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Comparative analysis of the efficacy and safety of modified FOLFOX-6 and DCF regimens as first-line treatment in advanced gastric cancer

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Abstract. The aim of this study was to retrospectively compare the efficacy and toxicity of the oxaliplatin + 5-fluorouracil (5-FU) + leucovorin (LV) regimen [modified (m) FOLFOX-6] with that of the docetaxel + cisplatin + 5-FU regimen (DCF) in patients with advanced gastric cancer (AGC). A total of 72 patients received DCF (75 mg/m^2 docetaxel and 75 mg/m^2 cisplatin on day 1 and 750 mg/m^2 5-FU on days 1-5) every 21 days, whereas 54 patients received mFOLFOX-6 (85 mg/m^2 oxaliplatin and 400 mg/m^2 LV as a 2-h infusion, followed by a 5-FU bolus of 400 mg/m^2 and 2,400 mg/m^2 5-FU as a 46-h continuous infusion) every 14 days. In the DCF arm, 55 (76.4%) of the patients received prophylactic granulocyte colony-stimulating factor (G-CSF), 48-72 h following completion of chemotherapy. The median follow-up of the study was 12.1 months. The overall response rate (ORR) was 37.0% for mFOLFOX-6 and 40.3% for DCF (P=0.72). The median time to progression was 6.5 and 6.2 months in the mFOLFOX-6 and DCF arms, respectively (P=0.70). The median overall survival was 11.4 and 13.5 months in the mFOLFOX-6 and DCF arms, respectively (P=0.72). The rates of hematological toxicity did not differ between the two arms. However, in the subgroup analysis, grade 3-4 neutropenia and febrile neutropenia were significantly more common among patients who had not received G-CSF prophylaxis in the DCF arm. The incidence of grade 3-4 nausea/vomiting and diarrhea were significantly higher in the DCF arm. In conclusion, the present study demonstrated that the efficacy of the mFOLFOX-6 regimen was comparable to that of the DCF regimen in AGC patients. In addition, the benefit of G-CSF prophylaxis in conjunction with the DCF regimen was demonstrated.

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Introduction

Gastric cancer is one of the most common causes of cancer-related mortality worldwide (1). Despite the decline in incidence and mortality rates over the last two decades, >40% of gastric cancer patients present with advanced-stage disease at diagnosis (2).

Several randomized trials demonstrated that palliative chemotherapy may relieve gastric cancer-related symptoms, prolong survival and improve the quality of life compared to best supportive care; therefore, it is offered as a routine treatment option to patients with a satisfactory performance status (3-5). A meta-analysis demonstrated that combination chemotherapy, particularly with three-drug combinations, is superior to monotherapy (6).

Since encouraging survival outcomes and better quality of life have been obtained with the docetaxel + cisplatin + 5-fluorouracil (5-FU) regimen (DCF) in several studies, this regimen has been widely used to treat advanced-stage gastric cancer (7,8). However, these studies reported that the incidence of grade 3-4 toxicity with DCF was higher compared to that with other combination regimens; therefore, this regimen has not been established as standard chemotherapy for advanced gastric cancer (AGC).

Although a number of different chemotherapeutic agents have been tested in AGC patients, there is currently no globally accepted standard chemotherapeutic regimen for the treatment of AGC. In addition, despite the introduction of new-generation chemotherapeutic agents and the significant increase in the proportion of patients receiving palliative chemotherapy over the last few years, overall survival (OS) has not increased in AGC patients (9).

Thus, first-line chemotherapy should be extensively investigated in these patients, to determine the optimal chemotherapeutic regimens that will improve patient survival and quality of life, with reduced toxicity.

In numerous phase II studies, combination chemotherapy with 5-FU, folinic acid (leucovorin; LV) and oxaliplatin (FOLFOX regimens), has exhibited considerable antitumor activity and a tolerable toxicity profile in AGC patients using different doses and schedules (10-14).

To address this issue, a retrospective analysis was conducted comparing baseline characteristics and treatment results with the oxaliplatin + 5-FU + LV regimen [modified (m)FOLFOX-6] and the DCF regimen in previously untreated patients with AGC.

Patients and methods

Patients. A total of 126 patients with AGC (unresectable or metastatic), who were treated with DCF or mFOLFOX-6 as first-line chemotherapy between June, 2010 and August, 2014 at the Department of Medical Oncology, Faculty of Medicine, Trakya University (Edirne, Turkey), were retrospectively reviewed. Patients who had received prior treatment, or exhibited insufficient hematological, hepatic and renal functions, were excluded from the analysis.

This retrospective study was approved by the Institutional Review Board of the Trakya University.

Treatment. In the DCF arm (n=72), the patients received 75 mg/m^2 docetaxel and 75 mg/m^2 cisplatin as an intravenous (i.v.) infusion on day 1 and 750 mg/m^2/day 5-FU as a continuous infusion for 5 days. The DCF protocol was repeated every 3 weeks, for up to 6 cycles. In the DCF arm, 55 (76.4%) of the patients received prophylactic granulocyte colony-stimulating factor (G-CSF) 48-72 h following completion of chemotherapy.

In the mFOLFOX6 arm (n=54), the patients received 85 mg/m^2 oxaliplatin and 400 mg/m^2 LV as an i.v. infusion over 2 h and a 5-FU bolus of 400 mg/m^2 as a 10-min infusion, followed by 2,400 mg/m^2 5-FU as a 46-h continuous infusion. The mFOLFOX-6 protocol was repeated every 2 weeks, for up to 12 cycles. Chemotherapy was continued until disease progression, unacceptable toxicity, patient refusal or the physician's decision. Demographic, medical and toxicity data were obtained from the medical and chemotherapy charts.

The performance status of the patients was estimated according to the Eastern Cooperative Oncology Group performance status (ECOG PS; http://ecog-acrin.org/resources/ecog-performance-status) scale.

Table I. Patient characteristics (n=126).

Characteristics	Chemotherapeutic regimen: mFOLFOX-6[a], no. (%) (n=54)	Chemotherapeutic regimen: DCF[b], no. (%) (n=72)	P-value
Age (years)			0.103
Median	58.5	56.0	
Range	32-80	27-78	
Gender			0.590
Male	42 (77.8)	53 (73.6)	
Female	12 (22.2)	19 (26.4)	
ECOG PS			<0.0001
0-1	26 (48.1)	61 (84.7)	
2	28 (51.9)	11 (15.3)	
Disease status			0.700
Locally advanced	3 (10)	2 (7.1)	
Metastatic	27 (90)	26 (92.9)	
Radical gastrectomy	13 (24.1)	19 (26.4)	
Any palliative surgery	19 (35.2)	14 (19.4)	
Adjuvant treatment			0.950
No	41 (75.9)	55 (76.4)	
Yes	13 (24.1)	17 (23.6)	
No. of metastatic sites			0.720
Locally advanced	5 (9.3)	4 (5.6)	
1	31 (57.4)	44 (61.1)	
≥2	18 (33.3)	24 (33.3)	
Organs most commonly involved			
Liver	26 (48.1)	39 (54.2)	0.500
Peritoneum	16 (29.6)	23 (31.9)	0.170
Lung	17 (31.5)	15 (20.8)	0.780
Presence of ascites	13 (24.1)	4 (5.6)	0.003

[a]Oxaliplatin + 5-FU + leucovorin. [b]Docetaxel + cisplatin + 5-FU. ECOG PS, Eastern Cooperative Oncology Group performance status; 5-FU, 5-fluorouracil.

Response to treatment. Response evaluation was performed every 8-12 weeks according to the Response Evaluation Criteria in Solid Tumors, version 1.1 (15) and the adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (16).

The time to progression (TTP) was measured from treatment initiation until the first evidence of disease progression. The OS was measured from treatment initiation until death or last control date. If a patient had succumbed to presumed progressive disease in the absence of radiographic evidence of progression, the date of death was used as the date of disease progression.

Statistical analysis. The baseline characteristics of the mFOLFOX-6 and DCF groups were compared by the χ^2 test (for categorical variables) or the two-sample t-test (for continuous variables). The Kaplan-Meier method was used to provide median point estimates, TTP and median OS, and the confidence intervals (CIs) were calculated with the Greenwood's formula. The log-rank test was used to determine the statistical significance of the differences between the groups. Survival curves were created with IBM SPSS software, version 20.0 (IBM Corp., Armonk, NY, USA). Safety analyses were performed using descriptive statistics. P<0.05 was considered to indicate statistically significant differences.

Results

Patient characteristics. A total of 126 patients were enrolled in this study, 54 and 72 of whom were treated with mFOLFOX-6

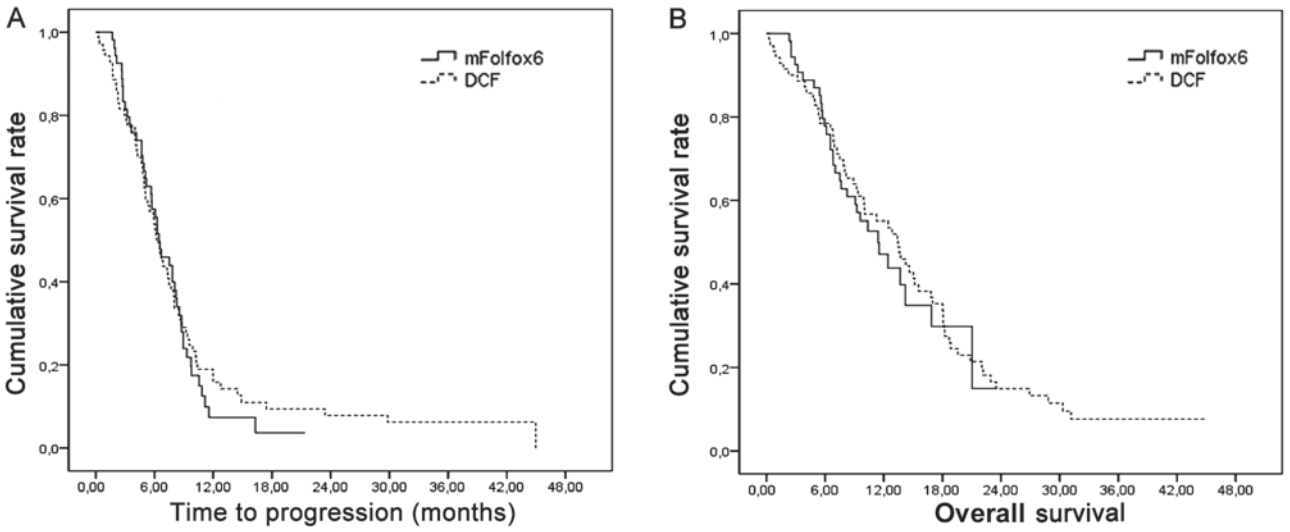

Figure 1. (A) Kaplan-Meier estimates of time to progression (TTP) according to chemotherapeutic regimen. The median TTP was 6.5 and 6.2 months in the oxaliplatin + 5-fluorouracil + leucovorin (mFOLFOX-6) and the docetaxel + cisplatin + 5-fluorouracil (DCF) arms, respectively (P>0.05). (B) Kaplan-Meier estimates of overall survival (OS) according to chemotherapeutic regimen. The median OS was 11.4 and 13.5 months in the mFOLFOX-6 and DCF arms, respectively (P>0.05).

Table II. Response to treatment according to chemotherapeutic regimen.

	Chemotherapeutic regimen		
Characteristics	mFOLFOX-6[a], no. (%) (n=54)	DCF[b], no. (%) (n=72)	P-value
Complete response	2 (3.7)	3 (4.2)	0.72
Partial response	18 (33.3)	26 (36.1)	
Stable disease	18 (33.3)	28 (38.9)	
Progressive disease	16 (29.7)	15 (20.8)	

[a]Oxaliplatin + 5-FU + leucovorin. [b]Docetaxel + cisplatin + 5-FU. 5-FU, 5-fluorouracil.

Table III. Toxicities according to the NCI CTC 2.0. criteria.

	Chemotherapeutic regimen		
Grade 3-4 adverse events	mFOLFOX-6[a], no. (%) (n=54)	DCF[b], no. (%) (n=72)	P-value
Non-hematological			
Nausea-vomiting	4 (7.4)	15 (20.8)	0.037
Diarrhea	3 (5.6)	14 (19.4)	0.024
Stomatitis	4 (7.4)	11 (15.3)	0.180
Peripheral neuropathy	3 (5.6)	3 (4.2)	0.710
Hematological			
Neutropenia	18 (33.3)	23 (31.9)	0.860
Febrile neutropenia	1 (1.9)	7 (9.7)	0.070
Anemia	2 (3.7)	5 (6.9)	0.430
Thrombocytopenia	3 (5.6)	5 (6.9)	0.750

[a]Oxaliplatin + 5-FU + leucovorin. [b]Docetaxel + cisplatin + 5-FU. NCI-CTC, National Cancer Institute Common Toxicity Criteria. 5-FU, 5-fluorouracil.

and DCF, respectively. The median follow-up was 12.1 months and it was not significantly different between the two groups (P=0.08). According to the ECOG PS scale, 28 (51.9%) of the patients in the mFOLFOX-6 arm and 11 (15.3%) of the patients in the DCF arm had a PS of 2 (P<0.0001). The baseline characteristics of the patients according to the first-line regimen are summarized in Table I.

Response to treatment. Patients were treated with a median of 10 and 6 cycles of mFOLFOX-6 and DCF, respectively.

The overall response rate (ORR) was 37.0 and 40.3% in the mFOLFOX-6 and DCF arms, respectively (P=0.72) (Table II). The median TTP was 6.5 (95% CI: 4.8-8.1) and 6.2 (95% CI: 5.2-7.2) months in the mFOLFOX-6 and DCF arms, respectively (P=0.70) and the median OS was 11.4 (95% CI: 7.9-14.9) and 13.5 (95% CI: 10.2-16.8) months in the mFOLFOX-6 and DCF arms, respectively (P=0.72) (Fig. 1).

Toxicities. The most commonly observed grade 3-4 hematological toxicity was neutropenia in both arms. The rate of grade 3-4 neutropenia did not differ significantly between the two arms (33.3% in the mFOLFOX-6 arm vs. 31.9% in the DCF arm; P=0.860). The rate of febrile neutropenia also did not differ significantly between the two arms (1.9% in the mFOLFOX-6 arm vs. 9.7% in the DCF arm; P=0.07).

However, in the DCF arm, 55 (76.4%) of the patients received primary G-CSF prophylaxis subcutaneously for 5 days. In the subgroup analysis, the incidence of grade 3-4 neutropenia was significantly higher among patients in the DCF arm who had not received G-CSF prophylaxis (18.2 vs. 76.5%, P<0.001).

Febrile neutropenia was also significantly more common among patients in the DCF arm who had not received G-CSF prophylaxis (3.6 vs. 29.4%, P=0.002). The rates of anemia and thrombocytopenia were similar between the two arms.

The most commonly encountered grade 3-4 non-hematological toxicities were nausea/vomiting, mucositis and diarrhea in both arms. Grade 3-4 nausea-vomiting was more frequent with DCF (20.8%) compared with mFOLFOX-6 (7.4%) (P=0.037). Grade 3-4 diarrhea was also more frequent with DCF (19.4%) compared with mFOLFOX-6 (5.6%) (P=0.024). The treatment-related toxicities are summarized in Table III. Dose reduction was required in 15 (27.8%) and 28 (38.9%) patients in the mFOLFOX-6 and DCF arms, respectively (P=0.19). Dose delays of at least 7 days were required in 15 (27.8%) and 17 (23.6%) patients in the mFOLFOX-6 and DCF arms, respectively (P=0.6). Treatment discontinuation due to toxicity was required in 2 (3.7%) and 9 (12.3%) patients in the mFOLFOX-6 and DCF arms, respectively (P=0.08). Treatment-related mortality was reported in 2 (3.7%) and 4 (5.6%) patients in the mFOLFOX-6 and DCF arms, respectively (P=0.62) (data not shown).

Discussion

Although AGC is considered to be relatively chemosensitive, systemic chemotherapy for patients with gastric cancer exerts a limited effect on OS. The majority of the patients have received palliative chemotherapy in recent years; however, OS did not increase as expected in patients with metastatic gastric cancer (9). In addition, there is currently no globally accepted chemotherapeutic regimen due to concerns regarding the toxicity of chemotherapy and the inconsistency in treatment response. In the face of the limited progress in the treatment options for AGC, the therapeutic trend is toward improved clinical efficacy and a more acceptable toxicity profile.

Thus, we aimed to investigate the efficacy and safety of mFOLFOX-6 and DCF as first-line regimens in AGC. To the best of our knowledge, this study is the first to compare the efficacy and safety of these two regimens as the first-line treatment of AGC in the English literature.

In this study, we observed that DCF and mFOLFOX-6 were associated with similar ORR, TTP and OS, with a different toxicity profile in the first-line stetting for patients with AGC.

The DCF regimen has been widely used for the treatment of AGC, with encouraging survival outcomes and improved quality of life, as reported by several recent studies; in these studies, the ORR was reported to be 36.6-43%, the TTP was 4.6-5.6 months and the OS was 9.2-10.4 months (7,8,17). In the present study, the DCF regimen exhibited good efficacy, with an ORR of 40.3%, a median TTP of 6.2 months and a median OS of 13.5 months. Thus, our efficacy results for the DCF arm were consistent with the literature.

Although DCF is commonly used in as first-line chemotherapy in metastatic gastric cancer worldwide, its tolerability is low due to toxicity. Therefore, evaluation of treatment benefits against chemotherapy-related toxicities is required and patients eligible for combination chemotherapy should be carefully selected.

In several trials, novel chemotherapeutic agents, such as capecitabine, taxanes, irinotecan and oxaliplatin, have been tested in AGC over the last few decades (18-20). In several studies conducted over the last decade, a number of different FOLFOX regimens have exhibited satisfactory clinical activity and acceptable toxicity in patients with AGC. The effectiveness of a variety of FOLFOX-6 regimens in the treatment of AGC has been recently evaluated, with a reported ORR of 40.2-48% a TTP of 5.4-6.2 months and an OS of 8.6-13 months (11,21-25). In the present study, the mFOLFOX-6 regimen exhibited good efficacy, with an ORR of 37.0%, a median TTP of 6.5 months and a median OS of 11.4 months. The results of the present study were similar to those previously reported by studies investigating FOLFOX-6 (11,21-25).

In terms of results, there was no significant difference between the DCF and mFOLFOX-6 arms; the ORR and efficacy data were comparable to the results of previous studies investigating the DCF and mFOLFOX regimens (7,8,17,21-25).

As regards toxicity, the two regimens were associated with a manageable toxicity profile. In the DCF arm, the incidence of grade 3-4 nausea/vomiting and diarrhea was significantly higher compared with that in the mFOLFOX-6 arm. The rate of grade 3-4 neutropenia was similar between the two arms. The lower hematological toxicity rates in the DCF arm of this study may be explained by 76.4% of the patients in the DCF arm receiving primary G-CSF prophylaxis. In the V325 trial, the rates of grade 3-4 neutropenia and febrile neutropenia were reported to be 82 and 29%, respectively (7). In the subgroup analysis of the present study, grade 3-4 neutropenia and febrile neutropenia were significantly more common among patients in the DCF arm not receiving primary G-CSF prophylaxis; our results were similar to those of the V325 study.

The benefits of administering primary G-CSF prophylaxis in conjunction with docetaxel-based chemotherapy have been reported by phase 3 trials in breast cancer patients. When comparing patients receiving docetaxel-based combination regimens, a significant reduction in the incidence of febrile neutropenia and other neutropenia-related complications was observed in patients receiving docetaxel-based combination regimens with primary prophylactic G-CSF (26,27). Recent European and American guidelines recommend the routine use of primary prophylaxis with G-CSF when using chemotherapeutic regimens associated with a risk of febrile neutropenia of ≥20%, such as DCF (28,29). The results of the V325 trial support the use of G-CSF in conjunction with the DCF protocol (7). In previous studies using FOLFOX-6 regimens for AGC, the rates of neutropenia, anemia and thrombocytopenia were 4.9-34.1, 1.2-20 and 0-7.3% respectively (21-25). The incidence of grade 3-4 adverse effects in the mFOLFOX-6 arm was similar to that reported by previous studies. Dose reduction, dose delays and treatment-related mortality was similar between the two arms.

This study had certain limitations due to the indirect comparison and retrospective design. First, the proportion of patients with an ECOG PS of 2 was significantly higher in the mFOLFOX-6 arm, although PS is not an accurate criterion for evaluating the general status of cancer patients. However, our results suggest that the mFOLFOX-6 regimen is an efficient and tolerable treatment option for AGC patients with an ECOG PS of 2. Second, adverse event data were limited to grade 3-4 toxicities. We were unable to compare grade 1-2 toxicities due to insufficient records in the medical charts. Finally, there was heterogeneity in the DCF

arm in terms of primary prophylaxis due to the physician's decision. However, despite these limitations, the results of this study may be considered as a major reference regarding the benefits of G-CSF use in conjunction with the DCF regimen.

In conclusion, there was no statistically significant difference between the DCF and mFOLFOX-6 arms in terms of treatment results. The present study demonstrated that the efficacy of mFOLFOX-6 was comparable to that of DCF in AGC patients and the toxicity analysis revealed that DCF was associated with worse non-hematological toxicities. Therefore, the mFOLFOX-6 regimen may be an effective and tolerable treatment option for AGC patients with an ECOG PS of 2.

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