Phase II study of epirubicin plus oxaliplatin and infusional 5-fluorouracil as first-line combination therapy in patients with metastatic or advanced gastric cancer

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The purpose of this study was to evaluate the efficacy and safety of an epirubicin, oxaliplatin and infusional 5-fluorouracil combination in patients with advanced gastric cancer. Patients with previously untreated advanced measurable gastric cancer received epirubicin (50 mg/m^2, day 1), oxaliplatin (130 mg/m^2 2-h infusion, day 1) and 5-fluorouracil (750 mg/m^2, 24-h infusion, day 1–3) every 3 weeks. The primary endpoint of this phase II study was the response rate according to Response Evaluation Criteria in Solid Tumors. Out of 48 patients, 46 were evaluable for efficacy and 48 for toxicity. A median of five cycles (range 1–6) was administered. The overall best response rate was 47.8% (95% confidence interval 33–63%) including 2.2% complete responses and 45.6% partial responses. The median time for progression and median overall survival was 5 (95% confidence interval 4.1–5.9) and 11 months (95% confidence interval 8.1–13.9), respectively. Grade 3/4 neutropenia and leukocytopenia were observed in 25 and 12.5% of patients, respectively. Grade 3/4 nonhematological toxicities included nausea (6.3%), vomiting (14.6%), neurological toxicity (10.4%) and mucositis (2.1%). The epirubicin, oxaliplatin and infusional 5-fluorouracil regimen was effective and well tolerated as a front-line chemotherapy for patients with metastatic or advanced gastric cancer, and should be evaluated further. *Anti-Cancer Drugs* 18:581–586 © 2007 Lippincott Williams & Wilkins.

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Introduction

Despite a remarkable decline of its incidence during the second half of the 20th century, gastric cancer remains the fourth most common cancer worldwide, with an estimated 934 000 new cases per year in 2002 (8.6% of new cancer cases). It is the second most common cause of death from cancer (700 000 deaths annually). Almost two-thirds of the cases occur in developing countries and 42% in China alone [1]. The only potentially curative treatment for localized gastric cancer is surgery. Unfortunately, the majority of patients have locally advanced or metastatic disease at presentation, which precludes resection. Systemic chemotherapy is widely accepted as palliative treatment, as it has been associated with a significantly superior median survival and a better quality of life in comparison with best supportive care alone [2]. Unresectable advanced or recurrent gastric cancers still have poor prognoses; however, results of survival have been unsatisfactory so far, with a median survival time ranging between 6 and 9 months [3–5].

In prospectively randomized studies, combination chemotherapy with epirubicin, cisplatin and continuous infusion of 5-fluorouracil (5-FU) (ECF) has led to significant response rates and survival benefit for patients with advanced gastric cancer [6,7]. The results of ECF were superior to those achieved with the former standard regimen consisting of 5-FU, doxorubicin and high-dose methotrexate. A potential drawback of ECF is the need for an indwelling catheter and external infusion pumps as a limiting factor in the acceptability of this type of regimen to patients. A meta-analysis showed that comparisons of 5-FU/cisplatin-containing regimens with versus without anthracyclines [hazard ratio (HR) = 0.77; 95% confidence interval (CI): 0.62–0.95] and 5-FU/anthracycline-containing combinations with versus without cisplatin (HR = 0.83; 95% CI: 0.76–0.91) both demonstrated a significant survival benefit for the three-drug combination [2].

Oxaliplatin is a third-generation diaminocyclohexane platinum compound proven in numerous clinical trials to be active in various tumor types. In contrast to cisplatin, oxaliplatin has demonstrated efficacy alone and in combination with 5-FU in advanced colorectal cancer. Many studies are ongoing to test the combination in

0959-4973

noncolorectal gastrointestinal tumors and other malignancies, including gastric cancer [8]. Oxaliplatin has a more favorable toxicity profile compared with cisplatin. The dose-limiting toxicity is a cumulative sensory peripheral neuropathy [9]. In the initial ECF regimen developed in the gastrointestinal unit of the Royal Marsden Hospital, infusion of 5-FU was administered from day 1 to day 21. We modified the schedule of infusion of 5-FU for 3 days, which is more comfortable for patients.

On the basis of the possible advantages, this phase II trial was designed to evaluate the efficacy and safety of epirubicin plus oxaliplatin and infusional 5-FU combination chemotherapy in first-line metastatic or advanced gastric cancer.

Patients and methods

Eligibility

Patients with advanced gastric cancer who had histologically confirmed and measurable target lesions not previously treated by systemic chemotherapy were enrolled onto the study. The patients were required to have measurable disease. Other eligibility criteria were: Eastern Cooperative Oncology Group performance status ≤ 2, a life expectancy > 3 months, age between 18 and 75 years, adequate bone marrow (absolute neutrophil count ≥ 1500 cells/mm^3, platelet count $\geq 100\,000$ cells/mm^3), hepatic function (aspartate aminotransferase/alanine aminotransferase) ≤ 3.0 times the upper normal limit (UNL), renal (serum creatinine $\leq 1.5 \times$ UNL) and liver (serum bilirubin $\leq 1.5 \times$ UNL) functions, a normal cardiac function, absence of second primary tumor other than nonmelanoma skin cancer or in-situ cervical carcinoma, no central nervous system involvement, no prior radiotherapy in parameter lesions, and no concurrent uncontrolled medical illness. The protocol was approved by the Ethics Committee of our centers and carried out according to the principles of the Declaration of Helsinki and good clinical practice guidelines, and all patients gave their written informed consent to participate in the trial.

Treatment schedules

Treatment consisted of epirubicin 50 mg/m^2 by intravenous bolus followed, 15 min later, by oxaliplatin 130 mg/m^2 as a 2-h infusion on day 1 and 5-FU 750 mg/m^2 as a 24-h continuous infusion on day 1 through day 3. Cycles were repeated every 3 weeks. Antiemetic treatment consisted of an antiserotonin agent in a 15-min infusion before starting chemotherapy. Treatment was postponed by a maximum of 2 weeks if the absolute neutrophil count was < 1500 cells/mm^3 or the platelet count was $< 100\,000$ cells/mm^3. A 25% drug dose reduction was planned in case of grade 4 neutropenic fever (absolute granulocyte count < 500 cells/mm^3 at the time of a documented temperature of 38°C or higher), as well as in case of grade 4 mucositis or grade 3 neurotoxicity. Chemotherapy was administered on an inpatient basis for a maximum of six cycles and was discontinued in case of unacceptable toxicity, treatment delay longer than 2 weeks, disease progression or patient refusal.

Pretreatment and follow-up studies

Pretreatment evaluation included clinical history and physical examination, automated blood cell count, biochemical profile, computed tomography of thorax and abdomen, and electrocardiogram. Endoscopy was performed only in case of complete remission of all measurable lesions. Blood counts were obtained twice a week; biochemical profile was repeated every 3 weeks. All measurable parameters of disease were reevaluated every 6 weeks, until the tumor progressed. Cardiac monitoring was performed at baseline with electrocardiograms repeated every cycle.

Evaluation

Patients were evaluated for response to chemotherapy every two cycles of treatment. Responses were assessed by at least two observers and were confirmed by an expert independent radiologist. The Response Evaluation Criteria in Solid Tumors were used to evaluate clinical response [10]. Assessment of time to progression (TTP) was determined by measuring the time interval from the beginning of treatment until the first documentation of progression regardless of the patient's treatment status. Overall survival (OS) was determined by measuring the time interval from the beginning of the treatment to the date of death or last contact. Toxicity was assessed in each treatment cycle of therapy using the National Cancer Institute Common Toxicity Criteria (version 2.0).

Statistical consideration

The primary endpoint of this study was to estimate the overall response rate of the regimen. Secondary end points were TTP, OS and safety. The Optimal Simon two-stage phase II design was used to determine the sample size. Interim analysis was carried out when the first 15 assessable patients had been recruited [11]. If more than five responses were observed, 31 additional patients were to be recruited; otherwise, the study was to be terminated. If more than 18 responses were observed in the 46 patients, the regimen was considered sufficiently active with a significance level of 5% and power of 80% to be submitted for further evaluation. TTP and OS were analyzed according to the Kaplan–Meier method, and were updated to 30 May 2006. Statistical computations were performed using SPSS (version 10.0). (SPSS, Chicago, Illinois, USA).

Results

Patients characteristics

From October 2002 to May 2006, 48 patients with a metastatic or advanced gastric cancer were entered onto

this trial. Forty-six patients were evaluated for efficacy and 48 patients for toxicity. The pretreatment characteristics of patients are listed in Table 1. None of the patients had received chemotherapy before for advanced disease. Two patients were excluded from the response analysis because they did not complete two cycles of chemotherapy and did not show early progression; both the patients refused continuation of treatment because of personal aspects after the first cycle.

Efficacy

Among the 46 assessable patients, we observed one (2.2%) complete response and 21 (45.6%) partial responses, for an overall response rate of 47.8% (95% CI: 33–63%). As per the intent-to-treat analysis, the overall response rate was 45.5% (95% CI: 31–61%). Eighteen (39.1%) patients had stable disease and six (13.0%) had progressive disease. Median TTP was 5 months (95% CI: 4.1–5.9 months) (Fig. 1) and median OS was 11 months (95% CI: 8.1–13.9 months) (Fig. 2). One- and 2-year survivals were 40.8 and 13.1%, respectively. Thirty-five patients had died at the time of the present evaluation. The median follow-up was 11.2 months (range: 6.8–31 months).

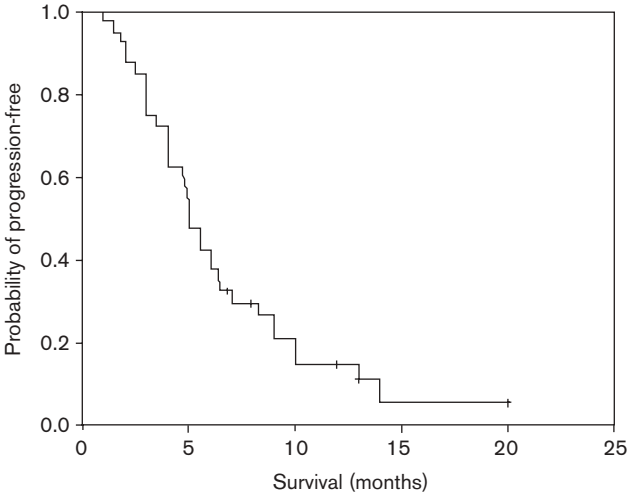
In total, 226 chemotherapy cycles were administered, with a median of five cycles per patient (range 1–6), and two (4.2%) patients received one cycle, four (8.3%) two cycles, two (4.2%) three cycles, nine (18.8%) four cycles, 12 (25%) five cycles and 19 (39.6%) six cycles. The planned dose intensity was 16.7 mg/m^2/week for epirubicin, 43.3 mg/m^2/week for oxaliplatin and 750 mg/m^2/week for 5-FU. Dose intensity for all 48 patients was 16.2 mg/m^2/week for epirubicin, 40.2 mg/m^2/week for oxaliplatin and 736.4 mg/m^2/week for 5-FU, with 97.4% of the planned epirubicin dose, 92.7% of the planned oxaliplatin dose and 98.2% of the planned 5-FU dose delivered. A total of 13 (27.1%) patients received second- and third-line chemotherapies: 10 taxane-based and four irinotecan-based.

Table 1 Baseline patient characteristics ($n=48$)

	No.	%
No. included	48	
Median age (years)	53 (21–71)	
Men/Women	33/15	68.7/31.3
ECOG performance status		
0	17	35.4
1	25	52.1
2	6	12.5
Disease status		
Newly diagnosed	38	79.2
Recurrent	10	20.8
Locally advanced	9	18.7
Metastatic	39	81.3
Histology		
Well differentiated adenocarcinoma	0	0
Moderately differentiated adenocarcinoma	11	22.9
Poorly differentiated adenocarcinoma	23	47.9
Signet ring cell	10	20.8
Mixed	4	8.3
Localization of the primary tumor		
Stomach	41	85.4
Esophagogastric junction	7	14.6
Sites of metastases		
Liver	21	43.8
Lymph nodes	16	33.3
Peritonum	11	23.0
Lung	2	4.2
Other	16	33.3
No. of involved sites		
1	30	62.5
2	14	29.2
3	4	8.3
≥ 4	0	0

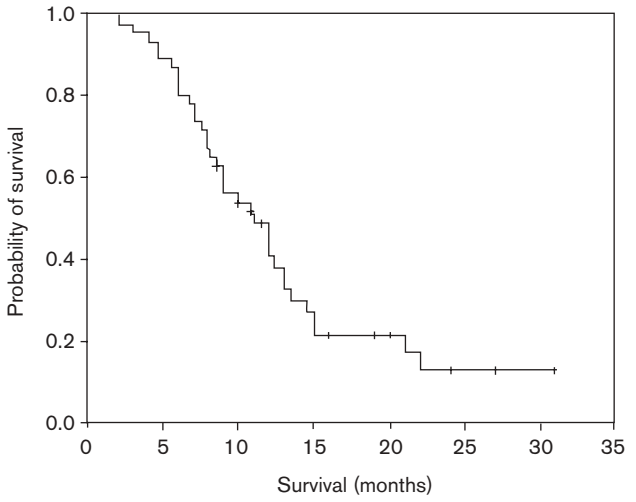
ECOG, Eastern Cooperative Oncology Group.

Fig. 1



Time to progression for all patients.

Fig. 2



Overall survival for all patients.

Table 2 Treatment-related adverse events according to NCI-CTC scale

	Grade (% of patients) ($n=48$)		Grade (% of cycles) ($n=226$)	
	1–2	3–4	1–2	3–4
Leukocytopenia	50	12.5	48.2	6.6
Neutropenia	35.4	25	36.7	12.4
Febrile neutropenia	4.2	0	0.9	0
Anemia	54.2	6.3	38.5	6.6
Thrombocytopenia	22.9	6.3	13.3	3.5
Nausea	77.1	6.3	79.2	3.5
Vomiting	66.7	14.6	58.0	12.0
Diarrhea	31.3	4.2	25.2	2.2
Constipation	29.2	0	19.9	0
Increased AST	25	0	12.0	0
Increased creatinine	2.1	0	0.9	0
Alopecia	89.6	NA	52.2	NA
Neurological toxicity	47.9	10.4	46.9	7.1
Mucositis	20.8	2.1	11.5	0.9
Fatigue	18.8	2.1	12.4	2.7

AST, aspartate aminotransferase; NA, not applicable; NCI-CTC, National Cancer Institute Common Toxicity Criteria.

Toxicity

A total of 226 cycles of epirubicin, oxaliplatin and infusional 5-fluorouracil (modified EOF) regimen was analyzed in 48 patients. The frequencies of hematological and nonhematological toxicities are shown in Table 2. Grade 3/4 hematological toxicities were neutropenia in 12 patients (25%) and in 28 cycles (12.4%). Grade 3/4 leukocytopenia was observed in six patients (12.5%) and in 15 cycles (6.6%), anemia in three patients (6.3%) and in 15 cycles (6.6%), and thrombocytopenia in three patients (6.3%) and in eight cycles (3.5%). No patient required platelet transfusion, hematopoietic growth factors support care in 38 (16.8%) cycles. The most common nonhematological toxicities were nausea, vomiting, alopecia and neurological toxicitity. Grade 3/4 nausea, vomiting and neurological toxicitity occurred in 6.3, 14.6 and 10.4% of patients, respectively. No serious adverse events were reported during the study and none of the patients died of the toxicity.

Although the protocol specified 21 days between cycles, 182 cycles (80.5%) received all treatment cycles within the protocol 21-day period. Thirty cycles (13.3%) were delayed for less than 7 days, 14 cycles (6.2%) were delayed for more than 7 days. Of these, 32 cycles (14.2%) were delayed for toxicity reasons.

Discussion

Oxaliplatin has demonstrated additive or synergistic activities with 5-FU, even in 5-FU-resistant cell lines [12] and in many tumor cell lines resistant to cisplatin [13]. In the study of Eriguchi *et al.* [14], oxaliplatin was able to inhibit cell growth and to induce apoptosis in five gastric cell lines, especially in the scirrhous type. Oxaliplatin has a better toxicity profile than cisplatin, its main and dose-limiting toxicity being acute, cumulative short-term sensory peripheral neuropathy, resulting in acral paresthesia/dysesthesia, exacerbated by cold [9]. The present study suggests that the combination of epirubicin plus oxaliplatin and infusional 5-FU is an effective and well-tolerated regimen for the first-line metastatic or advanced gastric cancer. This combination regimen demonstrated promising efficacy with a tumor response rate of 47.8%, a median TTP of 5 months and a median overall survival of 11 months. And this is comparable to the results reported from studies using FAMTX regimen (5-FU, doxorubicin, and high-dose methotrexate), ECF (epirubicin, cisplatin and infusion 5-FU), ELF (etiposide, leucovorin and 5-FU), FOLFOX [biweekly 5-FU/folinic acid (FA)/oxaliplatin], FUFOX [weekly 5-FU/folinic acid (FA)/oxaliplation], [6,15–18]. Two principal categories of oxaliplatin-based combinations exist in the treatment of advanced gastric cancer. The first is a double-drug combination with weekly and biweekly 5-FU/FA oxaliplatin, whereas the second is a triple-drug combination consists of fluoropyrimidine (infusional 5-FU and oral 5-FU prodrug)/anthracycline/oxaliplatin. Three phase II studies published previously had shown consistent results regarding the activity of biweekly oxaliplatin/5-FU/FA combinations. From those three studies, the regimens induced objective tumor responses at 45, 43 and 38% of patients, respectively. They were associated with a median TTP of 6.2, 5.6 and 7.1 months, respectively, and a median survival of 8.6, 9.6 and 11.2 months, respectively [16,19,20]. A result of weekly oxaliplatin/5-FU/FA combination showed a response rate of 54% with a median survival of 11.4 months and a median TTP of 6.5 months [17]. At the 2006 American Society of Clinical Oncology Meeting, Cunningham *et al.* [18] presented the final analysis of the REAL-2 trial, a randomized multicenter phase III study comparing capecitabine (X) with 5-FU and oxaliplatin (O) with cisplatin (C) in patients with advanced esophagogastric cancer. Treatment regimens were ECF, EOF, ECX or EOX. The primary aims of the study were a noninferiority comparison based on the per protocol population for the substitutions of capecitabine for 5-FU, and oxaliplatin for cisplatin, and a superiority analysis based on the intent-to-treat population comparing the individual experimental arms with the reference arm ECF. The results showed that there were no significant differences in response rates comparing ECF with EOF, ECX and EOX (41, 42, 46 and 48% respectively). Median survival was 9.9, 9.3, 9.9 and 11.2 months, respectively, with significant difference in median survival comparing ECF with EOX ($P = 0.025$). In the REAL-2 trial, infusion of 5-FU was administered from day 1 to day 21. We modified the schedule of infusion of 5-FU for 3 days, which is more comfortable for patients in China because of our patients being all inpatients and shortening the duration of hospitalization.

As a result of the modified treatment schedule in this study, the toxicity profile was moderate. The main

hematologica toxicity was leukocytopenia, neutropenia and anemia. Grade 3/4 neutropenia occurred in 12 patients (25%) or 28 cycles (12.4%), which is less than ECF and similar to EOF in the REAL-2 trial [6,21,18]. Only two patients developed febrile neutropenia but no treatment-related death occurred. Neurotoxicity was the most frequent toxicity that led to treatment discontinuation in a number of trials with oxaliplatin-based combinations. The rate of all grade neurotoxicity, however, was 58.3% in our study. In all, 10.4% of grade 3/4 neurotoxicity was also similar to EOF in the REAL-2 trial. This was less than one from biweekly oxaliplatin-based combination [16], which may be due to a relatively low cumulative dose of oxaliplatin in the present study with a median administered oxaliplatin dose of 602 mg/m^2. Other nonhematological toxicities were nausea, vomiting and alopecia, with grade 3/4 nausea in 6.3% of patients, vomiting in 14.6% of patients, which occurred less frequently when compared with cisplatin-based regimens such as ECF and DCF docetaxel, cisplatin and 5-(FU) [6,22].

5-FU plus cisplatin combination (CF) and epirubicin, 5-FU plus cisplatin (ECF) are considered as the reference regimen in phase III trials but their benefits remain limited owing to poor tolerability. We still do not know which is the best combination for treating advanced disease. New therapeutic strategies are needed to achieve a better clinical efficacy with an acceptable toxicity profile. A new generation of agents has been developed, including irinotecan, S-1, capecitabine, docetaxel, paclitaxel and oxaliplatin, which have shown promising activities in single-agent studies and when investigated in combination with other agents [23]. Oxaliplatin presents a better toxicity profile than cisplatin, being less nephrotoxic and ototoxic, and not requiring patient hydration. As expected, the peripheral neuropathy is the limiting toxicity. In phase I–II trials, the oxaliplatin-based regimens demonstrate a response rate ranging from 40 to 50% in chemonaive advanced gastric cancer patients and around 20% in cisplatin-pretreated patients. The REAL-2 study shows that oxaliplatin-containing triplets have a favorable safety profile compared with cisplatin-containing triplets; capecitabine is not inferior to infusion of 5-FU; oxaliplatin is not inferior to cisplatin; EOX is associated with improved efficacy versus reference ECF. Recently, a meta-analysis showed that best survival results are achieved with three-drug regimens containing 5-FU, an anthracycline and cisplatin [2]. Among these, regimens including 5-FU as bolus exhibit a higher rate of toxic deaths than regimens using a continuous infusion of 5-FU, such as epirubicin, cisplatin and continuous-infusion 5-FU. Oxaliplatin can be substituted for cisplatin in the treatment of gastric cancer, but it is not clear whether double-drug oxaliplatin-based regimens are better than triple-drug oxaliplatin-based regimens. No head-to-head randomized phase III study exists.

In conclusion, the modified EOF regimen was effective and well tolerated as a front-line chemotherapy for patients with advanced gastric cancer. With an activity at least comparable to other studies evaluating commonly used regimens or even more innovative combinations, and an acceptable safety profile, the modified EOF regimen is active and tolerable, and should be evaluated further. To better define the role of this combination in the management of gastric cancer, comparative trials with other active regimens (e.g. FOLFOX, DCF) should, however, be performed as well as a combination partner for investigational targeted agents (e.g. cetuximab, bevacizumab) in phase I/II trials.

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