

Clinical Research Paper

A phase II trial of epirubicin plus oxaliplatin and fluorouracil as first-line chemotherapy for advanced gastric cancer

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Key words: gastric neoplasm, chemotherapy, epirubicin, oxaliplatin, 5-fluorouracil, efficacy

Background and Objective: The prognosis of advanced gastric cancer (AGC) is poor. No standard chemotherapy regimens for AGC are available so far. Randomized studies have revealed that epirubicin plus oxaliplatin and 5-fluorouracil (5-FU) (EOF) regimen could improve the response rate and prolong survival in patients with AGC. This study was to evaluate the efficacy and toxicity of EOF regimen as first-line chemotherapy for AGC patients. **Methods:** Fifty-two patients with pathologically confirmed AGC were entered into the study. On day 1, patients were intravenously injected with 50 mg/m² epirubicin, infused with 85 mg/m² oxaliplatin over 2 h, infused with 400 mg/m² calcium folinate (CF) over 2 h, followed by a 46-h infusion of 5-FU at 2600 mg/m². The cycle was repeated every three weeks. Treatment efficacy was evaluated every two cycles based on the RECIST standard. All patients received at least two cycles of therapy. **Results:** Patients received a total of 220 cycles of treatment, and all were evaluable for efficacy and toxicity. The overall response rate was 46.15%. Three cases (5.77%) achieved complete response (CR), 21 (40.38%) achieved partial response (PR), 18 (34.62%) had stable disease (SD), and 10 had progression disease (PD). The median time to progression (TTP) was 6.5 months and the median survival time (MST) was 9.8 months. Hematologic toxicities included 14 cases (26.92%) of grades 3–4 neutropenia, two of which were accompanied with fever, and four cases of grade 3 thrombocytopenia. The main non-hematologic toxicities included six cases of grade 3 nausea and vomiting (11.54%), and 28 cases of grades 1–3 neurotoxicity (53.84%). No treatment related deaths occurred. **Conclusion:** EOF regimen is effective and well tolerated as first-line chemotherapy for AGC patients.

Gastric cancer is a common malignancy of the gastrointestinal tract in China, with the highest morbidity and the highest mortality rate.¹ Patients mostly present with no symptoms in the early stage, and are diagnosed at the advanced stage. Therefore, they often miss their chances for surgery. Chemotherapy is the primary treatment for advanced gastric cancer (AGC), there is yet no standard chemotherapy regime for AGC so far. It is critical to improve therapeutic efficacy, prolong survival as well as improve the quality of life of patients. This study was to evaluate the efficacy and toxicity of EOF regimen [epirubicin + oxaliplatin + 5-fluorouracil (5-FU)] as first-line chemotherapy for AGC patients.

Materials and Methods

General data. Fifty-two pathologically confirmed AGC patients treated in the First Affiliated Hospital of Nanchang University from June 2005 to June 2007 were entered into the study. Patients were treated with EOF as the first-line chemotherapy regime. There were 33 males and 19 females, aged from 28 to 68 years with a median age of 55 years. All patients had at least one detectable lesion and were reported to have distant metastasis or postoperative recurrence, or were unsuitable for surgery. Eighteen cases had poorly-differentiated adenocarcinoma, 13 had moderately-differentiated adenocarcinoma, 10 had mucinous adenocarcinoma, seven cases had signet-ring cell carcinoma, and four cases had tubular adenocarcinoma. The primary sites of AGC were cardia (18 cases), gastric antrum (23 cases) and gastric body (21 cases). Twenty-two cases had liver metastasis, nine cases had pulmonary metastasis, 26 cases had peritoneal lymph node metastasis, 13 cases had supraclavicular lymph node metastasis, five cases had pelvic metastasis, and one case had bone metastasis. A single metastatic site was noted in 34 cases, whereas two or more than two metastatic sites were noted in 18 cases. The enrollment criteria for the patients were as follows: Karnofsky score of ≥ 60 , expected survival of longer than three months, normal findings of routine blood tests and electrocardiogram (ECG) before the commencement of chemotherapy, liver and renal functions within 1.5 times of the normal ranges, no history of peripheral nerve diseases.

Treatment methods. On day 1, patients were intravenously injected with 50 mg/m² epirubicin, infused with 85 mg/m² oxaliplatin over 2 h, infused with 400 mg/m² calcium folinate (CF) over 2 h followed by a 46-h infusion of 5-fluorouracil at 2.6 g/m². The cycle was repeated every 21 days. Granisetron was given as antiemetic treatment

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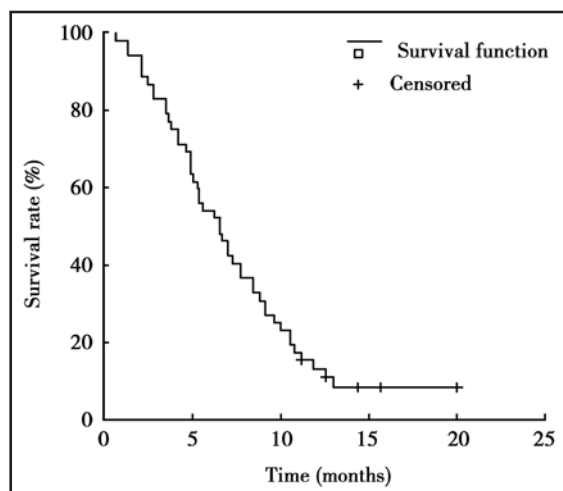


Figure 1. Kaplan-Meier curve of time to progression of 52 patients with advanced gastric cancer.

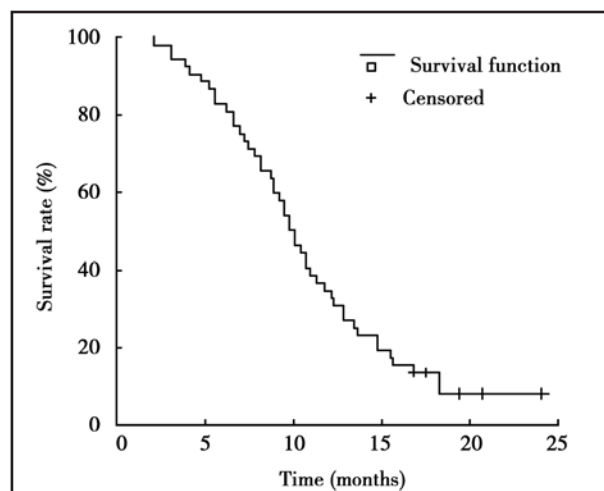


Figure 2. The overall survival curve of 52 patients with advanced gastric cancer.

before chemotherapy. Therapeutic efficacy was assessed after at least two cycles. All patients received at least two cycles of therapy. When the neutrophil count below 1.5×10^9 or platelet count below 75×10^9 occurred after chemotherapy, subsequent chemotherapy for the patient was postponed, but no longer than two weeks. When grade 4 neutropenic fever, grades 3–4 neurotoxicity, or grade 4 mucosa reaction appeared, the dose of chemotherapy was reduced by 25%. If grade 4 neutropenic fever occurred twice, the treatment was terminated. Granulocyte colony-stimulating factors were administered for patients who developed grades 3–4 myelosuppression.

Observation indices. The RECIST criteria were adopted to assess the therapeutic efficacy. Adverse reactions were categorized into grades 0–4 according to the evaluation standards for the toxicities of anticancer drugs proposed by World Health Organization (WHO). Time to tumor progression (TTP) was measured from the initiation of chemotherapy until disease progression. Overall survival time (OS) was measured from the initiation of chemotherapy until death/the last follow-up. Follow-ups were conducted through telephone calls or mails. The final follow-up was performed on the June 1, 2008. All patients were followed up and evaluable, with a median follow-up time of 16.8 months.

Statistical analysis. Statistical analyses were performed using SPSS13.0 software. Median survival time (MST) and median TTP were calculated using the Kaplan-Meier method, and corresponding curves were plotted.

Results

Therapeutic efficacy of EOF regimen. Fifty-two patients received a total of 220 cycles EOF regimen, ranged from two to seven cycles with a median of four cycles per patient. Three cases (5.77%) achieved complete remission (CR), 21 cases (40.38%) achieved partial remission (PR), 18 cases (34.62%) had stable disease (SD), and 10 cases (19.23%) had progressive disease (PD). The total efficacy rate was 46.20%, median TTP was 6.5 months (Fig. 1), and median OS was 9.8 months (Fig. 2).

Adverse reactions of EOF regimen. Major hematological toxicities included grades 3–4 neutropenia (26.92%), grades 3–4 thrombocytopenia (7.69%), grades 3–4 anemia (7.69%). Two patients

with grades 3–4 neutropenia developed pyrexia. Non-hematological toxicities were generally mild. The incidence of grades 1–3 peripheral neurotoxicity was 53.84%, and no grades 4 peripheral neurotoxicity occurred. No treatment was terminated due to gastrointestinal reactions, which were mostly grades 1–2. Alopecia appeared in most cases, most of which were grades 1–2 (Table 1). Chemotherapy for 24 patients was postponed, less than seven days in 19 cases and more than seven days in five cases, due to chemotherapy toxicities. The dose of chemotherapy was reduced in three patients. None of the patients terminated the therapy, and no chemotherapy-related death was reported.

Discussion

Gastric cancer is one of the most common malignancy in China. It is diagnosed at advanced stages for most patients, when surgery is no longer suitable. This leaves chemotherapy as one of the main approaches in the treatment of AGC. In 1980, Macdonald et al.² first reported the combined chemotherapy of 5-FU, adriamycin (ADM), and mitomycin C (MMC) (FAM regime) in treating 62 patients with AGC and achieved a remission rate of 42%. Subsequently FAM regime was used as the standard regime for treating AGC. In 1991, Cunningham et al.³ reported the use of epirubicin instead of doxorubicin and proposed ECF regime, which shows good therapeutic efficacy. ECF was used as a control regime in subsequent clinical studies for gastric cancer. However, conventional chemotherapy regimes based on 5-FU, anthracyclines and cisplatin, such as FAM, ELF, EAP, ECF and so on, cause severe side effects with short remission time. In recent years, newly drugs, such as taxols, oxaliplatin, CPT-11, capecitabine and so on, have been introduced. Each of those drugs alone has achieved an effective rate of greater than 20% for gastric cancer. The combination treatment containing those new drugs has further improved the therapeutic efficacy of AGC.

Oxaliplatin is a third generation platinum-based chemotherapy drug. It binds to DNA in the body more than ten times faster than cisplatin and is more stable, exerting stronger cytotoxic effects than cisplatin. Compared with cisplatin, oxaliplatin has a broader spectrum of anticancer activities, and has no cross resistance with cisplatin or carboplatin. One of its major toxic side-effects is neurotoxicity,

Table 1 Adverse events occurred in the 52 advanced gastric cancer patients after treatment with EOF regimen

Adverse events	Grade 0 (cases)	Grade I (cases)	Grade II (cases)	Grade III (cases)	Grade IV (cases)	Grade III/IV (%)	Incidence (%)
Anemia	35	7	6	4	0	7.69	32.69
Neutropenia	15	13	10	10	4	26.92	71.15
Thrombopenia	41	4	3	4	0	7.69	21.15
Nausea/vomiting	21	14	11	6	0	11.54	59.61
Diarrhea	44	4	4	0	0	0	15.38
Alopecia	19	16	15	2	0	3.85	63.46
Mucositis	48	2	2	0	0	0	7.69
Phlebitis	48	3	1	0	0	0	7.69
Hepatotoxicity	49	3	0	0	0	0	5.77
Peripheral neuritis	24	15	12	1	0	1.92	53.84
Hand-foot syndrome	49	3	0	0	0	0	5.77
Erythra	50	2	0	0	0	0	3.85
Change in ECG	49	3	0	0	0	0	5.77

which is mostly reversible. It has mild myelosuppression, no nephrotoxicity and mild gastrointestinal reaction. Furthermore, the use of oxaliplatin and 5-FU together exerts a synergistic effect. Al-Batran et al.⁴ conducted a stage III clinical study using FOLFOX as the first-line chemotherapy regime in treating patients with AGC and achieved a response rate (RR) of 34.8% and TTP of 5.8 months. Hence, on the basis of ECF regime, we replaced cisplatin with oxaliplatin in treating AGC patients to improve therapeutic efficacy and reduce side-effects.

Recently, it is reported by the REAL-2 study⁵ that the overall RR of EOF regime is 42.40%, the median TTP is 6.5 months, and MST is 9.3 months. Shen et al.⁶ adopted the EOF regime in treating 36 AGC patients. Patients achieved an overall RR of 41.7%, and 38.9% patients experienced a more than 20-point improvement in KPS score. The EOF regime shows good efficiency for AGC with good tolerance. We applied EOF regime as the first-line chemotherapy in treating 52 AGC patients. The overall RR was 46.20%, TTP was 6.5 months, and MST was 9.8 months, similar to other reports. We administered drugs differently from other studies. In the REAL-2 study, 200 mg/m² of 5-FU was given via intravenous infusion daily from day 1 to day 14. A dose of 130 mg/m² oxaliplatin was given on day 1. In the study conducted by Shen et al.,³ 500 mg/m² of 5-FU was given by continuous infusion for 22 h on day 1 to day 3. In this study, 5-FU was continuously given at 2.6 g/m² via a micropump for 46 h; whereas oxaliplatin was given at 85 mg/m². We previously used the modified FOLFOX regime based upon 5-FU administration for advanced colorectal cancer (ACC) and obtained good therapeutic efficacy.⁷

We found that hematological toxicities caused by EOF regimen were mainly grades 1–2. The incidence rates of grades 3–4 neutropenia, grades 3–4 anemia, and grades 3–4 thrombocytopenia were 19.23%, 7.69%, and 7.69%, respectively. Manifestations of non-hematological toxicities included nausea, vomiting, diarrhea, peripheral neurotoxicity, hand-foot syndrome, alopecia, most of which were grades 1–2. The incidence rates of grades 3–4 nausea and vomiting and grades 3–4 peripheral neurotoxicity were 11.54% and 1.92%. The majority of patients showed good tolerance. Compared

with the incidence rates of grades 3–4 neutropenia (29.90%) and grades 3–4 peripheral neurotoxicity (8.40%) in the REAL-2 study, the corresponding side reactions were lower in our study, which may be due to the reduced dose of oxaliplatin. In the V325 study, where docetaxel (DOC), cisplatin (DDP) and 5-FU (DCF regime) were used in treatment of AGC, the incidence rates of grades 3–4 neutropenia was up to 82% and neutropenic pyrexia was 29%.⁸ It is obvious that the hematological toxicities in our study were significantly milder than those in the DCF regime.

In our study, the use of EOF regime as the first-line treatment for AGC demonstrates good efficacy with tolerant toxicities, shortens hospitalization duration and lowers medical costs for patients, thus EOF is recommended for clinical applications.

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