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Modified Epirubicin, cisplatin, and 5-FU regimen as first-line chemotherapy in metastatic gastric or gastroesophageal junction adenocarcinoma: A Phase II study

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Abstract

Background: Epirubicin, cisplatin, and 5-FU (ECF) is one of the most commonly used first-line chemotherapy regimens in metastatic gastric cancer. However, due to protracted infusion schedule, need for special infusion pumps, and catheter-related complications, the practical utility and acceptability of standard ECF regimen are limited, particularly in resource-constrained settings including India. **Materials and Methods:** In the present study, we have used a more convenient modification of the standard ECF protocol (using 5 days intravenous infusion of 5-FU at a dose of 750 mg/m^2/day, given over 6 h through a peripheral venous line), in Indian patients with metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma. The primary endpoint was overall survival (OS). The secondary endpoints were overall response rate (ORR), progression-free survival (PFS), and toxicity profile. **Results:** Between January 2014 and December 2017, 107 patients were assigned and treated with this modified ECF regimen. The median age was 52 years (range, 34–62); 66.3% were males and 36.5% of the patients had ≥ 3 metastatic disease site involvement at baseline. Dose reductions due to toxicity were required in 14.9% of the patients. The ORR was 32.7%; median PFS and OS were 5.9 months (95% confidence interval [CI]: 4.7–6.9) and 10.4 months (95% CI: 8.4–11.8), respectively. Both the hematological and nonhematological toxicities were manageable, and there was no toxicity-related death. The most frequent Grade 3–4 adverse events were neutropenia (18.7%), febrile neutropenia (13.1%), mucositis (5.6%), and diarrhea (5.6%). **Conclusions:** In the present study, the modified ECF regimen demonstrated significant efficacy with an acceptable toxicity profile in Indian patients with metastatic gastric and GEJ adenocarcinoma. The survival outcomes of this modified schedule were comparable with those of the standard ECF regimen, as reported earlier. Clearly, this modified and more convenient ECF protocol should be explored and validated through large prospective randomized trials.

Key words: Gastric cancer, modified epirubicin, cisplatin and 5-FU regimen, systemic chemotherapy

Introduction

Gastric cancer is often diagnosed at an advanced stage, and patients with metastatic disease have a poor prognosis with a median survival of 3–5 months, if untreated.[1-3] Chemotherapy is the mainstay of treatment for these patients, and many drugs are active in the first-line treatment, such as fluoropyrimidines, platinum derives, epirubicin, taxanes, and irinotecan.[4-6] However, due to unsatisfactory results, no standard first-line regimen has been emerged.

In light of the data from different trials, fluorouracil (5-FU)- and cisplatin-based regimens (CF) are considered as reference regimens, and the epirubicin, cisplatin, and 5-FU (ECF) regimen is probably the most widely used and the best validated one, till date.[7,8] Webb *et al*. established the superiority of ECF regimen over FAMTX in advanced gastroesophageal cancer, in a randomized trial.[8] After this initial study, a series of randomized trials have been performed over the past two decades, using the same ECF protocol (epirubicin 50 mg/m^2 every 3 weeks, cisplatin 60 mg/m^2 every 3 weeks, and protracted venous infusion 5-FU at a dose of 200 mg/m^2/day for up to 6 months) as reference standard.[9,10] Later on, in a meta-analysis, Wagner *et al*. showed an improvement in weighted average survival of approximately 2 months with addition of anthracycline to CF regimen, and ECF became the reference standard for advanced/metastatic gastric cancer in many countries.[11]

The protracted intravenous (IV) infusion of 5-FU is expensive. Moreover, it needs special infusion pump as well as well-educated and motivated patients. In the present prospective study, we have used a modified ECF regimen, to make it more convenient for our patients, using 5 days IV infusion of 5-FU at a dose of 750 mg/m^2/day (given over 6 h through a peripheral venous line), every 3 weeks. To the best of our knowledge, this is the first ever reported data of this modified ECF schedule in Indian patients with metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma.

Materials and Methods

Patient selection

Patients older than 18 years of age were eligible for inclusion in this prospective single-center study if they had histologically confirmed metastatic adenocarcinoma of the stomach or GEJ; the Eastern Cooperative Oncology Group performance status ≤2; adequate renal, hepatic, and hematologic function; and measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST). Major exclusion criteria were previous chemotherapy for metastatic or locally advanced disease, poor organ function, and evidence of brain metastases.

Treatment assignment

Eligible patients were allocated to a modified ECF regimen which consisted of epirubicin 50 mg/m^2 (1-h IV infusion) plus cisplatin 60 mg/m^2 (1–2 h IV infusion) on day 1, followed by 5-FU 750 mg/m^2/day (continuous IV infusion over 6 h through a peripheral venous line) for 5 days, given every 3 weekly. All the patients also received appropriate hydration, premedication, and primary prophylactic granulocyte colony-stimulating factor. A 25% dose reduction in subsequent cycles was done

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in patients developing any Grade 4 toxicity. Treatment was continued until disease progression, unacceptable toxicity, or patient withdrawal.

Evaluation and outcomes

Before treatment assignment, a complete evaluation was carried out including full medical history, physical examination, complete blood count, serum biochemical analysis, electrocardiography, two-dimensional echocardiography, upper gastrointestinal endoscopy, and contrast-enhanced computed tomography (CECT) of the thorax, abdomen, and pelvis. CECT scans were repeated after 3 and 6 cycles of first-line chemotherapy, as a routine departmental strategy. After the active treatment phase of the study, subsequent CT scans have been performed every 12 weeks (±2 weeks) or whenever needed depending on the symptoms. Responses to chemotherapy were reported according to the RECIST 1.1. The adverse events were classified based on the National Cancer Institute of Canada Common Terminology Criteria for Adverse Events version 4.0. The primary endpoint was overall survival (OS). The secondary endpoints were overall response rate (ORR), progression-free survival (PFS), and toxicity profile.

Statistical analysis

The Kaplan–Meier method was used to estimate the survival distributions. All statistical analyses have been performed using IBM SPSS software version 17.0.

Results

Patient characteristics

Between January 2014 and December 2017, 107 patients were assigned to this modified ECF regimen as first-line chemotherapy, at the Department of Medical Oncology, Kidwai Memorial Institute of Oncology, Bengaluru, Karnataka, India. The baseline demographic parameters were depicted in Table 1.

Chemotherapy characteristics

The median number of first-line chemotherapy cycles received was 6 (range: 3–9). Dose reductions due to toxicity were done in 16 patients (14.9%). Second-line treatment with docetaxel was given in 31 patients (28.9%), and irinotecan was administered to 17 patients (15.8%).

Efficacy and survival

The ORR with this modified ECF regimen was 32.7% (0% complete response [CR] and 32.7% partial response [PR]). Disease stabilization was achieved in 37.4% of patients. The median PFS was 5.9 months (95% confidence interval [CI]: 4.7–6.9) [Figure 1], while the median OS was 10.4 months (95% CI: 8.4–11.8) [Figure 2]. Multivariate analysis showed that patient characteristics including gender, site of primary tumor, site, and number of metastatic sites had no significant impact on survival or response to chemotherapy.

Toxicity profile

The majority of hematological and nonhematological adverse events were of Grade 1 and 2 [Table 2]. The most frequent Grade 3–4 adverse events were neutropenia (18.7%), febrile neutropenia (13.1%), mucositis (5.6%), and diarrhea (5.6%).

Discussion

ECF is one of the most commonly used first-line systemic chemotherapy regimens, in advanced/metastatic gastric cancer.

Table 1: Patient characteristics at baseline

Variables	Modified ECF regimen (*n*=107), *n* (%)
Median age in years (range)	52 (34-62)
Male gender	71 (66.3)
ECOG performance status	
0-1	94 (87.8)
2	13 (12.2)
Site of primary tumor	
GEJ	12 (11.2)
Body of the stomach	69 (64.5)
Pylorus and antrum	26 (24.3)
Grade of primary tumor	
Grade I	8 (7.5)
Grade II	75 (70)
Grade III	24 (22.5)
Site of metastases	
Liver	67 (62.6)
Nonregional lymph node	35 (32.7)
Peritoneum	28 (26.2)
Lung	13 (12.1)
Ovary	5 (4.6)
Number of metastatic sites involved	
0 or 1	20 (18.7)
2	48 (44.8)
≥3	39 (36.5)

ECOG=Eastern Cooperative Oncology Group, GEJ=Gastric or gastroesophageal junction, ECF=Epirubicin, cisplatin, and fluorouracil

Table 2: Toxicity profile

Variables	Modified ECF regimen (*n*=107)	
	All grades, *n* (%)	Grade 3-4, *n* (%)
Anemia	22 (20.6)	-
Neutropenia	44 (41.1)	20 (18.7)
Febrile neutropenia	14 (13.1)	14 (13.1)
Thrombocytopenia	11 (10.3)	-
Nausea-vomiting	30 (28)	4 (3.7)
Fatigue	61 (57)	-
Mucositis	13 (12.1)	6 (5.6)
Diarrhea	15 (14)	6 (5.6)

ECF=Epirubicin, cisplatin, and fluorouracil

However, its practical applicability is limited (particularly in resource-constrained countries) due to its complex delivery schedule, need for special infusion pumps, catheter-related complications, and logistics. Consequently, several studies have investigated a modified version of the standard ECF regimen, with an aim to make it more convenient for the patients.

In a multicentric Phase II study, Felici *et al*. tried to use ECF regimen in a biweekly schedule and reported an ORR of 34.6% and median duration of response of 8 months.[12] Karapetis *et al*. conducted a Phase I and II trial of a modified version of ECF, utilizing 5-FU as a 24-h infusion on day 1 and day 8 of a 3-weekly cycle.[13] Dose-limiting toxicity of febrile neutropenia was encountered at 2000 mg/m^2 in the Phase I cohort, and for the Phase II part of the study (n = 29), the recommended dose of 5-FU was 1750 mg/m^2. The ORR was 45%, and the median OS was 10.7 months. Seventy-two percent of patients obtained clinical benefit with improvement in dysphagia grade or weight gain. However, at the same time, central venous catheter complications were observed in 12 (41%) patients. Finally, the authors concluded that this modified version of ECF regimen

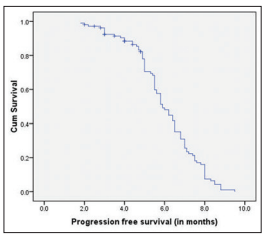

Figure 1: Kaplan–Meier estimates of progression-free survival (in months) of the patients (*n* = 107) treated with modified epirubicin, cisplatin, and 5-FU regimen

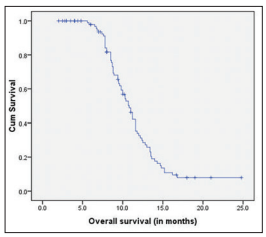

Figure 2: Kaplan–Meier estimates of overall survival (in months) of the patients (*n* = 107) treated with modified epirubicin, cisplatin, and 5-FU regimen

was associated with a response rate and survival similar to that reported with standard ECF regimen. Therefore, this modified regimen might provide an alternative option to standard ECF when a continuous ambulatory infusion pump was not feasible or not preferred by the patient.[13]

In 2005, Ozkan *et al*. published their experience with another modified version of ECF regimen, in 68 patients with metastatic gastric cancer.[14] They have used a much lesser cumulative dose of 5-FU (300 mg/m^2/day, given as a 15-min short infusion on days 1–5, every 4 weeks). Four patients achieved PR and 1 patient achieved CR (ORR: 7.3%); 16 patients had stable disease. Median PFS and OS were 3.1 months and 6 months, respectively. Grade 3–4 neutropenia was observed in 19 patients (27.9%), anemia in 12 patients (17.6%), and thrombocytopenia in 8 patients (11.7%). Finally, the authors concluded that the modified version of ECF regimen used in this study has inferior activity against metastatic gastric cancer. The most probable explanation for a much inferior ORR (7.3%) and median PFS (3.1 months) reported in this study was the use of a much lesser cumulative dose of 5-FU.[14] In a retrospective study, Ibrahim *et al*. investigated a more convenient and logical modification of the standard ECF protocol.[15] They used "5-day continuous IV infusion 5-FU" at a dose of 1000 mg/m^2/day. The ORR was 36.5%; the median PFS was 3.2 months, and the median OS was 7 months, with the modified ECF regimen (*n* = 41). Grade 3–4 neutropenia, thrombocytopenia, and mucositis were seen in 39%, 34%, and 31% of patients, respectively.[15]

In the present prospective study, we have used an almost similar modification of the ECF regimen as done by Ibrahim *et al*., to make it more convenient for our patients, using 5-day IV infusion of 5-FU at a dose of 750 mg/m^2/day (given over 6 h through a peripheral venous line), every 3 weeks. The ORR was 32.7%; median PFS and OS were 5.9 months and 10.4 months, respectively. Both the hematological and nonhematological toxicities were manageable. The survival outcomes and toxicity profile of this modified ECF regimen were quite comparable with the published reports of standard ECF regimen.[8-10] Moreover, it is possible to deliver this modified regimen through a peripheral venous line, which makes it more convenient and safe for our patients.

Conclusions

In the current prospective study, a modified ECF regimen with 5-day IV infusion of 5-FU (given over 6 h through a peripheral venous line) demonstrated significant clinical activity with an acceptable toxicity profile in Indian patients with metastatic gastric and GEJ adenocarcinoma. The survival outcomes of this modified schedule were quite comparable with those of the standard ECF regimen, as reported earlier. Clearly, these encouraging findings of this modified and more convenient ECF protocol should be tested and validated further, through large prospective randomized trials.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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