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Efficacy of Combined 5-Fluorouracil and Cisplatinum in Advanced Gastric Carcinomas. A Phase II Trial With Prognostic Factor Analysis

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Combined chemotherapy has demonstrated a degree of efficacy in gastric carcinoma. As 5-fluorouracil (5FU) and cisplatinum are two of the most active drugs, we have tested the efficacy of combined 5FU and cisplatinum in a prospective phase II trial. Cycles were administered every 4 weeks and consisted of 5FU 1000 mg/m²/day 5 days continuous intravenous (i.v.) infusion and cisplatinum 100 mg/m² on day 2. Cycles were repeated according to tolerance and efficacy. 87 patients entered the study, 57 with metastatic or recurrent tumour (M) and 30 with locally advanced gastric cancer (LAGC). The response rate for the 83 evaluable patients was 43% [95% confidence interval (CI) 30–56%]. There were four complete responses (5%), 32 partial responses (39%), 34 cases of stable disease and 13 cases of progressive disease. Responses were more frequent in patients with a good performance status ($P = 0.02$), with their primary located in the cardia ($P = 0.003$), with a non-linitis plastica tumour form ($P = 0.003$) or a tumour containing less than 50% of independent cells ($P = 0.016$). Median survival was 9 months for the total population. It was better in patients with a good performance status ($P = 0.01$), and those who did not have linitis plastica ($P = 0.005$). Toxicity was acceptable, although grade 3–4 neutropenia was reported in 22% of the cycles, mucositis in 14% and 3 patients died of septic complications. The combination of 5FU and cisplatinum is effective in terms of tumour response in advanced gastric cancer and warrants testing with the other active regimens.

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INTRODUCTION

CHEMOTHERAPY IN advanced gastric carcinomas is palliative, and has a limited effect [1, 2]. Among the agents with known anti-tumour activity, 5 fluorouracil (5FU) has been extensively used [3], and cisplatinum is one of the most active in terms of response rate (RR) [4, 5]. Many combinations have been tested, and a RR of more than 40% has been reported with a marginal effect on survival [1, 2]. The combination of 5FU, doxorubicin and mitomycin C (FAM) was reported to yield a 42% RR [6], but a randomised trial failed to demonstrate its superiority over 5FU alone [7]. The combination of high-dose methotrexate, 5FU and doxorubicin (FAMTX) initially afforded a 63% RR [8], but this was lower (39%) in a randomised trial of the Gastrointestinal Tract Cooperative Group of the European

Organisation for Research and Treatment of Cancer (EORTC) [9]. However, this trial demonstrated that the FAMTX protocol was more efficient than the FAM protocol, both in terms of RR and survival [9]. This protocol requires serum methotrexate determinations to guide leucovorin rescue, and its feasibility is limited by the logistics. It is difficult to foresee widespread use in the community practice setting. The combination of 5FU, doxorubicin and cisplatinum (FAP) has in our experience yielded a 35% RR, but we discontinued its use because of its haematological and digestive toxicity [10]. The combination of etoposide, doxorubicin and cisplatinum (EAP protocol) offered very encouraging results in selected patients, with a 63% RR [11], but this was not confirmed in a randomised trial comparing the EAP and the FAMTX protocol [12]. The EAP protocol is also highly toxic to the haematological system and overall poorly tolerated [12]. These results justified the investigation of other cisplatinum combinations. We have tested the combination of cisplatinum and a 5-day regimen of intravenous infusion 5FU because these two drugs are synergistic [13, 14], and the activity of this combination has been demonstrated in head and neck cancer [15]. After Lacave's experience [16, 17], our preliminary results were encouraging [18], and we decided to include more patients in this phase II study series. This report has not only focused on the efficacy and tolerance of this combination, but also the factors influencing RR and survival.

PATIENTS AND METHODS

Between January 1987 and August 1990, 87 patients with advanced gastric carcinoma were included in a prospective phase II trial. Two different groups were established according to tumour extension. The first group of patients had metastatic or locally recurrent gastric cancer (M group; $n = 57$). The second group had locally advanced gastric cancer (LAGC) and surgical exploration was prospectively envisaged after two to four cycles of chemotherapy, depending on tolerance and efficacy (LAGC group; $n = 30$).

The eligibility criteria for the patients in the M group were histologically-proven gastric carcinoma and measurable metastatic disease or an unresectable and measurable local recurrence WHO grade 0–3 performance status [19], age under 75 years, no cardiac or renal insufficiency, normal haematological tests (white blood cell count (WBC) > 4000/ml, neutrophils > 2000/ml, platelets > 100 000/ml) and no previous chemothreapy.

The eligibility criteria for patients in the LAGC group were unresectable gastric carcinoma determined at a previous surgical exploration ($n = 4$), and/or tumour located in the cardia region, and/or tumour diameter greater than 7 cm, and/or evidence of enlarged lymph nodes (diameter > 2cm) in the coeliac area at CAT scan; all other criteria were identical to those of the M group. The chemotherapy in this group was given with a neoadjuvant intent, and the detailed analysis of its efficacy, and of the secondary surgical treatment performed in this group is reported elsewhere (Rougier *et al.*, pp. 000).

The main patients' characteristics in each group are shown in Table 1. The median age was 57 years (range 22–75). The performance status was WHO grade 0–1 for 64 patients (74%), grade 2 for 16 (18%) and grade 3 for 7 (9%). Prior surgery to remove the primary was performed in 33/57 patients (58%) in the M group and was completely removed in 20/33. In contrast, only 4/30 patients in the LAGC group underwent surgery before their entry in this study, and all four tumours were unresectable. Pathological characteristics for each group are shown in Table 1. 33 of 87 patients had their primary tumour located in the cardia (38%). An infiltrative form, reminiscent of the macroscopic definition of linitis plastica (subgroup of the diffuse type), was found in 21/87 patients (24%). Among the histological types documented, 42/87 were well or moderately differentiated carcinoma (48%), 41/87 were poorly differentiated carcinoma (47%), and 34/87 had more than 50% independent cells (39%), as defined by Wantanabe *et al.* [20] and more recently by Maehara *et al.* [21]. For patients in the M group a measurable local recurrence and involved coeliac lymph nodes were present in 8 cases and distant metastases were present in the other 49 patients. The main metastastic sites are indicated in Table 2. 31 patients had a unique metastatic site and 18 patients had two or more metastatic sites.

All patients underwent a complete work-up prior to chemotherapy to evaluate the main tumour sites. An upper endoscopy was performed when the primary gastric tumour was present, and the tumour length was estimated as precisely as possible, as were the maximum thickness and the percentage of the circumference involved. It was completed by a barium series to measure the two maximum diameters of the tumour and by a CAT scan to measure, where possible, the maximum thickness of the gastric wall at the level of the tumour and its length. Abdominal metastases were evaluated by echography and CAT scan; lung metastases were evaluated by X-ray films and CAT scans. 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 the evolution at the other sites. Response to treatment was evaluated after a minimum of two cycles, unless evidence of tumour progression occurred after the first cycle, in which case, it was considered as a failure. After the first evaluation, patients were monitored every two cycles. WHO response criteria were used [19]: a complete response (CR) was defined as the 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 decrease of more than 50% of the sum of the product of the two maximal perpendicular diameters of the tumour sites if no new lesions were detected; stabilisation (SD) was defined as a decrease in the sum of these products of less than 50% or an increase of less than 25% without any new lesion; progressive disease (PD) was defined as an increase of over 25% or the appearance of new tumour sites.

A complete clinical examination was performed before inclusion and before each cycle as well as biological determinations including a blood cell count; serum ionogram, urea, creatinine, glucose, glutamic oxalacetic (GOT) and glutamic pyruvic (GPT) transaminases, alkaline phosphatase, bilirubin, and prothrombin time. CEA (carcinoembryonic antigen) and CA 19–9 were also measured, and an electrocardiogram and chest X-ray were performed before treatment and repeated according to the patient's symptoms. Toxicity was verified before each cycle and recorded according to WHO criteria [19].

Protocol

The chemotherapy regimen was administered every 4 weeks. It consisted of continuous intrevenous infusion of 5FU (Roche,) for 5 days at a dose of 1 g/m^2 and intravenous cisplatinum on day 2 at a dose of 100 mg/m^2. Blood counts were repeated weekly

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Table 1. Advanced gastric cancer: population of patients treated by the combination of intravenous 5FU + cisplatinum

	Metastatic group (n = 57)	Locally advanced Gastric (n = 30)	Total (n = 87)
Male/female	34/23	18/12	52/35
Median age (years)	56	60	57
Range	(29–74)	(22–75)	(22–75)
PS (OMS)			
0–1	38 (67%)	26 (87%)	64 (74%)
2	13 (23%)	3 (10%)	16 (18%)
3	6 (11%)	1 (3%)	7 (9%)
Tumour characteristics			
Localisations			
Cardia	18 (32%)	15 (50%)	33 (38%)
Other part of stomach	39 (68%)	15 (50%)	54(62%)
Histology			
Differentiation			
Well	3 (5%)	3 (10%)	6 (7%)
Moderate	24 (42%)	12 (40%)	36 (41%)
Poorly	26 (46%)	15 (50%)	41 (47%)
Unknown	4 (7%)		4 (5%)
Krückenberg tumor	5 (9%)	0 —	5 (6%)
Linitis plastica	14 (25%)	7 (23%)	21 (24%)
Independent cells (>50%)	20 (35%)	14 (47%)	34 (39%)
Prior treatment	34 (60%)	4 (13%)	38 (44%)
Surgery	33 (20 curative)	4*	37
Radiotherapy	1†	—	1
Chemotherapy	4†	—	4

* Explorative laparotomy only. †Adjuvant treatment. 5FU, 5-fluorouracil; PS, performance status.

Table 2. Advanced gastric cancer: tumour sites in patients with metastatic disease

	No. of patients
Solitary metastases	31
Liver	22
Peritoneum	6
Lymph nodes (distant)	2
Bones	1
Multiple metastases	18
Liver	9
Peritoneum	8
Lymph nodes (distant)	18
Bones	2
Lung	5
Ovary	5
Other	7

and doses were adapted to the toxicity: a reduction of 25% was planned in case of toxicity (WBC or platelets WHO grade >3) [19] and/or digestive toxicity (WHO grade 4) during the interval between two cycles. Cycles were delayed for 1 week if patients had less than 4000 WBC/ml and/or neutrophils were less than 2000/ml and/or less than 100 000 platelets/ml on day 1. Cisplatinum was cancelled in the event of neurological, otological and/or renal toxicity (grade ≥2).

Results are given with their 95% confidence interval (CI). Comparisons of response rates have been performed using the χ^2 method and the Mantel–Haenszel test [22]. Survival was calculated with the Kaplan–Meier method [23] and a comparison of survival has been performed using the log-rank test [24]. Prognostic factors for survival have been tested using the log-rank test adjusted on the main variables [24].

RESULTS

83 patients were evaluable for response with a median follow-up of 24 months. 1 patient in the M group was lost to follow-up after the first cycle and 3 in the LAGC group were not evaluable. One refused to continue and was lost to follow-up after one cycle, 1 had 5FU-related cardiac ischemia and was excluded

from the response analysis but not from the tolerance and survival analysis, and the last patient died after the first cycle of severe aplasia and septic complications.

The total number of cycles administered was 345 and the median number of cycles per patient was four in the overall series (range 1–11): four for the M group (range 1–11) and three for the LAGC group (range 1–6). The median dose of 5FU and cisplatinum received by the patients during the first two cycles was, respectively, 99 and 99.5% of planned doses with no difference, whatever the patient characteristics.

Secondary surgery, planned for patients with LAGC, was performed in 28/30 patients with complete resection of all macroscopic tumour in 23 patients (77%). However, most of the patients had an advanced gastric tumour at pathological examination, and the UICC stage of the cardia tumours were stage I–II in 4 cases, IIIA in 4, IIIB in 4 and IV in 2 cases. Secondary surgical excision of metastatic or recurrent disease was indicated in M patients after a good response to chemotherapy in 11 cases (19%) but was only macroscopically complete in 5 cases (9%).

Response to chemotherapy: 83 patients were evaluable after a minimum of two cycles and we observed 36 objective responses, 43% (95%; CI 30–56%). There were four CR (5%), 32 PR (39%), 34 SD (41%) and 13 PD (16%) (Table 3).

The main patients' characteristics have been tested by univariate analysis to estimate their influence on the RR (Table 4). The RR was higher for patients with a good performance status (performance status, PS 0–1/2–3) ($P = 0.02$), for tumours located in the cardia region ($P = 0.003$); for patients who did not have linitis plastica ($P = 0.003$), and for patients with adenocarcinomas containing less than 50% of independent cells ($P = 0.016$). However, a close correlation was found between the presence of independent cells and that of linitis plastica ($P = 0.0001$). The RR was higher, although not significantly, for patients in the LAGC group than for M ($P = 0.12$). The RR was lower for patients with two or more tumour sites ($P = 0.05$).

Survival was evaluable for 85 patients and 2 patients were lost to follow-up after the first cycle of chemotherapy and excluded. The overall survival of the entire group is reported in Figure 1; the median survival was 9 months.

Many factors influenced survival (Table 5). It was significantly better for the patients with a good performance status (grade 0–1 versus 2–3; $P = 0.01$; Fig 2), but this advantage ceased to be significant after adjustment for tumour extension (LAGC/M). Surivial was better for the patients with LAGC than for those with metastatic or recurrent disease ($P < 0.0001$; Figure 3), but the two groups were not comparable as a surgical excision was systematically planned for patients with LAGC and was complete in 60% of cases. Survival was also better for the patients without linitis plastica ($P = 0.005$), even after adjustment for tumour extension (Figure 4). In contrast, no difference was noted in survival according to the presence or the absence of more than 50% of independent cells in the tumour. Age and sex had no influence on survival.

Toxicity was evaluable for 342 cycles administered to 85 patients (2 lost to follow-up). The toxicity was mainly haematological and digestive and is reported in Table 6. Severe toxicity (WHO grade 3–4) occurred in 22% of the cycles for neutrophils, 21% of patients experienced vomiting and 14% mucositis. 11 patients experienced septic complications and 3 died of gram-negative septicaemia, 1 in the LAGC group and the other 2 in the M group. Neurological and otological grade 1 or 2 toxicity

Table 3. Tumour responses observed in patients with gastric cancer treated with combination intravenous 5FU and cisplatinum

	M		LAGC		Overall	
No. of evaluable patients	56		27		83	
Complete responses	3	38%	1	56%	4	43%
Partial responses	18		14		32	
Minor responses	7	39%	4	44%	11	41%
Stable disease	15		8		23	
Progressive disease	13	23%	–		13	16%

M, metastatic and local recurrence; LAGC, locally advanced gastric cancer without distant metastases.

Table 4. Factors influencing the response rate in patients with advanced gastric cancer treated with combination intravenous 5FU and cisplatinum

Factors	Response rate		P
Male/female	44/42		NS
Performance status WHO grade 0–1/2–3	51/23		0.02
for M and unresectable T	46/21		0.06
LAGC/M	56/38		0.12
Linitis/non-linitis	15/52		0.003
for M and unresectable T	14/45		0.02
Independent C./others	25/54		0.016
for M and unresectable T	13/49		0.005
Cardia/others	65/31		0.003
for M and unresectable T	50/29		0.11
Tumour extension			
Stomach ±LR only	20/35	57%	
One metastatic site	12/30	40%	0.05
Two or more metastatic sites	4/18	22%	

LAGC, locally advanced gastric carcinoma; M, metastatic or recurrent gastric carcinoma; T, tumour.

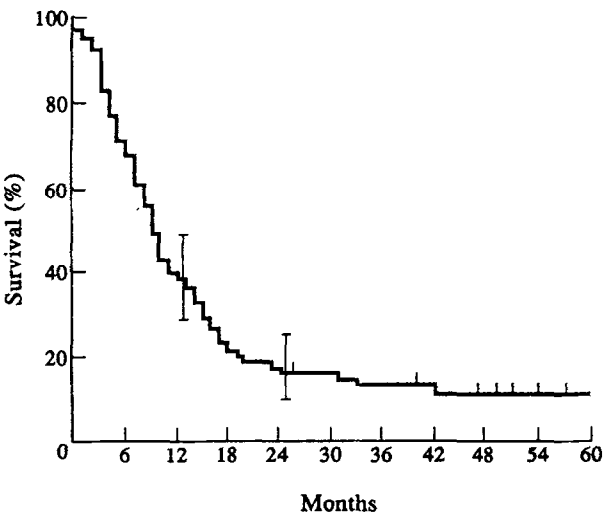

Figure 1. Overall survival of patients with gastric cancer treated with chemotherapy combining 5FU and cisplatinum. Kaplan–Meier method with 95% confidence interval; $n = 87$.

Table 5. Factors influencing the survival in patients with advanced gastric cancer treated with the combination 5FU and cisplatinum (n = 87)

Factors	Median survival (months)	One-year survival (%)	Two-year survival (%)	Log-rank test P
Age (years)				
≥60 (*n* = 47)	9	36	10	0.13
<60 (*n* = 40)	10	42	24	
Sex				
Female (*n* = 35)	7	31	10	0.1
Male (*n* = 52)	11	44	20	
Performance status				
0–1 (*n* = 64)	10	44	22	0.01
2–3 (*n* = 23)	6	26	0	
Tumour extension				
M (*n* = 57)	8	25	4	<0.0001
LAGC (*n* = 30)	16	67	42	
Site of the primary				
Cardia (*n* = 33)	11	48	18	0.3
Other part of the stomach (*n* = 45)	8	33	15	
Linitis				
Present (*n* = 21)	6	24	0	0.005
Absent (*n* = 66)	10	44	22	
Independent cells				
<50% (*n* = 53)	10	40	17	0.82
≥50% (*n* = 34)	8	38	15	

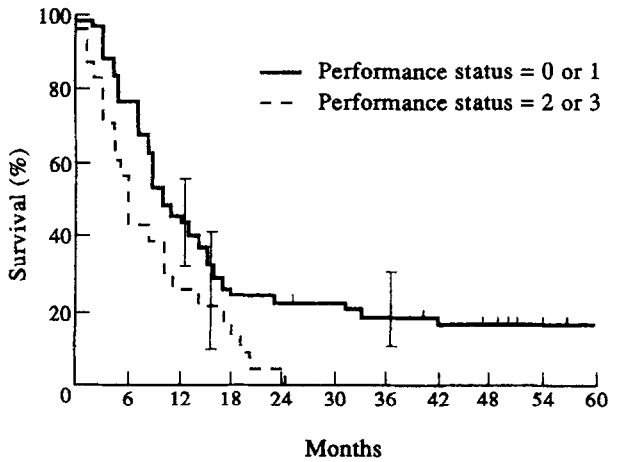

Figure 2. Survival of patients with gastric cancer treated with chemotherapy combining 5FU and cisplatinum according to their performance status: WHO grade 0–1 (*n* = 64) versus grade 2–3 (*n* = 23). Kaplan–Meier method with 95% confidence interval.

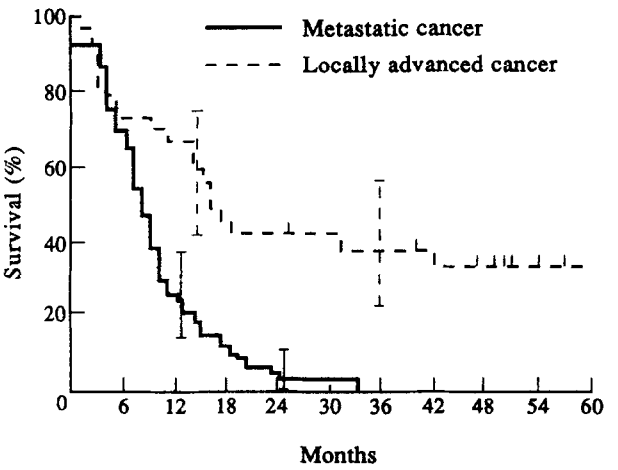

Figure 3. Survival of patients with gastric cancer treated with chemotherapy combining 5FU and cisplatinum, according to the tumour extension: metastatic (*n* = 57) versus locally advanced (*n* = 30). Kaplan–Meier method with 95% confidence interval.

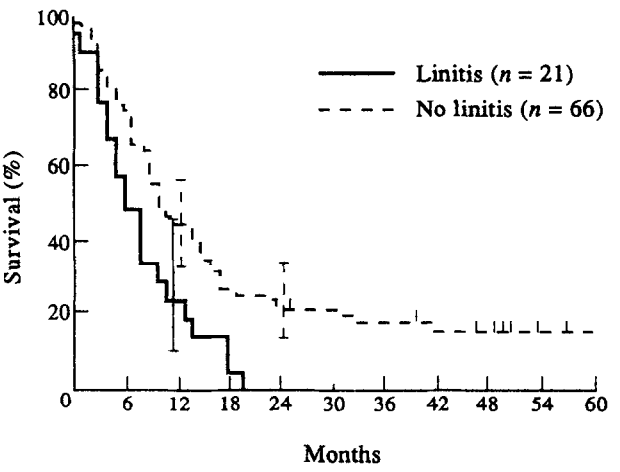

Figure 4. Survival of patients with gastric cancer treated with chemotherapy combining 5FU and cisplatinum, according to their histological type: linitis plastica (*n* = 21) versus non-limits (*n* = 66). Kaplan–Meier method with 95% confidence interval.

Table 6. Toxicity of combination 5FU + cisplatinum in patients with advanced gastric cancer. A total number of 342 cycles were administered in 85 evaluable patients (mean number per patient = four)

	WHO grade 0	1	2	3	4	3+4(%)
White blood cells	179	82	51	25	5	9%
Neutrophils	109	80	77	51	25	22%
Platelets	282	15	19	13	13	8%
Nausea/vomiting	56	73	140	70	3	21%
Mucositis	145	85	64	40	8	14%
Diarrhoea	287	28	21	5	1	2%

was observed in 11 and 4 cases, respectively, after a median of 7 cycles (range 2–9). There was no renal toxicity.

DISCUSSION

This phase II study confirms the efficacy of combined 5FU and cisplatinum (5FU–P) in advanced gastric cancer. The 43% response rate is not different from the RR reported by Lacave [17]. This RR is also in the same range as that of other more popular protocols, such as FAMTX [9] and EAP [11]. The advantage of the 5FU–P association lies in the simplicity of this protocol whose acceptable tolerance is well-known to all oncologists. Recently, a Korean study demonstrated that this combination yields a higher response rate than 5FU alone or the FAM combination, although the increase in survival was not statistically significant [25].

This study confirms that many factors influence response rate and survival. Lavin [26] demonstrated the importance of PS, and our study confirms that the RR was 2-fold higher for patients with a PS between 0 and 1 compared to patients with a PS of 2 to 3. This is a major prognostic factor which may bias the results and the interpretation of many trials, and may partially account for the discrepancies in the results reported in the literature. The histological pattern was another major factor influencing the RR in this trial. Patients with linitis plastica were poor responders, as were patients with carcinomas containing more than 50% of independent cells [20,21]. However, these two factors were strongly linked since all the patients with linitis except for one had independent cells in their tumour ($P < 0.0001$). The difference in RR according to tumour extension (LAGC versus M) was not significant, and was probably related to the better performance status in the LAGC group. It is remarkable that, in the German studies in which EAP was employed, the RR also seemed to be higher in the LAGC group than in M patients (100 versus 56%) [11]. This could be related to difficulties in evaluating the response in LAGC and to the better PS of these patients. The better RR observed in patients with a tumour located in the cardia compared to a tumour of the body or the gastric antrum was not related to a selection of patients in better condition, with less tumour sites, nor because more patients had locally advanced disease, but most probably to the histological characteristics, as there were less patients with linitis plastica in this group.

Survival in this trial was closely associated with tumour extension and patients with LAGC survived longer than patients with metastasis. This has already been reported in other studies [11, 26, 27], and explained by both the better performance status of the patients in the LAGC group and the frequent possibility of surgical resection after chemotherapy, which was macroscopically complete in 77% and curative in 60% of the LAGC group, preventing any valid comparison between the two groups. Survival was also related to the performance status, but this ceased to be true after adjustment for tumour extension as there were more patients in a poor general condition in the M group. Moreover, the results achieved with this regimen in patients in a poor condition (PS grade 2 or 3) were too unsatisfactory (median survival of 6 months) for it to be recommended in these patients. In this trail, patients with linitis plastica had a shorter survival than others, even after adjustment for tumour extension. This finding may influence the results of many trials, as this characteristic is not usually taken into account. It should be considered in future trials.

In conclusion, this study shows that the combination of 5FU and cisplatinum has shown some efficacy in terms of RR for the treatment of advanced gastric cancer. Its efficacy on survival has to be compared to that of other chemotherapy regimens, particularly the FAMTX combination and the ELF combination (5FU, folinic acid, etoposide) [28]. This is currently being tested in an ongoing phase III trial conducted by the EORTC Gastro-Intestinal Tract Cancer Cooperative Group.

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Neoadjuvant Chemotherapy in Locally Advanced Gastric Carcinoma—a Phase II Trial With Combined Continuous Intravenous 5-Fluorouracil and Bolus Cisplatinum

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Locally advanced gastric adenocarcinomas (LAGC) have a poor prognosis, particularly when tumours are bulky, located in the cardia or in the event of locoregional lymph node involvement. Patients bearing these tumours were entered in a phase II trial of neoadjuvant chemotherapy, combining continuous intravenous 5-fluorouracil (5FU) (1000 mg/m^2 for 5 days) and cisplatinum (CDDP) (100 mg/m^2 on day 2) repeated every 4 weeks, for one to six cycles according to response and tolerance. 30 patients have been entered, 26 after clinical evaluation (CAT scan and upper gastrointestinal endoscopy) and 4 with unresectable tumours at prior laparotomy. Median age was 60 years, 15/30 patients had a tumour of the cardia, 15/30 had enlarged lymph nodes and 7/30 had linitis plastica (diffuse type). A mean number of three cycles was administered (range 1–6). 27 of the 30 patients were evaluable for response. One patient achieved a complee response (CR) and 14 a partial response (56%; 95% confidence interval 38–74%). No patient had tumour progression, and only 1/6 with linitis plastica responded. 28 patients underwent surgery, and 23 had a macroscopically complete resection (77% of the 30 entered patients); RO resections were performed in 60% of the cases, mainly after an objective response (13/15 versus 4/12 in non-responders). No pathological CR were seen. Grade 4 neutropenia was observed in eight cycles (5 patients), with five septic complications and one death due to toxicity. Four postoperative complications were observed: 2 cases of severe pneumonia and 2 subphrenic abscesses. One postoperative death, due to intravascular disseminated coagulation, was observed at day 30. Median survival was 16 months and the 1-, 2- and 3-year survival was 67, 42 and 38%, respectively. Patients with linitis plastica had a significantly shorter survival ($P < 0.002$). We conclude that neodjuvant chemotherapy is feasible in LAGC, although randomised trials are warranted to demonstrate its efficacy on survival and resection rates.
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INTRODUCTION

ALTHOUGH LOCOREGIONAL gastric carcinoma is a potentially curable disease, less than 20% of patients will be cured by surgery alone [1, 2]. Even after a complete resection, only approximately 50% of the patients will be cured by surgery alone or followed by adjuvant chemotherapy [3–4].

In patients with locally advanced gastric cancer (LAGC) it is well established that resectability is one of the main prognostic factors, with longer survival if the tumour is amenable to surgery [5–7]. Unfortunately, in about half of the cases, the local extension prevents curative resection [8, 9], and when surgical resection is feasible, most patients (80%) will die from either