A phase II study of modified FOLFOX as first-line chemotherapy in elderly patients with advanced gastric cancer

Jian Guo Zhao[a], Feng Qiu[b], Jian Ping Xiong[b], Ling Zhang[b], Xiao Jun Xiang[b], Feng Yu[b], Jun Yan[b], Zhen Yu Zhan[b] and Miao Feng[b]

The aim of this study was to evaluate the efficacy and safety of biweekly oxaliplatin in combination with continuous infusional 5-fluorouracil and leucovorin (modified FOLFOX regimen) in elderly patients with advanced gastric cancer (AGC). Forty-six eligible patients older than 65 years with previously untreated AGC received oxaliplatin 85 mg/m^2 intravenously over a 2-h period on day 1, together with leucovorin 400 mg/m^2 over 2 h, followed by a 46-h infusion of 5-fluorouracil 2600 mg/m^2 every 2 weeks. All patients were evaluable for efficacy and toxicity. A median of seven cycles (range 1–12) was administered. The overall response rate was 45.6% [95% confidence interval (CI): 31–61%] with two complete responses, 19 partial responses, 15 stable diseases, and 10 progressions. Median time to progression was 6.2 months (95% CI: 4.6–7.8) and median overall survival was 9.8 months (95% CI: 8.2–11.4). Toxicity was fairly mild. Grade 3 toxicities included neutropenia (8.7%), nausea (4.3%), vomiting (4.3%), diarrhea (2.2%); and grade 4 toxicities occurred in none of the patients. Grades 1–2 peripheral neuropathy was reported in 43.5% of patients. The modified FOLFOX regimen is active, well tolerated as first-line chemotherapy for elderly patients aged above 65 years with AGC. *Anti-Cancer Drugs* 20:281–286 © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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[a]Department of Oncology, Shaoxing People's Hospital, Shaoxing and [b]Department of Oncology, The First Affiliated Hospital, Nanchang University, Nanchang, China

Correspondence to Dr Jian Ping Xiong, MD, Department of Oncology, The First Affiliated Hospital, Nanchang University, 17 Yongwaizheng Road, Nanchang 330006, China
Tel/fax: +86 791 8693861; e-mail: jpxiong@medmail.com.cn

Jian Guo Zhao and Feng Qiu contributed equally to this study

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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 and the second most common cause of death from cancer. Almost two-thirds of the cases occur in developing countries and 42% in China alone [1]. Current epidemiologic data indicate gastric cancer rarely occurs before the age of 40 years; its incidence increases rapidly in the sixth and seventh decades. However, patients older than 65 years have often been excluded from or underrepresented in the trials of new cancer therapies [2,3]. Although systemic chemotherapy has been confirmed to improve survival and quality of life in advanced gastric cancer (AGC) [4], few studies were conducted to offer a proper chemotherapy regimen to elderly patients.

So far, no gold standard regimen has been defined in AGC. ECF (epirubicin, cisplatin, and 5-FU) and DCF (docetaxel, cisplatin, and 5-FU) regimens are currently recommended as first-line chemotherapy in advanced disease because of significant survival benefits [5–7], but the severe hematological toxicity, particularly from DCF, made the administration difficult in elderly patients. In contrast, the PF [cisplatin and 5-fluorouracil (5-FU)] combination, also a widely used regimen, seemed to be less toxic. In 2003, Graziano *et al.* [8] showed that weekly PLF (cisplatin, leucovorin, and 5-FU) chemotherapy was an effective and safe alternative for elderly patients with AGC. However, there is a great need to improve the efficacy produced by this regimen.

Oxaliplatin is an alkylating agent that inhibits DNA replication by forming adducts between two adjacent guanines or guanine and adenine molecules. However, the adducts of oxaliplatin seem to be more effective than cisplatin adducts with regard to the inhibition of DNA synthesis. Oxaliplatin also showed additive or synergistic activity when associated with 5-FU, even in 5-FU-resistant cell lines. The combination of oxaliplatin, 5-FU, and leucovorin (LV) (FOLFOX) has been accepted as the standard first-line treatment in advanced colorectal cancer worldwide [9,10]. In published phase II trials, oxaliplatin-based regimens were also active and well tolerated in AGC, with a response rate ranging from 40 to 50% in chemonaive [11–16] and around 20% in

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cisplatin-pretreated patients [17]. Oxaliplatin has a more favorable toxicity profile compared with cisplatin. The dose-limiting toxicity is a cumulative sensory peripheral neuropathy.

This phase II study was designed to evaluate the activity and safety of the modified FOLFOX regimen for patients older than 65 years with AGC. Here, the schedule of 5-FU was altered by omitting bolus 5-FU and increasing the dose of infusional 5-FU to 2600 mg/m^2 to reduce hematological and gastrointestinal toxicities.

Patients and methods

Eligibility

Patients with AGC who had histologically confirmed and measurable target lesions were enrolled in the study. The patients were required to have measurable disease. Other eligibility criteria were: Eastern Cooperative Oncology Group performance status ≤ 2, a life expectancy more than 3 months, age above 65 years, adequate bone marrow, hepatic and renal function, a normal cardiac function, absence of second primary tumor other than nonmelanoma skin cancer or in-situ cervical carcinoma, no central nervous system involvement, and no concurrent uncontrolled medical illness. Previous adjuvant chemotherapy, if given, must have been completed at least 6 months before inclusion. Patients who received earlier adjuvant treatment with oxaliplatin were not eligible. The protocol was approved by the ethics committee 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

The modified FOLFOX consisted of LV 400 mg/m^2 as a 2-h infusion followed by a 46-h infusion of 5-FU 2600 mg/m^2, and oxaliplatin 85 mg/m^2 on day 1 given as a 2-h infusion. When LV and oxaliplatin were given concurrently through a Y-connector, both drugs were administered in 5% dextrose. Cycles were repeated every 2 weeks. Routine antiemetic prophylaxis with a 5-hydroxytryptamine-3 receptor antagonist was used for modified FOLFOX. Disposable and electronic pumps were used in all inpatients. Chemotherapy was delayed until recovery if absolute neutrophil count decreased to less than 1500 cells/mm^3 or platelet count decreased to less than 100 000 cells/mm^3 or for significant persisting nonhematologic toxicity. The 5-FU dose was reduced after the National Cancer Institute Common Toxicity Criteria (version 2.0) grade ≥ 3 diarrhea, stomatitis occurred. Oxaliplatin was reduced for grades 3–4 neutropenia, and in cases of persistent (≥ 14 days) paresthesia or temporary (7–14 days) painful paresthesia or functional impairment. In cases of persistent (≥ 14 days) painful paresthesia or functional impairment, oxaliplatin was omitted from the regimen until recovery. Chemotherapy was administered for a maximum of 12 cycles and was discontinued in case of unacceptable toxicity, disease progression, patient's refusal, or physician's decision.

Evaluation criteria

Physical examinations, blood counts, biochemical profile, and electrocardiogram were performed for every cycle. Tumor markers, and computed tomography scans or magnetic resonance images of measurable lesions were assessed at baseline and repeated for every three cycles of treatment. Responses were assessed by at least two observers, and were confirmed by an expert independent radiologist. Tumor assessment was performed for every three cycles of chemotherapy, or earlier when indicated clinically. The Response Evaluation Criteria in Solid Tumors were used to evaluate clinical response [18]. 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 and safety of the regimen. Secondary end points were TTP, OS. The Simon's optimal two-stage phase II design was used to determine the sample size [19]. Interim analysis was carried out when the first 15 assessable patients were recruited. 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. Statistical computations were performed using SPSS (version 10.0). (SPSS, Chicago, Illinois, USA).

Results

Patients characteristics

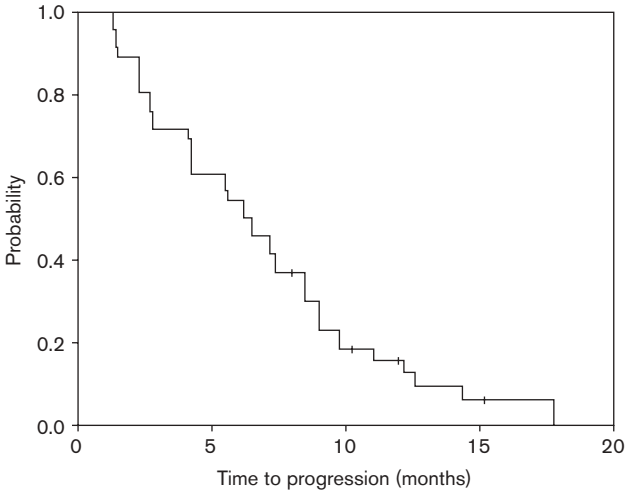
From March 2005 to August 2007, 46 elderly patients with a metastatic or AGC were enrolled in this trial. The median age was 71 (66–81) years. In all, 46 patients received three or more treatment cycles, and were eligible to be analyzed for efficacy and toxicity. The pretreatment characteristics of patients are listed in Table 1. At the closing date of 20 December 2007, the median follow-up time from the commencement of treatment was 13.5 months (range 3–30).

Table 1 Baseline patient characteristics ($n=46$)

	Number	%
Number of patients included	46	
Median age (years)	71 (66–81)	
Male/female	35/11	76.1/23.9
ECOG performance status		
0	13	28.3
1	22	47.8
2	11	23.9
Disease status		
Newly diagnosed	30	65.2
Recurrent	16	34.8
Locally advanced	12	26.1
Metastatic	34	73.9
Histology		
Well-differentiated adenocarcinoma	3	6.5
Moderately differentiated adenocarcinoma	7	15.2
Poor differentiated adenocarcinoma	25	54.3
Signet ring cell	5	10.9
Mixed	6	13.0
Sites of metastases		
Lymph node	18	39.1
Liver	15	32.6
Peritoneum	10	21.7
Lung	5	10.9
Other	9	19.6
Number of metastatic sites		
0 or 1	28	60.9
≥ 2	18	39.1
Primary adjuvant chemotherapy		
None	40	87.0
Yes	6	13.0

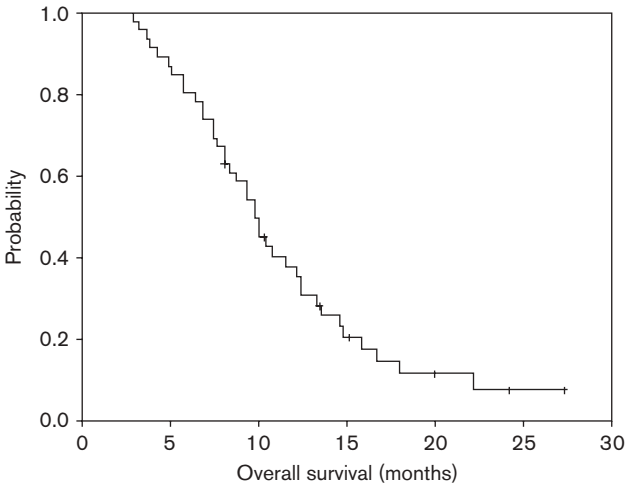
ECOG, Eastern Cooperative Oncology Group.

Fig. 1



Time to progression for all patients.

Fig. 2



Overall survival for all patients.

Efficacy

Among the 46 assessable patients, we observed two (4.3%) complete responses and 19 (41.3%) partial responses, for an overall response rate of 45.6% [95% confidence interval (CI): 31–61%]. Fifteen (32.6%) patients had stable disease and 10 (21.7%) had progressive disease. Median TTP was 6.2 months (95% CI: 4.6–7.8) (Fig. 1) and median OS was 9.8 months (95% CI: 8.2–11.4) (Fig. 2). One-year survival was 35.6% (95% CI: 22–50%). Thirty-nine patients had died at the time of the present evaluation. A total of 10 (21.8%) patients received second-line chemotherapies: seven taxane based and three irinotecan based.

Toxicity

In total, 319 chemotherapy cycles were administered, with a median of seven cycles per patient (range 1–12). Seventy-four percent of patients received at least six cycles and 33% of patients received at least nine cycles. The planned dose intensity was 42.5 mg/m^2/week for oxaliplatin, 200 mg/m^2/week for LV, and 1300 mg/m^2/week for 5-FU. The relative dose intensities of each drug were 98, 100, and 99%, respectively. Only one patient discontinued treatment because of febrile neutropenia. Although the protocol specified 14 days between cycles, 18 cycles (5.6%) were delayed for 2 days at the most and 25 cycles (7.8%) for more than 2 days. Of these, 29 cycles (9.1%) were delayed for toxicity reasons.

The frequencies of hematological and nonhematological toxicities are shown in Table 2. Grades 3–4 neutropenia occurred in four patients (8.7%), and one patient (2.2%) experienced febrile neutropenia. Grades 1–2 anemia and thrombocytopenia developed in 46 and 24% of the patients, respectively, but no one was reported with grades 3–4 anemia or thrombocytopenia. None of the patients required platelet transfusion and one patient received packed red blood cell transfusion. The most common nonhematological toxicities were nausea, vomiting, diarrhea, and neurological toxicity. Grades 1–2 vomiting, diarrhea, and neurotoxicity were reported in 37.0, 30.4 and 43.5% of the patients, respectively; and

grade 3 in 4.3, 2.2, 0%, respectively. Grade 4 toxicities occurred in none of the patients. No serious hepatic or renal function impairment was reported during the study and none of these elderly patients died of the toxicity.

Discussion

Systemic chemotherapy has been shown to prolong survival and to relieve symptoms in AGC. Though the optimal chemotherapy regimen has not yet been defined, ECF is a preferred reference regimen in Europe [4–6], whereas PF is a favored one in the United States [20]. Triple-drug regimens, such as ECF and DCF, seemed to be most effective in AGC, with response rates of 37–46%, median OS of 8.7–9.2 months [5–7]. However, the rate of grades 3–4 neutropenia accompanied was reported as high as 82% [7]. These combinations are difficult to deliver in elderly patients because of the severe hematological and nonhematological toxicities. The PF regimen seemed to be less toxic and has already proved to be safe and effective in elderly patients with AGC [8]; but in randomized phase III studies, PF showed no significant survival benefit when compared with FAMTX (5-FU, doxorubicin, and high-dose methotrexate) [20,21]. Obviously, new therapeutic strategies are needed to achieve a better clinical efficacy with an acceptable toxicity profile for elderly patients.

Oxaliplatin is a third-generation diaminocyclohexane platinum compound proven in numerous clinical trials to be active in various tumor types. Oxaliplatin in combination with 5-FU/LV has been widely used as standard first-line treatment in advanced colorectal cancer, [9,10]. This combination has also shown good activity as first-line treatment in patients with AGC, with response rates ranging from 38 to 56%, TTP 5.2 to 7.1 months, median OS 8.6 to 11.4 months [11–16]. In a previous phase II study, we modified the FOLFOX4 regimen by omitting bolus 5-FU and increasing the dose of infusional 5-FU to 2600 mg/m^2, and found it to be active and well tolerated in advanced colorectal cancer patients [22]. Therefore, we used this regimen to explore its efficacy and safety as first-line chemotherapy in elderly (> 65 years old) AGC patients.

This is the first evaluation of this schedule in AGC patients and it showed promising results. The overall response rate in 46 assessable patients was 45.6%, TTP was 6.2 months, and median OS was 9.8 months. So far, to the best of our knowledge, there are another three published phase II studies assessing oxaliplatin, 5-FU, and LV combination as first-line chemotherapy in elderly patients with AGC [23–25] (Table 3). One is the weekly oxaliplatin, 5-FU, and LV regimen reported by Santini *et al.* [23], in 2006, the other two are subsequent FOLFOX4 and modified FOLFOX4 regimens, respectively. In these trials, the authors observed a response rate of 32–52.5%, TTP of 5.0–6.4 months, and median OS of 9.0–10.0 months, which were similar to the data in this study. In addition, the median OS seemed to be longer when compared with 8.6 months produced by the PLF regimen in a previous study [8]. Unfortunately, up to date, randomized trials are still lacking in elderly AGC patients.

Table 2 Most common treatment-related toxicities according to NCI-CTC (*n*=46)

	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
Leucocytopenia	10 (21.7)	6 (13.0)	5 (10.7)	0
Neutropenia	7 (15.2)	4 (8.7)	4 (8.7)	0
Febrile neutropenia	0	0	1 (2.2)	0
Anemia	16 (34.8)	5 (10.7)	0	0
Thrombocytopenia	9 (19.6)	2 (4.3)	0	0
Nausea	16 (34.8)	7 (15.2)	2 (4.3)	0
Vomiting	12 (26.1)	5 (10.9)	2 (4.3)	0
Diarrhea	10 (21.7)	4 (8.7)	1 (2.2)	0
Stomotitis	5 (10.9)	2 (4.3)	0	0
ALT/AST elevation	9 (19.6)	1 (2.2)	0	0
Creatinine elevation	1 (2.2)	0	0	0
Neurological toxicitity	15 (32.6)	5 (10.9)	0	0
Alopecia	5 (10.7)	2 (4.3)	NA	NA

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

Table 3 Summary of the efficacy and toxicity of different oxaliplatin, LV, and 5-FU regimens as first-line chemotherapy in elderly AGC patients

Study	Oxaliplatin, LV, and 5-FU regimens (mg/m^2)	Number of evaluable patients	RR (%)	Median TTP (months)	Median OS (months)	Median number of cycles (range)	Grade 3/4 neutropenia (%)	Grade 1/2, 3/4 neurotoxicity (%)
Santini *et al.* [23]	40, 250, and 500 (bolus)[a]	42	45.2	5.0	9.0	12 (3–24)	4.8	30.9, 2.4
Nardi *et al.* [24]	85, 100, and 400 (bolus) + 600 (continuous infusion)[b,c]	31	32.0	6.4	–	8 (4–16)	19.0	45, 0
Liu *et al.* [25]	85, 200, and 1000 (continuous infusion)[b,c]	40	52.5	6.5	10.0	7 (1–10)	6.8	40.9, 2.3
Xiong *et al.* (this study)	85, 400, and 2600 (continuous infusion)[b]	46	45.6	6.2	9.8	7 (3–12)	8.7	43.5, 0

AGC, advanced gastric cancer; RR, response rate; TTP, time to progression; OS, overall survival.
[a]Weekly regimen.
[b]Biweekly regimen.
[c]LV and 5-FU were repeated for 2 consecutive days.

However, in a phase III study conducted by Al-Batran *et al.* [26], the stratification analysis indicated that for AGC patients older than 65 years, treatment with FLO (5-FU, LV, and oxaliplatin) resulted in statistically significant superior response rate (41.3 vs. 16.7%; $P=0.012$), time to treatment failure (5.4 vs. 2.3 months, $P < 0.001$), and PFS (6.0 vs. 3.1 months, $P=0.029$) and an improved OS (13.9 vs. 7.2 months) as compared with FLP (5-FU, LV, and cisplatin), respectively. FLO seemed to be associated with improved efficacy in elderly patients. It was concluded that oxaliplatin was at least as effective as cisplatin in patients with AGC. The conclusion was also confirmed by the REAL-2 study, in which a two-by-two design was used to evaluate the several modifications of ECF including substitution of oxaliplatin for cisplatin and substitution of capecitabine for 5-FU [27]. The hazard ratio for death in the oxaliplatin groups was 0.92 (95% CI: 0.80–1.10), well below the noninferiority margin of 1.23.

In addition, the efficacy of our regimen was also comparable with that of some other newer regimens. In the study conducted by Park *et al.* [28], patients received oxaliplatin 130 mg/m^2 over 2 h on day 1 plus oral capecitabine 1000 mg/m^2 twice daily on days 1–14, every 3 weeks (XELOX). PFS was 5.8 months, and OS was 11.9 months. Another promising combination of S-1 and cisplatin, has been assessed both in a Western and a Japanese population [29,30], with a response rate ranging from 51 to 54%, TTP 4.8 to 6.0 months, and OS 10.9 to 13.0 months. Recently, a weekly TCF (docetaxel, cisplatin, and 5-FU) regimen was evaluated in a randomized phase II study [31]. The response rate was 49%, and the hematological toxicity was markedly lower than that in the 3-weekly DCF arm [7] (febrile neutropenia, 4 vs. 29%), suggesting that weekly docetaxel-based regimens should be further explored.

As far as toxicity is concerned, the published phase II studies have shown the mild hematological toxicity of oxaliplatin, 5-FU, and LV regimens in elderly AGC patients [23–25]. The rates of grades 3–4 neutropenia were 4.8, 19, and 6.8%, respectively. In this modified FOLFOX regimen, we chose to omit bolus 5-FU and use an infusional 5-FU regimen to reduce hematological toxicity [32]. In the study N9741 [33], the infusional 5-FU in FOLFOX is associated with substantially less febrile neutropenia and less risk of early death than its delivery by bolus. A recent meta-analysis also showed [4] that regimens including 5-FU as bolus exhibit a higher rate of toxic deaths than regimens using a continuous infusion of 5-FU. In this study, grades 3–4 neutropenia occurred in only four (8.7%) patients, with one case of febrile neutropenia. Similarly, 6.8–11.6% of grades 3–4 neutropenia were reported with infusional 5-FU-based modified FOLFOX4 regimen [25,26], whereas up to 19–36% of grades 3–4 neutropenia were observed with bolus 5-FU-retained FOLFOX4 regimen [15,24].

It should not be ignored that oxaliplatin at a lower dose of 85 mg/m^2 also contributed to the reduced hematological toxicity. Furthermore, with a median of seven cycles administered, the relatively low cumulative dose of oxaliplatin did not result in severe neurological toxicity. Grades 1–2 neuropathy occurred in 43.5% of patients, and grades 3–4 occurred in none of the patients. In a number of trials with oxaliplatin-based therapies, neurotoxicity was the most frequent side effect that led to treatment discontinuation. In the randomized FOLFOX6 study [10], in which oxaliplatin was administered at a dose of 100 mg/m^2 for a median of 12 cycles, 34% of patients had grade 3 neurotoxicity. However, with the dose of oxaliplatin decreased to 85 mg/m^2, the rate of grades 3–4 neurotoxicity was reported as low as 0–2.3% in elderly AGC patients [24,25]. Interestingly, the dose-cumulative neurotoxicity profile of oxaliplatin led us to give some toxicity only to responder patients avoiding to induce toxicity in nonresponder patients. In this study, nausea and vomiting were also common nonhematological toxicities, but were mild and occurred less frequently as compared with cisplatin-based regimens. The relative dose intensities of oxaliplatin, LV, and 5-FU were 98, 100, and 99%, respectively, which may also indicate the good tolerability in elderly patients.

In conclusion, the modified FOLFOX regimen is active, well tolerated as first-line chemotherapy for elderly patients with AGC, and deserves to be studied further. Comparative trials with other active regimens (e.g. FLP, XELOX) should be carried out. In addition, targeted agents (e.g. cetuximab, bevacizumab) are also expected to be incorporated to optimize the efficacy.

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