Adjuvant Treatment of High-Risk, Radically Resected Gastric Cancer Patients With 5-Fluorouracil, Leucovorin, Cisplatin, and Epidoxorubicin in a Randomized Controlled Trial

Stefano Cascinu, Roberto Labianca, Carlo Barone, Armando Santoro, Carlo Carnaghi, Alessandra Cassano, Giordano D. Beretta, Vincenzo Catalano, Oscar Bertetto, Sandro Barni, Luciano Frontini, Enrico Aitini, Silvia Rota, Valter Torri, Irene Floriani

On behalf of the Italian Group for the Study of Digestive Tract Cancer

Background Promising findings obtained using a weekly regimen of 5-fluorouracil (5-FU), epidoxorubicin, leucovorin (LV), and cisplatin (PELFw) to treat locally advanced and metastatic gastric cancer prompted the Italian Group for the Study of Digestive Tract Cancer (GISCAD) to investigate the efficacy of this regimen as adjuvant treatment for high-risk radically resected gastric cancer patients.

Methods From January 1998 to January 2003, 400 gastric cancer patients at high risk for recurrence including patients with serosal invasion (stage pT3 N0) and/or lymph node metastasis (stage pT2 or pT3 N1, N2, or N3), were enrolled in a trial of adjuvant chemotherapies; 201 patients were randomly assigned to receive the PELFw regimen, consisting of eight weekly administrations of cisplatin (40 mg/m^2), LV (250 mg/m^2), epidoxorubicin (35 mg/m^2), 5-FU (500 mg/m^2), and glutathione (1.5 g/m^2) with the support of filgrastim, and 196 patients were assigned to a regimen consisting of six monthly administrations of a 5-day course of 5-FU (375 mg/m^2 daily) and LV (20 mg/m^2 daily, 5-FU/LV). Disease-free and overall survival were estimated and compared between arms using hazard ratios (HRs) and Kaplan–Meier estimates. All statistical tests were two-sided.

Results The 5-year survival rates were 52% in the PELFw arm and 50% in the 5-FU/LV arm. Compared with the 5-FU/LV regimen, the PELFw regimen did not reduce the risk of death (HR = 0.95, 95% confidence interval [CI] = 0.70 to 1.29) or relapse (HR = 0.98, 95% CI = 0.75 to 1.29). Less than 10% of patients in either arm experienced a grade 3 or 4 toxic episode. Neutropenia (occurring more often in the PELFw arm) and diarrhea and mucositis (more prevalent in the 5-FU/LV arm) were the most common serious side effects. Nevertheless, only 19 patients (9.4%) completed the treatment in the PELFw arm and 85 (43%) patients completed the treatment in the 5-FU/LV arm.

Conclusions Our study found no benefit from an intensive weekly chemotherapy in gastric cancer. The extent of toxicity experienced by the patients in the adjuvant setting suggests that, in gastric cancer, chemotherapy may be more safely administered preoperatively.

J Natl Cancer Inst 2007;99:601–7

Gastric cancer is still a major problem worldwide, despite a declining incidence in the Western countries. In fact, it remains the second most frequently diagnosed cancer worldwide, accounting for approximately 10% of all new cancer diagnoses and 12% of all cancer deaths (1). Although surgery remains the cornerstone of any curative procedure for gastric cancer, the 5-year survival rate for all patients receiving radical surgery is poor, ranging between

Affiliations of authors: Universita' Politecnica delle Marche, Ancona, Italy (SC); Azienda Ospedaliera "Ospedali Riuniti" di Bergamo, Bergamo, Italy (RL, GDB); Universita' Cattolica del Sacro Cuore, Roma, Italy (CB, AC); Istituto Humanitas, Milano, Italy (AS, CC); Azienda Ospedaliera "Ospedale S Salvatore," Pesaro, Italy (VC); Azienda Ospedaliera S Gerardo, Monza, Italy (OB); Azienda Ospedaliera Le Molinette, Torino, Italy (SB); Azienda Ospedaliera S Paolo, Milano, Italy (LF, EA); Azienda Ospedaliera "Ospedale Poma," Mantova, Italy (EA); GISCAD Centre (SR), Clinical Trials Unit and Cancer Clinical Research Laboratory (VT, IF), Mario Negri Institute, Milano, Italy.

Correspondence to: Stefano Cascinu, MD, Clinica di Oncologia Medica, Azienda Ospedaliero-Universitaria Ospedali Riuniti di Ancona; Universita' Politecnica delle Marche, Via Conca 60020 Ancona, Italy (e-mail: cascinu@yahoo.com).

See "Notes" following "References."

DOI: 10.1093/jnci/djk131

CONTEXT AND CAVEATS

Prior knowledge

The relative effectiveness of promising adjuvant chemotherapies for gastric cancer patients who have had surgery and are at high risk of recurrence was largely unknown.

Study design

This was a randomized trial comparing two treatment arms.

Contribution

This trial showed that a regimen consisting of cisplatin, leucovorin, epidoxorubicin, 5-fluorouracil, and glutathione was not more effective in prolonging survival of gastric cancer patients than a previously used regimen based on 5-fluorouracil and leucovorin.

Implications

Additional strategies that may include preoperative therapies that do not have the side effects associated with postoperative chemotherapy will be needed to treat gastric cancer patients who are at high risk.

Limitations

It was not feasible to include a control arm in this trial, and an unexpectedly high survival rate in both treatment arms, possibly due to the high quality of the gastric surgery that was performed, limited the statistical power of the study to detect differences in outcomes.

15% and 35% (2). In an attempt to improve postsurgery survival, a worldwide effort was undertaken to develop effective adjuvant therapies for gastric cancer patients who have undergone radical resection. Unfortunately, the majority of clinical trials that evaluated these therapies have had negative results (3,4). However, the trials were often underpowered, and most used first-generation 5-fluorouracil (5-FU)–based regimens, such as 5-FU, doxorubicin, and mitomycin C (FAM) or FAM-like regimens, that had previously been reported to have limited activity in patients with metastatic gastric cancer (5).

Large meta-analyses have addressed the question of postoperative chemotherapy (6–9). These seemed to suggest a small survival benefit for patients treated with adjuvant chemotherapy, but the relevance of these data to current clinical practice is limited due to lack of individual data recollection, publication bias, and differences in patient populations and entry criteria of the trials (10). Furthermore, none of the published meta-analyses included adjuvant trials that used the third generation of chemotherapies (i.e., cisplatin-based regimens) (11–14), which appear to be more active in patients with advanced gastric cancer than previous regimens (15,16).

In the early 1990s, a weekly intensive regimen that included cisplatin, epidoxorubicin, 5-FU, and leucovorin (LV)—referred to as PELFw—was evaluated in advanced gastric cancer patients by the Italian Group for the Study of Digestive Tract Cancer (GISCAD). PELFw-treated patients were found to have a clinical response rate of more than 50%, a survival time of approximately 11 months, and an acceptable level of toxicity (17–20). These promising findings prompted us in 1998 to design a multicenter phase III study to investigate the efficacy of this intensive treatment compared with that of a 5-FU–based chemotherapeutic regimen in curatively resected gastric cancer patients with serosa invasion or metastases to regional lymph nodes. We were aware that a control arm based on 5-FU could be problematic because there was only weak evidence of efficacy of adjuvant chemotherapy in gastric cancer. However, the results of the meta-analysis of adjuvant clinical trials in radically resected gastric cancer patients by Mari et al. (8) showing an estimated survival advantage of about 4% in patients receiving chemotherapy, the apparent role of 5-FU treatment in causing this benefit, and the likelihood that most patients would refuse to enroll in a control arm that lacked adjuvant therapy, especially when positive lymph nodes were diagnosed, led us to define a control arm with a 5-FU–based therapy, according to Machover's regimen (21). This regimen had been previously tested in gastric cancer patients, and its toxicity had been found to be acceptable and manageable (22).

Patients and Methods

Study Design and Eligibility

The study was a multicenter prospective randomized controlled phase III trial with two treatment arms. Treatment allocation was achieved by minimization with stratification according to institution and pathologic stage.

To be eligible, patients were required to have histologically proven adenocarcinoma of the stomach or gastroesophageal junction and have undergone (between 35 and 42 days before registration) complete resection of the neoplasm (defined as resection of all tumors with margins of the resection testing negative for carcinoma [R0]). Patients were also required to have experienced serosa invasion (pT3 stage) or metastases to the regional lymph nodes (23). Additional requirements for eligibility were an Eastern Cooperative Oncology Group performance status between 0 and 1 and adequate hematologic (leukocyte count > 4000/mL, platelet count > 100 000/mL), hepatic (serum bilirubin level < 1.5 mg/dL), renal (serum creatinine concentration < 1.5 mg/dL), and cardiac (New York Heart Association class < II) functions. Patients were excluded if they experienced metastasis to locations other than regional lymph nodes, had had previous malignancies other than superficial skin cancer or in situ cervical carcinoma, or if their caloric intake was inadequate (<1500 kcal/day by oral alimentation). To continue to be eligible, patients had to begin chemotherapy within 2 weeks of registration. Thus, no more than 8 weeks were allowed between surgery and the start of treatment. All patients provided written informed consent, and the trial was approved by the local ethics committees at each participating institution.

Surgical Procedures

The surgical procedures suggested in the protocol were total or subtotal gastrectomy with curative intent and en bloc resection of the tumor with negative margins. Surgeons were free to perform either D1 (lymphadenectomy of the perigastric lymph nodes) or D2 (extensive en bloc resection of second echelon lymph nodes) resection. The operating surgeon completed an assessment form to define the extent of lymphadenectomy, and the completed form was sent to the pathologist along with the surgery report. However, no quality control was performed on surgery or pathology.

Treatment Plan

In the 5-FU/LV treatment arm, patients were given a 5-day course of 6S-LV (20 mg/m^2 by means of an intravenous bolus injection) followed by daily infusion of 375 mg/m^2 5-FU for a period of 15 minutes. This cycle was repeated every 28 days for a total of six cycles.

PELFw consisted of once a week administration of cisplatin (40 mg/m^2 as a 30-minute infusion in 250 mL of normal saline solution), 5-FU (500 mg/m^2 as a 15-minute infusion), and epidoxorubicin (35 mg/m^2 by intravenous bolus). In addition, 6S-LV was administered at a dose of 250 mg/m^2 diluted in 250 mL of normal saline solution in a 4-hour infusion concurrent with hydration; to prevent cisplatin-associated neurotoxicity, glutathione was given at a dose of 1.5 g/m^2 in 100 mL of normal saline solution for a period of 15 minutes immediately before each cisplatin administration. We had previously established the efficacy of this treatment in preventing toxicity in gastric cancer patients (17). For the patients assigned to PELFw treatment, standard intravenous hydration was performed: 2 hours before initiation of cisplatin infusion, patients were hydrated with 1500 mL of 0.9% sodium chloride to which 20 mEq of potassium chloride and 15 mEq of magnesium sulphate had been added. Posthydration was continued for 2 hours with 1000 mL of normal saline solution. The antiemetic regimen for all patients receiving PELFw consisted of dexamethasone (20 mg in 50 mL of saline given as an intravenous infusion for a period of 15 minutes, beginning 45 minutes before cisplatin) and ondansetron (8 mg in a 50 mL of saline solution as an intravenous infusion for a period of 15 minutes immediately following dexamethasone). Patients in the PELFw arm also received filgrastim administered by subcutaneous injection at a dose of 5 μg/kg with the injection beginning the day before each chemotherapy administration and continuing until the day after. This supportive treatment was needed to maintain a schedule of weekly administration of chemotherapy without delays due to neutropenia. In our experience, none of the patients can continue their weekly cycles without filgrastim (18). It was planned that patients would receive eight weekly treatments as postoperative therapy in the PELFw arm.

Full doses of anticancer drugs were given if the leucocyte count was 4000/μL or more and the platelet count was greater than 100 000/μL; when the leucocyte and platelet counts were less than this but were either grade 1 or 2, we delayed the treatment by a week or until a complete recovery occurred. If grade 3 or 4 neutropenia or thrombocytopenia occurred, subsequent doses of cytotoxic drugs were reduced to 75% of the planned dose. If grade 2 or 3 mucositis or diarrhea occurred, treatment was delayed by a week or until normalization. If grade 4 nonhematologic toxicities occurred, patients were removed from the study.

Postoperative Baseline and Follow-up

Patients were given a standardized postoperative baseline assessment that included a complete medical history and physical examination, a hemogram, and renal and hepatic function tests. An abdominal computed tomography (CT) scan and a chest x-ray were required after surgery. Before each chemotherapy cycle, the hemogram and the renal and hepatic tests were repeated. All adverse events were graded using the National Cancer Institute Common Toxicity Criteria, version 2.0.

Follow-up of both groups was from the end of adjuvant chemotherapy and was performed at 3-month intervals for 2 years, then at 6-month intervals for 3 years, and then yearly for the next 2 years. It consisted of a physical examination, a complete blood count, liver function tests (bilirubin, alkaline phosphatase, gamma glutamyl transpeptidase, and lactate dehydrogenase), and an abdominal CT scan. The patients also underwent chest x-rays every 6 months after adjuvant therapy for 2 years and then every 12 months for the next 3 years. The site and date of the first recurrence and, if the patient died, the date of death were recorded. Disease recurrence was ascertained by clinical, radiologic, and, if possible, histologic examination.

Statistical Analysis

The primary endpoint of the trial was overall survival. Secondary endpoints were disease-free survival and toxicity. Disease-free survival was measured from the date of random assignment to the date of the first occurrence of a neoplastic event (relapse or second malignancy) or the date of death from any cause. Relapse was coded as local if tumor was detected in the surgical anastomosis, residual stomach, or gastric bed; as regional if tumor was detected in the peritoneal cavity (including the intra-abdominal lymph nodes and peritoneum); and as distant if metastases were detected outside the peritoneal cavity. If no progression was reported and no death occurred, data on disease-free survival were censored at the date when the absence of relapse was confirmed. Overall survival was measured from the date of random assignment to the date of death from any cause or to the date of the last follow-up.

We calculated that a sample size of 400 patients with 200 patients in each arm with a follow-up time of 3 years was needed to observe the 250 events (deaths) required to test the hypothesis that PELFw treatment would lead to a 15% improvement in survival. We estimated that this sample size would provide the study with 90% power to detect a 15% increase in 5-year survival when 5-year survival was 20% in the 5-FU/LV arm and 35% in the PELFw arm, with two-sided type I error of .05. The planned duration of accrual was 5 years. At inclusion, the clinical variables were described as means or frequencies. Comparison of the two groups based on patient characteristics was performed using the Student's *t* test and the chi-square test. Disease-free and overall survival curves for all the eligible patients in an intention-to-treat analysis were estimated using the Kaplan–Meier method and compared using the log-rank test. All statistical tests were two-sided.

The study was monitored by the data and safety monitoring committee of GISCAD. An interim analysis of recurrence rate and survival that was performed after the enrollment of 250 patients resulted in the continuation of the study until the planned time for the reporting of final data.

Results

Patient Characteristics

Between January 1998 and January 2003, 400 patients were enrolled. Three patients were considered to be ineligible at the time of treatment allocation: two because they had a positive surgical margin and one due to the presence of a tumor with involved lymph nodes but that had invaded only submucosa (pT1 N1).

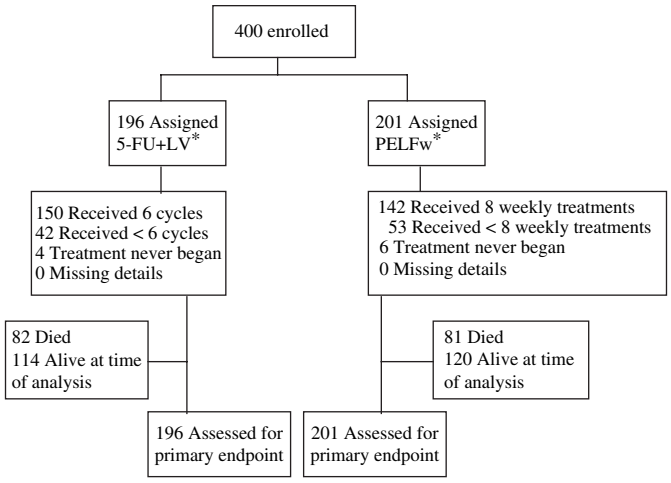

Fig. 1. Trial flow chart. *Three patients were ineligible, two with positive margins and one with a pT1 stage.

Therefore, the analyses were carried out on an intention-to-treat basis with the remaining 397 enrolled patients, of whom 196 were in the control arm and 201 were in the PELFw arm (Fig. 1). Of the two patients with positive margins, one relapsed at 6 months after surgery and the other at 8 months after surgery, and, with palliative therapy, their survival was 12 and 16 months, respectively. The patient with the stage pT1 N1 tumor was alive without tumor relapse 5 years after surgery.

Patient and tumor characteristics were well balanced in the two arms (Table 1). Tumor was located in the upper third of the stomach in approximately 30% of the patients in both arms. More than 90% of the patients had involved lymph nodes, and the majority (80%) of them presented with an intestinal-type histology while only 20% of patients had a diffuse type. Median age was similar in both arms (58 and 59 years in the PELFw and 5-FU/LV arms, respectively).

Table 1. Characteristics of the patients in 5-FU/LV and PELFw arms*

Characteristic	5-FU/LV	PELFw
Median age (y)	59	58
Male/female ratio	61/39	67/33
Surgery procedure		
Subtotal gastrectomy	40%	42%
Total gastrectomy	60%	58%
Examined lymph nodes†		
<15	23.5%	19.5%
>15	76.5%	80.5%
<25	49%	53%
>25	51%	47%
Primary localization of tumor in the stomach		
Upper third	30%	35%
Middle third	42%	42%
Lower third	28%	23%
Primary tumor stage‡		
T3 N0	7%	6%
T any N1	21%	19%
T any N2	42%	39%
T any N3	30%	36%
Histologic characteristics		
Intestinal	80%	78%
Diffuse	20%	22%

* Of the 401 enrolled patients, 196 were assigned to the 5-FU arm and 201 were assigned to the PELFw arm. 5-FU/LV = 5-fluorouracil and leucovorin; PELFw = cisplatin, epidoxorubicin, 5-fluorouracil, and leucovorin.

† The median number of examined lymph nodes for patients undergoing 5-FU and PELFw treatment was 25 and 23, respectively.

‡ T3 N0 = serosal but no lymph nodes involvement; N1 = from 1 to 6 involved lymph nodes; N2 = from 7 to 15 involved lymph nodes; N3 = more than 16 lymph nodes involved.

Surgical Procedures

A D0 lymphadenectomy, which is a less than complete dissection of the perigastric lymph nodes, was performed in 85 patients (21%), and a D1–D2 lymphadenectomy was performed in the remaining patients. The median number of lymph nodes removed per patient was 25 in the 5-FU/LV arm and 23 in PELFw arm.

Chemotherapy

Among the 196 patients allocated to the 5-FU/LV arm, 150 (77%) completed the treatment and 42 (23%) stopped chemotherapy because of toxicity (n = 20), progressive disease (n = 10), or refusal of further treatment (n = 12). Four patients allocated to the 5-FU/LV arm never started chemotherapy. Of these, two patients had a delay because of wound healing complications and two refused treatment because of their assignment to the 5-FU/LV arm. Among the 150 patients in the 5-FU/LV arm who completed treatment, a dose reduction was required in 21 patients, a delay in administration of cytotoxic drugs in 26, and both a dose and a time modification in 18 patients.

Among the 201 patients allocated to the PELFw arm, 142 (72%) completed the treatment and 53 (28%) stopped chemotherapy because of toxicity (n = 32), progressive disease (n = 7), or refusal of further treatment (n = 14). Six patients assigned to the PELFw arm never started chemotherapy. Among the 142 patients who completed treatment, a dose modification was required in 13 patients, a time modification in 53 patients, and both a dose and a time modification were needed in 57 patients. Thus, only 19 patients (9.4%) completed the treatment according to the planned dose and timing.

Toxicity

Toxic effects experienced during treatment were recorded according to National Cancer Institute Common Toxicity Criteria grade (Table 2). Neutropenia was more frequent in patients treated with the PELFw regimen: 27 patients experienced grade 3 or 4 neutropenia in the PELFw arm compared with 17 in the 5-FU/LV arm. In the PELFw arm, 13 patients suffered from anemia grade 3 or 4 compared with only one in the 5-FU arm. Grade 3 or 4 diarrhea occurred in 15 and 5 patients in the 5-FU/LV and PELFw arms, respectively, whereas grade 3 or 4 mucositis occurred in 16 and 0 patients, respectively. Overall, apart from alopecia, a severe toxic episode (grade 3 or 4) was reported at least once in 2159 patients in the PELFw arm and in 1456 patients in the 5-FU/LV arm.

Overall and Disease-Free Survival

Median follow-up time was 54 months, and 163 patients (41%) had died as of December 1, 2005. Kaplan–Meier estimates of

Table 2. Number of patients experiencing different chemotherapy-related toxic effects according to National Cancer Institute Common Toxicity Criteria grade, version 2.0*

	No. of patients experiencing toxicity of given grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Neutropenia					
5-FU/LV*	157	12	10	11	6
PELFw	157	8	9	11	16
Thrombocytopenia					
5-FU/LV	189	5	1	1	0
PELFw	132	41	20	5	3
Anemia					
5-FU/LV	160	27	8	1	0
PELFw	81	50	57	12	1
Diarrhea					
5-FU/LV	146	27	8	10	5
PELFw	160	20	16	4	1
Nausea/vomiting					
5-FU/LV	91	66	30	9	0
PELFw	114	47	30	10	0
Mucositis					
5-FU/LV	105	47	28	13	3
PELFw	141	47	13	0	0
Neurotoxicity					
5-FU/LV	195	1	0	0	0
PELFw	134	52	12	3	0
Alopecia					
5-FU/LV	190	6	0	0	0
PELFw	45	45	34	45	32

* 5-FU/LV regimen consisted of 5-fluorouracil and leucovorin; PELFw consisted of cisplatin, epidoxorubicin, 5-FU, and LV.

cumulative overall survival and progression-free survival were derived for patients in the two treament arms (Fig. 2). The 5-year overall survival rate was 52% in the PELFw arm and 50% in the 5-FU/LV arm. Median survival was 60 months in the 5-FU/LV arm, whereas in the PELFw arm, 59% of patients were alive at the time of statistical analysis (hazard ratio [HR] for death in PELFw arm compared with 5-FU arm = 0.95, 95% confidence interval [CI] = 0.70 to 1.29 based on the log-rank test).

As shown in Table 3, 156 patients were found to have metastases (systemic recurrence) at first sign of relapse, whereas in 14 patients relapse was determined to be due to locoregional recurrence. Thirteen patients had both locoregional recurrence and metastatic disease, the first sign of recurrence. There was no difference in the pattern of recurrence among the two treatment groups. The 5-year disease-free survival rates were 41% in the PELFw arm and 40% in the 5-FU/LV arm. The median disease-free survival was 42 months in both arms (hazard ratio for relapse in PELFw arm compared with 5-FU arm = 0 .98, 95% CI = 0.75 to 1.29).

Discussion

The present trial focused on gastric cancer patients with the highest risk for recurrence: about 75% of patients in both arms were N2–N3 stage, that is, had metastases in at least seven regional lymph nodes. Earle and Maroun (7) have suggested that patients with the highest risk of recurrence might benefit most from adjuvant treatment strategies. However, the results of this randomized trial showed that the addition of cisplatin and epidoxorubicin to a 5-FU/LV regimen did not improve survival of patients with curatively resected gastric cancer.

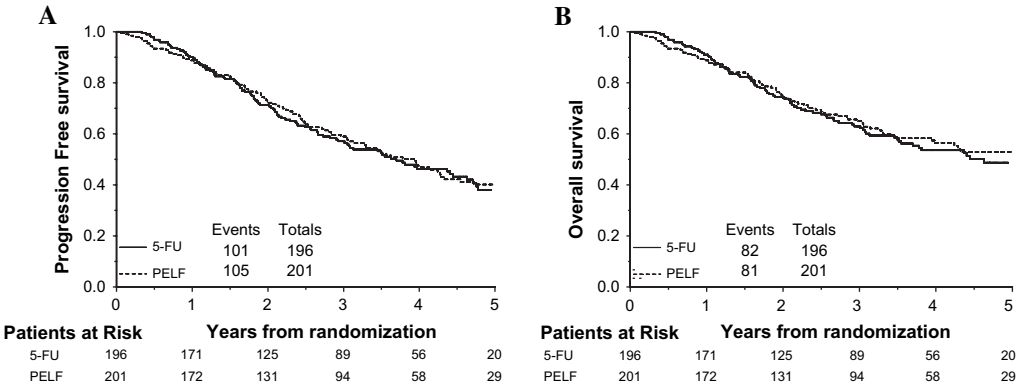

Fig. 2. Progression-free survival and overall survival according to treatment arm. Kaplan–Meier survival curves showing progression-free survival (**A**) and overall (**B**) survival in gastric cancer patients treated with 5-FU/LV (5-fluorouracil and leucovorin) or PELFw, (cisplatin, epidoxorubicin, 5-FU, and LV). Progression was locoregional recurrence or metastatic disease as ascertained by clinical, radiologic, and, in some cases, histologic examinations. EST = estimated fraction of patients alive; CI = confidence interval.

	PROGRESSION-FREE SURVIVAL (A)						OVERALL SURVIVAL (B)					
	5-FU			PELFw			5-FU			PELFw		
YEARS	EST	95% CI		EST	95% CI		EST	95% CI		EST	95% CI	
1	0.800	0.790	0.810	0.790	0.780	0.800	0.910	0.900	0.920	0.887	0.877	0.897
2	0.585	0.575	0.595	0.586	0.576	0.596	0.742	0.732	0.752	0.740	0.730	0.750
3	0.518	0.507	0.528	0.494	0.484	0.504	0.622	0.612	0.632	0.651	0.641	0.661
4	0.466	0.456	0.476	0.449	0.439	0.459	0.529	0.518	0.539	0.567	0.557	0.577
5	0.414	0.404	0.424	0.439	0.429	0.449	0.480	0.470	0.491	0.532	0.522	0.542

Table 3. Number of patients experiencing locoregional recurrence, systemic cancer, and death in the 5-FU/LV and PELFw treatment arms*

Event	No. of patients (%)	
	5-FU	PELFw
Locoregional	5 (6)	9 (10)
Systemic recurrence	77 (86)	79 (84)
Locoregional and systemic recurrence	7 (8)	6 (6)
Total	89 (45)	94 (46)
Death	82 (42)	81 (40)

* 5-FU/LV consisted of 5-fluorouracil and leucovorin; PELFw consisted of cisplatin, epidoxorubicin, 5-FU, and LV. Of the 401 enrolled patients, 196 were assigned to the 5-FU arm and 201 were assigned to the PELFw arm.

In this trial, the 5-year survival rate was 50% in both arms, much higher than in previous studies that reported 5-year survival for patients whose stage of disease was similar to that of our patients that ranged from 20% to 30% (3). The unexpectedly long survival time in our trial may be due to several factors, among them, the high quality of surgery (number of D1 and D2 resections) observed in our trial. Although in treating patients in the trial, surgeons were free to perform any type of surgical resection as long as a complete macroscopic clearance and a free section line at microscopic exploration were obtained, a high number of lymph nodes were examined in both arms, and in more than 75% of patients at least 15 lymph nodes were resected (data not shown). Also, 50% of patients received a D2 resection. These characteristics of the surgery may also have contributed to the low incidence of local recurrence in our trial (only 2.5% and 4.5% of patients experienced local recurrence in the 5-FU/LV arm and in the PELFw arm, respectively).

The low rate of local recurrence that we observed may be of clinical relevance to the management of patients with radically resected gastric cancer because the previously reported positive results in survival obtained by treating gastric cancer patients with chemoradiotherapy were, as suggested by Macdonald et al. (24), mainly due to a reduction in local recurrences compared with the surgical control arm (23). Thus, one could argue that chemoradiotherapy should be limited to patients receiving a suboptimal surgery (less than a D1 dissection) and that the addition of chemoradiotherapy may confer no benefit to patients receiving a D1 or D2 dissection. This opinion was at the basis of several comments (25–27) about the suboptimal surgery performed in the trial reported by Macdonald et al. (24), in which about half of the patients received a D0 resection. It was suggested that the survival benefit conferred by chemoradiotherapy observed in the trial would only be reproducible among gastric cancer patients receiving less than adequate surgery. This suggestion was supported in a subgroup analysis of the trial reported by Macdonald et al. (24), which indicated that the survival benefit for chemoradiotherapy was limited to patients treated with suboptimal surgery (i.e., D0 or D1 resection).

Although our study was not specifically designed to consider subgroups, we retrospectively assessed the role of the intensive weekly chemotherapy according to quality of surgery. In our series, only 85 patients received a D0 resection (i.e., a clearance of the lymphatics that is less than a complete dissection of the perigastric lymph nodes). However, we did not find any statistically significant difference in disease-free survival and overall survival of different treatment arms in this group of patients (data not shown). On the basis of data from the Italian Trials in Medical Oncology trial, which suggested a benefit from chemotherapy in patients with six or more involved lymph nodes (13), we also analyzed this category of patients (representing the majority of the patients in our trial), and we were not able to find any difference in overall survival or disease-free survival between the two treatment arms (data not shown).

The high survival rate (50% 5-year survival in both arms) rendered our statistical design inappropriate. As designed, the trial was powered to detect a 15% increase in 5-year survival with an expected 5-year survival of only 20% for the control arm. A 5-year survival of 20% was chosen on the basis of the pathologic stages of the patients (about 70% of the enrolled patients had stage IIIb or IV gastric cancer).

Another limitation was the poor compliance with treatment in both arms. Despite the fact that 72% of patients completed the treatment in the experimental arm, only 14% did so without time and dose modifications. Even in the 5-FU/LV arm, where patients were treated with a regimen that is generally well tolerated, only 50% were able to complete the treatment. The poor compliance suggests that, after gastrectomy, patients tolerate poorly even those chemotherapeutic regimens whose toxicity is low; this was recently suggested by Bouche et al. (11), who used a 5-FU/cisplatin combination that was less toxic than PELFw to treat gastrectomy patients. Further evidence that postoperative regimens are poorly tolerated was obtained in the trial reported by Cunningham et al. (28), where the same drugs in the preoperative and postoperative setting were administered to patients with gastric and lower esophageal adenocarcinomas; whereas 82% of patients completed preoperative treatment, only 42% completed postoperative treatment.

In conclusion, our study did not show any benefit of an intensive adjuvant chemotherapy for curatively resected gastric cancer patients compared with a standard regimen using 5-FU. Furthermore, toxicity associated with postoperative chemotherapy as reported in our trial and in other studies as well as the encouraging results of the trial of Cunningham et al. (28), where an absolute improvement in 5-year survival of 13% was reported in patients treated with perioperative chemotherapy, suggest that it may be preferable to move toward preoperative approaches.

References

(1) Jemal A, Siegel R, Ward E, Murray T, Xu J, Smigal C, et al. Cancer statistics 2006. CA Cancer J Clin 2006;56:106–30.

(2) Dicken BJ, Bigam DL, Cass C, Mackey JR, Joy AA, Hamilton SM. Gastric adenocarcinoma. Review and considerations for future directions. Ann Surg 2005;241:27–39.

(3) Lim L, Michael M, Leong T. Adjuvant therapy in gastric cancer. J Clin Oncol 2005;23:6220–32.

(4) Shimada K, Ajani JA. Adjuvant therapy for gastric carcinoma patients in the last 15 years. Cancer 1999;86:1657–68.

(5) Jansen EPM, Boot H, Verheij M, van de Velde CJH. Optimal locoregional treatment in gastric cancer. J Clin Oncol 2005;23:4509–17.

(6) Hermans J, Bonekamp JJ, Boon M, Bunt AMG, Ohyama S, Sasako M, et al. Adjuvant chemotherapy after curative resection for gastric cancer: a meta-analysis of randomised trials. J Clin Oncol 1993;11:1441–7.

(7) Earle C, Maroun J. Adjuvant chemotherapy after curative resection for gastric cancer in non-Asian patients: revisiting a meta-analysis of randomised trials. Eur J Cancer 1999;35:1059–64.
(8) Mari E, Floriani I, Tinazzi A, Buda A, Belfiglio M, Valentini M, et al. Efficacy of adjuvant chemotherapy after curative resection for gastric cancer: a meta-analysis of published randomised trials. Ann Oncol 2000; 11:837–43.
(9) Panzini I, Gianni L, Fattori PP, Tassinari D, Imola M, Fabbri P, et al. Adjuvant chemotherapy in gastric cancer: a meta-analysis of randomized trials and a comparison with previous meta-analyses. Tumori 2002;88:21–7.
(10) Janunger KG, Hafstrom L, Glimelius B. Chemotherapy in gastric cancer: a review and updated meta-analysis. Eur J Surg 2002;168:597–608.
(11) Bouche O, Ychou M, Burtin P, Bedenne L, Ducreux M, Lebreton G, et al. Adjuvant chemotherapy with 5-fluorouracil and cisplatin compared with surgery alone for gastric cancer: 7-year results of the FFCD randomised phase III trial (8801). Ann Oncol 2005;16:1488–97.
(12) Chipponi J, Huguier M, Pezet D, Basso N, Hay JM, Quandalle P, et al. Randomised trial of adjuvant chemotherapy after curative resection for gastric cancer. Am J Surg 2004;187:440–5.
(13) Bajetta E, Buzzoni R, Mariani L, Beretta E, Bozzetti F, Bordogna G, et al. Adjuvant chemotherapy in gastric cancer: 5-year results of a randomised study by the Italian Trials in Medical Oncology (ITMO) Group. Ann Oncol 2002;13:299–307.
(14) Di Costanzo F, Gasperoni S, Manzione L, Tonato M, Bisagni G, Bravi S, et al. Postoperative chemotherapy in resected gastric cancer: follow-up vs PELF. Results of an Italian intergroup (GOIRC and GISCAD) study. Proc Am Soc Clin Oncol 2003;18:1189.
(15) Webb A, Cunningham D, Scaffe J, Harper P, Norman A, Joffe JK, et al. Randomised trial comparing epirubicin, cisplatin and fluorouracil versus fluorouracil, doxorubicin, and methotrexate in advanced esophageal cancer. J Clin Oncol 1997;15:261–7.
(16) Cocconi G, Carlini P, Gamboni A, Gasperoni S, Rodino C, Zironi S, et al. Cisplatin, epirubicin, leucovorin and 5-fluorouracil (PELF) is more active than 5-fluorouracil, doxorubicin and methotrexate (FAMTX) in advanced gastric cancer. Ann Oncol 2003;14:1258–63.
(17) Cascinu S, Cordella L, Del Ferro E, Fronzoni M, Catalano G. Neuroprotective effect of reduced glutathione on cisplatin-based chemotherapy in advanced gastric cancer: a randomised double-blind placebo-controlled trial. J Clin Oncol 1995;13:26–32.
(18) Cascinu S, Labianca R, Alessandroni P, Marcellini M, Silva RR, Pancera G, 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;5:3313–9.
(19) Cascinu S, Labianca R, Graziano F, Pancera G, Barni S, Frontini L, et al. Intensive weekly chemotherapy for locally advanced gastric cancer using 5-fluorouracil, cisplatin, epidoxorubicin, 6S-leucovorin, glutathione and filgrastim: a report from the Italian Group for the study of Digestive tract Cancer (GISCAD). Br J Cancer 1998;78:390–3.
(20) Cascinu S, Scartozzi M, Labianca R, Catalano V, Silva RR, Barni S, et al. High curative resection rate with weekly cisplatin, 5-fluorouracil, epidoxorubicin, 6S-leucovorin, glutathione and filgrastim in patients with locally advanced, unresectable gastric cancer: a report from the Italian Group for the Study of Digestive Tract Cancer (GISCAD). Br J Cancer 2004;90: 1521–5.
(21) Machover D, Grison D, Goldschmidt E, Zittoun J, Lotz JP, Metzger G, et al. Fluorouracil combined with the pure (6S)-stereoisomer of folinic acid in high doses for treatment of patients with advanced colorectal carcinoma: a phase I-II study. J Natl Cancer Inst 1992;84: 321–7.
(22) Schipper DL, Wagener DJT. Chemotherapy of gastric cancer. Anticancer drugs 1996;7:137–49.
(23) International Union Against Cancer. TNM classification of malignant tumors. 6th ed. New York (NY): Wiley-Liss; 2002.
(24) Macdonald JS, Smalley SR, Benedetti J, Hundahl SA, Estes NC, Stemmermann GN, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med 2001;345:725–30.
(25) Atkins CD. Adjuvant chemoradiotherapy for gastric cancer. N Engl J Med 2002;346:210–1.
(26) Abraham I, Dhar P, Praseedom RK. Adjuvant chemoradiotherapy for gastric cancer. N Engl J Med 2002;346:210–1.
(27) Berney CR, Merrett ND. Adjuvant chemoradiotherapy for gastric cancer. N Engl J Med 2002;346:210–1.
(28) Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJH, Nicolson M, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. New Engl J Med 2006;355: 11–20.

Notes

The following investigators participated in this study and are to be considered as co-authors: Universita' Cattolica, Roma: Carlo Barone, Alessandra Cassano, Carmelo Pozzo; Istituto Humanitas, Milano: Armando Santoro, Carlo Carnaghi, Lorenza Rimassa; Azienda Ospedaliera "Ospedali Riuniti" di Bergamo, Bergamo: Roberto Labianca, Giordano Beretta, Stefania Mosconi; Azienda Ospedaliera "Ospedale S. Salvatore", Pesaro: Vincenzo Catalano, Paolo Giordani; Azienda Ospedaliera "S Gerardo", Monza: Antonio Ardizzoia; Azienda Ospedaliera di Treviglio (BG): Sandro Barni; Azienda Ospedaliera "Le Molinette", Torino: Oscar Bertetto; Azienda Ospedaliera "S. Paolo", Milano: Luciano Frontini, Paolo Foa; Azienda Ospedaliera "Poma", Mantova: Enrico Aitini, Carla Rabbi; Istituto Nazionale sul Cancro, Genova: Silvana Chiara; Azienda Ospedaliera di Reggio Calabria: Giampietro Gasparini, Mario Nardi; Azienda Ospedaliera S Maria della Misericordia, Udine: Mauro Mansutti; Ospedale di Trescore, Bergamo: Ermenegildo Arnoldi; Azienda Ospedaliera Sacco, Milano: Elena Piazza; Policlinico Umberto I, Roma: Enrico Cortesi; Azienda Ospedaliera di Parma: Francesca Pucci; Ospedale Profili, Fabriano: Rosa Rita Silva; Policlinico Umberto I, Udine: Alberto Sobrero; Ospedale degli Infermi, Rimini: Alberto Ravaioli.

The study sponsor had no role in the design of the study; the collection, analysis, and interpretation of the data; the writing of the manuscript; or the decision to submit the manuscript for publication.

Manuscript received July 29, 2006; revised February 1, 2007; accepted March 8, 2007.