Dicle Tıp Dergisi / Dicle Med J (2022) 49 (3) : 468-476

www.diclemedj.org

Original Article / Özgün Araştırma

Retrospective Comparison of Chemotherapy Plus Anti-HER2 Therapies at First-line Treatment in Patients with Metastatic Gastric Adenocarcinoma

Fatih Gurler[1], **Aysegul İlhan Gulesen**[1], **Berna Oksuzoglu**[1]

1 Department of Medical Oncology, UHS Dr Abdurrahman Yurtaslan Oncology Training & Research Hospital, Ankara, Turkey

Received: 20.06.2022; Revised: 01.09.2022; Accepted: 01.09.2022

Abstract

Aim: We aimed to compare the efficacy and the safety of cisplatin plus 5-FU plus trastuzumab and mFOLFOX-6 plus trastuzumab at first-line treatment in HER2-positive metastatic gastric cancer.

Method: It was a retrospective observational monocentric study. Patients diagnosed with HER2-positive metastatic gastric adenocarcinoma between January 2013 and December 2020 in Dr AY Ankara Oncology TRH were screened. Patients treated at least one cycle of treatment with either CF-T or mFOLFOX-T were included. Survival outcomes and treatment compliance of patients were compared between groups.

Results: Of 52 patients, 55.8% (n=29) of patients were treated with CF-T, and 44.2% (n=23) with mFOLFOX-T. The median age at diagnosis was 60 years (IQR: 52-70) in the CF-T and 64 years (IQR: 59-70) in the mFOLFOX-T groups. De novo metastatic disease comprised 96.6% (n=28) of patients in the CF-T and 69.6% (n=16) in the mFOLFOX-T groups (p=0.016). Both IHC3+ and ISH positivity were observed 82.8% (n=24) of patients in the CF-T and 56.5% (n=13) in mFOLFOX-T groups (p=0.038). The mPFS was 10.4 months (95% CI 8.7-12.2) in the CF-T and 6.5 months (95% CI 5.5-7.6) in the mFOLFOX-T groups (p=0.532). The mOS was 12.2 months (95% CI 11.3-13.2) in the CF-T and 12.5 months (95% CI 9.8-15.5) in the mFOLFOX-T groups (p=0.974). No statistically significant difference regarding at least one dose reduction (31.0% vs 21.7%, p=0.453) and at least one dose delay (24.1% vs 21.7%, p=0.838) was observed between groups.

Conclusion: It was revealed that CF-T and mFOLFOX6-T had similar efficacy and tolerability in patients with HER2-positive metastatic gastric adenocarcinoma.

Keywords: metastatic gastric cancer, anti-HER2, FOLFOX, CF

DOI: 10.5798/dicletip.1170175

Correspondence / Yazışma Adresi: *Fatih Gürler, Dept. of Medical Oncology, University of Health Sciences, Dr. Abdurrahman Yurtaslan Oncology Training & Research Hospital, Yenimahalle/Ankara, Turkey e-mail: fatih_gurler@yahoo.com*

Metastatik Mide Adenokarsinom Hastalarında Birinci Basamak Tedavide Kemoterapi ve Anti-HER2 Tedavi Kombinasyonlarının Retrospektif Karşılaştırılması

Öz

Amaç: HER2-pozitif metastatik mide karsinomu hastalarında birinci basamak tedavi olarak sisplatin + 5-FU + trastuzumab tedavisi ile mFOLFOX6 + trastuzumab tedavilerinin etkinliklerinin ve güvenliliklerinin karşılaştırılmasını amaçladık.

Yöntemler: Çalışma retrospektif gözlemsel tek merkez çalışmasıdır. Ocak 2013 ile Aralık 2020 tarihleri arasında Dr. AY Ankara Onkoloji EAH'nde HER2-pozitif metastatik mide adenokarsinom tanısı alan hastalar taranmıştır. CF-T veya mFOLFOX-T tedavilerinden en az bir siklus tedavi almış hastalar dahil edilmiştir. Gruplar arasında sağkalım ve tedavi kompliyansı sonuçları karşılaştırılmıştır.

Bulgular: Elli iki hastanın %55,8'i (n=29) CF-T ile %44,2'si (n=23) mFOLFOX-T ile tedavi edilmiştir. Ortanca yaş CF-T grubunda 60 yıl (IQR: 52-70) ve mFOLFOX-T grubunda 64 yıldır (IQR: 59-70). De novo metastatik hastalık CF-T grubunun %96,6'sını, mFOLFOX-T grubunun %69,6'sını (n=16) oluşturmaktadır (p=0,016). Hem İHK3+ hem İSH pozitifliği CF-T grubunun %82,8'inde (n=24) mFOLFOX-T grubunun%56,5'inde (n=13) gözlenmiştir (p=0,038). Ortanca PFS CF-T grubunda 10,4 ay (%95 CI 8,7-12,2) ve mFOLFOX-T grubunda 6,5 aydı (%95 CI 5,5-7,6)(p=0,532). Ortanca OS CF-T grubunda 12,2 ay (%95 CI 11,3-13,2) ve mFOLFOX-T grubunda 12,5 aydı (%95 CI 9,8-15,5) (p=0,974). En az bir doz azaltma (%31,0% vs 21,7, p=0,453) ve en az bir doz erteleme (%24,1% vs %21,7, p=0,838) açısından gruplar arasında istatistiksel anlamlı fark yoktu.

Sonuç: Bu çalışma ile HER2-pozitif metastatik mide adenokarsinom hastalarında CF-T ve mFOLFOX-T tedavilerinin benzer etkinlik ve tolere edilebilirliğe sahip oldukları gösterilmiştir.

Anahtar kelimeler: metastatik mide kanseri, anti-HER2, FOLFOX, CF.

INTRODUCTION

Gastric cancer (GC) is the fifth in incidence and the fourth in cancer-related death worldwide[1]. HER2 overexpression or amplification was observed approximately 15%-20% of gastric cancers, and more common in intestinal-type, the cancer genome atlas chromosomal instability (TCGA CIN) subtype, and gastroesophageal junction cancers[2,3]. Chemotherapy plus HER2-directed therapy is the recommended contemporary treatment[4]. In TOGA trial, adding trastuzumab (T) to fluoropyrimidine (F/X) plus cisplatin (C) improved PFS (HR 0.71, 95% CI 0.59-0.85, p=0.0002) and OS (HR 0.74, 95% CI 0.60-0.91, p=0.0046)[5]. With the practice-changing results of TOGA trial, CF-trastuzumab has become the standard treatment in HER2-positive mGC. In the REAL-2 trial, it was shown that oxaliplatin could be substituted for cisplatin with a similar clinical outcome and a favourable toxicity profile[6]. Another phase III trial and meta-analyses also suggested that oxaliplatin was more tolerable with the same efficacy[7-10]. With the increasing trend towards oxaliplatin, three phase II trials were conducted with XELOX or FOLFOX plus T in HER2-positive advanced GC. The mPFS varied between 7.1 and 9.8 months, and the mOS varied between 13.8 and 21.0 months in these trials[11-13]. Although there was a heterogeneity of patients between groups suggestive of selection bias, it was observed that XELOX-T or FOLFOX-T was an effective and tolerable treatment in HER2-positive advanced GC. The evaluation of treatment from TOGA regimen to oxaliplatin-based doublet chemotherapy plus T regimens makes it an obligation to compare the efficacies and safety profiles of these regimens. However, no randomized controlled trial compares XELOX-T or FOLFOX-T and CF-T in HER2-positive mGC. Only indirect comparisons can be carried out with the TOGA trial and above-mentioned phase

II trials. In addition, a few retrospective studies compared different chemotherapeutic agents plus T in HER2-positive GC[14-16].

It was aimed to compare the clinical outcomes of CF-T and mFOLFOX-6-T in HER2-positive mGC retrospectively.

METHOD

Patients

It is an observational retrospective monocentric study. Patients who admitted to "UHS Dr Abdurrahman Yurtaslan Oncology Training & Research Hospital" between January 2013 and December 2020 with metastatic gastric or gastroesophageal junction adenocarcinoma were screened. The inclusion criteria: adenocarcinoma histopathology, ≥18 years, and treated with at least one cycle of chemotherapy, HER2-positivity with in situ hybridization-ISH (immunohistochemistry-IHC 2+ and IHC3+), and adequate systolic cardiac function (EF>55%). ISH was applied even IHC3+ in accordance with local regulations. The exclusion criteria: a second malignancy or histopathology other than adenocarcinoma or HER2-negativity (IHC0, IHC1+ and ISH negativity with IHC2+ or IHC3+). Patients' records were reviewed. The definition of PFS was the time between the beginning of therapy to progression, or death (in months), and OS was the time between the beginning of therapy and the patient's last visit or death (in months).

Chemotherapeutic Agents

Cisplatin plus 5-Fluorouracil plus trastuzumab and modified FOLFOX-6 plus trastuzumab regimens were used as a routine treatment procedure in our clinic (Supplementary table SI). Any selection criteria were defined for either CF-T or FOLFOX-T. They were treated as a routine care upon the physicians' choices.

Statistical Analysis

The statistical analyses were carried out using SPSS®, v22.0. The homogeneity and the distribution of the variables were shown with descriptive analysis. Median (range and IQR) was used in reporting non-categorical variables. Pearson's chi-squared test or Fisher's Exact test was used in reporting categorical variables. Survival curves were created with the Kaplan-Meier, and the comparisons were done with the log-rank test. Cox regression analyses were carried out to estimate progression and death. The tests were bidirectional, and the $p<0.05$ value was accepted as significant.

The ethics committee approval was obtained from The Ethics Committee of "UHS Dr Abdurrahman Yurtaslan Oncology Training & Research Hospital" (08.06.2022, 2022-06/1875).

RESULTS

Fifty-two patients were included in the study. At all, 55.8% (n=29) of patients were treated with CF-T, and 44.2% (n=23) of patients were with mFOLFOX-T. The median age at diagnosis was 60 years (IQR: 52-70) in the CF-T and 64 years (IQR: 59-70) in the mFOLFOX-T groups. De novo metastatic disease comprised 96.6% (n=28) of patients in the CF-T and 69.6% (n=16) in the mFOLFOX-T groups (p=0.016). The liver was the most common metastatic region, with a percentage of 75.9 in the CF-T and 78.3 in the mFOLFOX-T groups, the difference was not significant. Both IHC3+ and ISH positivity were observed 82.8% (n=24) of patients in the CF-T and 56.5% (n=13) in mFOLFOX-T groups (p=0.038). Other clinicopathological features were similar in between groups (Table I).

Table I: Patient characteristics

Variable	CF-T	mFOLFOX6-T	*P* value
Number of patients, *n* (%)	29 (55.8)	23 (44.2)	
Median age, *years* (IQR)	60 (52-70)	64 (59-70)	
Elderly, *n* (%)			
<65 years old	18 (62.1)	13 (56.5)	0.686
≥65 years old	11 (37.9)	10 (43.5)	
Sex, *n* (%)			
Female	2 (6.9)	6 (26.1)	0,118
Male	27 (93.1)	17 (73.9)	
ECOG PS, *n* (%)			
0-1	26 (89.7)	21 (91.3)	1.000
2	3 (10.3)	2 (8.7)	
Metastatic condition at initial diagnosis, *n* (%)			
Non-metastatic	**1 (3.4)**	**7 (30.4)**	**0.016**
Metastatic	**28 (96.6)**	**16 (69.6)**	
Metastatic regions, *n* (%)			
Liver	22 (75.9)	18 (78.3)	1.000
Peritoneum	6 (20.7)	6 (26.1)	0.646
Bone	7 (24.1)	1 (4.3)	0.064
Others	12 (41.4)	14 (60.9)	0.163
No. of metastatic sites, *n* (%)			
<2	11 (37.9)	9 (39.1)	0.930
≥2	18 (62.1)	14 (60.9)	
Primary tumor localization, *n* (%)			
Cardia + GEJ	10 (34.5)	10 (43.5)	0.319
Fundus + Corpus	12 (41.4)	5 (21.7)	
Antrum + Pylorus	7 (24.1)	8 (34.8)	
Differentiation, *n* (%)			
Well + Moderate	16 (55.2)	13 (56.5)	0.922
Poor	13 (44.8)	10 (43.5)	
HER2 status, *n* (%)			
IHC3+ and ISH positive	**24 (82.8)**	**13 (56.5)**	**0.038**
IHC 2+ and ISH positive	**5 (17.2)**	**10 (43.5)**	
Histopathology, *n* (%)			
Intestinal	18 (62.1)	19 (82.6)	0.147
Diffuse	9 (31.0)	2 (8.7)	
Mixed	2 (6.9)	2 (8.7)	

The median duration of follow-up was 12.8 months (min-max: 2.0-44.5) in the CF-T and 14.1 months (min-max: 5.9-36.0) in the mFOLFOX-T groups. The objective response rates were 20.7% vs 21.7%, and the disease control rates were 75.9% vs 82.6% in the CF-T and mFOLFOX-T groups, respectively (p=0.927 and p=0.735, respectively) (Table II).

Table II: Treatment exposure and best response rates with first-line treatment

Parameters	CF-T	mFOLFOX6-T	*P* value
Median duration of follow up, *months* (min-max)	12.8(2.0-44.5)	14.1 (5.9-36.0)	
Median duration of 1st line treatment, *months* (min-max)	6.8 (0.7-27.9)	5.7 (2.4-22.3)	
Objective response rate, *n* (%)	6 (20.7)	5 (21.7)	0.927
Disease control rate, *n* (%)	22 (75.9)	19 (82.6)	0.735
≥1 dose reduction, *n* (%)	9 (31.0)	5 (21.7)	0.453
≥1 dose delay (%), *n* (%)	7 (24.1)	5 (21.7)	0.838
Treatment cessation, *n* (%)	1 (3.4)	0 (0.0)	
Second-line treatment, *n* (%)			
None	14 (48.4)	12 (52.2)	0.780
Single agent chemotherapy	9 (31.0)	6 (26.1)	0.696
Doublet chemotherapy	6 (20.6)	5 (21.7)	0.927

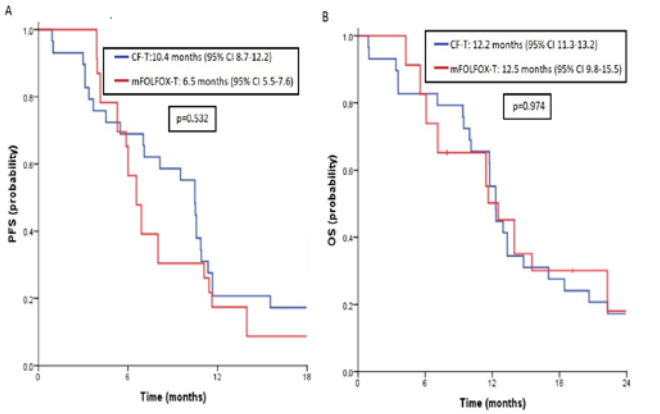

Fig. 1. Kaplan-Meier curves of PFS with first-line treatment (A), and OS (B) in patients with metastatic gastric adenocarcinoma.

The mPFS was 10.4 months (95% CI 8.7-12.2) in the CF-T and 6.5 months (95% CI 5.5-7.6) in the

mFOLFOX-T groups (p=0.532) (Fig. 1A). In univariate analyses, geriatric age (≥65 years old) (HR 2.86, 95% CI 1.42-5.75, p=0.003), an ECOG PS of 2 (HR 3.17, 95% CI 1.20-8.41, p=0.020), metastatic disease at initial diagnosis (HR 3.63, 95% CI 1.39-9.44, p=0.008), IHC3+ and ISH positivity (HR 2.01, 95% CI 1.03-3.92, p=0.041) variables increased progression. On the other hand, fundus and corpus tumor localization (HR 0.48, HR 0.23-0.99, p=0.046) and antrum and pylorus tumor localization (HR 0.40, 95% CI 0.10-0.85, p=0.018) variables decreased progression. The mFOLFOX-T chemotherapy variable did not affect progression in the univariate analysis. In the multivariate analysis, only an ECOG PS of 2 (HR 2.91, 95% CI 1.10-7.73, p=0.032 variables increased progression (Table III).

Table III: Univariate and multivariate Cox regression analyses to estimate progression

Variable	Univariate			Multivariate		
	HR	95% CI	P value	HR	95% CI	P value
Elderly						
<65 years old	Ref					
≥65 years old	2.86	1.42-5.75	0.003	2.01	0.96-4.22	0.066
Sex						
Female	Ref					
Male	1.02	0.45-2.29	0.955	-	-	-
ECOG PS						
0-1	**Ref**					
2	**3.17**	**1.20-8.41**	**0.020**	**2.91**	**1.10-7.73**	**0.032**
Metastatic condition at initial diagnosis						
Non-metastatic	Ref					
Metastatic	3.63	1.39-9.44	0.008	2.86	0.89-9.17	0.077
Metastatic regions						
Liver	0.87	0.45-1.69	0.696	-	-	-
Peritoneum	1.68	0.86-3.29	0.125	-	-	-
Bone	0.86	0.40-1.87	0.720	-	-	-
Others	1.22	0.70-2.12	0.482	-	-	-
No. of metastatic sites						
<2	Ref					
≥2	1.21	0.68-2.12	0.501	-	-	-
Primary tumor localization						
Cardia + GEJ	Ref					
Fundus + Corpus	0.48	0.23-0.99	0.046	0.68	0.32-1.46	0.323
Antrum + Pylorus	0.40	0.18-0.85	0.018	0.50	0.22-1.13	0.096
Differentiation, *n* (%)						
Well + Moderate	Ref					
Poor	1.48	0.84-2.60	0.175	-	-	-
HER2 status						
IHC 2+ and ISH positive	Ref					
IHC3+ and ISH positive	2.01	1.03-3.92	0.041	1.02	0.46-2.29	0.955
Histopathology						
Intestinal	Ref					
Diffuse	0.92	0.46-1.84	0.815	-	-	-
Mixed	1.40	0.49-4.01	0.532	-	-	-
First-line chemotherapy						
CF-trastuzumab	Ref					
mFOLFOX6-trastuzumab	1.20	0.68-2.09	0.541	-	-	-

The mOS was 12.2 months (95% CI 11.3-13.2) in the CF-T and 12.5 months (95% CI 9.8-15.5) in the mFOLFOX-T groups (p=0.974) (Fig. 1B). In univariate analyses, an ECOG PS of 2 (HR 8.15, 95% CI 2.71-24.50, p<0.001), metastatic disease at initial diagnosis (HR 2.76, 95% CI 1.22-6.27, p=0.015), peritoneal metastasis (HR 2.99, 95% CI 1.49-6.04, p=0.002), and poor differentiation (HR 2.70, 1.45-5.00, p=0.002) variables increased the death. The mFOLFOX-T chemotherapy variable did not affect death in the univariate analysis. In the multivariate analysis, an ECOG PS of 2 (HR 10.97, 95% CI 3.40-35.41, p<0.001), and peritoneal metastasis (HR 2.47, 95% CI 1.16-5.27, p=0.019) variables increased the death (Table IV).

Table IV: Univariate and multivariate Cox regression analyses to estimate death

Variable	Univariate			Multivariate		
	HR	95% CI	P value	HR	95% CI	P value
Elderly						
<65 years old	Ref			-	-	-
≥65 years old	1.51	0.84-2.71	0.178			
Sex						
Female	Ref			-	-	-
Male	1.28	0.59-2.76	0.532			
ECOG PS						
0-1	**Ref**					
2	**8.15**	**2.71-24.50**	**<0.001**	**10.97**	**3.40-35.41**	**<0.001**
Metastatic condition at initial diagnosis						
Non-metastatic	Ref					
Metastatic	2.76	1.22-6.27	0.015	1.73	0.70-4.27	0.233
Metastatic regions						
Liver	0.80	0.41-1.56	0.514	-	-	-
Peritoneum	**2.99**	**1.49-6.04**	**0.002**	**2.47**	**1.16-5.27**	**0.019**
Bone	0.84	0.39-1.81	0.657	-	-	-
Others	1.03	0.58-1.82	0.929	-	-	-
No. of metastatic sites						
<2	Ref			-	-	-
≥2	1.25	0.70-2.23	0.458			
Primary tumor localization						
Cardia + GEJ	Ref					
Fundus + Corpus	0.83	1.41-1.67	0.596	-	-	-
Antrum + Pylorus	0.56	0.27-1.16	0.119	-	-	-
Differentiation						
Well + Moderate	Ref					
Poor	2.70	1.45-5.00	0.002	1.89	0.94-3.79	0.072
HER2 status						
IHC 2+ and ISH positive	Ref			-	-	-
IHC3+ and ISH positive	1.52	0.82-2.83	0.183			
Histopathology						
Intestinal	Ref					
Diffuse	1.58	0.79-3.17	0.197	-	-	-
Mixed	0.70	0.17-2.94	0.624	-	-	-
First-line chemotherapy						
CF-trastuzumab	Ref					
mFOLFOX6-trastuzumab	0.99	0.55-1.77	0.975	-	-	-

No statistically significant difference regarding at least one dose reduction (31.0% vs 21.7%, p=0.453) and at least one dose delay (24.1% vs 21.7%, p=0.838) was observed between the CF-T and the mFOLFOX-T groups. While treatment cessation was carried out in 3.4% (n=1) of patients in the CF-T group, no treatment cessation was done in the mFOLFOX-T group. After progression, 48.4% (n=14) of patients in the CF-T and 52.2% (n=12) in the mFOLFOX-T groups could not receive second-line treatment (p=780). At all, 31.0% (n=9) of patients in the CF-T and 26.1% (n=6) in the mFOLFOX-T groups were treated with single-agent chemotherapy, and 20.6% (n=6) of patients in the CF-T and 21.7% (n=5) in the mFOLFOX-T groups were treated with doublet agent chemotherapy at second-line treatment (p=0.696 and p=0.927, respectively) (Table II).

Supplementary table S1. Treatment regimens

Regimen	Schedule
Cisplatin plus 5-FU plus trastuzumab	Cisplatin 80 mg/m^2 (iv) on day 1 plus 5-fluorouracil 800 mg/m^2/day (iv) on 1-5 days plus trastuzumab (iv) 8 mg/kg on day 1 of the first cycle, followed by 6 mg/kg, repeated in every 3 weeks.
Modified FOLFOX-6 plus trastuzumab	Oxaliplatin 85mg/m^2 (iv) plus folinic acid 400 mg/m^2 (iv) plus 5-fluorouracil 400 mg/m^2 (iv bolus)on day 1, and followed by 5-fluorouracil 2400 mg/m^2 (iv infusion over 46 hours) plus trastuzumab (iv) 6 mg/kg on day 1 of the first cycle, followed by 4 mg/kg, repeated in every 2 weeks.

DISCUSSION

This study suggested that CF-T and mFOLFOX6-T had similar efficacy and tolerability in HER2-positive mGC.

In the TOGA trial, it was reported that the mOS was 13.8 months (95% CI 12-16), the mPFS was 6.7 months (95% CI 6-8), and the ORR was 47% in the chemotherapy plus T arm[5]. In our study, the mOS was 12.2 months (95% CI 11.3-13.2), the mPFS was 10.4 months (95% CI 8.7-12.2), and the ORR was 20.7% in the CF-T group. In The TOGA trial, 97% of the patients had metastatic disease, and in our study, all had metastatic disease. In the TOGA trial, 87% of the patients were treated with capecitabine plus cisplatin with T in the chemotherapy plus T arm; in our study, all of the patients were treated with 5-FU in the CF-T group. These differences may be counted as the numerically lower mOS and ORR in our study than in the TOGA trial. On the other hand, the PFS in the TOGA trial was numerically lower than in our study. In the TOGA trial, 45% of the patients were reported as FISH positive and IHC3+ in the chemotherapy plus T arm. In our study, 82.8% of the patients were reported as FISH positive and IHC3+ in the CF-T group. This histologic subtype was shown to be more responsive to T treatment than other HER2-positive subtypes. The numerically higher mPFS of our study may result from this difference.

In a phase II trial conducted by Hong et al., it was observed that the mOS was 19.5 months (95% CI 15.5-26.0), the mPFS was 9.2 months (95% CI 6.5-11.6), and the ORR was 46% with XELOX-T[12]. In our study, the mOS was 12.5 months (95% CI 9.8-15.5), the mPFS was 6.5 months (95% CI 5.5-7.6), and the ORR was 21.7% in the mFOLFOX-T group. In the study conducted by Hong et al., it was observed that 13.7% of the patients had locally advanced disease, capecitabine was used as a fluoropyrimidine, and capecitabine plus T was continued until progression after six cycles of treatment. In our study, no maintenance therapy was used after six cycles of treatment. These differences may be counted as a potential reason for our study's numerically lower survival outcomes. In the second phase II trial carried out by Ryu et al. in patients treated with XELOX-T, it was obtained that the mOS was 21.0 months (95% CI 6.4-35.7), the mPFS was 9.8 months (95% CI 7.0-12.6), and the ORR was 68%[11]. In this trial, 4% of the patients had locally advanced disease, eight cycles of XELOX-T and two more cycles of X-T were administered, and 49% of the patients had liver metastasis (78.3% of the patients in

the mFOLFOX6-T group of our study). These differences may be counted as some of the reasons for the numerically higher mOS and mPFS than in our study. In the HERXO trial, it was observed that the mOS was 13.8 months (95% CI 10.1-17.4), the mPFS was 7.1 months (95% CI 5.5-8.7), and the ORR was 46.7% in patients treated with XELOX-T[13]. In this study, 2% of patients had locally advanced disease, and capecitabine maintenance was administered until disease progression. The mOS and the mPFS were similar in our study and the HERXO trial.

In a retrospective French study conducted by Soularue et al., (85% mFOLFOX6-T, 15% XELOX-T) it was reported that the mOS was 17.3 months (95% CI 13.5-32.3), mPFS was 9.0 months (95% CI 5.6-12.0), and the ORR was %41[15]. In this retrospective French study, 50% of the patients had liver metastasis (while 78.3% of the patients had liver metastasis in the mFOLFOX-T group of our study), and T was administered beyond six cycles and beyond progression. These differences may be counted as some of the reasons for numerically higher mOS than in our study. However, this retrospective French study is vital that the mFOLFOX-T regimen was predominantly used one. In the Agamenon registry, it was reported that the mOS was 16.5 months (95% CI 12.3-24.5), and the mPFS was 9.6 months (95% CI 7.7-12.9) in the FOLFOX-T arm[14]. In this study, it was observed that trastuzumab was administered until progression, unlike in our study. In a retrospective study comparing mFOLFOX-T and CF-T, it was revealed that an improved PFS (mPFS: 9.4 months vs 7.3 months, p=0.024) and a similar OS (mOS: 18.4 months vs 15.1 months, p=0.640) were obtained with mFOLFOX-T regimen over CF-T regimen[16]. In this retrospective study, T maintenance was allowed. Furthermore, metastasis patterns of the patients and IHC/FISH subtypes were not reported, so a direct comparison of this study and our study may not be appropriate. On the other hand, in our study mPFS was numerically lower in the mFOLFOX-T group than in the CF-T group. There may be some reasons for this trend. First, 82.8% of the patients in the CF-T and 56.5% in the mFOLFOX-T groups were reported as FISH positive and IHC3+ (p=0.038). This histologic subtype was shown to be more responsive to trastuzumab treatment than other HER2-positive subtypes. Second, there were more de novo metastatic disease (96.6% vs 69.5%, p=0.016) in the CF-T group than in the mFOLFOX-T group. In addition, in our study, treatment compliance of the patients was well. The treatment cessation was conducted in 3.4% of the patients in the mCF-T arm, and no treatment cessation was accomplished in the mFOLFOX-T arm. This result was consisted with the previous studies.

Some limitations are in this study. It was a retrospective, monocentric study. The number of patients was small. Adverse events other than treatment compliance could not be obtained.

In conclusion, the current study suggested that CF-T and mFOLFOX6-T had similar efficacy and tolerability in HER2-positive GC. Further prospective trials with large patient groups are needed.

Ethics Committee Approval: The ethics committee approval was obtained from The Ethics Committee of "UHS Dr Abdurrahman Yurtaslan Oncology Training & Research Hospital" (08.06.2022, 2022-06/1875).

Conflict of Interest: The author declares no conflict of interest.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71:209-49.

2. Bass AJ, Thorsson V, Shmulevich I, et al. Comprehensive molecular characterization of gastric adenocarcinoma. Nature. 2014;513:202.

3. Van Cutsem E, Bang Y-J, Feng-Yi F, et al. HER2 screening data from ToGA: targeting HER2 in gastric and gastroesophageal junction cancer. Gastric cancer. 2015;18:476-84.

4. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Gastric Cancer Version 2.2022 — January 11, 2022 (https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf).

5. Bang Y-J, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet. 2010;376:687-97.

6. Cunningham D, Starling N, Rao S, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med. 2008;358:36-46.

7. Al-Batran S-E, Hartmann JT, Probst S, et al. Phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil, leucovorin plus either oxaliplatin or cisplatin: a study of the Arbeitsgemeinschaft Internistische Onkologie. J Clin Oncol. 2008;26:1435-42.

8. Okines A, Norman A, McCloud P, Kang Y-K, Cunningham D. Meta-analysis of the REAL-2 and ML17032 trials: evaluating capecitabine-based combination chemotherapy and infused 5-fluorouracil-based combination chemotherapy for the treatment of advanced oesophago-gastric cancer. Ann Oncol. 2009;20:1529-34.

9. Montagnani F, Turrisi G, Marinozzi C, Aliberti C, Fiorentini G. Effectiveness and safety of oxaliplatin compared to cisplatin for advanced, unresectable gastric cancer: a systematic review and meta-analysis. Gastric Cancer. 2011;14:50-5.

10. Değirmencioğlu S, Ünal OÜ, Oktay E. Comparison of oral capecitabine alone versus platinum combinations in elderly metastatic gastric cancer patients. Dicle Med J. 2019;46:567-73.

11. Ryu M-H, Yoo C, Kim JG, et al. Multicenter phase II study of trastuzumab in combination with capecitabine and oxaliplatin for advanced gastric cancer. Eur J Cancer. 2015;51:482-8.

12. Gong J, Liu T, Fan Q, et al. Optimal regimen of trastuzumab in combination with oxaliplatin/capecitabine in first-line treatment of HER2-positive advanced gastric cancer (CGOG1001): a multicenter, phase II trial. BMC cancer. 2016;16:1-9.

13. Rivera F, Romero C, Jimenez-Fonseca P, et al. Phase II study to evaluate the efficacy of Trastuzumab in combination with Capecitabine and Oxaliplatin in first-line treatment of HER2-positive advanced gastric cancer: HERXO trial. Cancer Chemother Pharmacol. 2019;83:1175-81.

14. Jimenez-Fonseca P, Carmona-Bayonas A, Martinez-Torron A, et al. External validity of clinical trials with diverse trastuzumab-based chemotherapy regimens in advanced gastroesophageal adenocarcinoma: data from the AGAMENON-SEOM registry. Ther Adv Med Oncol. 2021;13:17588359211019672.

15. Soularue E, Cohen R, Tournigand C, et al. Efficacy and safety of trastuzumab in combination with oxaliplatin and fluorouracil-based chemotherapy for patients with HER2-positive metastatic gastric and gastro-oesophageal junction adenocarcinoma patients: a retrospective study. Bull Cancer. 2015;102:324-31.

16. Esen SA, Ergun Y, Erol C, et al. First-line treatment of patients with HER2-positive metastatic gastric and gastroesophageal junction cancer. Bosn J Basic Med Sci. 2022. Apr 17. Epub ahead of print.