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Adjuvant chemotherapy with epirubicin, leucovorin, 5-fluorouracil and etoposide regimen in resected gastric cancer patients: a randomized phase III trial by the Gruppo Oncologico Italia Meridionale (GOIM 9602 Study)

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Background: This randomized, multicenter, phase III trial evaluated the efficacy and safety of the combination of epirubicin, leucovorin, 5-fluorouracil and etoposide (ELFE regimen) as adjuvant therapy for radically resected gastric cancer patients.

Patients and methods: From June 1996 to June 2001, 228 stage IB–IIIB gastric cancer patients were enrolled. All patients received a total or subtotal gastrectomy with at least a D1 lymphoadenectomy and were randomly assigned to receive surgery alone or surgery followed by chemotherapy.

Results: A total number of 630 cycles was delivered with a median number of 5. With a median follow-up of 60 months, the 5-year overall survival (OS) was 48% in the treatment arm and 43.5% in the control arm [hazard ratio (HR) 0.91; 95% confidence interval (CI) 0.69–1.21; $P = 0.610$); the 5-year disease-free survival (DFS) was 44% in the treatment arm and 39% in the control arm (HR 0.88; 95% CI 0.78–0.91; $P = 0.305$). In node-positive patients, the 5-year OS was 41% in the treatment arm and 34% in the control arm (HR 0.84; 95% CI 0.69–1.01; $P = 0.068$), while the 5-year DFS was 39% in the treatment arm and 31% in the control arm (HR 0.88; 95% CI 0.78–0.91; $P = 0.051$). The most common grade 3–4 toxic effects according to World Health Organization criteria were hematological and gastrointestinal.

Conclusions: In radically resected gastric cancer patients, adjuvant chemotherapy with ELFE regimen does not improve OS over surgery alone.

Key words: adjuvant chemotherapy, ELFE regimen, gastric cancer

introduction

Surgery is the only potentially curative treatment of localized gastric cancer [1]. However, also among patients who undergo a curative resection, the outcome remains poor, with a 5-year survival rate ranging between 20% and 30% [2–5]. In an attempt to improve these disappointing results, different adjuvant chemotherapy regimens have been proposed and evaluated in clinical trials. To date, no definitive conclusions have been drawn from these studies because the majority of these has failed to show a clear survival benefit over surgery alone. However, several recent meta-analyses indicate a small but statistically significant benefit in 5-year overall survival (OS) between 3% and 5% [6–11]. The relevance of these data in the current clinical practice is restrained by a number of limitations; therefore, adjuvant chemotherapy for gastric cancer should be considered still investigational, and the potential reduction in risk of death should be confirmed in a well-designed large prospective randomized trial by using more active regimens in metastatic or locally advanced disease [12]. In the mid-90s, Gruppo Oncologico Italia Meridionale evaluated in a phase II study the efficacy and tolerability of the association of epirubicin, leucovorin, 5-fluorouracil and

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etoposide (ELFE regimen) in previously untreated advanced gastric cancer patients. Four complete responses (8%) and 21 partial responses (41%) were observed, with an overall response rate of 49%. The median duration of response and survival were 6 and 8 months, respectively. Responder patients showed a significantly better median survival duration than nonresponders (12 versus 4 months, respectively; $P < 0.0001$); furthermore, toxicity was mild [13]. Following these results, we designed a randomized phase III study to evaluate the efficacy of ELFE regimen in the adjuvant treatment of resectable gastric cancer with unfavourable prognostic factors.

patients and methods

elegibility criteria

Patients with histologically confirmed adenocarcinoma of the stomach or the gastroesophageal junction were enrolled in the study. All patients gave their written informed consent to be enrolled in this trial, which was revised and approved by Bari's Istituto Oncologico Ethics Committee. Inclusion criteria were the following: R0 surgery defined as the removal of all macroscopic tumoral tissue; no evidence of distant metastases; the absence of microscopic residual tumor; free resection margins and a D1 lymphadenectomy with resection of all perigastric lymph nodes and some celiac, splenic or splenic hilar, hepatic artery and cardial lymph nodes depending on the location of the tumor in the stomach or gastroesophageal junction; surgery done within the previous 6 weeks; stage IB, II, IIIA and IIIB according to the tumor–node–metastasis system of the American Joint Committee for Cancer Staging of 1992; age <70 years; performance status according to Eastern Cooperative Oncology Group scale of zero to two and absence of preexisting renal, hepatic, hematologic or cardiac dysfunction. The postoperative baseline evaluation included physical examination, serum chemistry tests, chest-X-ray, abdominal computed tomography (CT) scan and echocardiography. At each chemotherapy cycle, the serum chemistry tests were repeated.

treatment

After surgery and staging, all patients were stratified by nodal involvement and centrally, randomly assigned to receive surgery alone (control arm) or chemotherapy (treatment arm).

The ELFE regimen consisted of epirubicin 60 mg/m^2 on day 1, leucovorin 100 mg/m^2 on days 1–5, fluorouracil 375 mg/m^2 on days 1–5, etoposide 80 mg/m^2 on days 1–3, and cycles repeated every 3 weeks for six times. Toxicity was graded according to World Health Organization (WHO) scoring system. If grade 3 myelotoxicity was recorded, the treatment was delayed by a week and, in the case of persistent grade 3 myelotoxicity, the dose was reduced by 25%. In the case of grade 4 myelotoxicity the treatment was definitively stopped. If grade 3 gastrointestinal toxicity was observed, the treatment was delayed by 1 week and then continued with a dose reduction of 25%; in the case of persistent grade 3 gastrointestinal toxicity after 1 week of delay or in the case of grade 4 gastrointestinal toxicity, the treatment was definitively stopped. During the follow-up, the patients underwent a physical examination, serum chemistry tests and abdominal ultrasonography every 3 months, chest X-ray, abdominal CT scan every 6 months and esophagogastroscopy every year.

statistical considerations

The primary end point of the study was the OS that was measured from the date of randomization to the date of death from any cause or the date of the last follow-up. The secondary end points were the disease-free survival (DFS) and toxicity. The DFS was measured from the date of randomization to the date of the first occurrence of a neoplastic event (relapse or second malignancy) or the date of death from any cause or the date of the last follow-up in the case of living patients without evidence of disease. The sample size was designed to provide the study with 80% power to detect a difference between 5-year OS of 20% in the surgery-alone arm and 35% in the chemotherapy arm [hazard ratio (HR) for death of 0.65], with two-sided α error of 0.05 and a β error of 0.2. Therefore, with a duration of accrual of 5 years and a duration of follow-up time of 5 years, the planned sample size was 226 patients including an estimated drop out rate of 10%. DFS and OS curves were estimated using the Kaplan–Meier method and compared using the log-rank test (unadjusted analysis) for all the eligible patients on an intention-to-treat basis. The independent significance of every prognostic variable related to OS and DFS was determined by multivariate analysis, using the Cox proportional hazards model with results reported as relative HR of death and relapse with corresponding 95% confidence interval (CI) and P value. The following covariates were included in the multivariate analysis: tumor differentiation, location of tumor, depth of invasion, nodal status and adjuvant chemotherapy.

results

From June 1996 to June 2001, 228 patients were enrolled by six centers in Southern Italy. Three patients were considered inelegible: two had metastatic disease (control arm) and one had positive surgical margins (treatment arm). Therefore, the final analysis was carried out on an intention-to-treat basis with the remaining 225 enrolled elegible patients: 113 patients were allocated to surgery alone while 112 patients were allocated to surgery followed by adjuvant chemotherapy. Table 1 shows patients' and tumours' characteristics and surgery procedures. The two arms were well balanced without any significant difference. In particular, ~60% of patients received a total gastrectomy and 80% of patients had 16 or more resected nodes; the median number of removed lymph nodes per patient was 22 in the treatment arm and 23 in the control arm. Among the 112 patients treated with chemotherapy, a total number of 630 cycles of chemotherapy was delivered with a median number of 5 (range 1–6): 82% of patients completed therapy as planned and 18% stopped chemotherapy because of toxicity: 6% after five cycles, 7% after four cycles, 2% after three cycles, 2% after two cycles and 1% after one cycle. Among 92 patients who received six cycles, 61% of patients received full dose chemotherapy, while 31% of patients required dose reduction. The most frequent life-threatening toxic effects were haematological and gastrointestinal (Table 2). According to WHO classification, grade 3–4 neutropenia was experienced by 26% of the patients, while diarrhea (26%), nausea and vomiting (20%) and mucositis (13%) were the most common gastrointestinal toxic effects. No treatment-related deaths were observed. The median follow-up time was 60 months with a range of 10–91. Figures 1 and 2 show the OS and DFS curves according to the treatment. The 5-year OS rate was 48% in the treatment group and 43.5% in the control arm with a relative risk reduction of 9% and an absolute benefit in survival of 4.5%. This difference was not statistically significant (HR 0.91; 95% CI 0.69–1.21; $P = 0.610$). The 5-year DFS rate was 44% in the treatment group and 39% in the control arm with a relative

Table 1. Patients' and tumours' characteristics and surgery procedures

Characteristics	Surgery + ELFE (n = 112)	Surgery (n = 113)
Age/years	63 (39–70)	62 (41–70)
Median (range)		
Sex no. (%)		
Male	66 (59)	65 (58)
Female	46 (41)	48 (42)
ECOG PS		
0	74 (66)	73 (65)
1	29 (26)	31 (27)
2	9 (8)	9 (8)
Histology differentiation		
Well/moderately	68 (61)	65 (58)
Poorly	44 (39)	48 (42)
Location of tumor (%)		
Cardia	15 (13)	14 (12)
Stomach	97 (87)	99 (88)
Depth of invasion		
T1	3 (3)	5 (4)
T2	19 (17)	18 (16)
T3	69 (62)	73 (65)
T4	21 (18)	17 (15)
Nodal status		
N0	32 (28)	30 (27)
N1	38 (34)	39 (34)
N2	42 (38)	44 (39)
Stage		
IB	1 (1)	3 (3)
II	38 (34)	35 (31)
IIIA	39 (35)	36 (32)
IIIB	35 (30)	39 (34)
Surgery (%)		
Total	70 (62)	74 (65)
Subtotal	42 (38)	39 (35)
Extent of nodes dissection (%)		
≤15	24 (21)	23 (20)
16–25	71 (64)	74 (65)
≥26	17 (15)	16 (14)
Median (SE)	18 (1.5)	19 (1.0)

ELFE, epirubicin, leucovorin, 5-fluorouracil and etoposide; ECOG PS, Eastern Cooperative Oncology Group performance status; SE, standard error.

Table 2. Toxicity of chemotherapy according to WHO grade

Adverse event	Grade 3 (%)	Grade 4 (%)
Neutropenia	25 (22)	5 (4)
Thrombocytopenia	12 (11)	2 (2)
Anemia	11 (10)	0
Diarrhea	22 (20)	7 (6)
Mucositis	11 (10)	2 (2)
Nausea and vomiting	20 (18)	0
Cardiac	2 (2)	0

WHO, World Health Organization.

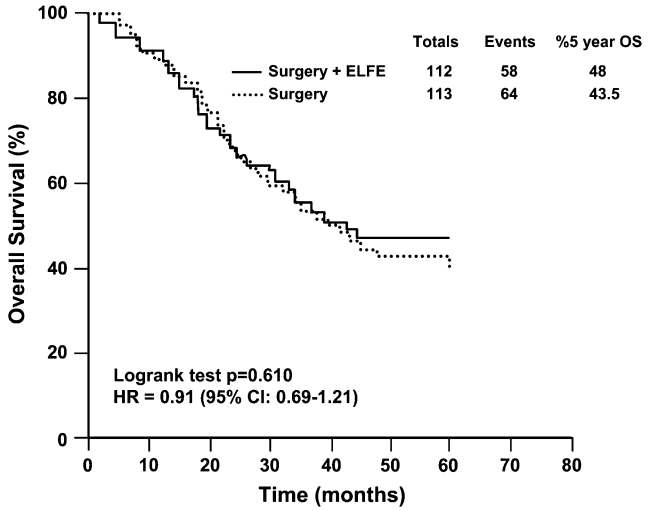

Figure 1. Overall survival by arm Intention-to-treatment population.

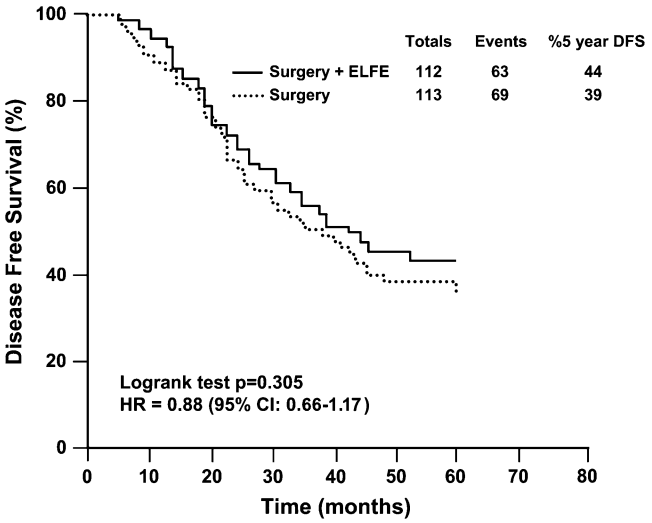

Figure 2. Disease-free survival by arm Intention-to-treatment population.

risk reduction of 12% and an absolute benefit in DFS of 5%. Also, this difference was not statistically significant (HR 0.88; 95% CI 0.66–1.17; P = 0.305). The most frequent cause of death during the follow-up was tumor-related death with 50 patients died in the chemotherapy arm and 58 patients died in the surgery-alone arm. In the relapsed patients, metastases were the most frequent site of first recurrence followed by locoregional recurrence. There was no difference in the pattern of recurrences between the two groups. The present trial was not designed specifically to consider subgroups; however, in an exploratory analysis, the only patient category that seemed to benefit more from adjuvant chemotherapy was that with lymph nodes involvement. In fact, the 5-year survival rate was 41% in the treatment group and 34% in the control arm with a relative risk reduction of 16% and an absolute benefit in of 7%; however, this difference was not statistically significant (HR 0.84; 95% CI 0.69–1.01; P = 0.068). Furthermore, in the same subgroup of node-positive patients, the 5-year DFS rate was 39% in the treatment group and

31% in the control arm with a relative risk reduction of 14% and an absolute benefit in DFS of 8% with a trend towards a statistical significant (HR 0.88; 95% CI 0.78–0.91; $P = 0.051$); (Figures 3 and 4). The results of Cox model showed that the only covariates independently associated with OS and DFS were the depth of invasion and the nodal status.

discussion

This randomized trial showed that adjuvant chemotherapy with six courses of ELFE failed to improve significantly the survival of patients with gastric cancer in comparison with surgery alone. In fact, the primary end point of the study was not reached because ELFE produced an absolute difference in OS at 5 years of 4.5% and this advantage was not statistically significant. The statistical assumptions and the accrual would have changed if we have correctly predicted the survival of the surgical control arm. In fact, in designing this study, we set a 15% difference in 5-year survival between the two arms as clinically significant, which could be modestly and reasonably expected on the basis of the results from previous studies. To prove a statistical significance in the 15% difference in 5-year survival (35% for the chemotherapy and 20% for the surgery-alone arm) with two-sided type I error of 0.05 and type II error of 0.2, a 5-year accrual time and 5-year follow-up, a sample size of at least 103 patients per arm was necessary [12]. The number of patients enrolled (228 patients) was sufficient to detect the planned difference. However, the observed survival difference was smaller than that planned, partly because of much better than expected prognosis of the surgery-alone arm, with a 5-year OS rate of 43.5%. The statistical assumptions and the accrual would have changed if we have had correctly predicted the survival of the surgical control arm. In fact, this study was designed in 1996 and the statistical drawing was affected from the available survival data which showed a 5-year OS ranging between 20% and 30% [2–5], whether in more recent trials the 5-year OS of surgery arm was better ranging between 39% and 48% [14–16]. Therefore, our study may not have sufficient statistical power for detecting smaller, yet still clinically significant survival benefits from chemotherapy as indicated from recent meta-analyses. The meta-analysis of Earle and Maroun [9] reported an odds ratio (OR) for death in the treated patients of 0.80 (95% CI 0.66–0.97), corresponding to a 20% reduction in the relative risk of death with an absolute survival benefit of 4%. Mari et al. [10] reported data from 3568 patients showing an HR of death of 0.82 (95% CI 0.75–0.89) which represented a 18% reduction in the relative risk of death, with an absolute survival effect of 2%–4%. Finally, in the meta-analysis of Pansini et al. [11] was observed a statistically significant reduction in the risk of death with an OR in treated patients being 0.72 (95% CI 0.62–0.84) [11]. These meta-analyses indicate a potential survival benefit of adjuvant chemotherapy in resected gastric cancer with an overall absolute increase at 5-year survival of ~4%. However, no definitive conclusion has yet been drawn from randomized clinical trials of adjuvant chemotherapy for gastric cancer published after these meta-analyses. In the Italian Trials in Medical Oncology study, there was a relative risk reduction of 7% in OS with an absolute difference of 4% [14]. The 7 years result of Federation Francophone de Cancerologie Digestive randomized phase III trial showed a relative risk reduction of 26% for OS with a an absolute difference of 9.5% [15]. Furthermore, another French study demonstrated that adjuvant chemotherapy was unable to improve the OS after surgery with a 5-year survival rate of 39% in the control and chemotherapy groups [16]. Our study showed that the observed survival difference (4.5%), although smaller than that planned, was not different from results of other published trials obtained with cisplatin-based regimens. Although this trial was not designed to consider subgroups, in an exploratory analysis, the only subgroup with a trend to benefit from chemotherapy was the node-positive population: the 5-year DFS of the patients treated with chemotherapy was comparatively better than that of the control patients (39% versus 31%). This result supports the evidence from the meta-analysis of Earle and Maroun [9] reporting an OR for death in node-positive treated patients of 0.70; however,

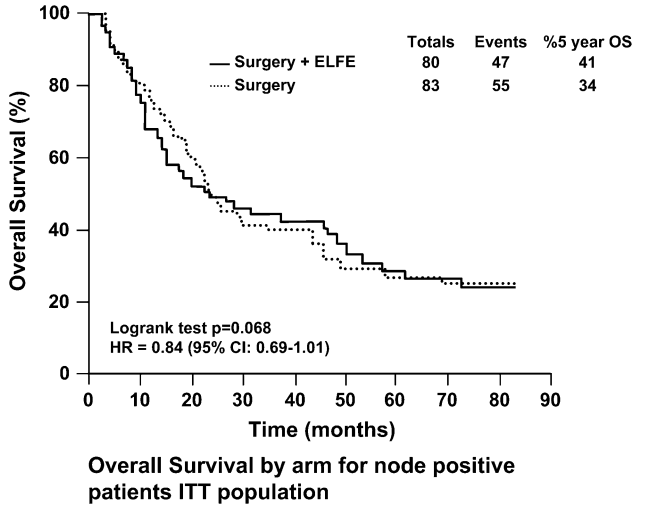

Figure 3. Overall survival by arm for node-positive patients—Intention-to-treatment population.

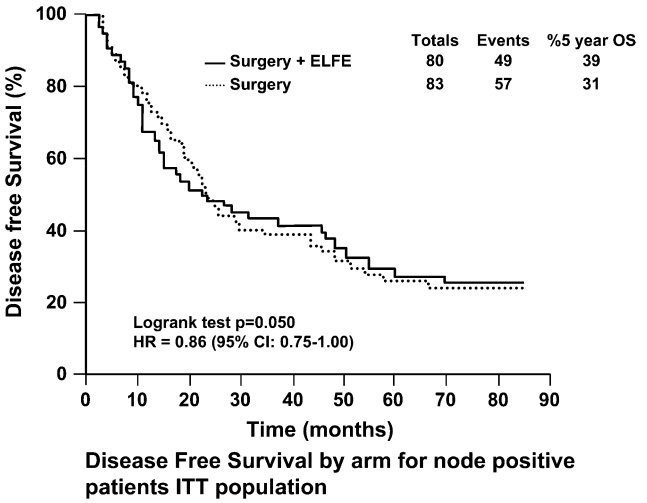

Figure 4. Disease-free survival by arm for node-positive patients—Intention-to-treatment population.

it must be interpreted with caution, because it is based on a retrospective analysis of a subgroup of patients. The difficulty in obtaining a good compliance with treatment is a major problem of adjuvant chemotherapy studies; the potential survival benefit should be balanced against the toxicity induced by the treatment. Many regimens studied in clinical adjuvant trials have recorded significant toxic effects without any survival benefit. Instead, the toxicity of our chemotherapy regimen was mild as confirmed by the observation that 61% of patients received full drug doses. Despite the large number of trials, the evidence supporting the usefulness of adjuvant chemotherapy in radically resected gastric cancer is not yet definitive and, at present, no standard adjuvant regimen has been established [17]. The advent of new regimens inducing higher response rate indicates that gastric cancer is a chemosensitive tumor [18]. However, there are a number of questions to which it will be mandatory to answer. The optimal timing of administration of chemotherapy (preoperative or postoperative) has become of increased interest. Recently the MRC Adjuvant Gastric Infusional Chemotherapy trial, with a median follow-up of 5 years showed that preoperative chemotherapy with epirubicin, cisplatin, continuous infusion fluorouracil combination regimen reported a significant improved OS and DFS compared with the control arm [19]. The quality of surgery is another critical point [20, 21]. In fact, the efficacy of adjuvant chemotherapy must be tested in relationship with adequate surgery before it may be considered as standard therapy. The role of radiotherapy also needs to be determined. The USA Intergroup phase III study showed a significant OS and local control benefit with postoperative adjuvant chemoradiation versus surgery alone in resected adenocarcinoma of stomach and gastrointestinal junction [22]. Finally, there are several newer drug associations incorporating taxanes, irinotecan and/or oxaliplatin with an interesting activity that supports their evaluation in the adjuvant setting [23–26]. In conclusion, although an improvement of 4.5% in 5-year survival was shown in our study, this result failed to reach statistical significance and therefore ELFE regimen cannot be recommended as adjuvant treatment of patients with resected gastric cancer.

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