

5-Fluorouracil, Epirubicin and Cisplatin in the Treatment of Metastatic Gastric Carcinoma: A Retrospective Analysis of 68 Patients

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Abstract

BACKGROUND: Gastric cancer is one of the most common types of cancer and one of the most frequent causes of cancer-related death. The majority of gastric cancers show distant metastasis at the time of diagnosis. At present, there is no general agreement over one standard chemotherapy regimen for metastatic gastric cancer. **AIMS:** 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. **SETTING AND DESIGN:** Medical Oncology Department of Uludag University Faculty of Medicine, Bursa; retrospective study. **MATERIAL AND METHODS:** Sixty-eight patients received 5-FU 300 mg/m² on Days 1-5, epirubicin 50 mg/m² on Day 1 and cisplatin 60 mg/m² on Day 1, every 4 weeks. A median of 3.5 cycles was administered. The response rate, time to disease progression, survival and toxic effects were analyzed. **STATISTICAL ANALYSIS USED:** Overall survival and time to progression were estimated using Kaplan-Meier method. **RESULTS:** There were 4 partial responses and 1 complete response (overall response rate 7.3%); 16 patients had stable disease. Median progression-free and overall survival rates were 3.1 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 27.9%, anemia in 17.6%, and thrombocytopenia in 11.7% of patients. Non-hematological toxicity was mild and manageable. **CONCLUSIONS:** We concluded that FEP combination as used at the doses and schedules in this study has inferior activity against metastatic gastric cancer.

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. The incidence of gastric cancer is particularly high in Asia, South America, and Eastern Europe. In some countries there is a wide variation in the incidence of this disease. For example, the incidence of gastric cancer is four times higher in Southern India compared with Northern India. ^[1]

At the time of diagnosis, approximately 50% of patients with gastric cancer have metastatic disease. A number of randomized clinical trials have established the role of chemotherapy in the treatment of these patients. In the four trials that compared chemotherapy plus best supportive care with best supportive care alone, patients who received chemotherapy had longer survival times.^[2-5] However, a standard combination chemotherapy regimen for advanced gastric cancer has not been well established.

Combination regimens with 5-FU and cisplatin showed promising activity in Phase II trials and are frequently used throughout Europe. Epirubicin was included in this combination because of anticipated enhanced cytotoxicity. In a randomized Phase III study a regimen consisting of epirubicin, cisplatin and infusional 5-FU (ECF) showed superior response rates and significantly prolonged survival compared with the historic reference regimen 5-FU, doxorubicin and methotrexate (FAMTX). Therefore, the ECF regimen has represented a step ahead in the treatment of advanced gastric cancer. 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. As an alternative, some European investigators have adopted the use of weekly or biweekly 24- to 48-hour infusions of 5-FU to ease the administration of treatment.

To reduce the catheter line-associated morbidity of ECF, we modified this regimen and administered 5-FU as a short infusion. In this article, we report our experience in patients with metastatic gastric cancer treated with short infusion of 5-FU, epirubicin and cisplatin (FEP) regimen.

Materials and Methods

Patients with metastatic gastric cancer treated with FEP, as first-line chemotherapy from May 1999 to August 2003 at Uludag University Faculty of Medicine, Department of Medical Oncology were analyzed retrospectively. Patients treated with FEP if they fulfilled the following eligibility criteria: (1) a diagnosis of histologically or cytologically proven gastric cancer; (2) bidimensionally measurable disease using computed tomography; (3) no previous chemotherapy or radiotherapy; (4) adequate bone marrow and organ functions (leukocyte count $\geq 4000/\text{mm}^3$, platelet count $\geq 100000/\text{mm}^3$, serum creatinine level $< 1.5 \text{ mg/dl}$, bilirubin $\leq 1.5 \text{ mg/dl}$, and transaminase $\leq 2.5 \text{ X}$ upper normal limits [$\leq 5 \text{ X}$ upper normal limits if liver metastases were present]); (5) Eastern Cooperative Oncology Group performance status ≤ 2 ; (6) normal cardiac function; (7) no other severe medical condition; (8) a life expectancy of at least 3 months; (9) all patients were required to provide written informed consent for treatment. There were no age restrictions. The study was approved by the local ethical committee.

Epirubicin (50 mg/m^2) and cisplatin (60 mg/m^2) were administered on Day 1. Epirubicin was given as a 5-min 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-min short infusion on Days 1-5. Treatment was repeated 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.^[8] Prior to each course of chemotherapy, all patients were required to have adequate haemopoietic recovery (neutrophil count $> 2000/\text{mm}^3$, platelet count $> 100000/\text{mm}^3$). 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 value was less than 40 ml/min.

Objective response to chemotherapy was classified according to WHO criteria.^[8] A chest radiography 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 the beginning of chemotherapy until the date of death. Overall survival and time to progression were estimated using the Kaplan-Meier method.

Table 1: Patient characteristics

Characteristics	No
No. of patients	68
Male/female	48/20
Median age (years)	58 (31-78)
ECOG performance status	
0-1	53
2	15
Metastatic sites	
Liver	48
Peritoneum	28
Distant lymph nodes	10
Lung	7
Ovary	3

Result

Sixty-eight eligible patients (48 males, 20 females) received a total of 243 cycles of FEP, with a median of 3.5 cycles per patient (range 1-6 cycles). Patients' characteristics are summarized in Table 1. The median age was 58 yrs (range 31-78) and the median ECOG performance status was 1 (range 0-2). Metastatic sites were liver (n = 48), peritoneum (n= 28), lymph node (n = 10), lung (n = 7), and ovary (n = 3). Patients with peritoneal metastasis had other measurable metastatic lesions. Alkaline phosphatase level was ≥ 100 U/L in 50 patients (73.5%).

Grade 3-4 neutropenia was observed in 19 patients (27.9%), anemia in 12 patients (17.6%), and thrombocytopenia in 8 patients (11.7%) (Table 2). Febrile neutropenia was observed in 2 (2.9%) patients. Grade 3-4 vomiting occurred in 9 patients (13.2%), Grade 3 mucositis in 3 patients (4.4%) and Grade 2 diarrhea in 4 patients (5.8%). One episode of Grade 2 nephrotoxicity developed in one patient (1.4%) with prerenal azotemia but this was reversed with intravenous hydration within 72 h. Six patients required dose reductions of at least one drug. No treatment-related toxic deaths occurred.

Objective response was seen in 5 patients (7.3%), with 1 patient achieving a complete response and 4 showing partial response. Sixteen patients (23.5%) remained stable, whereas 47 (69%) progressed. The median progression-free and overall survivals were 3.1 months (95% CI, 1.9-4) and 6 months (95% CI, 4.2-7), respectively.

Discussion

We retrospectively analyzed 68 patients with metastatic gastric cancer treated with FEP. In this analysis, the response rate (7.3%) and survival rates are relatively lower than those reported in previous studies evaluating active regimens such as FAMTX, ECF or EAP (etoposide, doxorubicin, cisplatin).^[9-11] Short infusion 5-FU may be partially responsible for this low response

rate in our study. It was shown that continuous intravenous infusion of 5-FU showed comparable or higher response rates with fewer adverse effects with bolus intravenous administration.^[12] Infusional 5-FU as used in the ECF protocol might improve the treatment results. However, this necessitates the use of infusion pumps and the presence of permanent central venous access, increasing the cost and complexity of treatment as well as the risk of line-related complications. Alternative regimens, such as weekly 24-hour administration of 5-FU/folinic acid could be alternatives to protracted venous infusion of 5-FU as used in the ECF regimen in order to improve patients' acceptance. The combination of a weekly high dose of 5-FU/folinic acid plus cisplatin was evaluated in a randomized Phase II trial (EORTC 40953 trial).^[13] In this trial, patients receiving biomodulated 5-FU fared significantly better with respect to survival and response rate. The addition of cisplatin added comparatively little.

The protracted intravenous infusion of 5-FU may be replaced by oral 5-FU pro-drugs such as UFT or capecitabine. A Phase II trial of epirubicin, cisplatin, UFT and leucovorin showed a 57.5% response rate and 15 months median survival duration.^[14] Capecitabine offers the possibility of continuous tumor exposure to 5-FU by preferential activation at the tumor site. In a Japanese trial of 60 patients with previously untreated advanced gastric cancer, intermittent capecitabine (828 mg/m² twice daily for 3 weeks followed by 1 week of rest) led to a response rate of 25.5% and a median survival of 8.8 months.^[15] Capecitabine is currently under investigation in a British Phase III trial.^[16] This four-arm trial is evaluating capecitabine plus 5-FU and oxaliplatin plus cisplatin in patients with advanced esophago-gastric cancer.

Modulation of 5-FU by folinic acid may also improve the response rates and survival. Cocconi *et al*^[17] have shown that cisplatin, epirubicin, leucovorin and 5-FU (PELF) 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.

Recently, four poor prognostic factors, including performance status ≥ 2 , alkaline phosphatase level ≥ 100 U/L, liver and peritoneal metastases have been identified by Chau *et al* in patients receiving first-line chemotherapy for locally advanced or metastatic esophago-gastric cancer.^[18] In our series, peritoneal metastases were present in 28 patients (41%) and liver

Table 2: WHO Grade 3 and 4 Toxicities (n = 68)

Toxicity	Grade 3 n (%)	Grade 4 n (%)
Neutropenia	16 (23.5)	3 (4.4)
Anemia	10 (14.7)	2 (2.9)
Thrombocytopenia	6 (8.8)	2 (2.9)
Mucositis	3 (4.4)	-
Vomiting	5 (7.3)	4 (5.8)

WHO: World Health Organization

metastases in 48 patients (70.5%). Alkaline phosphatase level was ≥ 100 U/L in 50 patients (73.5%). These poor prognostic parameters might also explain the disappointing treatment results.

This study demonstrated that FEP is well-tolerated regimen for patients with metastatic gastric cancer. We observed Grade 3 or 4 neutropenia in 27.9% of patients. However, febrile neutropenia occurred in only two (3%) patients. Grade 3-4 anemia and thrombocytopenia were observed in 17.6% and 11.7% of patients, respectively. These results are comparable to those with infusional 5-FU regimens. Non-hematological toxicity was mild and manageable.

This study has limitations because it was not randomized or prospective. However, we think that the negative results of our study provide additional evidence for the general opinion that the first generation treatment regimens in metastatic gastric cancer are of very little value. Therefore, new agents that are more active and less toxic are required. Phase II studies of new drugs including the taxanes, irinotecan, oxaliplatin, and capecitabine have shown encouraging results in the treatment of patients with advanced gastric cancer. Response rates up to 65% have been demonstrated in Phase II trials evaluating combination regimens of these new agents. [19-24]

In conclusion, the treatment of gastric cancer remains a great challenge to an oncologist. FEP combination as used at the doses and schedules in this study has demonstrated unsatisfactory activity against metastatic gastric cancer. Administration of new cytotoxic drugs in the treatment of gastric cancer may improve the poor prognosis of this disease in the future.

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