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

Ph. Rougier, M. Mahjoubi, Ph. Lasser, M. Ducreux, J. Oliveira, M. Ychou, J.P. Pignon, D. Elias, S. Bellefqih, C. Bognel, A. Lusinchi, E. Cvitkovic and J.-P. Droz

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

distant metastases (30–50%) or locoregional recurrence (40–80%) [1, 7, 10].

This failure rate is particularly high when tumours are located in the cardia [11], when there is locoregional lymph node involvement [2], when tumours are larger than 7 cm [12], and for infiltrative types such as linitis plastica [13–15]. These cases, which have a cure rate of less than 10%, correspond to clinical stages III and IV of the UICC classification [8]. Based on these data, the promising results of chemotherapy in advanced gastric cancer [16], and previous reports on the potential efficacy of neoadjuvant chemotherapy [17, 18], we investigated the feasibility and efficacy of pre-operative chemotherapy in locally advanced gastric cancers in order to decrease the tumour mass, to improve the resectability rate and to evaluate the toxicity of such an approach and its impact on overall survival.

The combination of 5-fluorouracil (5FU) and cisplatinum is efficacious, and well tolerated in patients with metastatic gastric carcinoma [19–21]. We tested the same regimen in LAGC prior to surgical excision (neoadjuvant chemotherapy) and conducted a prospective phase II trial to identify factors influencing the response rate and survival.

PATIENTS AND METHODS

From December 1986 to December 1989, 30 consecutive patients with LAGC were entered in this phase II trial. Eligibility criteria were histologically-proven adenocarcinoma of the stomach that was either unresectable at prior laparotomy, or locally advanced, as evidence by involvement of abdominal lymph nodes at computed tomography (CT) scan (larger than 2 cm), or when the tumour size was greater than 7 cm, or when tumours were located in the cardia. Patients were to have no evidence of distant metastases, performance status (PS) < 3 (WHO grade), age < 76 years, an adequate blood count (white blood cell count > 4000/ml; platelets > 100 000/ml), no renal or hepatic insufficiency (creatinine < 135μmol/l; bilirubin < 35 μmol/l), no prior chemotherapy or radiation therapy and no second malignancy.

All patients had to have measurable disease on CT scan and at upper digestive endoscopy, at which the tumour size, its thickness and the percentage of the gastric circumference involved had to be carefully evaluated. All patients gave their informed consent.

Pretreatment evaluation included a complete physical examination, an upper digestive endoscopy and an abdominal CT scan. A thoracic CT scan was also performed for tumours of the cardia. Usual blood chemistry tests, serum lactic dehydrogenase (LDH), carcino-embryonic antigen (CEA) and carbohydrate antigen (CA 19–9) were performed prior to each cycle. A complete blood and platelet count was performed every week to assess haematological toxicity.

Pathological specimens were classified as well, moderately and poorly differentiated carcinoma; however, we have also individualised the cases with linitis plastica [22], and those containing more than 50% of independent cells (or signet-ring cells) [23, 24].

The chemotherapy regimen was 1 g/m^2/day 5FU in continuous intravenous (i.v.) infusion for 5 consecutive days, and 100 mg/m^2/day CDDP on day 2 in a 1-h infusion with hyperhydration. Cycles were repeated every 4 weeks according to haematological, digestive and renal tolerance. Toxicity was assessed using WHO criteria. The evaluation of response was performed 4 weeks after the second cycle according to WHO criteria. However, in the event of tumour progression after the first cycle, patients were taken off the study and considered as failures. These patients were submitted to surgery as soon as possible provided they were free of distant metastatic disease. The duration of treatment was dependent on response and toxicity. For patients who achieved disease stabilisation, or an objective response, an additional cycle was planned. Surgery was performed 4 weeks after the third cycle (12 weeks after the initiation of preoperative chemotherapy).

Surgery consisted, when it was possible, of a complete excision of tumour and an extensive lymphadenectomy (R2 type). Postoperative adjuvant treatments were prescribed according to the prior response to chemotherapy, to the type of surgery and to pathological extension. For responders (Figure 1), when no tumour was documented pathologically or when tumour only invaded the submucosa with no regional lymph node involvement, no further treatment was performed. When lymph node involvement and/or extension through the serosa and/or invasion of blood and lymphatic channels existed, three more cycles of systemic chemotherapy were given (total number of cycles was six); when only incomplete resection was possible, postoperative chemotherapy was indicated combined with radiation therapy (45–55 Gy, 22–25 fractions) delivered at the site of the residual tumour. For non-responders and when surgery was complete, no further treatment was carried out. If only palliative surgery was possible because of incomplete resection, unresectability or evidence of distant metastases, patients were submitted to radiation therapy and/or to another chemotherapy regimen.

Statistical methods

Tumour response and toxicity were evaluated using WHO criteria [25]. The disease-free interval was calculated from the day of surgery to the day of relapse; the time to disease progression was calculated from the first day of chemotherapy to the day of cancer progression; overall survival was calculated from the start of chemotherapy [26]. The following eight items were used for the univariate analysis: age, sex, PS, location, tumour size, histological type, extension and the presence or

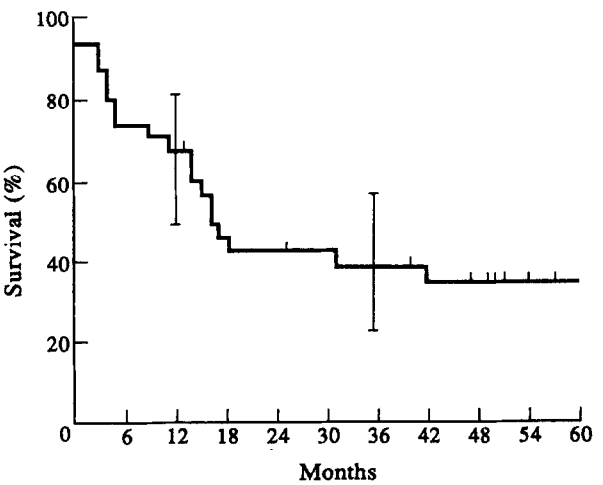

Figure 1. Survival curve (Kaplan–Meier) of patients (n = 30) receiving pre-operative chemotherapy (5-FU + cisplatinum) for locally advanced gastric cancer.

Correspondence to Ph. Rougier.
The authors are at the Gastro-Intestinal Unit, Institut Gustave Roussy, 94805 Villejuif Cedex, France.
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absence of linitis plastica. A comparison of response rates was performed using the χ^2 method and the Mantel–Haenszel test [27]. Survival comparisons were determined by the log-rank test [28].

RESULTS

Patients' characteristics are summarised in Table 1. It is of interest to note that 15 of the 30 patients had poorly differentiated adenocarcinoma with more than 50% of independent cells (signet-ring cells) and 7 had linitis plastica.

Rate of response to chemotherapy

The median number of cycles administered per patient was three (range one to six). However, of the 30 patients entered, 3 were not evaluable for response: 1 patient was lost to follow-up immediately after the first cycle and died 1 month later of an unknown cause; 1 patient experienced severe neutropenia, septicaemia, mucositis, diarrhoea and died on the 15th day of her first cycle. The third patient had her chemotherapy interrupted on the first day of treatment because of a chest pain evocative of a coronary spasm. She underwent surgery 2 weeks after this cardiac event without complications.

The rate of response to chemotherapy was evaluable in 27 patients. There was one complete response (CR) at upper digestive endoscopy with negative forceps biopsies and normal CT scan, and 14 partial responses (PR). The overall response rate (RR) was 56% [95% confidence interval (CI) 38–74%]. 4 patients had a minor response (MR), 8 patients were stabilised (SD) and there were no cases of tumour progression or degradation in PS. However, if we consider all but 1 patient, namely the patient lost to follow-up after the first cycle, the RR was 52%.

Table 1. Patients' characteristics

	No. of patients
Total number of patients	30
Median age (range) (years)	60 (22–75)
Male/female	18/12
Performance status (WHO)	
0–1	26
2	3
3	1
Unresectable disease surgically proven	4
Locally advanced disease clinically suspected	26
Location of primary	
Cardia	15
Other	15
Median tumour size (range)	80 mm (60–140)
Median percentage of circumference involvement (range)	73% (40–100)
Enlarged lymph nodes at CAT scan	15
Histology	
Well or moderately differentiated	15
Poorly differentiated with independent cells	15
Linitis plastica	7/30

CAT, computed axial tomography.

Table 2. Factors influencing the response rate to pre-operative chemotherapy in locally advanced gastric carcinomas in 27 evaluable patients

Variable	Number of patients (%)	Objective response rate (%)	*P*
Location of the tumour			
Cardia	13 (48)	79	0.01
Other	14 (52)	31	
Independent cells (more than 50%)			
Yes	13 (48)	43	0.17
No	14 (52)	69	
Linitis			
Yes	6 (22)	17	0.09
No	21 (78)	67	
Performance status (WHO)			
≤ 1	24 (89)	58	0.41
< 1	3 (11)	33	
Sex			
Male	17 (63)	56	0.65
Female	10 (37)	50	

The RR was analysed according to the patient characteristics: patients who had a tumour in the cardia, and patients with no or less than 50% of independent cells had a better RR than the others. In contrast, only one response was observed among the 6 evaluable patients with linitis plastica (Table 2).

Surgery

2 patients did not undergo surgery (1 early toxicity-related death and 1 lost to follow-up), thus 28 patients had an intervention, and 23/28 (82%) patients had a macroscopically complete resection considered curative (R0 resection) (six partial gastrectomy, two total gastrectomy, 10 extended total gastrectomy and five esogastrectomy). One patient had a cephalic duodenopancreatectomy associated with a colectomy, but the resection was not complete due to peritoneal carcinomatosis. Another patient with peritoneal carcinomatosis had a bypass procedure, and 3 patients had only an explorative laparotomy because of peritoneal carcinomatosis. Thus, 77% of the 30 patients entered in the study had a R0-R1 resection, 3% had a macroscopically incomplete resection (R2 resection), 13% were unresectable and 7% were not operated on.

Of the 23 patients who had a macroscopically complete resection, 5 were found to have microscopically positive margins (R1 resection). After completion of the treatment programme with chemotherapy and surgery, 18 of the 28 patients who had undergone surgery had no evidence of disease (NED), i.e. 60% of the patients entered in this study (18/30).

Of the 4 patients whose tumour was not resectable at a prior laparotomy, 2 achieved an objective response to chemotherapy followed by curative resection of tumour. The other 2 patients,

who had linitis plastica with local peritoneal extension, were unresponsive to chemotherapy, and their tumours were unresectable at second laparotomy.

Resectability was higher in patients with an objective response to chemotherapy and this is reported in Table 3. Of the 15 responders (CR + PR), residual tumour was completely resected in 13; surgical resection was incomplete in the other 2 patients because of postive margins. Of the 12 patients who failed to achieve an objective response to chemotherapy, 8 underwent surgery with a curative intent, but complete resection was only possible in 4 of them; 3 of the remaining patients had positive margins and 1 had local peritoneal carcinomatosis. The patient who had cardiac toxicity had a curative resection. Thus, 87% (CI 60–100%) of the patients with an objective response had a complete resection (R0) and had NED after surgery compared to 33% of the non-responders (CI 17–50%) ($\chi = 8.34$; $P < 0.01$).

Pathological findings

No pathological complete response was found. In the patient who had a clinical CR, no macroscopic evidence of tumour was found at surgery. A partial gastrectomy was performed, and only small foci of active tumour located in the mucosa with major areas of necrosis and fibrosis without metastatic lymph nodes were disclosed at histopathological exmaination. An extended lymph node dissection (type R2) was performed in all patients with resectable disease; the number of lymph nodes analysed was between 9 and 52 (median 19), and the number of metastatic lymph nodes was between 1 and 32 (median 5)

The TNM stage of the 23 patients resected was T3-T4 tumour in 19 (82%), N1 in 8 (35%) and N2 in 9 patients (39%). The UICC stage for the 28 patients who underwent surgery was not different according to the location of the primary. Cardia tumours comprised 4 stage I–II; 4 stage IIIA; 4 stage IIIB and 2 stage IV; non-cardia tumours comprised 3 stage I–II; 4 stage IIIA; 3 stage IIIB and 4 stage IV. Thus, 75% of the patients had advanced disease (stage (III and IV) even after chemotherapy.

Toxicity of chemotherapy

Eighty-seven cycles were evaluable for toxicity in 29 patients. Haematological toxicity consisted of grade 3 neutropenia in 13 cycles (8 patients) and grade 4 in eight cycles (5 patients). There were five episodes of febrile aplasia with documented sepsis; 1 of these patients experienced an irreversible septic shock which occurred at the time of the haematological nadir with grade 4 mucositis and diarrhoea and died 15 days after the first cycle of chemotherapy. Alopecia grade 3 was noted in 2 patients. Other toxicities were mild and are reported in Table 4.

Table 3. Results of surgical treatment after neoadjuvant chemotherapy according to tumour response in patients with locally advanced gatric carcinoma

Type of response	Operated patients	Unresectable tumours	Type of resection R2	R1 + R0	R0	6 months survival
OR ($n = 15$)	15	0	0	15	13	93%
NR ($n = 12$)	12	4	1	7	04	42%
NE ($n = 3$)	1	0	0	1	1	33%
Total ($n = 30$)	28 (93%)	4 (13%)	1 (3%)	23 (77%)	18 (60%)	

OR, objective response; NR, non-responders; NE, non-evaluable. R0, microscopically complete resection; R1, macroscopically complete resection; R2, macroscopically uncomplete resection.

Table 4. Toxicity of chemotherapy observed in 29 patients (total number of cycles = 87)

	Number of cycles with toxicity grade (WHO) 1	2	3	4
Leucopenia	22	12	4	4
Neutropenia	19	20	13	8
Thrombocytopenia	5	3	2	4
Nausea, emesis	11	45	21	0
Mucositis	12	12	9	4
Diarrhoea	10	3	2	0
Infection	0	1	4	1*
Renal toxicity	1	0	0	0
Cardiac toxicity	1	0	0	0
Neurologial toxicity	2	0	0	0

*Irreversible septic shock.

Postoperative complications

One patient died 1 month after a partial gastrectomy due to a haemorrhagic complications related to intra-vascular disseminated coagulation (IDC) with anastomotic leakage. 2 patients experienced severe postoperative pneumonia which required intensive antibiotherapy. Finally, 2 patients developed a subphrenic abscess that was surgically drained and subsequently resolved.

Follow-up

With a median follow-up of 48 months (range 1–63), 14 (61%) of the 23 patients with NED relapsed after chemotherapy and/or surgery.

According to the tumour response, the patient who achieved the clinical CR did not receive any postoperative treatment and is still alive and disease free at 72 months. 12 out of the 14 PR had NED after surgery; 3 did not receive further treatment. The remaining 9 patients received two to four additional cycles of chemotherapy, 1 patient had radiotherapy and 2 had radiotherapy plus chemotherapy. Three of the 12 PR are still alive and disease-free 52, 55 and 60 months after the beginning of preoperative chemotherapy. The two PR, who underwent palliative resection (positive margin), received both radiation therapy and chemotherapy; their disease progressed 3 and 12 months after the completion of therapy, and they survived 17 and 48+ months.

The 4 patients stabilised after chemotherapy and who had NED after surgery did not receive any adjuvant treatment. 3 of them relapsed after surgery, and 1 patient is disease-free at 51 months.

According to the quality of resection, of the 23 patients who had a macroscopically complete resection, 13 failed during the follow-up period: 3 had a local recurrence, 8 distant metastases and 2 both local and distant metastases.

Finally, 6 patients with a R0 resection are disease-free more than 3 years after surgery (2 did not responsed to CT and 4 were responders). Another patient, who had only a palliative resection, received complementary external radiotherapy and is

Table 5. Univariate analysis of the prognostic factors influencing the survial

Variable	Number of patients	Two-year survival	*P* (log-rank test)
Age			
≥ 60 years	16	54%	0.07
< 60 years	14	27%	
Sex			
Male	18	48%	0.40
Female	12	31%	
Location			
Cardia	15	41%	0.66
Other	15	55%	
Linitis			
Yes	7	0%	0.002
No	23	55%	
Independent cells (more than 50%)			
Yes	13	33%	0.57
No	17	51%	
Performance status			
0–1	26	48%	0.0001
> 1	4	0%	

still alive and disease-free at 52 months. Thus, 7 (23%) of the initial 30 patients had NED at 3 years.

The median survival for the overall population is 16 months and the overall survival is 67, 42 and 38% at 1, 2 and 3 years, respectively (Figure 1). Survival was better after R0 resection than after R1–2 resection (median 30 months and 16 months, respectively). There was no difference in survival between patients with tumour of the cardia and others ($P = 0.8$).

Factors influencing survival are shown in Table 5. The two significant predictive factors of survival were the performance status ($P = 0.0001$) (Figure 2) and the histological type: the

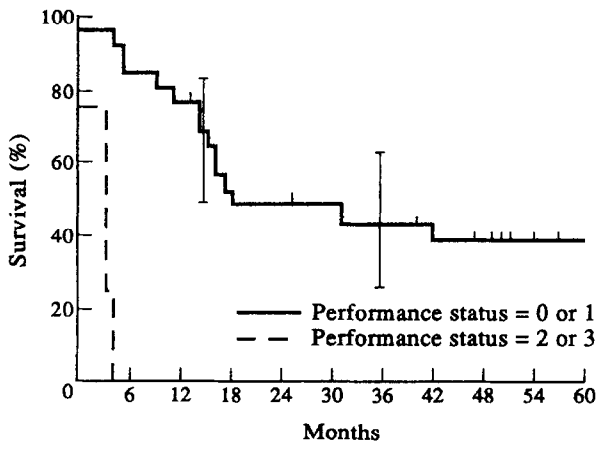

Figure 2. Survival curves (Kaplan–Meier) of patients receiving pre-operative chemotherapy (5-FU + cisplatinum) for locally advanced gastric cancer according to their performance status; PS 0–1 versus PS 2 ($P = 0.0001$).

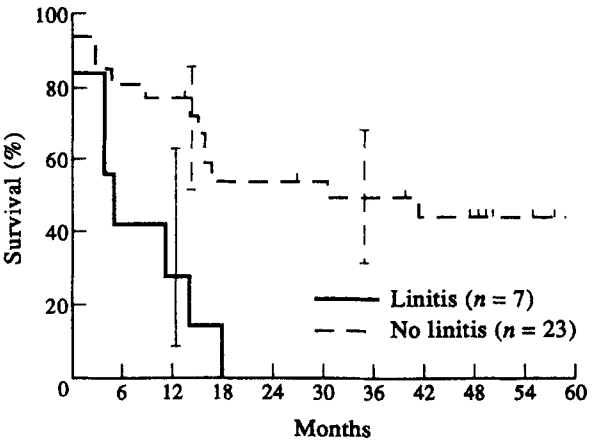

Figure 3. Survival curves (Kaplan–Meier) of patients receiving pre-operative chemotherapy (5-FU + cisplatinum) for locally advanced gastric cancer according to their histological pattern; linitis plastica versus non-linitis ($P = 0.002$).

survival of patients without linitis plastica was significantly longer ($P = 0.002$) than that of those with linitis (Figure 3).

DISCUSSION

Pre-operative (or neoadjuvant) chemotherapy has two main aims in gastric cancer, namely to decrease the tumour mass or its extension and thereby facilitate surgical resection in locally advanced disease, and to prolong the survival of patients. These two aims will be discussed separately.

Resectability

In a retrospective study, Baba and colleagues [29] reported that, among 275 patients with gastric carcinoma, only 142 (51%) had extensive curative surgery. More recently, Rohde and colleagues [8] reported that complete resection was only possible in 740 (54%) of 1360 patients with gastric cancer. Furthermore, they reported that in 186/845 cases (22%), classified as complete resection by the surgeons, the histopathological examination of specimens revealed tumour at the resection margins (R1 resection). Recently, Sue-Ling and colleagues [9] reported a 53% curative resection rate for patients treated between 1985 and 1989, which was higher than that of previous periods. When compared to these data, the results of the present study partially support the ability of chemotherapy to increase resectability of locally advanced gastric carcinoma.

In this series, which included patients with a large tumour, enlarged lymph nodes at CT scan in 50% of the cases, and with tumour located in the cardia in half of them, 60% of patients had a curative resection (R0 resection) after neoadjuvant chemotherapy with cisplatin and 5-FU; 17% had microscopically positive margins (R1 resection) and only 13% of the lesions were totally unresectable. Thus, the resection rate was 77% in our experience, which is comparable to that reported by Ajani and colleagues, who conducted two phase II trials on neoadjuvant chemotherapy with two different platinum combinations [30, 31]. Interestingly, we found that the curative resection rate was higher for patients who had an objective response to chemotherapy (86%; CI 60–100%).

Of our patients, who were selected according to criteria of advanced disease based on previous studies on prognostic factors studies [2, 11, 12], we undoubtedly treated several patients with tumours amenable to surgery without any chemotherapy.

Consequently, even if the likelihood of a benefit in terms of resectability seems probable, it had to be confirmed in a randomised trial. Recently, such a trial was conducted in stage IV patients and partially reported; it suggested a higher rate of curative resection after neodjuvant chemotherapy [32], but it failed, probably by a lack of power, to demonstrate an increase in survial.

In this series, only 4 of the 30 patients eligible for the study had surgically staged unresectable tumour prior to the chemotherapy, and 2 of them underwent successful resection after chemotherapy which seems clearly beneficial for these cases as in other reports. Few clinical trials have investigated surgically proven unresectable gastric cancer. Plukker and colleagues [18] was one of the first authors to report the positive effect of pre-operative chemotherapy in these patients. He used a combination of 5FU and methotrexate which rendered tumours resectable in 7/17 patients after chemotherapy.

The largest trial with such a design was reported by Wilke and colleagues [17] who treated 33 patients with surgically proven unresectable tumours with aggressive chemotherapy combining etoposide, doxorbicin and cisplatin (EAP). Their results were impressive with 70% OR and 21% CR; 19 of the 23 patients who achieved an OR underwent second-look laparotomy for removal of the primary tumour, and 15 patients were able to have a complete resection (of whom 5 had a pathologically-proven CR). The resectability rate for surgery with a curative intent, in this group of patients with initially inoperable gastric tumours, was 45%. Thus, this trial clearly demonstrated the role of pre-operative chemotherapy on resectability. These results have been partially confirmed by Lerner and colleagues [33], who applied the same protocol in 28 patients with advanced gastric carcinoma, and reported a 43% response rate (12/28) but only 3 CR. He, however, reported a benefit in terms of resectability, as 4 of the 11 patients with unresectable tumour had NED after chemotherapy and surgery. However, the EAP regimen cannot be recommended as neoadjuvant chemotherapy since it has not demonstrated its superiority over other protocols, and its haematological toxicity and lethality are severe [33]. In a randomised trail comparing FAMTX (5FU, doxorubicin, methotrexate) to EAP, Kelsen and colleagues [34] demonstrated that FAMTX was as active as EAP but far less toxic. The EORTC gastrointestinal groups [35] recently reported the results of a randomised phase III trial testing the FAMTX regimen versus the FAM regimen (5FU, doxorubicin and mitomycin C). Although they demonstrated a significant advantage in terms of survival and response for the FAMTX arm, they failed to show a significant improvement in resectability in both arms.

The ability to obtain an objective response with chemotherapy seems to be one of the main factors influencing resectability. 13 patients of the 15 responders in our study had NED after chemotherapy and surgery, whereas only 4 of the 12 non-responders were able to achieve the same results. Similar data were reported by Wilke and colleagues and Pluker and colleagues [17, 18]. These results open the way for the development of new chemotherapy regimens able to increase the objective response rate consistently and perhaps surgical resectability. In our opinion, the highest priority should be given to investigational new combinations in this field, and perhaps to intensive chemotherapy with haematopoetic growth factor rescue. The relationship between response and resectability is also an argument for a better selection of patients in future trials to avoid including patients with a poor performance status and/or with linitis plastica in neoadjuvant chemotherapy studies. From our experience, these patients have a very low response rate and a low probability of resectability.

Survival

Since experiences with adjuvant chemotherapy have failed to demonstrate a significant survival advantage [36], it is worthwhile evaluating the impact of neoadjuvant chemotherapy on survival. Theoretical considerations and experimental data [37, 38] have shown a possible benefit of the pre-operative chemotherapy approach.

In most of the reported series, the median survival of patients with locally advanced unresectable gastric cancer was dramatically low, ranging between 4 and 8 months, depending on whether they were palliatively treated or not [39, 40]. In contrast, the survival of patients undergoing curative resection is far better, but the cumulative 5-year survival rate does not exceed 20% (range 5–40%) when they are treated by surgery alone [1, 10, 41].

In the present study, as in others [15, 17, 18], the median survival seems significantly higher than that of historical controls but no firm conclusion can be drawn regarding the effect of neoadjuvant chemotherapy on survival.

In effect, since unresectability was not surgically proven in all of these studies, and as the relapse rate remained unsatisfactorily high (range 40–80%, despite pre- and post-operative chemotherapy), it is impossible to affirm whether extended surgery alone would have achieved the same results or not. Obviously, only randomised trials, comparing pre-operative chemotherapy and immediate surgical excision, in a population of patients with locally advanced disease, is likely to establish the exact benefit of neodjuvant chemotherapy.

These randomised trials are urgently needed as the toxicity of pre-operative chemotherapy is far from negligible. In our experience, 8 patients had grade 4 neutropenia and 1 patient died of septicaemia (3.3%). Toxicity-related deaths have also been reported by others [17, 18, 33], and should to be taken into account in the design of future trials.

The techniques used for patients selection in this study, mainly endoscopy and CT scan, have probably underestimated the extent of the tumour [8, 42], even if CT scan seems able to estimate the locoregional extension to adjacent organs in 80–90% of the cases [43]. Although unsophisticated, this selection approach is satisfactory since 75% of our cases had stage III or IV gastric cancer after chemotherapy at surgery. In future trials, more accurate techniques such as endoscopic ultrasonography and pretherapeutic surgical laparoscopy would be more reliabe for the selection of locally advanced cancers to be included in prospective studies.

In conclusion, neoadjuvant chemotherapy is feasible and may be proposed for patients with proven unresectable gastric cancer at a prior laporatomy. For patients with locally advanced cancer, not proven unresectable, only randomised studies comparing pre-operative chemotherapy versus surgery alone can be recommended. These studies will have to be stratified for the main prognostic factors (performance status, histology).

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