

Comparison of the efficacy of mFOLFOX-6 and mDCF regimens in the treatment of metastatic gastric cancer: a multicenter retrospective study

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Abstract

Background: Metastatic gastric cancer (GC) and gastroesophageal junction (GEJ) cancer are associated with a poor prognosis. Recent advancements in treatment have incorporated trastuzumab, anti-PD-1 agents, and anti-claudin therapies alongside chemotherapy (ChT), significantly improving outcomes. Contemporary studies predominantly employ doublet ChT as the backbone for these regimens, although historically triplet ChT regimens have been favored, particularly in younger patients requiring rapid tumor shrinkage.

Objective: The aim of this study was to compare the efficacy of mFOLFOX-6 and mDCF regimens in the treatment of advanced GC and GEJ adenocarcinoma.

Design: This was a retrospective multicenter study.

Methods: Patient data were obtained from the databases of 25 hospitals across Turkey. Demographic and clinicopathological characteristics were documented. Overall survival (OS) and progression-free survival (PFS) were analyzed using the Kaplan–Meier method, and group discrepancies were assessed with log-rank test.

Results: A total of 493 patients were included in the analysis, with similar baseline characteristics between the two groups. The objective response rate was 36.3% in the mDCF group and 38% in the mFOLFOX-6 group ($p=0.7$). The median PFS was 6 months for mDCF and 7 months for mFOLFOX-6 ($p=0.2$), while the median OS was 12 months for mDCF and 11 months for mFOLFOX-6 ($p=0.4$). Grade 3–4 neutropenia occurred in 27.6% of patients treated with mDCF versus 17.8% with mFOLFOX-6 ($p=0.01$). Likewise, grade 3–4 anemia was more frequent in the mDCF group (9.5%) compared to the mFOLFOX-6 group (4.8%; $p=0.04$).

Conclusion: Modified FOLFOX-6 demonstrated comparable efficacy to mDCF in the treatment of advanced GC and GEJ adenocarcinoma. Moreover, mFOLFOX-6 was associated with a lower incidence of hematological adverse effects.

Keywords: chemotherapy, gastric cancer, metastasis, quality of life, survivorship, toxicity management

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Introduction

Gastric and gastroesophageal junction (GEJ) cancers rank as the fourth leading cause of cancer-related mortality globally.¹ In over half of the cases, curative treatment is not feasible due to late-stage diagnosis or the presence of significant comorbidities.² Advanced-stage gastric cancer (GC) is associated with a poor prognosis, with a median overall survival (OS) of approximately 1 year.³ Adenocarcinoma is the most common pathological subtype encountered. Chemotherapy (ChT) remains the cornerstone of treatment for advanced disease. Recent advancements in the management of metastatic GC include the incorporation of targeted therapies such as trastuzumab,⁴ nivolumab,⁵ pembrolizumab,⁶ and zolbetuximab^{7,8} into ChT regimens. The addition of nivolumab to chemotherapy improved both progression-free survival (PFS) and OS, with a more pronounced benefit observed in patients with high PD-L1 expression. In patients with PD-L1 $\geq 5\%$, the median OS (mOS) was 14.4 months in the nivolumab plus chemotherapy group compared to 11.1 months in the chemotherapy-alone group. Notably, the 3-year OS rates were 21% versus 10%, suggesting that a subset of patients may experience long-term benefit.⁵ Similarly, the addition of zolbetuximab to chemotherapy resulted in an improvement in mOS by approximately 3 months (16.4 vs 13.7 months), with 3-year OS rates of 20% versus 11%.^{7,9}

Despite advancements in treatment, 30%–40% of GCs remain negative for HER-2, PD-L1, and Claudin 18.2, leaving ChT as the sole therapeutic option for these patients.^{10,11} The combination of cisplatin and fluoropyrimidine forms the backbone of standard ChT regimens. Intensification of oxaliplatin and fluoropyrimidine with the addition of docetaxel has been shown to improve response rates, time to progression, and OS.¹² Moreover, substituting cisplatin with oxaliplatin in chemotherapy regimens has led to significant improvements in tolerability. Oxaliplatin is associated with lower incidences of grade 3–4 neutropenia, alopecia, renal toxicity, and thromboembolism compared to cisplatin.¹³

No direct comparison exists between the mFOLFOX-6 and mDCF regimens. To explore whether treatment intensification with triplet regimens provides additional benefit in advanced GC, we compared mFOLFOX-6 and mDCF as first-line options in a real-world cohort.

Materials and methods

Study design and patients

This multicenter, cross-sectional, retrospective study conducted by the Turkish Oncology Group enrolled patients from 25 centers across various regions of Turkey (Supplemental Appendix List 1). Data were collected from hospital electronic databases spanning the period from 2015 to 2023. Eligible participants were aged 18 years or older with unresectable or metastatic gastric or GEJ adenocarcinoma confirmed by histology. Inclusion criteria required patients to be HER-2 negative and treatment-naïve for metastatic disease, though prior ChT, radiotherapy, or chemoradiotherapy in the adjuvant or neoadjuvant setting was permitted. Exclusion criteria included HER-2-positive tumors, prior ChT for metastatic disease, age below 18 years, and tumors with a squamous component.

Data were collected on patients' age at diagnosis, sex, ECOG performance status (PS), tumor location, grade, histological subtype, presence of liver, peritoneal, lung, or bone metastases, metastatic status (de novo or recurrent), first-line treatment regimen, treatment response, and survival outcomes from hospital databases. The study included patients who had received at least one cycle of either the mFOLFOX-6 regimen—comprising oxaliplatin (85 mg/m²) and leucovorin (400 mg/m²) administered as a 2-h intravenous infusion, followed by a 5-FU bolus (400 mg/m²) over 10 min and a continuous 46-h infusion of 5-FU (2400 mg/m²)—or the mDCF regimen, which consisted of docetaxel (40 mg/m²), cisplatin (40 mg/m²), and a 48-h continuous intravenous infusion of 5-FU (2000 mg/m²). Both chemotherapy regimens were delivered biweekly. Chemotherapy dose reductions and treatment interruptions were made based on clinical judgment.

Treatment response was evaluated every 8–12 weeks using computed tomography (CT) or 18F-FDG PET-CT, following RECIST 1.1 criteria. Complete remission (CR) was defined as absence of disease, partial response (PR) as $\geq 30\%$ tumor reduction without progression, and progressive disease (PD) as $\geq 20\%$ increase or new lesions. Stable disease included cases not meeting CR, PR, or PD criteria. Objective response rate (ORR) was the sum of CR and PR. Response assessments were based on institutional radiology reports. PFS was defined as the time from the initiation of treatment to disease

progression or death, whichever occurred first. OS was defined as the time from the start of treatment to death. For PFS, patients were censored at the date of last contact. For OS, the patients were censored at the last known date of being alive as documented in the database. The follow-up duration was calculated from the date of chemotherapy initiation for metastatic disease to the date of the last follow-up.

Adverse events were identified from patient records, focusing solely on hematological toxicities. These were documented by the treating physicians at each center and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 published by the National Cancer Institute (NCI), Bethesda, Maryland, USA.

Statistical analysis

This study did not include a formal sample size calculation. Continuous variables are presented as medians with full ranges, while categorical variables are reported as frequencies and percentages. The Kolmogorov–Smirnov test was used to assess the normality of distribution. Normally distributed continuous variables are presented as mean values, and non-normally distributed variables are reported as medians. Minimum and maximum values are also provided. Associations between categorical variables were assessed using the Chi-square (χ^2) test. Survival analyses were performed using the Kaplan–Meier method, and differences in outcomes were evaluated with the log-rank test. All statistical analyses were conducted using SPSS version 25 (IBM Corp., NY, USA), and a p -value ≤ 0.05 was considered statistically significant.

Results

A total of 493 patients were included in the study, with a median age of 60 years (range: 26–88). The majority had an ECOG PS of 0 or 1 (51.1% with PS 1, and 24.3% with PS 0). Approximately 20% of the patients had GEJ cancer, while the remaining had GC. Nearly 75% were metastatic at diagnosis, with the liver being the most common metastatic site. Among the patients, 54.8% received the mFOLFOX-6 regimen, while 45.2% received mDCF. Patient demographic and clinical characteristics are detailed in Table 1.

The median number of chemotherapy cycles was 6 (range: 1–38) for the mDCF group and 6 (range: 1–21) for the mFOLFOX-6 group ($p=0.3$). The objective response rate (ORR) was comparable between the two groups, at 36.3% for mDCF and 38% for mFOLFOX-6 ($p=0.7$). Additional response rates are summarized in Table 2.

The median follow-up duration was 9 months (range: 1–84). The median PFS (mPFS) was 6 months for mDCF and 7 months for mFOLFOX-6 ($p=0.2$, Figure 1).

The mOS was 12 months for patients receiving mDCF and 11 months for those receiving mFOLFOX-6 ($p=0.4$, Figure 2).

Although mPFS and mOS were similar between the two treatment groups, we conducted a subgroup analysis to evaluate whether specific patient populations derived greater benefit from the triplet regimen (Supplemental Tables 1–3).

In summary, overall efficacy was similar between the two regimens; however, mFOLFOX-6 provided greater mPFS (hazard ratio (HR): 0.7; 95% confidence interval (CI): 0.53–0.95; $p=0.02$) and ORR (36.5% vs 24.6%, $p=0.038$) benefit in patients with an ECOG PS of 1, while mDCF was associated with improved OS in patients who developed grade 3–4 anemia (HR: 0.3; 95% CI: 0.1–0.6; $p=0.002$). Notably, patients receiving mDCF also exhibited higher ORR in the presence of grade 3–4 anemia (36% vs 8.3%; $p=0.03$) and neutropenia (39% vs 17%; $p=0.02$).

Hematological toxicities varied between the regimens. Grade 3–4 neutropenia occurred in 27.6% of patients in the mDCF group compared to 17.8% in the mFOLFOX-6 group ($p=0.01$), while any-grade neutropenia was reported in 48% of patients on mDCF versus 37.9% on mFOLFOX-6 ($p=0.02$). Grade 3–4 thrombocytopenia was observed in 5.9% of the mDCF group and 5.6% of the mFOLFOX-6 group ($p=0.8$), with any-grade thrombocytopenia affecting 26.7% of patients on mDCF and 24.5% on mFOLFOX-6 ($p=0.5$). Grade 3–4 anemia occurred in 9.5% of patients in the mDCF group compared to 4.8% in the mFOLFOX-6 group ($p=0.04$), while any-grade anemia was noted in 54.8% of the mDCF group and 47.2% of the mFOLFOX-6 group ($p=0.09$).

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Table 1. Patient demographic and clinical characteristics.

	Number (%)		
	Total population (n = 493)	mDCF (n = 223)	mFOLFOX (n = 270)
Age, years			
Median	60	59	61
Min-max	26–88	29–84	26–88
Sex			
Male	340 (69)	159 (71.3)	181 (67)
Female	153 (31)	64 (28.7)	89 (33)
ECOG PS			
0	120 (24.3)	42 (23.6)	78 (32.2)
1	252 (51.1)	122 (68.5)	130 (53.7)
2	46 (9.3)	12 (6.7)	34 (14)
3	2 (0.4)	2 (1.1)	0 (0)
Unknown	73 (14.8)		
Tumor location			
GEJ	98 (19.9)	45 (20.5)	53 (19.9)
Gastric	357 (72.5)	161 (73.5)	196 (73.7)
Unknown	30 (6.2)	13 (6)	17 (6.4)
Missing	8 (1.4)		
Grade			
1	59 (12)	27 (23.1)	32 (18.8)
2	116 (23.5)	47 (40.2)	69 (40.6)
3	112 (22.7)	43 (36.8)	69 (40.6)
Unknown	206 (41.8)		
Histology			
Diffuse adenoca	228 (46.2)	93 (49.7)	135 (52.3)
Intestinal adenoca	144 (29.2)	54 (28.9)	90 (34.9)
Linitis plastica	26 (5.3)	12 (6.4)	14 (5.4)
Other	47 (9.5)	28 (15)	19 (7.4)
Missing	48 (9.8)		
At the time of diagnosis			
Local/locally advanced	120 (24.3)	61 (27.4)	59 (21.9)
Metastatic	373 (75.7)	162 (72.6)	211 (78.1)

(Continued)

Table 1. (Continued)

	Number (%)		
	Total population (<i>n</i> = 493)	mDCF (<i>n</i> = 223)	mFOLFOX (<i>n</i> = 270)
Liver metastases			
Yes	243 (49.3)	106 (48)	137 (50.7)
No	248 (50.3)	115 (52)	133 (49.3)
Unknown	2 (0.4)		
Lung metastases			
Yes	82 (16.6)	31 (14)	51 (19)
No	408 (82.8)	190 (86)	218 (81)
Unknown	3 (0.6)		
Ascites			
Yes	168 (34.1)	77 (33)	95 (35.2)
No	323 (65.5)	148 (67)	175 (64.8)
Unknown	2 (0.4)		
Bone metastasis			
Yes	63 (12.8)	32 (14.3)	31 (11.5)
No	430 (87.2)	191 (85.7)	239 (88.5)
Unknown			
GEJ, gastroesophageal junction; PS, performance status.			

Discussion

In our study, the efficacy outcomes including OS, PFS, and ORR were comparable between the mDCF and mFOLFOX-6 regimens in the treatment of metastatic gastric and GEJ adenocarcinoma. Hematologic adverse events were observed more frequently in patients receiving the mDCF regimen. To date, there is no prospective randomized controlled trial directly comparing mDCF and mFOLFOX-6 in the first-line treatment of advanced metastatic GC.

A meta-analysis (*n* = 1294) revealed that substituting oxaliplatin for cisplatin in advanced inoperable GC significantly improved OS (HR: 0.88, 95% CI: 0.78–0.99).¹⁴ In contrast, another study found capecitabine plus oxaliplatin as effective as fluorouracil plus cisplatin.¹³ However, in HER2-positive advanced esophagogastric cancer, oxaliplatin-based ChT

Table 2. The response rates of study groups.

	Number (%)	
	mDCF (<i>n</i> = 223)	mFOLFOX-6 (<i>n</i> = 263)
Complete response	6 (2.7)	16 (6.1)
Partial response	75 (33.6)	84 (31.9)
Stable disease	38 (17)	59 (22.4)
Progressive disease	104 (46.6)	104 (39.5)

improved OS compared to cisplatin-based ChT.¹⁵ Based on these findings, we hypothesized that the oxaliplatin-based two-drug mFOLFOX-6 regimen could offer efficacy comparable to the cisplatin-based three-drug mDCF regimen in the treatment of inoperable or metastatic GC.

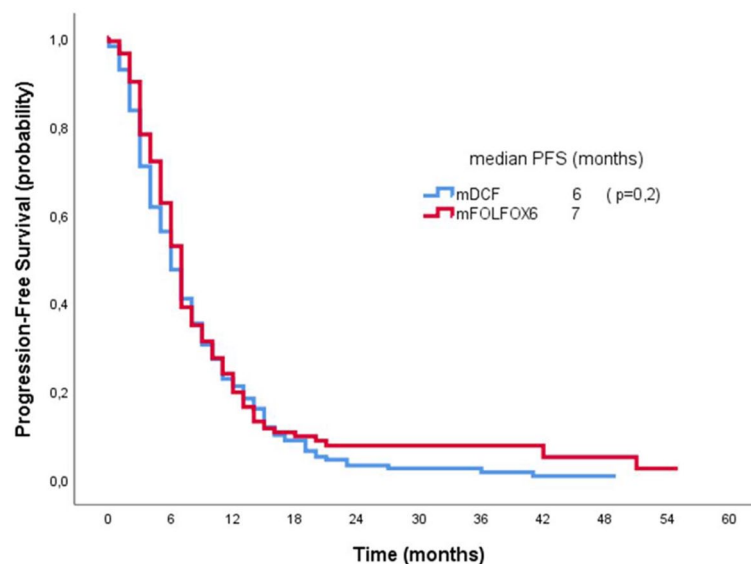


Figure 1. PFS for mDCF and mFOLFOX-6.
PFS, progression-free survival.

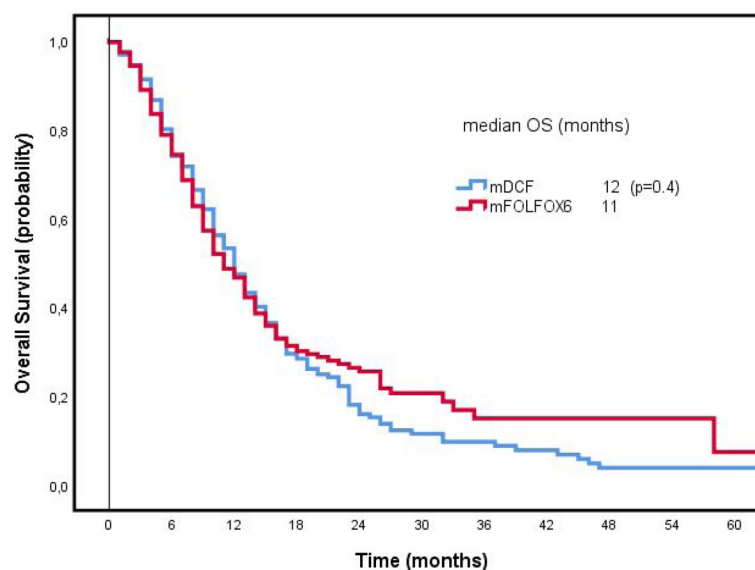


Figure 2. OS for mDCF and mFOLFOX-6.
OS, overall survival.

A retrospective, single-center study ($n=104$) reported similar survival outcomes between FOLFOX-4 and mDCF (12.6 and 13.5 months, respectively; $p=0.1$).¹⁶ While the results align with those of our study, there are key differences: the cited study utilized FOLFOX-4, which includes a lower dose of 5-FU compared to the FOLFOX-6 regimen used in our study. Given that FOLFOX-6 is commonly preferred

in GC research, we chose mFOLFOX-6 for this study. In another study involving 70 patients, mOS (13.9 vs 10.4 months) and mPFS (5.2 vs 6.4 months) were similar between the mDCF and mFOLFOX-6 groups ($p=0.1$).¹⁷ Although the dosages were identical and findings consistent with ours, the smaller sample size and monocentric design limit the generalizability compared to our multicenter study. Additionally,

Table 3. Summary of similar studies.

Study	Type	Year	Treatment regime	Patient (number)	PFS (months)	OS (months)	ORR (%)	Neutropenia (grade 3–4 vs all grades)	Thrombocytopenia (grade 3–4 vs all grades)	Anemia (grade 3– vs all grades)
Van Cutsem et al. ¹⁹	Phase III prospective	2006	DCF vs CF	445	5.6 vs 3.7	9.2 vs 8.6	37% vs 25%	82% vs 57%	8% vs 13%	18% vs 26%
Shah et al. ²⁵	Phase II prospective	2015	DCF vs mDCF	85	9.7 vs 6.5	18.8 vs 12.6	49% vs 33%	56% vs 45%	4% vs 3%	11% vs 39%
Pourghasemian et al. ¹⁶	Retrospective monocenter	2020	FOLFOX-4 vs mDCF	104	6.79 vs 7.97	12.6 vs 13.5	47 vs 35	19.1% vs 64.9%	10.6% vs 33.3%	NR
Acikgoz et al. ¹⁷	Retrospective monocenter	2021	FOLFOX-6 vs mDCF	70	6.4 vs 5.2	10.4 vs 13.9	NR	NR	NR	NR
Hacıbekiroğlu et al. ²¹	Retrospective monocenter	2015	FOLFOX-6 vs DCF	126	6.5 vs 6.2	11.4 vs 13.5	37% vs 40.3%	33.3% vs 31.9%	5.6% vs 6.9%	3.7% vs 6.9%
ORR, overall response rate; OS, overall survival; PFS, progression-free survival; NR, not reached.										

a meta-analysis of 715 Chinese patients found similar efficacy between DCF and FOLFOX regimens. This meta-analysis included both FOLFOX-4 and FOLFOX-6 regimens, with DCF (not mDCF) as the comparator.¹⁸ In summary, these studies, including our own study, indicate that FOLFOX-based and mDCF regimens yield similar survival outcomes in the treatment of advanced GC.

The rationale for using triplet regimens is the need for early objective response in patients at risk of organ dysfunction, like liver or lung involvement. In our study, ORR was 36.3% in the mDCF group and 38% in the mFOLFOX-6 group ($p=0.7$). These results align with the ORR of 37% for DCF in the TAX-325 study, which showed a higher response rate in the DCF group than CF.¹⁹ In a systematic review of 1311 patients with advanced GC treated with mDCF, ORR ranged from 27% to 78%, although dosing variations were noted.²⁰ Consistent with our findings, a retrospective study reported ORR of 37% for mFOLFOX-6 and 40.3% for mDCF ($p=0.7$).²¹ These results indicate that mFOLFOX-6 and mDCF have comparable ORR, further supporting their similar survival benefits. A summary of these studies is in Table 3.

Although we observed no overall benefit of mDCF over mFOLFOX-6 in terms of PFS, OS, or ORR, we conducted subgroup analyses to explore whether certain patient populations might derive greater benefit from the mDCF regimen. To the best of our knowledge, this is the first

study to perform a detailed subgroup analysis comparing mDCF and mFOLFOX-6 in terms of all three efficacy endpoints.

In the ORR subgroup analysis, patients with GEJ tumors and those with grade 3–4 anemia or neutropenia showed higher response rates in the mDCF group than in the mFOLFOX-6 group. However, these results should be interpreted with caution due to small subgroup sizes. For example, grade 3–4 anemia was seen in 10% with mDCF and 4.8% with mFOLFOX-6, and about 20% of patients in both groups had GEJ tumors. Regarding OS, the only subgroup that showed survival benefit with mDCF was patients who developed grade 3–4 anemia (13 vs 6 months). However, this observation is also limited by the small number of patients involved, as previously noted.

In contrast to our findings, the GASTFOX¹² trial demonstrated a survival benefit from adding docetaxel to FOLFOX in the overall population, particularly in patients with ECOG PS 0, younger age, and intestinal-type tumors. While our study did not show a survival benefit for mDCF in the overall cohort, their findings suggest that selected subgroups may benefit from treatment intensification—an effect not observed in our analysis. Although cross-trial comparisons must be made with caution, differences may relate to the platinum used: mDCF included cisplatin, while oxaliplatin used in FLOT. The study design may also play a role, as GASTFOX was prospective and randomized, while our study was retrospective

and cross-sectional. Also, triplet chemotherapy is not always better than doublets in metastatic GC. For example, the CALGB 80403 trial reported that the triplet regimen of epirubicin, cisplatin, and fluorouracil achieved similar OS compared to FOLFOX, and FOLFOX was associated with improved tolerability, which is consistent with the findings of our study.²²

The management of metastatic gastric GEJ cancers has significantly advanced in recent years. The incorporation of targeted therapies—such as trastuzumab and zolbetuximab—and immune checkpoint inhibitors like nivolumab and pembrolizumab into chemotherapy regimens has led to improved survival in biomarker-selected populations. In these settings, oxaliplatin combined with capecitabine or fluorouracil is commonly used as the chemotherapy backbone. This approach is both feasible and rational, especially considering that intensification with mDCF has not demonstrated additional clinical benefit in our study.

For patients ineligible for targeted therapies or immunotherapy, and in cases where treatment intensification is considered appropriate, a triplet regimen including fluorouracil, oxaliplatin, and docetaxel may be a viable option. Similar to the GASTROX trial, in the AIO-FLOT3 trial, FLOT showed promising survival outcomes in patients with oligometastatic disease, particularly in scenarios where high response rates and potential resectability are desired.²³ These findings suggest that when treatment intensification is clinically indicated, FLOT may be a more effective alternative to mDCF.

In our study, grade 3–4 neutropenia was significantly more frequent in the mDCF group compared to the mFOLFOX-6 group (27.6% vs 17.8%, $p=0.01$). Contrary to our findings, a smaller single-center study ($n=126$) reported similar rates of neutropenia between the two regimens, though its limited scope may introduce potential bias.²¹ In another retrospective analysis, neutropenia occurred in 64.9% of patients treated with mDCF and 19.1% of those receiving mFOLFOX-4 ($p<0.001$).¹⁶ The lower incidence of neutropenia in the mFOLFOX-4 arm of that study compared to our mFOLFOX-6 group (19.1% vs 37.9%) may reflect differences in study design and the lower 5-FU dose in FOLFOX-4 versus mFOLFOX-6.

In our study, grade 3–4 and any-grade thrombocytopenia rates were similar between mDCF and mFOLFOX-6. One study reported any-grade thrombocytopenia in 18% of FOLFOX patients, comparable to our 24.5%.⁷ A retrospective analysis reported any-grade thrombocytopenia in one-third of patients with mDCF and 10% with FOLFOX-4, possibly due to the lower 5-FU dose and smaller FOLFOX-4 sample ($n=47$).¹⁶ In a multicenter phase II study, any-grade thrombocytopenia was 23% and grade 3–4 was 4% with mDCF.²⁴ These findings align with our rates of 26.7% and 5.9%, suggesting an acceptable thrombocytopenia profile.

Anemia is a relatively uncommon but notable side effect reported in studies of advanced GC treatment. In a systematic review, the incidence of grade 3–4 anemia was reported as 8.9% in patients receiving mDCF regimens.²⁰ Similarly, a meta-analysis showed any-grade anemia in 43% with DCF and 21% with FOLFOX ($p=0.0001$).¹⁸ In our study, the incidence of grade 3–4 anemia was higher in the mDCF group compared to the mFOLFOX-6 group (9.5% vs 4.8%), consistent with the literature showing a higher anemia rate with mDCF.

These findings suggest that mFOLFOX-6 may offer a comparable therapeutic efficacy to mDCF, while being associated with a lower incidence of hematologic toxicity. Likewise, in older and frail patients with advanced gastroesophageal cancer, dose-reduced capecitabine and oxaliplatin regimens have demonstrated reduced toxicity without compromising oncologic efficacy.²⁵ In the GASTFOX trial, the TFOX regimen was associated with a survival benefit; however, this came at the cost of increased toxicity, with serious treatment-related adverse events occurring in 27% of patients in the TFOX arm compared to 13% in the FOLFOX arm.

Our study has several limitations. First, its retrospective design may introduce potential biases that could affect the findings. Second, we were unable to assess non-hematological toxicities such as neuropathy, vomiting, diarrhea, alopecia, and stomatitis, limiting a comprehensive evaluation of adverse events. Third, data on treatment discontinuation or delays across patient groups were not available, which may have influenced treatment outcomes. Lastly, we acknowledge that adjustments for multiple comparisons were not performed in our analysis.

Conclusion

This study demonstrated that mFOLFOX-6 achieved comparable PFS, OS, and ORR to mDCF in the treatment of metastatic gastric or GEJ adenocarcinomas. Furthermore, mFOLFOX-6 was associated with fewer hematological side effects, including neutropenia and grade 3–4 anemia. Based on these findings, modified FOLFOX-6 should be considered the preferred regimen for the treatment of unresectable or metastatic gastric or GEJ cancers.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of the Faculty of Medicine, University Hospital Harran (application number: HRÜ-22.24.06). We obtained documentation of permission from the participating centers and, based on these, applied for and received ethical approval. In our country, obtaining individual ethical approval from each participating center is not required for retrospective studies. The requirement for formal consent was waived by the approving ethics committee due to the retrospective nature of this study.

Consent for publication

Not applicable.

Author contributions

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Supplemental material

Supplemental material for this article is available online.

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