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5-Fluorouracil, epirubicin and cisplatin (FEP) in the treatment of metastatic gastric carcinoma

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ABSTRACT

In this retrospective study, we evaluated the activity and toxicity of the combination of 5-fluorouracil (5-FU), epirubicin and cisplatin (FEP) in previously untreated patients with metastatic gastric cancer. Sixty-five patients received 5-FU 300 mg/m^2 on days 1-5, epirubicin 50 mg/m^2 on day 1 and cisplatin 60 mg/m^2 on day 1, every 4 weeks. A median of 4 cycles was administered. There were 4 partial responses and 1 complete response (overall response rate 7.6%); 16 patients had stable disease. Median progression-free and overall survival rates were 3 months (95% CI 1.9-4) and 6 months (95% CI 4.2-7), respectively. The principal toxicity was myelosuppression. Grade 3-4 neutropenia occurred in 29.2%, anemia in 18.4%, and thrombocytopenia in 12.3% of patients. Non-hematological toxicity was mild and manageable. We concluded that FEP combination as used at the doses and schedules in this study has inferior activity against metastatic gastric cancer. [Turk J Cancer 2005;35(3):132-135].

KEY WORDS:

Metastatic gastric cancer, 5-Fluorouracil, epirubicin, cisplatin

INTRODUCTION

Gastric cancer is the second most common cancer in the world and one of the most frequent causes of cancer related mortality. At the time of diagnosis, approximately 50% of patients with gastric cancer have metastatic disease. Palliative chemotherapy is the only reasonable therapeutic option in these patients. Combination chemotherapy results in a significant survival advantage in patients with advanced gastric cancer compared with best supportive care in randomized clinical trials (1-3). However, standard combination chemotherapy regimen for advanced gastric cancer has not been well established.

In this article, we report our experience in patients with metastatic gastric cancer treated with 5-fluorouracil (5-FU), epirubicin and cisplatin (FEP) regimen. The choice of drugs for this regimen is based on their single agent activity in upper gastrointestinal cancer and on the synergy between 5-FU and cisplatin (4,5). Epirubicin is included because of anticipated enhanced cytotoxicity in combination with the other two drugs. Evidence for this enhanced cytotoxicity was provided by a randomized trial in advanced gastric cancer demonstrating a survival benefit from the addition of epirubicin to a combination of bolus 5-FU and cisplatin (6).

PATIENTS AND METHODS

Main eligibility criteria for administration of chemotherapy included; histologically proven metastatic gastric adenocarcinoma, measurable disease, Eastern Cooperative

Oncology Group performance status ≤2, a life expectancy >3 months, leukocyte count ≥4000/mm^3, platelet count ≥100000/mm^3, serum creatinine level <1.5 mg/dl, biluribin ≤1.5 mg/dl, and transaminase ≤2.5 X upper normal limits (≤5 X upper normal limits if liver metastases were present). There were no age restrictions. Patients who had received chemotherapy, with symptomatic cardiac disease or recent history of myocardial infarction or arrhythmia and active infections, were excluded.

Epirubicin (50 mg/m^2) and cisplatin (60 mg/m^2) were administered on day 1. Epirubicin was given as a 5-minute bolus injection. Cisplatin was administered as a 4-hour infusion with standard pre- and post-hydration protocols, magnesium and potassium supplementation and intravenous antiemetic therapy (5-HT3 antagonist and dexamethasone). 5-FU (300 mg/m^2) was administered as a 15-minute short infusion on days 1-5. Treatment was repeated at every four weeks. A maximum of six cycles of chemotherapy were planned unless disease had progressed or intolerable toxicities had occurred before.

Toxicity was scored according to standard World Health Organization (WHO) criteria (7). Prior to each course of chemotherapy, all patients were required to have adequate hemopoietic recovery (neutrophil count >2,000/mm^3, platelet count >100,000/mm^3). If this was not possible, chemotherapy was delayed until recovery of the neutrophil and platelet counts to the above levels. A second episode of treatment delay due to myelosuppression or an episode of neutropenic sepsis required a 25% dose reduction on subsequent treatments. A 25% dose reduction of 5-FU was applied in the case of grade 3 diarrhea or mucositis and 50% dose reduction in the case of grade 4. Cisplatin was discontinued when the glomerular filtration rate was less than 40 ml/min.

Objective response to chemotherapy was classified according to WHO criteria (7). A chest radiograph and abdominal computed tomography scan were repeated after cycles 2, 4, and 6 or whenever clinically indicated. Time to progression was measured in all patients from the beginning of chemotherapy to the first evidence of progression. Overall survival was calculated from beginning of chemotherapy until the date of death.

The primary objective of the study was determining the response rate, whereas secondary objective was to evaluate the survival and toxicity. Overall survival and time to progression were estimated using Kaplan-Meier method.

RESULTS

Sixty-five eligible patients (45 males, 20 females) received a total of 234 cycles of FEP, with a median of 4 cycles per patient (range 1-6 cycles). Patient characteristics are summarized in table 1. The median age was 56 years (range 31-73) and the median ECOG performance status was 1 (range 0-2). Metastatic sites were liver (n=39), peritoneum (n=28), distant lymph nodes (n=5), lung (n=4), and ovary (n=3). Patients with peritoneal metastasis had other measurable metastatic lesions.

Grade 3-4 neutropenia was observed in 19 patients (29.2%), anemia in 12 patients (18.4%), and thrombocytopenia in 8 patients (12.3%) (Table 2). Febrile neutropenia was observed in 2 (3%) patients. Grade 3-4 vomiting occurred in 8 patients (12.3%), grade 3 mucositis in 3 patients (4.6%) and grade 2 diarrhea in 4 patients (6.1%). One episode of grade 2 nephrotoxicity developed in one patient (1.5%) with prerenal azotemia but this was reversed with intravenous hydration within 72 hours Six patients required dose reductions of at least one drug. No treatment-related toxic deaths occurred.

Objective response was seen in five patients (7.6%), with one patient achieving a complete response and 4 showing partial response. Sixteen patients (24.6%) remained stable, whereas 44 (67.6%) progressed. The median progression-free and overall survivals were 3 months (95% CI, 1.9-4) and 6 months (95% CI, 4.2-7), respectively.

Table 1
Patient characteristics

Characteristics	N
No. of patients	65
Male/female	45/20
Median age (yrs)	56 (31-73)
ECOG performance status	
0-1	50
2	15
Metastatic sites	
Liver	39
Peritoneum	28
Distant lymph nodes	5
Lung	4
Ovary	3

Table 2
WHO Grade 3-4 Toxicities (n=65)

Toxicity	n (%)
Neutropenia	19 (29.2)
Anemia	12 (18.4)
Thrombocytopenia	8 (12.3)
Mucositis	3 (4.6)
Vomiting	8 (12.3)

DISCUSSION

During the 1980s, the reference treatment for advanced gastric cancer was the combination of 5-FU, doxorubicin and mitomycin-C (FAM). In 1991, however, a study by the European Organization for Research and Treatment of Cancer (8) showed better response rates and improved survival by combining 5-FU, doxorubicin and methotrexate (FAMTX) compared with the results achieved with FAM. In a phase II study, involving 128 patients, the ECF (epirubicin, cisplatin, protracted continuous infusion of 5-FU) regimen was associated with a response rate of 71% (9). This encouraging response rate led to a randomized trial of 274 patients in which ECF was compared to FAMTX. ECF resulted in a significantly better overall response rate (46% vs. 21%); median survival (8.7 months vs. 6.1 months) compared with FAMTX, with less myelosuppression, less mucositis and better quality of life (10). Therefore, the ECF regimen has represented a step ahead in the treatment of advanced gastric cancer.

The response rate observed in our study was 7.6%, resulting in a median progression-free survival of 3 months and in a median overall survival of 6 months. The response rate and survival rate seen with FEP in this study are relatively lower than those reported in previous studies evaluating active regimens such as FAMTX, ECF or EAP (etoposide, doxorubicin, cisplatin) (8,9,11). In a randomized trial comparing etoposide, epirubicin, cisplatin to FEP in advanced gastric cancer, İçli et al. (12) also reported relatively low response rate (15.3%) in the FEP arm. Short infusion 5-FU may be partially responsible for this low response rate in our study. However, there is little evidence to suggest that infusional 5-FU is superior to bolus administration specifically in gastric cancer and the improved response rates with ECF compared to FAMTX may be related to the use of cisplatin in the former regimen. This low response rate also might be due to the substitution of epirubicin for doxorubicin, which could have a lower efficacy than doxorubicin against gastric cancer. Pentheroudakis et al. (13) reported a relatively higher response rate with a combination of non-infusional 5-FU, doxorubicin and cisplatin in patients with advanced gastro-esophageal adenocarcinoma. The overall response rate was 47% in their study. Median progression free and overall survival rate were 5 months and 8 months, respectively. Additionally, the low response rate in our study may be due to the fact that all patients had metastatic disease.

Modulation of 5-FU by leucovorin may improve treatment results. Cocconi et al. (14) showed that PELF (cisplatin, epirubicin, leucovorin and 5-FU) was more active than FAMTX in advanced gastric carcinoma. In their study, the overall response rates to PELF and FAMTX were 39% and 22%, respectively. The survival rates after 12 months (30.8% vs. 22.4%) and 24 months (15.7% vs. 9.5%) were also higher among patients receiving PELF.

Some authors suggest that ECF regimen should be regarded as a reference treatment in advanced gastric cancer (15,16). Despite higher response rates and lower toxicity, a potential drawback of the ECF regimen may be the poor patient acceptability of the indwelling catheter and presence of the external infusion pump. The protracted venous infusion of 5-FU may be replaced by oral UFT plus leucovorin, which has a proven clinical activity in advanced gastric carcinoma. A phase II trial of epirubicin, cisplatin, UFT and leucovorin showed a 57.5% response rate and 15 months median survival duration (17).

It was reported that the short infusion of 5-FU is associated with more severe hematological toxicity than that with infusion regimens (18). We observed grade 3 or 4 neutropenia in 29.2% of patients. However, febrile neutropenia occurred in only two (3%) patients. Grade 3-4 anemia and thrombocytopenia were observed in 18.4% and 12.3% of patients, respectively. These results are comparable to those with infusional 5-FU regimens. Non-hematological toxicity was mild and manageable.

In conclusion, FEP combination as used at the doses and schedules in this study has inferior activity against metastatic gastric cancer.

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