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Original Paper

A Phase II Study of 5-Fluorouracil, Leucovorin and Cisplatin (FLP) for Metastatic Gastric Cancer

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The modulation of 5-fluorouracil (5-FU) with folinic acid (leucovorin, LV) is more efficacious than 5-FU alone in the treatment of metastatic colorectal cancer, and the combination of 5-FU with cisplatin is currently one of the most active regimens in advanced gastric cancer. A phase II study was therefore conducted to test the efficacy and toxicity of the combination of 5-FU, LV and cisplatin (FLP) in metastatic gastric cancer. 28 patients entered the study. Metastatic sites were observed in the liver (in 21 patients), the peritoneum (in 8), the lymph nodes (in 7) or the bones (in 1) and a local recurrence was noted in 4 cases. The performance status (using World Health Organisation criteria) was 0 for 13 patients and 1 or 2 for the others. Cycles of treatment were administered every 28 days and consisted of LV 200 mg/m²/day for 5 days followed by 5-FU 400 mg/m²/day for 5 days with cisplatin 100 mg/m² on day 2. The response rate for the 27 evaluable patients was 51.8% (95% confidence interval (CI), 33–70.6%). There were four complete responses (14.8%) and 10 partial responses (37%). Median survival was 11 months and 4 patients were alive at 2 years. Both response rate and survival were better for patients with a good performance status. The overall toxicity was very low, except for 1 patient who died of dehydration and cardiac failure. In conclusion, the FLP protocol was effective and well tolerated in patients with metastatic gastric cancer. Copyright © 1996 Published by Elsevier Science Ltd

Key words: gastric cancer, chemotherapy, phase II study

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INTRODUCTION

In recent years, some progress has been reported in the palliative chemotherapy of advanced gastric carcinoma. The combination of 5-fluorouracil (5-FU), doxorubicin and high-dose methotrexate (FAMTX) has been demonstrated to be more effective than the FAM protocol (the combination of 5-FU, doxorubicin and mitomycin) in a randomised study [1], both in terms of objective tumour responses and survival. The combination of etoposide, doxorubicin and cisplatin (EAP) also showed impressive results in a phase II trial with very selected patients [2], but these results were not confirmed when compared with FAMTX protocol in a randomised study [3]. The combination of 5-FU in continuous infusion with cisplatin (FP) has also been well documented in phase II studies, with a response rate of about 40%, but with some haematological and digestive toxicity [4, 5]. We can therefore consider that the combination of these two drugs, 5-FU and cisplatin, is one of the more effective polychemotherapies in gastric cancer, and in fact, these drugs are associated with epirubicin in the ECF regimen, another active regimen in gastric cancer [6, 7].

The modulation of 5-FU with folinic acid has been widely documented in both biochemical and clinical studies [8, 9]. In colorectal cancer, the 5-day regimen of 5-FU and leucovorin (LV) has been demonstrated to be more effective than 5-FU alone in terms of response rate and survival in some studies [10, 11]. Based on this superiority in colorectal cancer, we undertook a prospective study to test the effectiveness and safety of the combination of 5-FU–LV and cisplatin (FLP) in a phase II trial, anticipating that this schedule could be less toxic than the FP regimen, but with comparable efficacy.

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PATIENTS AND METHODS

Patient selection

Between January 1990 and November 1993, 28 patients with metastatic gastric cancer were entered into this prospective phase II trial. All patients had to have histologically proven gastric carcinoma and measurable metastatic disease, according to World Health Organisation (WHO) criteria [12], or a non-resectable local recurrence. Additional criteria included a performance status of WHO grade 0–2, normal haematological tests (neutrophils > 2000/ml, platelets > 100000/ml), normal cardiac and renal function (creatinine < 120 μmol/l), and no previous experience of chemotherapy. All patients provided informed consent.

Methods

The following chemotherapy regimen was used. D-Leucovorin (D-LV) 200 mg/m^2/day on days 1–5 given intravenously as a short infusion (15 min), immediately followed by 5-FU 400 mg/m^2/day on days 1–5 given as a 1 h infusion and cisplatin 100 mg/m^2 on day 2 given as a 1 h infusion with hyperhydration and anti-emetics. Cycles were repeated every 28 days if neutrophil levels were > 1500/ml, platelet levels > 100000/ml and creatinine levels < 120 μmol/l. In addition, the creatinine clearance was measured before each cycle and the dose of cisplatin was reduced by 25% if creatinine clearance was between 40 and 60 ml/min (with normal plasma levels of creatinine) and stopped if it was less than 40 ml/min.

All patients underwent a complete clinical investigation prior to treatment to evaluate the main metastatic sites. An upper endoscopy was performed whenever the primary tumour was not resected or when a local recurrence was suspected. A computer tomography (CT) scan was always used to evaluate abdominal and thoracic metastases. Bone metastases and/or peritoneal or pleural effusions were not considered evaluable metastatic sites, but were taken into account for progression or regression, in parallel with other metastatic sites. Response to treatment was evaluated after two or three cycles and then after every two cycles. Complete blood cell counts, levels of serum creatinine, electrolytes and tumour markers (CEA and CA19-9), and liver function tests were evaluated before each cycle, along with a complete clinical examination. WHO criteria were used for the definition of response and response duration [12]. A complete response (CR) was defined as complete disappearance of all clinical and radiological signs of tumour for a duration of over 4 weeks; a partial response (PR) was defined as a 50% or more decrease in the sum of the products of the two largest perpendicular diameters of all measurable lesions, if no new lesion was detected; no change (NC) was defined as a decrease in total tumour size of less than 50% or a less than 25% increase in the size of one or more measurable lesions. Response rates were compared using the chi squared method or Fisher's Exact test, and the Mantel–Haenszel test [13]. Survival rates, calculated using the Kaplan–Meier method, were compared using the logrank test [14].

Toxicity was evaluated before each cycle and reported according to WHO criteria [12]. All patients who had received at least one course of chemotherapy were considered evaluable for toxicity.

The response to chemotherapy was estimated after the first three cycles. In the case of objective tumour response or stabilisation with no more than grade 2 toxicity, three more cycles were planned. For patients responding after six cycles, an attempt was made to administer further cycles until limiting renal or neurological toxicity from high-dose cisplatin occurred.

Chemotherapy was stopped if there was progression or unacceptable toxicity. Some patients experienced second-line chemotherapy with FAMTX or ELF combinations [15].

RESULTS

Response rate

28 patients were assessed for toxicity and 27 were evaluable for response (there was 1 toxic death before evaluation). The main patient characteristics are summarised in Table 1. A total of 141 treatment cycles were administered and the median number of cycles per patient was five (range two–eight). 7 patients required a dose reduction (25%) but only 2 a dose delay of 1 week. Overall, at least 90% of the treatment planned was administered per cycle. The usual reason for patients stopping treatment was progression or a limitant toxicity, mainly after six cycles. Response to chemotherapy was evaluable after a minimum of two cycles in 27 patients: 4 CR (14.8%) and 10 PR (37%) were observed with an overall response rate of 51.8% (95% CI, 33–70.6%). The median duration of objective response was 7 months (range 3–20). No response was observed for second-line chemotherapy (FAMTX or ELF). The main patient characteristics have been tested by univariate analysis to estimate their influence on the response rate (Table 2). Patients with a good performance status (grade 0 versus 1–2), or with only one metastatic

Table 1. Patient characteristics

	n
Male/female	24/4
Median age in years (range)	64 (40–78)
Performance status (WHO)	
0	13
1	9
2	6
Localisation of primary tumour	
Cardia	11
Other parts of stomach	17
Prior resection of primary tumour	
Yes	13
No	15
Histological differentiation	
Well or moderate	13
Poor	12
Unknown	3
Sites of metastases	
Liver	21
Peritoneal	8
Local recurrence	4
Lymph nodes	7
Bone	1
Multiple metastases	10
CEA > normal	13
CA19-9 > normal	11
CEA and/or CA19-9 > normal	18

WHO, World Health Organisation.

Table 2. Factors influencing the tumour response in patients with metastatic gastric cancer treated with the combination of 5-fluorouracil–leucovorin–cisplatin

Factors	Responses (*n*)	χ^2 test (*P*)
Age (years)		
≤ 65 (*n* = 13)	6	NS
> 65 (*n* = 14)	8	
Performance status		
Grade 0 (*n* = 13)	10	0.014
Grade 1–2 (*n* = 14)	4	
CEA (normal = 10 ng/ml)		
≤ normal (*n* = 15)	6	NS
> normal (*n* = 12)	8	
CA19-9 (normal = 60 IU/ml)		
≤ normal (*n* = 17)	10	NS
> normal (*n* = 10)	4	
Primary tumour		
Non-resected (*n* = 15)	8	NS
Prior resection (*n* = 12)	6	
Site of primary tumour		
Cardia (*n* = 11)	8	0.077
Non-cardia (*n* = 16)	6	
Number of metastatic sites		
One site (*n* = 17)	12	0.015
> one site (*n* = 10)	2	
Histological differentiation		
Well/moderate (*n* = 12)	9	0.016
Poor (*n* = 12)	3	
Unknown (*n* = 3)		

NS, non-significant.

site, or with moderate or high histological differentiation showed a significantly higher response rate ($P < 0.05$). For tumours located in the cardia region, the response rate tended to be higher, but was not statistically significant ($P = 0.077$).

Survival

27 of the 28 patients are dead and 1 is still alive at 29 months after a PR and is undergoing third-line chemotherapy. The cause of death was tumour progression for 26 patients and toxicity from chemotherapy for 1. The overall survival of the entire group is shown in Figure 1; the median survival was 11 months. 4 patients were alive at 2 years and the longest survival was 37.5 months. This patient presented with a histologically proven adenocarcinoma of the cardia junction, with at least one measurable hepatic metastasis and retroperitoneal lymph nodes. A CR was observed after five cycles of chemotherapy using gastroscopy with biopsies, a CT scan and tumour markers. This CR was confirmed by surgery involving a total gastrectomy with R2 lymph node removal and liver biopsy in the site of the metastasis seen on the CT scan before chemotherapy. Every sample showed a pathological CR, with no detection of cancer cells. Duration of the CR was 20 months after surgery, until a liver recurrence appeared, located at the site of the previous metastasis. The metastatic disease rapidly became extensive, despite second-line FAMTX chemotherapy and the patient died of tumour progression.

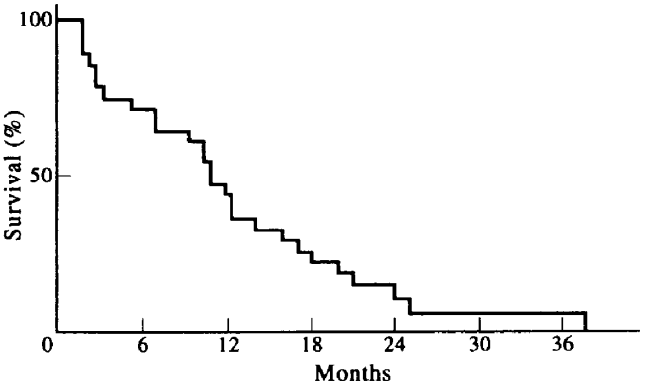

Figure 1. Overall survival of patients with metastatic gastric cancer treated with chemotherapy combining 5-fluorouracil, leucovorin and cisplatin. Kaplan–Meier method; *n* = 28.

We tested the main pretherapeutic factors that could influence survival (Table 3): performance status was the only significant prognostic factor (Figure 2), with a better survival for patients with grade 0 and grade 1 or 2.

Toxicity

The toxicity was mainly gastrointestinal and is reported in Table 4. 4 patients experienced grade 3 or 4 toxicity, with 1 dying of toxicity. He was 75 years old and had been previously operated on for resection of primary gastric tumour with synchronous hepatic metastases. After the first cycle of FLP, he presented with grade 3 digestive toxicity (vomiting and diarrhoea) and a 30% reduction was made in the dose of chemotherapy for the following cycles. Despite this dose reduction, after the third cycle, he experienced severe diarrhoea and vomiting, associated with neutopenic fever (grade 3), and stayed at home for 1 week without treatment. When he was hospitalised, he presented with severe dehydration with hypotension, and died of cardiac failure. He was the only case of toxic death and neutropenic fever. In all of the other cases, toxicity was at acceptable levels, and prolonged hospitalisation was not required.

DISCUSSION

This phase II study confirms the efficacy and safety of the FLP combination in metastatic gastric cancer. It also confirms the results previously obtained with the combination of 5-FU in continuous infusion and cisplatin [4, 5], with a comparable response rate (respectively 51.8% and 37%). This response rate is also in the same range as that for FAMTX (33–41%), which can be considered as standard chemotherapy for gastric cancer. These results can be compared with another active regimen, first described by Findlay and colleagues [6], combining a prolonged intravenous infusion of 5-FU with cisplatin and epirubicin administered every 3 weeks (ECF). Recently, a phase II multicentre trial [7] confirmed the activity of ECF in terms of the response rate (56%) with mild toxicity (no toxic death).

In our study, the median survival of 11 months seems particularly encouraging when compared with the median survival reported in similar trials with other active protocols, such as FP (8 months), FAMTX (7–10 months) and ECF (9 months) [1, 4, 7].

Concerning the factors that influence response rate and survival, this study confirms the results, reported by Rougier,

Table 3. Factors influencing the survival of patients with metastatic gastric cancer treated with the combination of 5-fluorouracil–leucovorin–cisplatin

Factors	Median survival (months)	1-year survival (%)	Logrank test (*P*)
Age (years)			
≤ 65 (*n* = 13)	10.5	38	0.45*
> 65 (*n* = 15)	11	38	
Performance status			
Grade 0 (*n* = 13)	18	62	0.003
Grade 1–2 (*n* = 15)	5.5	20	
CEA (normal = 10 ng/ml)			
≤ normal (*n* = 15)	10.5	20	0.14*
> normal (*n* = 13)	14	62	
CA19-9 (normal = 60 IU/ml)			
≤ normal (*n* = 17)	11	41	0.95*
> normal (*n* = 11)	10.5	36	
Primary tumour			
Non-resected (*n* = 15)	12	47	0.47*
Prior resection (*n* = 13)	11	35	
Site of primary tumour			
Cardia (*n* = 11)	16	55	0.069*
Non-cardia (*n* = 17)	10.5	29	
Number of metastatic sites			
One site (*n* = 18)	12.5	56	0.24*
> one site (*n* = 10)	3.5	18	
Histological differentiation			
Well/moderate (*n* = 13)	12.5	54	0.61*
Poor (*n* = 12)	9.5	20	
Unknown (*n* = 3)			

* Not statistically significant.

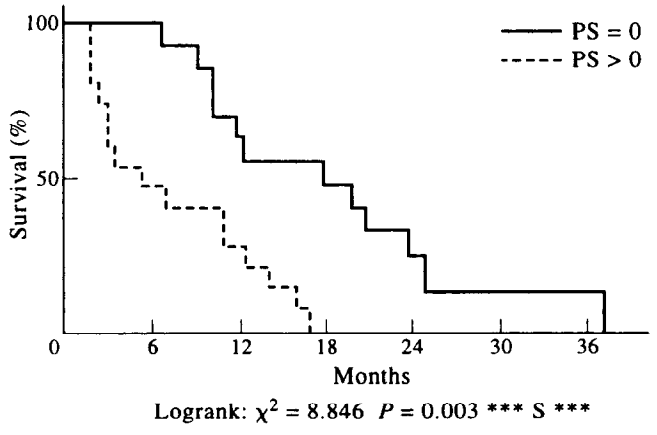

Figure 2. Survival of patients with metastatic gastric cancer treated with chemotherapy combining 5-fluorouracil, leucovorin and cisplatin according to their performance status: World Health Organisation grade 0 (*n* = 13) versus grade 1–2 (*n* =15). Kaplan–Meier method.

Table 4. Maximal toxicity grade (WHO) for each patient treated with the combination of 5-fluorouracil–leucovorin–cisplatin

	Number of patients with toxicity of WHO grade				
	0	1	2	3	4
White blood cells	24	1	2	1	0
Platelets	27	0	0	1	0
Mucositis	20	5	3	0	0
Nausea/vomiting	9	5	11	1	2
Diarrhoea	23	2	1	0	2
Renal function	21	5	1	1	0
Neuropathy	25	1	2	0	0

WHO, World Health Organisation.

that were achieved with the FP protocol, notably the importance of preformance status before treatment. The median survival was 18 months when the performance status was 0, but only 5.5 months when it was grade 1 or 2. Location of the tumour with respect to the cardia junction was not a statistically significant factor, but there was a trend towards better results in terms of both response and survival (*P* was equal to 0.077 and 0.069, respectively). This lack of significance is probably due to a lack of power in our statistical study.

In our experience, the FLP regimen was well tolerated, excepted for 1 patient, who was 75 years old and who died of toxicity. We consider there was a relatively good ratio between efficacy and tolerance for this FLP regimen in the treatment of metastatic gastric carcinoma that is a non-curable disease. The choice of the best regimen for metastatic gastric cancer is unclear. Two randomised trials comparing FAMTX with no

chemotherapy [16, 17] have shown a significant gain in survival, suggesting a real efficacy for chemotherapy. Another phase III study [18] compared the FP regimen to 5-FU alone and showed both a significantly better response rate and a longer time to progression, but no advantage for overall survival. Very recently, preliminary results of a phase III trial conducted by the Gastrointestinal Tract Cooperative Group of the European Organisation for Research and Treatment of Cancer (EORTC) and comparing FAMTX, FP and ELF regimens, were reported [19], with no significant difference detected between these three treatments. Based on these conclusions, we are now conducting a multicentre, randomised phase II trial comparing FP and FLP combinations in term of efficacy, toxicity and quality of life.

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