Phase II trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) as first-line treatment for advanced gastric cancer

Weiguo Cao[a], Weiping Yang[b], Guying Lou[a], Jinsong Jiang[a], Mei Geng[a], Wenqi Xi[a], Hao Li[a], Tao Ma[b] and Yening Jin[a]

The efficacy of chemotherapy for advanced gastric cancer with palliative intent compared with supportive care alone is now widely accepted. However, the best choice of chemotherapy regimen for patients with advanced gastric cancer is still a matter of controversy and requires further investigation. This study is performed to evaluate the efficacy and safety of the FOLFOXIRI regimen (oxaliplatin 85 mg/m^2 as a 2-h intravenous infusion, irinotecan 165 mg/m^2 as a 90-min infusion, leucovorin 200 mg/m^2 as a 2-h infusion, 5-fluorouracil 3200 mg/m^2 as a 48-h continuous infusion on day 1, every 2 weeks) as first-line treatment for advanced gastric cancer. Forty-seven (95.9%) of the 49 patients were assessable for response. Two cases of complete response and 29 cases of partial response were confirmed, giving an overall response rate of 63.3% [95% confidence interval (CI): 49.8–76.8%]. The median time to progression and overall survival for all patients were 7.3 months (95% CI: 6.0–8.6 months) and 11.9 months (95% CI: 9.4–14.4 months), respectively. The estimate of overall survival at 12 months was 42.9% (95% CI: 29.0–56.7%). Most patients experienced neutropenia during their course of therapy with 49% of patients ($n=23$) for grade 3/4 neutropenia. Grade 3 nausea/vomiting, stomatitis, and diarrhea were observed in 20 (42.6%), two (4.3%), and five (10.6%) patients, respectively. Yet, no grade 4 nonhematologic toxicity was observed. The FOLFOXIRI combination is a tolerated treatment modality with promising activity in previously untreated advanced gastric cancer patients. *Anti-Cancer Drugs* **20:287–293** © **2009 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Departments of [a]Oncology and [b]General Surgery, Ruijin Hospital, Medical School of Shanghai Jiaotong University, Shanghai, China

Correspondence to Dr Yening Jin, MD, Ruijin Hospital, Medical School of Shanghai Jiaotong University, No. 197, Rui Jin Er Lu, Shanghai 200025, China
Tel: +86 21 6415 5988; fax: +86 21 6415 5115; e-mail: rjyyzlk@gmail.com

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Introduction

Although the incidence of gastric carcinoma has fallen in most Western countries, it remains a significant problem in terms of global health and is the second most common cause of cancer mortality worldwide [1]. Gastric cancer is often diagnosed at a very advanced stage, with approximately half of all patients presenting with unresectable, locally advanced, or metastatic disease. Four randomized studies comparing best-supportive care with best-supportive care plus chemotherapy for advanced gastric cancer (AGC) have shown that chemotherapy can improve survival and quality of life (QoL) [2–5]. Since then, various combination chemotherapy regimens were tested in trials in patients with AGC.

Irinotecan (CPT-11, Camptosar; Pfizer Oncology, New York, USA), a camptothecin analog, acts as an antitumor agent by inhibiting the eukaryotic enzyme DNA topoisomerase I [6,7]. Irinotecan has shown high activity as a monotherapy in gastric cancer patients with overall response rate (ORR) from 18 to 43% [8,9]. Phase II studies with irinotecan plus 5-fluorouracil (5-FU) and leucovorin (LV, also referred to as folinic acid) showed ORR from 36 to 40%, with median survival time between 10.7 and 11.6 months [10–12].

Oxaliplatin (L-OHP, Eloxatin, Sanofi-aventis, New York, USA) is an alkylating agent that inhibits DNA replication by forming adducts between two adjacent guanines or guanine and adenine molecules. The adducts of oxaliplatin, however, seem to be more effective than cisplatin adducts with regard to the inhibition of DNA synthesis [13–15]. Oxaliplatin has a more favorable safety profile compared with cisplatin; benefits of oxaliplatin include neurotoxicity, renal toxicity and its dose-limiting toxicity is a cumulative sensory peripheral neuropathy [16]. Oxaliplatin has shown a notable activity against colorectal cancer in combination with 5-FU and LV, which led to several phase II trials in gastric cancer. The oxaliplatin/5-FU/LV regimen yielded RRs in the range of 38–40% with median survival time from 8 to 11 months with tolerable toxicity [17–20].

In an attempt to develop a more active and efficacious chemotherapy regimen, two newer agents, irinotecan and oxaliplatin, were combined with 5-FU and LV in a phase I

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trial, which showed a safe toxicity profile in patients with advanced solid tumors [21]. Furthermore, combinations of irinotecan, oxaliplatin, 5-FU, and LV have been tested in advanced colorectal [22,23] and pancreatic [24] cancer, showing high ORR and tolerable toxicity. We studied a three-drug combination of irinotecan, oxaliplatin, and 5-FU/LV (FOLFOXIRI) using the different treatment sequence: oxaliplatin → irinotecan → 5-FU, because an in-vitro study on three human gastric cancer cell lines (AZ-521, MKN-45, and NUGC-4) showed that greater than additive effects were observed in all of the cell lines when cells were treated with oxaliplatin followed by SN-38, whereas such effects were observed only in NUGC-4 cells in the reverse sequence. These results suggest that SN-38 may kill the cells recovering from the G(1) block produced by oxaliplatin as they progress into the S phase [25]. On the basis of these encouraging results, we conducted a phase II trial to assess the efficacy and safety of infusional fluorouracil, LV, oxaliplatin, and irinotecan (FOLFOXIRI) as first-line treatment for AGC.

Patients and methods

Eligibility criteria

All the patients involved in this study had histologically confirmed metastatic or recurrent gastric adenocarcinoma with at least one unidimensionally measurable lesion (i.e. a diameter ≥ 1 cm, as assessed by spiral computed tomography). The patients were 18–75 years of age with a performance status of 0–2 on the Eastern Cooperative Oncology Group scale. In addition, adequate hematological (absolute neutrophil count $\geq 1.5 \times 10^9$/l, platelet count $\geq 100 \times 10^9$/l, hemoglobin ≥ 9 g/dl), renal (serum creatinine ≤ 1.5 mg/dl and creatinine clearance ≥ 50 ml/min), and hepatic (total bilirubin ≤ 2.0 mg/dl and serum transaminase level ≤ 3 times the upper limit of the normal range) levels were also required. Patients who had received adjuvant chemotherapy completed 4 weeks before entry were eligible. Patients were ineligible if they had previously received palliative chemotherapy or radiation therapy, or had other severe medical illnesses, central nervous system metastasis, another active malignancy, or history of anaphylaxis to drugs. The institutional review board of the author's institution approved the protocol, and written informed consent was obtained from all patients before enrollment.

Study treatment

Patients received oxaliplatin 85 mg/m^2 diluted in 500 ml 5% dextrose as a 2-h intravenous (i.v.) infusion followed by irinotecan 165 mg/m^2 diluted in 500 ml 5% dextrose as a 90-min infusion. After LV 200 mg/m^2 was given in a 2-h infusion, 5-FU 3200 mg/m^2 was administered as a 48-h continuous infusion. Treatment was repeated every 2 weeks (Fig. 1). Treatment was administered biweekly until evidence of progression, unacceptable toxicity, patient refusal, or for a maximum of 12 cycles. Treatment was delayed when, on the planned day of treatment, the neutrophil count was less than 1000 mm^3, the platelet count was less than 100 000 mm^3, or persistent diarrhea or stomatitis grade greater than 1 were present. In the case of peripheral neurotoxicity grade greater than 2 National Cancer Institute Common Toxicity Criteria, oxaliplatin was interrupted. In the case of previous dose-limiting toxic effects, treatment was continued after resolution with doses of irinotecan, oxaliplatin, and 5-FU reduced by 25%, except in the case of grade 3–4 diarrhea, when only irinotecan and 5-FU doses were reduced by 25%. In the case of life-threatening toxic effects (grade 3 or 4 toxicity), treatment was definitively interrupted for 2 weeks if it cannot recover 2 weeks later, or continued at doses reduced by 50% if it can recover within 2 weeks.

To prevent nausea and vomiting, 5-HT$_3$ antagonists i.v. plus dexamethasone 16 mg i.v. were administered before chemotherapy, and 5-HT$_3$ antagonists were given orally at

Fig. 1

Drug	Day 1	Day 2	Day 3
L-OHP	85 mg/m^2 i.v. 2 h		
CPT-11	165 mg/m^2 i.v. 1.5 h		
LV	200 mg/m^2 i.v. 2 h		
5-FU	3200 mg/m^2 i.v. 48 h continuous infusion		
Repeated every 2 weeks			

Treatment schedule. 5-FU, 5-fluorouracil; CPT-11, irinotecan; L-OHP, oxaliplatin; LV, leucovorin; i.v., intravenous.

standard doses in the 2 days following chemotherapy. Atropine 0.25 mg was administered subcutaneously in case of cholinergic syndrome, and was given prophylactically in the following cycles. Loperamide 2 mg orally every 2 h and oral rehydration was prescribed in case of delayed diarrhea. No prophylactic granulocyte colony stimulating factors were recommended for neutropenia.

Efficacy assessment

The primary endpoint of this study was response rate (RR), and secondary objectives were toxicity, overall survival (OS), time to progression (TTP), and QoL [26]. Before entering the study, all patients received physical examination, full blood count, and serum chemistry analyses. Chest radiograph, ECG, upper gastrointestinal endoscopies, abdominal computer tomographic (CT) scans, and other appropriate procedures were also performed as needed. Patients were given a physical examination, a subjective/objective symptom evaluation, and blood tests twice weekly. Comprehensive biochemistry blood examination was performed every 4 weeks. After every two cycles of treatment, response was evaluated using Response Evaluation Criteria in Solid Tumors. Of the lesions observed before treatment, a maximum of five measurable lesions from each metastasized organ up to a total of 10 lesions were selected as target lesions. In cases of partial or complete response (CR), a confirmative CT scan was performed 4 weeks later and this was followed by a CT scan after every two treatment cycles. Toxicity was graded according to Version 2.0 of the National Cancer Institute-Common Toxicity Criteria. Patients' QoL was assessed at baseline and every cycle, using the European Organisation for Research and Treatment of Cancer QLQ-C30 self-administered questionnaire. The Global Health Status/QoL scale was selected as the primary endpoint [26]. Tumor-related symptoms were assessed at baseline and before each cycle.

Statistical analysis

The current trial used a two-stage optimal design, as proposed by Simon, with an 80% power to accept the hypothesis and a 5% significance to reject the hypothesis [27]. In addition, the current trial was designed to detect a RR of 40% as compared with a minimal, clinically meaningful RR of 20%. Allowing for a follow-up loss rate of 10%, the total sample size was 48 patients with a measurable disease. All enrolled patients were included in the intention-to-treat analysis of efficacy. The duration of response, TTP, and survival analyses were all estimated by using the Kaplan–Meier method [28]. The duration of response was defined as the interval from the onset of a CR or a partial response until the evidence of disease progression was found. Meanwhile, the TTP was calculated from the initiation of chemotherapy to the date of disease progression, whereas the OS was measured from the initiation of chemotherapy to the date of the last follow-up or death. The statistical data were obtained using an SPSS software package (SPSS 11.5 Inc., Chicago, Illinois, USA).

Results

Patient characteristics

From March 2006 to June 2007, a total of 49 patients were enrolled in this study from the department of Medical Oncology and Radiotherapy, Shanghai Ruijin Hospital, Medical School of Shanghai Jiaotong University. The characteristics of the patients are summarized in Table 1. The median age was 55 (range, 22–74) years, with 33 males and 16 females. The majority of the patients (91.8%) had either Eastern Cooperative Oncology Group performance status 0 or 1. Thirty-two (65.3%) patients presented with metastatic disease, whereas 17 patients presented with recurrent disease after prior gastrectomy (total or subtotal gastrectomy of the primary tumor). Twenty-nine (59.2%) patients were diagnosed with poorly differentiated adenocarcinoma. Distant lymph nodes, peritoneum, or liver were the most common sites of the metastatic disease. No patients had received prior chemotherapy or radiotherapy.

Efficacy and survival

Forty-seven (95.9%) of the 49 patients were assessable for response, of the two patients not assessable, both were lost to follow-up after the first cycle of the treatment. All efficacy data are reported using the intention-to-treat principle. Two cases of CR and 29 cases of partial response were confirmed, giving an ORR of 63.3% [95%

Table 1 Patient characteristics

Characteristics	No. of patients $n=49$ (%)
Age (years)	
Median (range)	55 (22–74)
Male/female	33/16
ECOG performance status	
0	7 (14.3)
1	38 (77.6)
2	4 (8.2)
Disease status	
Metastatic	32 (65.3)
Recurrent	17 (34.7)
Location of primary tumor	
Upper[a]	7 (14.3)
Middle and lower	42 (85.7)
Histology	
Well-differentiated AC	3 (6.1)
Moderately differentiated AC	13 (26.5)
Poorly differentiated AC	29 (59.2)
Signet ring cell carcinoma	4 (8.2)
Metastatic sites	
Lymph node	41 (83.7)
Liver	14 (28.6)
Peritoneum	13 (26.5)
Ovary	4 (8.2)
Others (bone, kidney, pancreas)	3 (6.1)
Number of metastases	
1	18 (36.7)
2	21 (42.9)
≥ 3	11 (22.4)

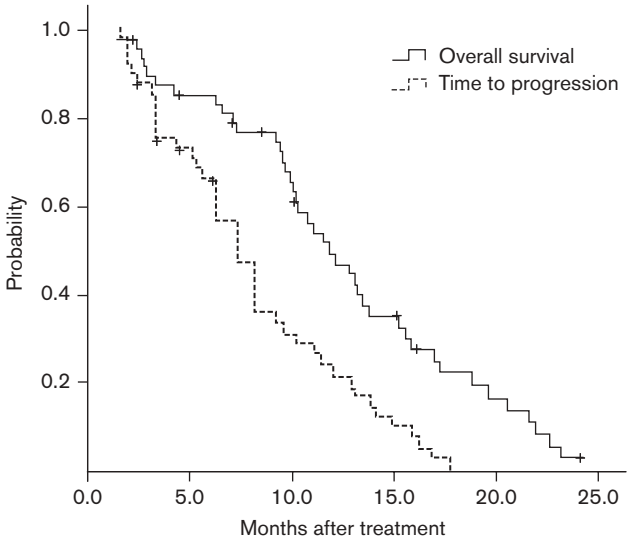
AC, adenocarcinoma; ECOG, Eastern Cooperative Oncology Group.
[a]Upper, gastroesophageal junction.

Table 2 Tumor response (intention-to-treat analysis)

Response	Number (n=49, %)
Confirmed response	31 (63.3)[a]
Complete response	2 (4.1)
Partial response	29 (59.2)
Stable disease	10 (20.4)
Progressive disease	8 (16.3)
Not assessable	2 (4.1)

[a]95% confidential interval=49.8–76.8%.

Fig. 2



Time to disease progression and overall survival for all patients.

confidence interval (CI): 49.8–76.8%](Table 2). There was no difference in RR between patients with metastatic disease and recurrent disease (65.6 vs. 58.8%). Of 31 responses, 21 were patients with metastatic disease, 10 were patients with recurrent disease; two (6.5%) were observed after two cycles, 22 (71.0%) were observed after four cycles, four (12.9%) after six cycles, and three (9.7%) after eight cycles of chemotherapy. The median follow-up period was 12.1 months. The median TTP for all patients was 7.3 months (95% CI: 6.0–8.6 months). The estimated median OS was 11.9 months (95% CI: 9.4–14.4 months) (Fig. 2). The estimate of OS at 12 months was 42.9% (95% CI: 29.0–56.7%). There were three patients successfully undergoing radical gastrectomy after four cycles of chemotherapy, and all lived longer than 1 year.

Toxicity

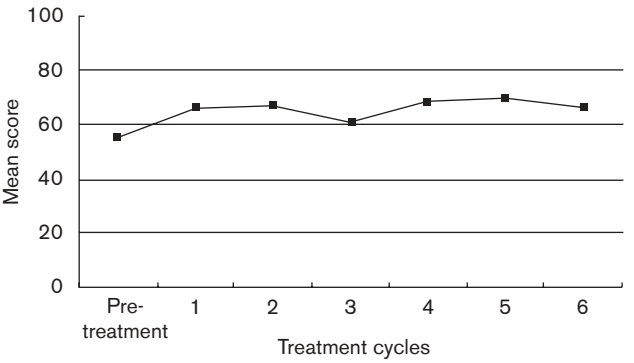
Forty-seven (95.9%) patients were assessable for safety. Toxic effects observed during the study are listed in Table 3. The most common toxic effects were anemia, neutropenia, diarrhea, nausea and vomiting, and stomatitis. Most patients experienced neutropenia during their course of therapy with 38% of patients (n=18) for grade 3

Table 3 Toxicities of irinotecan plus oxaliplatin and 5-fluorouracil/leucovorin combination chemotherapy (by patients)

	Grade (n, % of patients, n=47)[a]			
	1	2	3	4
Hematologic				
Anemia	4 (8.5)	3 (6.4)	1 (2.1)	–
Neutropenia	10 (21.3)	5 (10.6)	18 (38.3)	5 (10.6)
Febrile neutropenia	9 (19.1)	6 (12.8)	2 (4.3)	–
Thrombocytopenia	2 (4.3)	1 (2.1)	–	–
Nonhematologic				
Anorexia	6 (12.8)	2 (4.3)	–	–
Nausea/vomiting	9 (19.1)	8 (17.0)	20 (42.6)	–
Stomatitis	4 (8.5)	2 (4.3)	2 (4.3)	–
Alopecia	3 (6.4)	6 (12.8)	–	–
Diarrhea	11 (23.4)	12 (25.5)	5 (10.6)	–
Constipation	1 (2.1)	–	–	–
Skin rash	2 (4.3)	1 (2.1)	–	–
Peripheral neuropathy	23 (48.9)	6 (12.8)	–	–
Elevated transaminase	4 (8.5)	3 (6.4)	–	–
Elevated creatinine	1 (2.1)	–	–	–
Hyperbilirubinaemia	1 (2.1)	–	–	–

[a]National Cancer Institute-Common Toxicity Criteria (NCI-CTC) Version 2.0.

Fig. 3



Variation of the Global Health Status mean scale score during treatment with FOLFOXIRI regimen.

and 11% (n=5) for grade 4 neutropenia. Grade 1 or 2 neutropenia was detected in 32% of patients (n=15). Grade 3 anemia and febrile neutropenia were documented in one (2.1%) and two (4.3%) patients, respectively. Nausea/vomiting, stomatitis, diarrhea, and peripheral neuropathy were the most common nonhematological toxicities. Grade 3 nausea/vomiting, stomatitis, and diarrhea were observed in 20 (42.6%), two (4.3%), and five (10.6%) patients, respectively. However, no grade 4 nonhematologic toxicity was observed in this study. Although peripheral neuropathy was commonly observed, most patients had mild (grade 1 in 48.9%, grade 2 in 12.8% of patients) symptoms, and no patients had severe peripheral neuropathy requiring treatment interruptions. Mild-to-moderate diarrhea, which was reversible and manageable, developed in 59.6% of the patients. Twelve (25.5%) patients required dose reductions of at least one

drug because of grade 3 or 4 nonhematologic toxic effects; six (12.8%) patients were delayed for more than 1 week because of nonhematologic toxic effects. No patients were discontinued from the study because of toxic effects. There were no treatment-related deaths during this study.

Quality of life

Forty-two (85.7) patients were assessable for QoL. The Global Health Status/QoL mean scale score changed a little, with a mild to moderate improvement (between 5.8 and 14.1 score) during the treatment (Fig. 3).

Discussion

AGC still has a poor prognosis, with a median survival of just 7–10 months. Several combination regimens of chemotherapy have been developed, but the survival advantage seems to be marginal, and no worldwide standard regimens have been established so far. Recent meta-analysis has been carried out to assess the efficacy and tolerability of chemotherapy in patients with AGC. Analysis of chemotherapy versus best supportive care (hazard ratio: 0.39, 95% CI: 0.28–0.52) and combination versus single agent, mainly 5-FU, (hazard ratio: 0.83, 95% CI: 0.74–0.93) showed significant OS results in favor of chemotherapy and combination chemotherapy [29]. However, there is no single, global standard regimen for the first-line treatment of advanced disease. The best choice of chemotherapy regimen for patients with AGC is still a matter of controversy and requires further investigation [30]. The phase III trial, V-325 trial, compared DCF (docetaxel, cisplatin, and 5-FU) with the reference regimen of CF (cisplatin and 5-FU) and showed significant superiority of DCF in terms of survival (9.2 vs. 8.6 months), TTP (5.6 vs. 3.7 months), and RR (37 vs. 25%) than CF arm [31]. As DCF is an intensive combination with the incidence of grade 3–4 neutropenia of 82%, the benefit-to-risk ratio should be cautiously determined in incorporating the regimen in practice, especially in an elderly population. Therefore, we studied the combination of 5-FU with irinotecan and oxaliplatin in order to develop a potentially efficacious front-line chemotherapy of AGC with acceptable toxicity.

This phase II study showed that oxaliplatin 85 mg/m^2 in a 2-h i.v. infusion followed by irinotecan 165 mg/m^2 in a 90-min infusion, LV 200 mg/m^2 in a 2-h infusion, 5-FU 3200 mg/m^2 in a 48-h continuous infusion, repeated every 2 weeks (FOLFOXIRI regimen) was active and well-tolerated as first-line therapy in patients with AGC. The ORR was 63.3%, after a median follow-up of 12.1 months, median TTP was 7.3 months, and median OS was 11.9 months. These findings can be compared with two phase II studies (using similar patient populations) investigating the efficacy of FOLFOXIRI regimen as first-line therapy in patients with AGC, which reported the ORR of 67% and median TTP of 9.6 months and median OS of 14.8 months [32], and ORR of 67% and median TTP of 8.2 months and median OS of 10.2 months [33]. The ORR was higher than two phase II studies of weekly or biweekly FOLFIRI regimen (irinotecan, 5-FU/LV) in patients with previously untreated AGC by Blanke *et al.* [34] (63 vs. 22%) and Rosati *et al.* [35] (63 vs. 36%). It needs to be confirmed by the randomized study whether the combination chemotherapy of FOLFOXIRI (the addition of oxaliplatin to FOLFIRI) was more effective than the FOLFIRI regimen as the first-line treatment for AGC. Park *et al.* [36], however, found that the addition of cisplatin has no clear advantage over ILF (irinotecan 150 mg/m^2 on day 1, LV 20 mg/m^2 and a 22-h infusion of 5-FU 1000 mg/m^2 on days 1 and 2) as the first-line treatment for AGC in a recently published randomized phase II study. We knew that oxaliplatin has significant activity against some cisplatin-resistant tumors and a favorable safety profile over cisplatin [37]. Even the results of the REAL-2 study showed that there were no significant differences in RRs comparing ECF (epirubicin, cisplatin, and 5-FU) with EOF (epirubicin, oxaliplatin, and 5-FU), ECX (epirubicin, cisplatin, and capecitabine) and EOX (epirubicin, oxaliplatin, and capecitabine) (41, 42, 46, and 48%, respectively). Oxaliplatin was associated with lower incidences of grade 3 or 4 neutropenia, renal toxicity, and thromboembolism, as compared with cisplatin [38]. However, a phase III study that compared LV/5-FU and cisplatin with LV/5-FU and oxaliplatin in AGC patients showed that superior efficacy and safety were achieved with oxaliplatin-based chemotherapy [39].

We adopted a simplified FOLFOXIRI regimen by administering 5-FU as a 48-h continuous infusion without any bolus to reduce the related toxic effects, thus favoring its combination with optimal doses of irinotecan and oxaliplatin, so that it could be administered more easily in clinical practice, which was designed by Masi *et al.* [23] for colorectal cancer patients. There is a pharmacokinetic change, whether it may dramatically reduce the efficacy of the regimen by affecting drug-binding protein saturation in the blood needs to be studied. In this study, we found that 49% ($n=23$) and 43% ($n=20$) of patients experienced grade 3/4 neutropenia and nausea/vomiting during their course of therapy, respectively. Other groups have evaluated similar three-drug combinations in gastric and nongastric cancer patients, associating irinotecan and oxaliplatin with different schedules of 5-FU/LV. All these studies have confirmed the feasibility of these combinations, with neutropenia and diarrhea being the dose-limiting toxic effects. Lee *et al.* [32] reported grade 3/4 neutropenia and emesis in 52 and 44% of patients with AGC, respectively. Masi *et al.* [23] reported grade 3/4 neutropenia, diarrhea and stomatitis in 59, 16, and 6% of patients with metastatic colorectal cancer, respectively. Conroy *et al.*

[24] reported grade 3/4 neutropenia, nausea, vomiting, and diarrhea in 52, 20, 17, and 17% of patients with advanced pancreatic cancer, respectively. Compared with the combination of irinotecan and bolus administration of FU, followed by continuous infusion of 5-FU [24], only continuous infusion of 5-FU was associated with lower incidence rate of grade 3 diarrhea in this study. The oxaliplatin may cause peripheral neuropathy as well as acute events such as pharyngolaryngeal dysesthesias precipitated by exposure to cold, and the incidence of peripheral neuropathy increases with increased cumulative drugs dose [40]. In this study, 12.8% grade 2 neurotoxicity was observed, which is relatively lower; perhaps it was because of the key that we taught patients strategies to avoid cold exposure during or after chemotherapy administration.

In conclusion, the FOLFOXIRI combination is a tolerated treatment modality with promising activity in previously untreated AGC patients. The combination has been planned to be tested versus FOLFIRI and FOLFOX regimen in randomized phase II trials, in order to confirm whether the addition of oxaliplatin can have some advantages over FOLFIRI in AGC patients.

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Conflicts of interest: none declared.

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