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Epidoxorubicin and high dose leucovorin plus 5-fluorouracil in advanced gastric cancer: a phase II study

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We conducted a multicentric phase II study on advanced gastric cancer to determine the efficacy and toxicity of treatment with epidoxorubicin (EPI) plus high doses of leucovorin (LV) and 5-fluorouracil (5-FU). Thirty-seven patients with measurable disease were enrolled into the trial and treated with EPI 75 mg/m² on day 1 and LV 200 mg/m² plus 5-FU 450 mg/m² from day 1 to 3, the cycle being repeated every 3–4 weeks from a median of five cycles per patients. The response rate was 49% in 35 evaluable patients, with two complete remissions and 15 partial responses. Median response duration was 12.4 months; median survival for responding patients was 17.3 months, which was significantly longer than 8.7 months for non-responding patients. General toxicity was usually mild, myelotoxicity was moderate and there was no evidence of cardiac toxicity. These results show that EPI–LV–5-FU is an effective regimen for advanced gastric carcinoma. The efficacy of this combination should now be tested as an adjuvant therapy in resectable gastric cancer.

Key words: Advanced gastric cancer, chemotherapy, epidoxorubicin, 5-fluorouracil, leucovorin, phase II study.

Introduction

Gastric cancer represents the third most common cause of cancer deaths in Italy.[1] In 1988, 17 000 new cases were diagnosed but only 25% of these were candidates for curative surgery. At diagnosis, 75% of patients present either locally advanced or disseminated disease.[2–3]

In therapeutic terms, three stages of gastric cancer can be identified: (i) local disease treatable by surgery and with radio-, chemo- or immunotherapy as adjuvant treatment; (ii) locally advanced, non-resectable disease in which chemotherapy can considerably improve the survival of patients; (iii) disseminated disease for which surgery and/or chemotherapy are largely palliative and symptomatic.[4] Of the agents that have been adequately tested in patients previously untreated with chemotherapy, the following have induced response rates of about 20%: cisplatin, fluorouracil (5-FU), carmustine, mitomycin, doxorubicin (Dx) and its analog, epidoxorubicin (EPI).[4–8]

The most widely used chemotherapy regimen is the combination of 5-FU, Dx and mitomycin (FAM);[9] a variety of FAM modifications, replacing mitomycin with other drugs or Dx with EpiDx, have also been investigated.[10] These regimens, when used in patients with advanced gastric carcinoma, usually achieve 30–50% overall response rates, but complete responses are rare.

In a recent report Preusser *et al.* described impressive results with a combination of etoposide, Dx and cisplatin (EAP) in advanced gastric cancer, obtaining a response rate above 60%.[11] This regimen, however, which can be applied only to selected patients, is significantly more toxic than other conventional treatments for gastric cancer and is associated with a high risk of death.[12] Its contribution to prolonging patients' survival time has, therefore, been minimal.

The combination of leucovorin (LV) and 5-FU, to produce a biochemical modulation of 5-FU activity, represents another innovation in the chemotherapy of gastric carcinoma. Zaniboni *et al.* added LV to a FAM schedule and obtained an overall response rate of 46%, but with a significant incidence of myelosuppression.[13]

Thus complete responses are rarely observed and response duration tends to be short-lasting in unresectable gastric cancer, due to the disease's advanced stage and the toxicity of treatments.

Our attempt to achieve a high response rate together with a low treatment-related toxicity led us to employ an EPI–LV–5-FU combination. This choice was based on the better therapeutic index of EPI than of Dx, even in advanced gastric cancer,[10,14] and on the modulation of 5-FU activity by LV.[15]

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Patients and methods

Between October 1988 and February 1991, we recruited 37 advanced gastric cancer subjects, all of whom gave their informed signed consent. All patients had primary gastric adenocarcinoma with histological proof of surgically unresectable, locally advanced and/or metastatic disease. Lesions had to be measurable at one site at least by radiograph or computed tomographic scan or ultrasound or physical examination. The patients' life expectancy had to be >6 months, their age <75 years and their Karnofsky performance status >40.[16] Other criteria for entry into the study included the following: no prior chemotherapy or radiation therapy directed at the site of measurable disease; leukocyte count $\geq 4000/mm^3$; platelet count $>100\,000/mm^3$; bilirubin level <2.0 mg/dl; creatinine level <1.5 mg/dl; no active cardiac disease. The main characteristics of 35 evaluable patients are summarized in Table 1. The site of major measurable lesion was the liver in 13 patients (37%), abdominal mass in 11 (31%), lymph nodes in seven (20%), bone in two (6%) and the lung in two (6%).

The EPI–LV–5-FU regimen was administered over 3 days then repeated every 3–4 weeks, as follows: EPI 75 mg/m^2 intravenously (about 30 min) on day 1, and both LV 200 mg/m^2 (1 h) and 5-FU 450 mg/m^2 (30 min) on days 1, 2 and 3. Blood counts were obtained 2 weeks after drug administration and, when needed, immediately before each treatment. In patients in whom myelosuppression delayed proceeding with the next chemotherapy course, treatment was resumed as soon as the leukocyte count exceeded $2500/mm^3$ and the platelet $75\,000/mm^3$. On day 1, all patients received antiemetic pretreatment with Ondasetron 8 mg (i.v.) and Methylprednisolone 125 mg (i.v.) Response was evaluated at least every two cycles, and WHO criteria[17] were used for defining response, response duration, survival time and treatment-related toxicity.

Table 1. Clinical characteristics of patients

Evaluable patients (gender)	35 (28M–7F)
Median age in years (range)	58 (38–72)
Performance status (Karnofsky)	
(40–60)	4 (11%)
(60–80)	16 (46%)
(80–100)	15 (43%)
Predominant lesion site:	
locoregional only	11 (31%)
liver	13 (37%)
lymph nodes	7 (20%)
lung	2 (6%)
bone	2 (6%)

Results

Thirty-five of the 37 patients who entered this study had an adequate trial and could be assessed for both response and toxicity. One patient refused to continue the therapy and another died of brain metastases before the second treatment course.

The 35 evaluable patients underwent a total of 185 cycles of chemotherapy (median: five per patient; range: four to seven).

Responses became apparent after a median of three cycles (range: two to five) and are summarized in Table 2. There were two (6%) complete (CR) and 15 (43%) partial responses (PR), for an overall response rate of 49% (95% confidence limits: 33–65). Stable disease (SD) was observed in nine (25.5%), whereas the remaining nine patients (25.5%) had progressive disease (PD). Table 2 also lists response rates by dominant site. We found no evidence for any preferential site for response. CR occurred in one patient with liver metastases and in one with lymph node localization. For all 35 patients median duration of response was 12.4 months and median survival was 13 months (range 6–27). The median survival duration of responding patients was 17.3 months which was significantly longer ($p < 0.001$) than the 8.7 months of non-responding patients.

The toxicity of the EPI–LV–5-FU regimen is shown in Table 3. Myelosuppression tended to be cumulative, with lower and more prolonged nadirs after five cycles. However, no patient had severe myelosuppression (WHO toxicity grade >3). Moreover, none required hospitalization for severe infection. Infections (mainly pulmonary) experienced by five patients were all manageable on an outpatient basis. Gastrointestinal toxicity was mild: only two patients had grade 3 diarrhea, and nausea, vomiting or mucositis were not major problems. Alopecia was frequent but it was reversible in all

Table 2. Tumor response by dominant measurable site

Localization	(No.)	CR	PR	SD	PD
Locoregional	(11)	—	5 (45%)	4 (37%)	2 (18%)
Liver	(13)	1 (8%)	5 (38%)	4 (31%)	3 (23%)
Lymph nodes	(7)	1 (14%)	3 (43%)	1 (14%)	2 (29%)
Lung	(2)	—	1 (50%)	—	1 (50%)
Bone	(2)	—	1 (50%)	—	1 (50%)

Table 3. Toxicity of EPI–LV–5-FU regimen

Toxicity grade[a]	Number of patients				
	0	1	2	3	4
Leukopenia	9	7	13	6	—
Thrombocytopenia	18	10	5	2	—
Anemia	14	10	11	—	—
Nausea/vomiting	20	11	4	—	—
Diarrhea	25	3	6	2	—
Mucositis	29	5	1	—	—
Cardiac	30	3	2	—	—

[a]According to World Health Organization criteria.[16]

patients. The mean total dose of EPI administered was 375 mg/m^2 (range 300–525 mg/m^2) and no evidence of cardiac toxicity was recorded.

Discussion

Recent years have witnessed numerous attempts to develop effective combination chemotherapy regimens for the treatment of advanced gastric cancer. The most striking feature of these trials is the high order of activity shown by several regimens. Studies with FAM, FAP or FAMe[7,9,10] report response rates of 40–50%, with a median duration of survival ranging from 7.5 to 10.5 months. A response rate more than 60% with an 8 month median survival time has been found by Preusser *et al.*[11] with the EAP combination, though accompanied by severe infections and myelosuppression. Chemotherapy regimens involving biochemical modulation of antimetabolites in the treatment of advanced gastric cancer have also aroused interest. Using folinic acid to increase the effective cytotoxicity of 5-FU, Machover *et al.*[11] observed responses in 13 (48%) of 27 patients, but a complete response in only one.

Our phase II trial yielded an objective response rate of 49%, with a median survival time of 13 months for all patients and 17.3 months for responders. Response was associated with symptom control and responding patients showed marked improvement in performance status. Overall survival rates were longer with the EPI–LV–5-FU regimen than with FAM, FAMe or FAP combinations.[18–20] Our regimen, moreover was well tolerated; myelosuppression was not a problem and substituting EPI for Dx served to eliminate Dx-related cardiac toxicity.

In future trials, we plan to prolong the therapy in responding patients, thus hoping to further increase survival time. Moreover, if our results are confirmed on a larger sample of patients, we should like to apply this schedule as adjuvant post-surgical treatment in earlier stages of gastric cancer.

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