of the new agents, and anthracycline was generally omitted. Given the frequent reports of high objective response rates (as much as 40% or more) and acceptable toxicity profiles [16, 17, 19], some of these new combinations are now being compared with conventional (typically ECF or similar) combinations in phase III studies in an attempt to identify those that will become the future conventional therapies for the treatment of advanced gastric carcinoma and possibly adjuvant therapy in the 21st century. Paradoxically, the clinical research effort involved in recognising the new status of such combinations has been increased by the fact that the availability of such a large number of active agents has multiplied the number of theoretical trials.

Acknowledgements

The Medical Oncology Units of Sassari, Ferrara, Vigevano and Fivizzano contributed some patients to this study.

References

1. Wils JA, Klein HO, Wagener DJ et al. Sequential high-dose methotrexate and fluorouracil combined with doxorubicin—a step ahead in the treatment of advanced gastric cancer: a trial of the European Organization for Research and Treatment of Cancer Gastrointestinal Tract Cooperative Group. J Clin Oncol 1991; 9: 827–831.
2. Cocconi G, Bella M, Zironi S et al. Fluorouraciul, doxorubicin, and mitomycin combination versus PELF chemotherapy in advanced gastric cancer: a prospective randomized trial of the Italian Oncology Group for Clinical Research. J Clin Oncol 1994; 12: 2687–2693.
3. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. Cancer 1981; 47: 207–234.
4. Kaplan EI, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958; 53: 457–481.
5. Songun I, Keizer HJ, Hermans J et al. Chemotherapy for operable gastric cancer: results of the Dutch randomized FAMTX trial. Eur J Cancer 1999; 35: 558–562.
6. Vanhoefer U, Roogier P, Wilke H et al. Final results of a randomized phase III trial of sequential high-dose methotrexate, fluorouracil, and doxorubicin versus etoposide, leucovorin, and fluorouracil versus infusional fluorouracil and cisplatin in advanced gastric cancer: a trial of the Euro-

pean Organization for Research and Treatment of Cancer Gastrointestinal Tract Cooperative Group. J Clin Oncol 2000; 18: 2648–2657.

7. Cascinu S, Labianca R, Alessandroni P et al. Intensive weekly chemotherapy for advanced gastric cancer using fluorouracil, cisplatin, epidoxorubicin, 6s-leucovorin, glutathione, and filgrastim: a report from the Italian Group for the Study of Digestive Tract Cancer. J Clin Oncol 1997; 15: 3313–3310.
8. Cervantes A, Villar-Grimalt A, Abad A et al. 5-Fluorouracil, folinic acid, epidoxorucin and cisplatin (FLEP) combination chemotherapy in advanced measurable gastric cancer. A phase II trial of the Spanish Cooperative Group for Gastrointestinal Tumor Therapy (TTD). Ann Oncol 1993; 4: 753–757.
9. Massuti B, Cervantes A, Aranda E et al. A phase II multicentric randomized trial in advanced gastric cancer (GC): fluorouracil + leucovorin + epirubicin + cisplatin (FLEP) vs fluorouracil + adriamycin + methotrexate + leucovorin (FAMTX): response and survival report. Proceedings of the Sixth International Congress on Anti-cancer Treatment, Paris, France, February 6–9, 1996. Paris, Service d'Oncologic Méfical, Hospital Pitié-Salpetrière 1996; 120 (Abstr UI:97614417).
10. Findlay M, Cunningham D, Norman A et al. A phase II study in advanced gastro-esophageal cancer using epirubicin and cisplatin in combination with continuous infusion 5-fluorouracil (ELF). Ann Oncol 1994; 5: 609–616.
11. Zaniboni A, Barni S, Labianca R et al. Epirubicin, cisplatin, and continuous infusion 5-fluorouracil is an active and safe regimen for patients with advanced gastric cancer. An Italian Group for the Study of Digestive Tract Cancer (GISCAD) report. Cancer 1995; 76: 1694–1699.
12. Webb A, Cunningham D, Scarffe JH et al. Randomized trial comparing epirubicin, cisplatin and fluorouracil versus fluorouracil, doxorubicin and methotrexate in advanced esophagogastric cancer. J Clin Oncol 1997; 15: 261–267.
13. Waters JS, Norman A, Cunningham D et al. Long-term survival after epirubicin, cisplatin and fluorouracil for gastric cancer: results of a randomised trial. Br J Cancer 1999; 80: 269–272.
14. Ross P, Nicolson M, Cunningham D et al. Prospective randomized trial comparing mitomycin, cisplatin, and protracted venous infusion of fluorouracil (PVI 5-FU) with epirubicin, cisplatin, and PVI 5-FU in advanced esophagogastric cancer. J Clin Oncol 2002; 20; 1996–2004.
15. Hasham-Jiwa N, Kasakura Y, Ajani JA. Brief review of advances in the treatment of gastric carcinoma in North America and Europe, 1995–2001. Int J Clin Oncol 2002; 7: 219–224.
16. Kim YH, Shin SW, Kim BS et al. Paclitaxel, 5-fluorouracil, and cisplatin combination chemotherapy for the treatment of advanced gastric carcinoma. Cancer 1999; 85: 295–301.
17. Roth AD, Maibach R, Martinelli G et al. Docetaxel (Taxotere®)–cisplatin (TC): an effective drug combination in gastric carcinoma. Swiss Group for Clinical Cancer Research (SAKK), and the European Institute of Oncology (EIO). Ann Oncol 2000; 11: 301–306.
18. Pozzo C, Bugat R, Peschel C et al. Irinotecan in combination with CDDP or 5-FU and folinic acid is active in patients with advanced gastric or gastro–oesophageal junction adenocarcinoma: final results of a randomised phase II study. Proc Am Soc Clin Oncol 2001; 20: 134a (Abstr 531).
19. Artru P, André T, Tigaud JM et al. Oxaliplatin (OXA), 5-fluoro-uracil (FU) and folinic acid (FA) (FOLFOX 6) in advanced/metastatic gastric carcinoma (A/MGC) patients (Pts): final results of a multicenter phase II study. Proc Am Soc Clin Oncol 2001; 20: 164a (Abstr 654).