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Phase II study of combination chemotherapy of 5-fluorouracil, low-dose leucovorin, and oxaliplatin (FLOX regimen) in pretreated advanced gastric cancer

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Background: This phase II study describes the efficacy and safety of combination chemotherapy of 5-fluorouracil (5-FU), low-dose leucovorin, and oxaliplatin (FLOX regimen) for pretreated advanced gastric cancer.
Patients and methods: Patients who had been previously treated with greater than or equal to one regimen were enrolled. Patients received an oxaliplatin 75 mg/m^2 on day 1, 5-FU 1000 mg/m^2 on days 1–3, and leucovorin 20 mg/m^2 on days 1–3, every 3 weeks. The primary end point was overall survival (OS).
Results: Among the 52 patients enrolled, 26 patients were treated as second line, and the remaining 26 patients were enrolled as third- or fourth line. A total of 203 cycles of chemotherapy were administered with the median being three cycles (range 1–15) per patient. The median OS was 6.6 months [95% confidence interval (CI) 4.5–8.8] and the median progression-free survival was 2.5 months (95% CI 1.9–3.0). The response rate was 4% (95% CI 0–9%), and the disease control rate was 48% (95% CI 34–62%). The most common toxic effects of grade 3/4 were neutropenia (16%) and vomiting (6%).
Conclusions: The FLOX regimen showed modest activity as a salvage treatment in pretreated advanced gastric cancer with a favorable compliance.
Key words: advanced gastric cancer, 5-fluorouracil, leucovorin, oxaliplatin, salvage chemotherapy

introduction

Gastric cancer is a leading cause of cancer deaths worldwide; it ranks second in global cancer mortality following lung cancer [1]. In gastric cancer, the prolongation of patients' survival and improvement of the quality of life are challenges for the oncologists. Gastric cancer is considered to be moderately chemotherapy responsive, and combination chemotherapy is the standard approach in the treatment of metastatic gastric cancer. For first-line chemotherapy, many combination regimens have shown a response rate of 35%–45%. The median progression-free survival (PFS) has been 5–6 months, which means many patients eventually develop progressive disease (PD). Recent advances in chemotherapy have enabled many patients to maintain good performance status (PS) after first-line chemotherapy. There is an urgent need for second-line or even third-line salvage chemotherapy. Until now, there has been no standard second-line chemotherapy, although various chemotherapy regimens have been tried [2]. Cisplatin-based regimens have shown response rates of 19%–45% [3–5]; paclitaxel-based regimens have shown response rates of 22%–27% [6, 7]; and irinotecan-based regimens have shown response rates of 27%–52% [8, 9]. However, antitumor responses and response durations were heterogeneous among regimens, depending on the previous chemotherapy, and considerable toxicity accompanied most of these regimens. Therefore, survival prolongation while maintaining good clinical conditions should be the goals of salvage chemotherapy in pretreated gastric cancer.

Oxaliplatin is a third-generation platinum compound that acts as an alkylating agent, inhibiting DNA replication by forming guanine adducts [10]. Oxaliplatin has been shown to exhibit antitumor activity against cancer cell lines with acquired cisplatin resistance as well as clinical tumors that are intrinsically resistant to cisplatin and carboplatin [11, 12]. Only a few studies of oxaliplatin in the treatment of advanced gastric cancer are available. In regard to first-line chemotherapy in phase II studies, some combinations of oxaliplatin with 5-fluorouracil (5-FU) have shown a response rate and overall survival (OS) of 40% and 10 months, respectively [13–15]. These combinations showed low incidences of grade 3/4 toxic effects. The FOLFOX regimen also has some activity in

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cisplatin-pretreated patients. On the basis of these data, we planned a 5-FU, low-dose leucovorin, and oxaliplatin (FLOX) regimen that involves oxaliplatin combined with continuous infusion of 5-FU and low-dose leucovorin as salvage treatment for those who had failed previous chemotherapy treatments.

patients and methods

patient eligibility

Patients with histologically confirmed recurrent or metastatic gastric adenocarcinoma were considered eligible when they met all the following criteria: (i) age ≥18 years; (ii) Eastern Cooperative Oncology Group (ECOG) performance scale ≤2; (iii) evaluable disease with or without measurable lesions; (iv) disease progression after previous chemotherapies within 3 months before entry, with the maximum number of previous regimens being three in total, including neo-adjuvant or adjuvant chemotherapy; and (v) adequate hematological, renal, and hepatic functions. The latter was defined as neutrophil ≥1500/μl, platelet ≥100 000/μl, serum creatinine ≤1.5 mg/dl, total bilirubin ≤1.25 (or 1.5) × upper limit of normal (ULN) in the absence (or presence) of liver metastasis, and serum transaminase ≤2.5 (or 5.0) × ULN in the absence (or presence) of liver metastasis. Patients were excluded if they had concurrent malignancy within the past 5 years (excluding basal cell carcinoma of the skin or cervical carcinoma *in situ*), peripheral neuropathy as determined by the National Cancer Institute common toxicity criteria (NCI—CTC) grade ≥2, symptomatic metastasis to central nervous system, or uncontrolled significant comorbid conditions. All patients gave informed consent before enrollment.

treatment

Chemotherapy consisted of an i.v. injection of a bolus of leucovorin 20 mg/m^2 on days 1–3 and continuous i.v. infusion of 5-FU 1000 mg/m^2 on days 1–3. Oxaliplatin was administered at 75 mg/m^2 as a 2-h infusion on day 1 before the start of leucovorin and 5-FU infusion. The cycle was repeated every 3 weeks. Patients were premedicated with routine antiemetics. In the case of hematologic toxicity, the next cycle was delayed until the recovery of the neutrophil count ≥1500/μl and platelet count ≥100 000/μl. Prophylactic use of granulocyte-colony stimulating factor (G-CSF) was not allowed, but G-CSF was indicated when patients developed grade 4 neutropenia. The dose of oxaliplatin and 5-FU was reduced by 20% for subsequent courses if greater than or equal to grade 4 hematologic or greater than or equal to grade 3 nonhematologic toxicity occurred in the previous cycle. Dose reescalation was not allowed. Patients who required >4 weeks of rest for recovery from any toxicity other than alopecia or anemia or who required dose reduction of more than one step (20% from initial dose) were withdrawn from the study. Chemotherapy was continued until there was disease progression, occurrence of unacceptable toxicity, or the patient withdrew from the study.

patient evaluation

Baseline evaluations included a complete medical history with physical examination, PS, complete blood count (CBC), serum chemistries, carcinoembryonic antigen (CEA), urine analysis, creatinine clearance, and electrocardiography. A radiological examination of each lesion was done within 3 weeks before the treatment. Fiberoptic gastroduodenoscopy and positron emission tomography were planned for the evaluation of complete responders of all evaluable lesions.

A physical examination, PS, CEA, and laboratory evaluation (CBC, serum chemistries, and urinalysis) were evaluated before each subsequent cycle. For tumor response evaluation, imaging studies were repeated every two cycles. Treatment response was evaluated using spiral computed tomography according to the guidelines of the Response Evaluation Criteria in Solid Tumors Committee. The response was analyzed by intention-to-treat (ITT) analysis. Patients were considered to be assessable for response when they had received a minimum of two cycles of treatment with at least one tumor measurement or when they had evidence of early disease progression clinically or radiologically within two cycles. All the patients were evaluated for adverse events from the time of their first treatment cycle. Adverse events were evaluated weekly and recorded as a grade according to the NCI—CTC (version 3.0) for each patient. PFS was defined from the start of the treatment to the disease progression or death of any cause, and OS was calculated from the treatment start to death of any cause.

biostatistics

The primary aim of this study was to test the hypothesis that OS would improve by 50% compared with historical controls. The study was designed to have a 90% power to show an improvement in OS from 3.5 to 5.3 months with a 10% type I error, using two-sided testing, and assuming exponential OS times. According to Minimax phase II design, a sample size of 47 patients was required. Considering a 10% drop out rate, 52 patients were needed for this trial. The secondary aims included response rate, safety, PFS, and 1-year survival rate. Time-dependent variables were analyzed using the Kaplan–Meier method and compared using the log-rank test. Multivariate analysis was carried out using Cox proportional hazards regression model. Exact 95% confidence interval (CI) was provided for proportions.

results

patient characteristics

From April 2004 to May 2007, a total of 52 patients were enrolled, and all but one patient were assessable for tumor response. One patient was excluded from the study because he refused radiological examination after two cycles of chemotherapy. Patient characteristics are summarized in Table 1. The median age was 58 years. Twenty-six patients (50%) got FLOX as second-line treatment, and 26 patients (50%) got FLOX as third- or fourth-line treatment. Twenty-four patients (46%) had prior gastrectomy, among whom 16 patients (31%) got curative resection. The main metastatic sites were the peritoneum (n = 28), abdominal lymph nodes (n = 27), and liver (n = 15). Median value of the prechemotherapy level of CEA was 2.7 (range 0.2–11,531 ng/ml).

Previous chemotherapy histories of our patients are summarized in Table 2. The median cycle number of previous first-line chemotherapy was 6 (range 2–16 cycles) with a median dose intensity of 0.95 (range 0.57–1.0). The overall response rate of first-line chemotherapy was 31%. Twenty-six patients received second-line chemotherapy with the median number of cycles being 4 (range 1–9). The median dose intensity was 1.0 (range 0.6–1.0). Overall response rate of previous second-line chemotherapy was 22%. The median cycle number of previous third-line chemotherapy in eight patients was 4 (range 2–10). With a median dose intensity of 1.0 (range 0.87–1.0), the overall response rate was 13%. This implies that the patients enrolled in this study got enough doses and cycles of previous chemotherapy.

treatment summary

Treatment is summarized in Table 3. A total of 203 cycles were administered, with a median of three cycles (range 1–15) per patient. The median dose intensity of oxaliplatin was

Table 1. Patient characteristics

Characteristics	Number of patients	%
Number of enrolled patients	52	
Number of assessable patients	51	
Number of patients with measurable lesion	43	83
Sex		
Male	34	65
Female	18	35
Age (median), years	58 (37–75)	
ECOG		
0–1	23	45
2	29	56
Histology		
Well to moderately differentiated	15	29
Poorly differentiated	24	46
Signet ring cell	8	15
Unknown	5	10
Number of previous chemotherapy regimen		
1	26	50
2	18	35
3	8	15
Previous operation		
Unresectable	28	54
Radical	16	31
Palliative	8	15
Number of metastatic sites		
1	12	23
2	20	39
≥3	20	38
Disease site		
Abdominal lymph nodes	27	52
Peritoneum	28	54
Liver	15	29
Lung	5	10
Bone	6	12
Ovary	2	4

ECOG = Eastern Cooperative Oncology Group.

25 mg/m^2/week (range 15–29 mg/m^2/week), and the median intensity of 5-FU was 324 mg/m^2/week (range 196–351 mg/m^2/week). The relative dose intensity of oxaliplatin and 5-FU were 0.97 and 0.98, respectively. Four patients were subjected to dose reduction due to grade 3 nonhematologic toxic effects: liver enzyme elevation, mucositis, peripheral neuropathy, and nausea, respectively. Twenty-five total cycles were delayed in 14 patients (27%) due to liver enzyme elevation ($n = 1$), infection ($n = 1$), mucositis ($n = 1$), and by patients' preference ($n = 11$). After PD on this regimen, 17 patients of second-line treatment (65%) were transferred to the third-line salvage chemotherapy: taxane monotherapy ($n = 7$), cisplatin plus irinotecan ($n = 9$), and 5-FU agents ($n = 1$). Six patients (23%) who receive FLOX regimen as the third- or fourth line were transferred to further salvage chemotherapy: taxane monotherapy ($n = 3$), oral 5-FU agents ($n = 1$), and cisplatin plus irinotecan ($n = 2$).

Table 2. Summary of prior chemotherapy history

Treatment group	Number of enrolled patients	Median cycle (range)	Median RDI (range)
First line	52		
Cisplatin based	17	6 (2–16)	0.9 (0.57–1)
Others[1]	35	8 (2–12)	0.97 (0.59–1)
Second line	26		
Cisplatin based	3	9 (2–9)	0.98 (0.77–1)
Others[2]	23	4 (1–9)	1 (0.6–1)
Third line	8		
Cisplatin based	–	–	–
Others[3]	8	4 (2–10)	1 (0.87–1)

[1]5-FU + leucovorin + taxotere, 5-FU + leucovorin + taxol, S-1, capecitabine + doxorubicin, taxol + S-1, 5-FU + doxoribicin, taxotere + S-1, taxotere + capecitabine, herceptin + cisplatin + capecitabine.
[2]5-FU + leucovorin + taxol, S-1, capecitabine + doxorubicin, capecitabine, taxol, sutene.
[3]Capecitabine, capecitabine + doxorubicin, S-1, taxol.
RDI, relative dose intensity.

efficacy

With a median follow-up duration of 6 months (range 1–17 months), 48 patients had disease progression, and 41 patients (85%) died from cancer progression.

The median OS was 6.6 months (95% CI 4.5–8.8 months). When we evaluated the OS according to the previous treatment, OS was 6.6 months (95% CI 3.4–9.8 months) for the second-line treatment group and 6.4 months (95% CI 3.9–8.8 months) for greater than or equal to third-line treatment group ($P = 0.506$) (Figure 1).

One-year survival rate of all patients was 30% (38% for the second-line group, 21% for the third-line group, and 0% for the fourth-line group). The median PFS was 2.5 months (95% CI 1.9–3.0 months) by ITT analysis. When we evaluated the PFS according to the previous treatment, it was 3.0 months (95% CI 0.8–5.2 months) for the second-line treatment group and 2.3 months (95% CI 1.0–3.6 months) for greater than or equal to third-line treatment group ($P = 0.167$) (Figure 2).

When we compared survival according to clinical parameters by multivariate analysis, only initial CEA level (≤5.0 ng/ml) ($P = 0.020$) was a favorable factor for OS, and a good ECOG PS (≤1) ($P = 0.078$) showed a favorable trend for longer survival. For PFS, only initial CEA level (≤5.0 ng/ml) ($P = 0.038$) was a significant favorable factor.

Response to therapy was assessable in all but one patient, who withdrew after the second cycle without any response evaluation. The overall objective response rates are summarized in Table 4. Of the 52 assessable patients, 2 achieved a partial response (PR) and 23 patients had stable disease (SD). The overall response rate was 4% (95% CI 0–9%), and the disease control rate (DCR) was 48% (95% CI 34–62%). The two patients who achieved PR had received cisplatin as their first-line treatment. Their response duration was 15.8 and 3.6 months.

DCR was evaluated separately by the previous treatment as *post hoc* analysis. Among the 26 patients receiving second-line

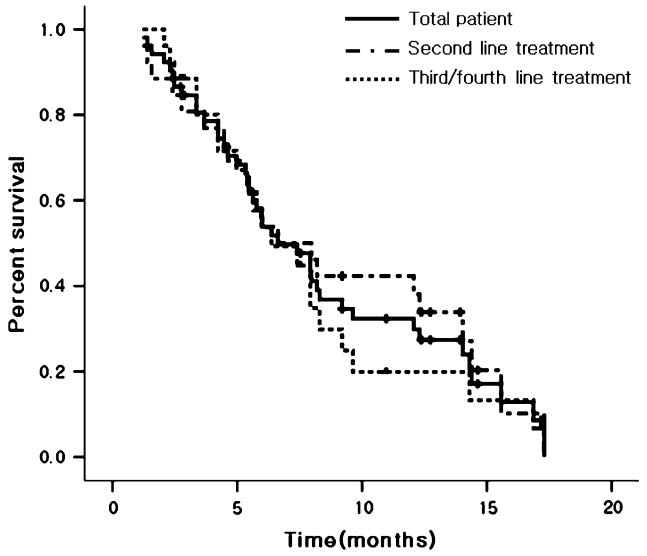

Figure 1. Analysis of overall survival according to previous treatments.

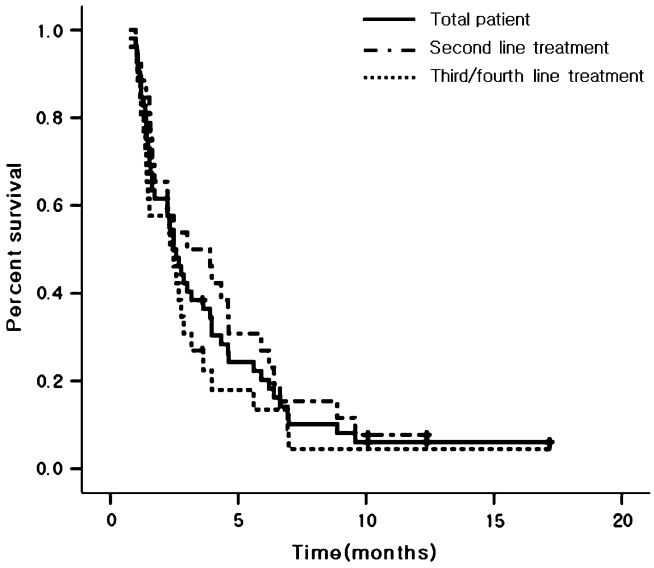

Figure 2. Analysis of progression-free survival according to previous treatments.

treatment, the DCR was 58% (95% CI 37–78%). The median duration of SD was 3.9 months (range 0.9–12.4 months). Of the 26 patients in the greater than or equal to third-line treatment group, the DCR was 38% (95% CI 18–59%), and the median duration of SD was 2.3 months (range 1.4–6.9).

toxicity

The toxicity profile is summarized in Table 5. There was no case of treatment-related mortality. The most common grade 3/4 hematologic toxicity was neutropenia, which was found in 16% of patients. Leukopenia and anemia of grade 3/4 were also observed in 8% and 4% of the patients, respectively. Twenty-three patients required G-CSF support, but none of them suffered febrile neutropenia. The median frequency of G-CSF administration of all the patients was 2 (range 1–10). Nineteen patients received a transfusion. The median unit of red blood cell transfused was 2 packs (range 1–6).

The most common grade 3 nonhematological toxic effects were vomiting (6%), nausea (4%), and mucositis (4%). Grade 3 peripheral neuropathy was observed in two patients (4%). Using Fisher's exact test, we compared the incidence of grade 3/4 toxicity between the second-line treatment group and greater than or equal to third-line treatment group. There were no significant differences in the incidence of neutropenia, vomiting, or peripheral neuropathy between the two groups.

discussion

There are no randomized controlled trials that have indicated a benefit of the second-line chemotherapy compared with supportive care alone. But responders to second-line chemotherapy survive longer compared with nonresponders, and symptomatic benefit may be obtained from the second-line therapy [2]. This study evaluated the clinical feasibility of oxaliplatin combined with 5-FU in previously treated patients with advanced gastric cancer. In this study, we adopted oxaliplatin 75 mg/m^2 instead of oxaliplatin ≥85 mg/m^2. We did this because more patients were expected to receive this regimen as the third- or fourth line of treatment. Therefore, we assumed that a lower dose of oxaliplatin would be reasonable considering patient safety and tolerability.

The oxaliplatin, 5-FU, and leucovorin combination is accepted in patients who are refractory to 5-FU and leucovorin in colorectal cancer [16]. This combination (FOLFOX) is on the basis of a bimonthly schedule, and the response rate of various combinations of FOLFOX is 20%–46%. Recently, oxaliplatin in various combinations with 5-FU and leucovorin were tried as first-line treatments for advanced gastric cancer, and the reported response rates were 38%–45% [13–15]. On the contrary to colorectal cancer, *in vitro* antitumor activity is reported to have a strict sequence dependency of oxaliplatin followed by 5-FU in gastric cancer, which was the basis of our protocol development [17].

The other point to mention is that, in this study, the primary end point was OS. However, in advanced gastric cancer with prior treatment, the traditional measured primary end point of phase II study is response rate, which is poorly correlated with patients' survival. A recent Japanese study demonstrated that the response of a primary gastric mass is poorly correlated with that of a metastatic lesion [18]. Moreover, gastric cancer often progresses as nonmeasurable disease. Locoregional or peritoneal metastasis comprises ~50% of the initial recurrence of gastric cancer in Korean patients, most of which cannot be assessed by conventional imaging [19]. Therefore, we concentrated on survival rather than response rate to measure the clinical benefit of the salvage chemotherapy in previously treated patients. When we initiated this study, most of studies of the second-line treatment of advanced gastric cancer after failing previous active combination chemotherapy reported the median survival time of 2.5–5.0 months [3, 4,20–23]. This is underestimated considering a recent pooled analysis reported in American Society of Clinical Oncology Gastrointestinal Symposium 2004 (5.6 months). However, on designing this trial, patients

Table 3. Treatment summary and dose intensity

Treatment group	Total patients ($n = 52$)	Second line ($n = 26$)	Third line ($n = 18$)	Fourth line ($n = 8$)
Treatment cycle				
Median (range)	3 (1–15)	4 (1–12)	2 (1–15)	3 (1–4)
Treatment delay				
Total cycle	203	123	59	21
Delayed cycle	25	15	4	3
Median delayed week	1 (1–3)	2 (1–3)	1 (1–3)	2 (1–3)
Number of dose modification (cycle)	14	10	1	3
Median dose intensity mg/m$^{2/}$/week (range)				
5-FU	324 (196–351)	314 (227–342)	333 (283–351)	311 (196–333)
Oxaliplatin	25 (15–29)	24 (17–26)	25 (21–29)	23 (15–25)
Relative dose intensity (range)				
5-FU	0.97 (0.59–1)	0.94 (0.68–1)	1 (0.85–1)	0.93 (0.59–1)
Oxaliplatin	0.98 (0.59–1)	0.94 (0.68–1)	1 (0.85–1)	0.93 (0.59–1)

5-FU, 5-fluorouracil.

Table 4. Response evaluation by intention-to-treat analysis

	Number of total patients ($n = 52$)		Second-line treatment ($n = 26$)		Third- and fourth-line treatment ($n = 26$)	
	Measurable ($n = 43$)	Nonmeasurable ($n = 9$)	Measurable ($n = 20$)	Nonmeasurable ($n = 6$)	Measurable ($n = 23$)	Nonmeasurable ($n = 3$)
Complete response	–	–	–	–	–	–
Partial response	2	–	1	–	1	–
Stable disease	18	5	10	4	8	1
Progressive disease	22	4	8	2	14	2
NA	1	–	1	–	0	–
ORR (%)	5		5		4	
DCR (%)	47		55		39	

NA, not available; ORR, overall response rate; DCR, disease control rate.

were allowed to receive not only second-line treatment but also third- or fourth-line treatment of oxaliplatin. Moreover, we anticipated considerable patients of modest PS (ECOG grade 2) to be enrolled. Therefore, we assumed that the historical control of 3.5 months could be a reference. Our study was designed to prove an increment of OS by 50% to 5.3 months. We thought this was somewhat high considering the patients' general condition and prior exposure to chemotherapy. Nevertheless, we believe that this survival parameter is currently the minimum range for acceptance of any new regimen aiming at second- or third-line treatment of gastric cancer [20, 21, 23]. In this study, the median OS was 6.6 months (95% CI 4.5–8.8). We can presume that good PS maintained throughout the treatment duration enabled many patients to be transferred to another chemotherapy regimens.

The third point to consider is that overall response rate was only 4% with 48% DCR. Toxicity, especially nonhematologic toxicity, however, was quite low. Toxicity profile and its incidence did not show any differences between the second-line group and greater than or equal to the third-line treatment group. Kim et al. [24] reported the OFL-CL regimen (oxaliplatin 85 mg/m^2 and infusion of high-dose 5-FU and leucovorin) with a response rate of 26% and median survival of 7.3 months in patients previously treated with platinum. Schmid et al. [22] combined oxaliplatin 130 mg/m^2 with thymidylate synthase inhibitor, raltitrexed, as second-line treatment, but its response rate was only 5% and median survival was 4.5 months [25]. Although there is little evidence that a higher oxaliplatin dose guarantees higher response rate, we think our poor response can be explained by the fact that half the patients got FLOX regimen as third- or fourth-line treatment with high tumor burden. Moreover, we can also indicate that the FLOX regimen could be recommended for previously cisplatin-exposed patients because two responders had previous cisplatin treatment; this is consistent with a previous study [24]. PS, retreatment after failure of a nonplatinum-based regimen, and previous response with first-line therapy are known predictive factors for response to second-line chemotherapy [2]. These factors, however, were not correlated with PFS or OS in our study. Neither PFS nor OS was affected by previous exposure to cisplatin. Therefore, we could indicate that the FLOX regimen is also an acceptable option in terms of patient survival for salvage chemotherapy in pretreated patients.

Table 5. Toxicity profiles per patient ($n = 52$) according to the NCI—CTC grade (version 3.0)

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 3/4 (%)
Hematologic toxicity					
Anemia	22	25	2 (4)	–	2 (4)
Neutropenia	5	11	6 (12)	2 (4)	8 (16)
Thrombocytopenia	9	3	–	–	–
Nonhematologic toxicity					
Diarrhea	8	1	1 (2)	–	1 (2)
Anorexia	8	5	1 (2)	–	1 (2)
Nausea	6	6	2 (4)	–	2 (4)
Vomiting	6	4	3 (6)	–	3 (6)
Mucositis	12	1	2 (4)	–	2 (4)
Constipation	3	2	–	–	–
Skin rash	2	–	–	–	–
Peripheral neuropathy	3	3	2 (4)	–	2 (4)
Elevated creatinine	1	2	2 (4)	–	2 (4)
Elevated aminotransferase	7	4	1 (2)	–	1 (2)
Hyperbilirubinemia	–	2	1 (2)	–	1 (2)

One of the main adverse effects of oxaliplatin is peripheral neuropathy. The cumulative dose of oxaliplatin (>540 mg/m^2) is an important factor in the development of peripheral neuropathy [25]. Even considering 20 (38%) cisplatin-pretreated patients in our study, neuropathy of grades 2–3 was noticed in only five patients. This may be due to a low cumulative dose of oxaliplatin (median 175 mg/m^2). Severe diarrhea and stomatitis were rare. Nausea and vomiting were the most common nonhematological toxicity, which was consistent with other reports. In conclusion, using the FLOX regimen, high DCR prolonged OS. Furthermore, its lower toxicity and preserved PS made many patients ($n = 23$, 48%) eligible for the next regimen. This FLOX regimen afforded a comparable survival profile and acceptable toxic effects in pretreated patients of advanced gastric cancer. Randomized clinical trial is needed to clarify if this regimen can be applied as salvage chemotherapy.

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