EJMI

DOI: 10.14744/ejmi.2023.22472
EJMI 2023;7(3):274–282

Research Article

The Comparison of FLOT vs. mDCF Regimens in Neoadjuvant Setting for Locally-advanced Gastric Cancer

Muslih Urun,[1] Suleyman Sahin,[2] Yonca Yilmaz Urun,[3] Abdullah Sakin[4]

[1]Department of Medical Oncology, Yuzuncu Yil University Faculty of Medicine, Van, Türkiye
[2]Department of Medical Oncology, Eskişehir Acıbadem Hospital, Eskişehir, Türkiye
[3]Department of Gastroenterology, Yuzuncu Yil University Faculty of Medicine, Van, Türkiye
[4]Department of Medical Oncology, Medipol University, Istanbul, Türkiye

Abstract

Objectives: To compare the pathological tumor response and survival of mDCF (modified docetaxel+cisplatin+5-flourosil) vs. FLOT (5-flourosil+oxaliplatin+dosataxel) regimens in the neoadjuvant setting for patients with locally-advanced gastric adenocarcinoma.

Methods: A total of 72 patients, 44 males and 28 females, who were diagnosed with locally-advanced gastric adenocarcinoma and treated with neoadjuvant chemotherapy were included. Postoperative pathological tumor response, disease free survival (DFS) and overall survival (OS) were compared between the two treatment groups (FLOT and mDCF group).

Results: Median DFS was 19.0 months in the FLOT arm (long rank p=0.218), while median DFS could not be reached in the mDCF arm. Rate of DFS in 6, 12,18 and 24 months were 95,4%, 80,9%, 63% and 42% in FLOT group, respectively. In mDCF group, rate of DFS in 6, 12, 18 and 24 months were 100%, 88%, 71,2% and 62,2%, respectively. Median OS was not reached in both groups (long rank p=0.514). There was no significant difference between the treatment regimens (mDCF and FLOT) in terms of response to the treatment, DFS, and OS.

Conclusion: Since no significant difference was observed between the regimens in terms of treatment response and survival, we think that cisplatin can be preferred instead of oxaliplatin as a part of neoadjuvant treatment regimen in elderly patients with diabetic neuropathy or high risk of neuropathy.

Keywords: Chemotherapy, cisplatin, gastric cancer, neoadjuvant, oxaliplatin

Cite This Article: *Urun M, Sahin S, Yilmaz Urun Y, Sakin A. The Comparison of FLOT vs. mDCF Regimens in Neoadjuvant Setting for Locally-advanced Gastric Cancer. EJMI 2023;7(3):274–282.*

Although the incidence of gastric cancer (GC) has declined steadily since the 1930s, it still remains one of the leading causes of deaths, being the fifth most common cancer and the third most common cause of cancer-related deaths worldwide.[1]

High mortality rate is mainly due to its increased recurrence risk and high prevalence of advanced-stage disease at the time of diagnosis. In population-based series in Western populations, the 5-year survival rate for patients with completely resected stage I GC is approximately 70-75% but drops to below 35% after stage IIb disease.[2] Early-stage resectable GC is usually asymptomatic and is rarely detected outside of a screening program which is not widely performed except in some countries with high incidence of GC, such as Japan, Korea, Venezuela, and Chile.[3]

Address for correspondence: Muslih Urun, MD. Department of Medical Oncology, Yuzuncu Yil University Faculty of Medicine, 65030, Van, Turkey
Phone: +90 530 775 38 38 **E-mail:** muslihurun@gmail.com

Submitted Date: June 07, 2023 **Revision Date:** August 23, 2023 **Accepted Date:** September 09, 2023 **Available Online Date:** September 19, 2023

For patients with potentially resectable GC, randomized controlled trials and meta-analyses have shown that neoadjuvant therapies provide a significant survival advantage over surgery alone.[4-6]

However, one of the important problem is that patients who need to undergo neoadjuvant treatment are operated by general surgeons, without consulting a medical oncologist. NCCN strongly recommends Neoadjuvant Chemotherapy (NACt) for most patients who have potentially resectable GC with tumor size equal to or greater than T2 and/or node positive disease.[7]

Although there are no randomized controlled trials comparing any form of adjuvant therapy to NACt and demonstrating an Overall Survival (OS) advantage, NACt is recommended because patients are more likely to be medically fit to receive preoperative therapy, further preventing patients from unnecessary morbidity due to gastrectomy if evidence of distant metastasis occurs after NACt.[8]

For locally-advanced GC, the phase III MAGIC study performed in 2006 which demonstrated survival benefit of NACt over surgery alone has been a milestone in this area, leading to a positive trend towards NACt, and the results of this study were supported by recent clinical trials from. [4] Moreover, recent studies have shown that NACt is well tolerated and does not affect postoperative morbidity and mortality in GC patients.[9,10]

In patients with GC receiving NACt, the rate of pathological complete response (PCR) or the degree of tumor regression are considered to be the most important factors affecting OS.[11] Although tumor response is the main target of neoadjuvant treatment intent, tolerability and side-effect profile of the chemotherapeutics are the key factors limiting the goal of treatment.

The best chemotherapy regimen for NACt has not yet been established and the method of drug administration differs between centers. Herein we aimed to compare the effects of NACt with modified docetaxel + cisplatin + 5-flourouracil (mDCF) vs. 5-flourouracil+leucovorin+oxaliplatin+docetaxel (FLOT) regimens on postoperative tumor response and its prognostic impact on survival for patients with locally-advanced GC.

Methods

Study Design and Centers

This was a multi-center and retrospective analysis of patients with GC who were followed up and treated between 2014 and 2018 at 2 major medical oncology clinics of Van Province in Turkey as follows; Van Yüzüncü Yıl University Faculty of Medicine and Van Training and Research Hospital. The patients were divided into 2 groups according to the NACt protocol as follows; mDCF and FLOT. Postoperative pathological tumor response and its associated prognostic impact on survival were compared between the groups.

Inclusion and Exclusion Criteria

The following parameters were defined as the inclusion criteria; patients equal to or greater than 18 years old, had locally-advanced disease (stage II and III), ECOG PS 0 or 1, histologically biopsy-proven adenocarcinoma, and those with complete data required for the study. Patients under the age of 18 years, metastatic disease at presentation, tumors which had non-adenocarcinoma histology, and those with missing data were excluded from the study.

Staging and Response Evaluation

In our center, patients diagnosed with GC are clinically staged by contrast-enhanced thoraco-abdominal computed tomography (TABT) before and after NACt with physicians' choice of FLOT or mDCF regimen up to 6 cycles. All the radiological evaluations after NACt and decisions for operation were made in multidisciplinary team meeting which included a medical oncologist, general surgeon, pathologist, radiologist, and radiation oncologist.

Treatment Regimens and Schedules

FLOT; Docetaxel (60 mg/m^2), oxaliplatin (85 mg/m^2), leucovorin (200 mg/m^2), and 5-fluorouracil (2600 mg/m^2, via a port catheter, continuous infusion over 24 hours), all given on day 1, administered once every 2 weeks, for 4 cycles.

mDCF; Docetaxel 60 (mg/m^2, IV, on day 1), cisplatin (50 mg/m^2, IV, on day 1), Folinic acid (400 mg/m^2, IV, on day 1), 5-fluorouracil (400 mg/m^2, IV, on day 1), 5-fluorouracil (2400 mg/m^2, via a port catheter, continuous infusion for 46 hours), IV, administered once every 2 weeks, for up to 4-6 cycles.

Tumor Regression Grade (TRG) and Becker Criteria

Pathological response assessment and Tumor Regression Grade (TRG) was made according to Becker criteria as follows; Grade 1: Full tumor regression (0% residual tumor per tumor bed), Grade 1b: Subtotal tumor regression (residual tumor per tumor bed <10%), Grade 2: Partial tumor regression (10-50% residual tumor per tumor bed), and Grade 3: Minimum or no tumor regression (residual tumor per tumor bed >50%).[12]

Statistical Analysis

SPSS 22.0 for Windows program was used for all statistical analysis. Descriptive statistics were presented as numbers

and percentages for categorical variables, mean, standard deviation, median, minimum, and maximum for numerical variables. Comparisons of numerical variables between two independent groups were made with the Student's t-Test if the normal distribution condition was met, and with the Mann Whitney U test if otherwise. The ratios in the groups were analyzed with the Chi-square test. Survival rates were calculated by Kaplan Meier Analysis. Risk factors were analyzed by Cox Regression Analysis. Values with p<0.250 in univariate analysis were evaluated in multivariate analysis with forward stepwise method. Statistical alpha significance level was accepted as p<0.05. Disease-Free Survival (DFS) was calculated as the time from the end of NACt to the date of first relapse. Overall Survival (OS) was calculated from the date of diagnosis to the date of death or last follow up.

Results

Demographic Features

A total of 72 patients, 44 male and 28 female, were included in the study. Median age was 55 years (range: 39-75). About 15.3% of patients had hypertension and 8.3% had diabetes mellitus. In the study population, 54.2% of the patients were current smoker. ECOG PS was 0 in 98.6% of the patients. The rates of clinical stage II and III disease were 6.9% and 93.1%, respectively. According to the Lauran classification, 86.1% of the patients had intestinal-type adenocarcinoma. 66,7% of the patients (n=48) had upper gastric cancer, 29,2% of the patients (n=21) had mid-gastric cancer and 4,2% of the patients (n=3) had lower gastric cancer. Number of upper gastric cancer was significantly higher than other localisations (p=0,049). In FLOT group, 4 patients (8,9%) had signet-ring cell carcinoma, 38 patients (84,4%) had adenocarcinoma and 3 patients (6,7%) had mucinous carcinoma. In mDCF group, 3 patients (11,1%) had signet-ring cell carcinoma, 18 patients (%66,7) had adenocarcinoma and 6 patients (22,2%) had mucinous carcinoma. There was no significantly difference between FLOT group an mDCF group in terms of histological features of the tumor. Number of the treatment cycles were not significantly different between FLOT and mDCF groups (p>0,05). 79,2% of all patients (n=57) completed the treatment. There was no significantly difference between FLOT and mDCF group in terms of completion of treatment. Complete remission was reached at 6 patients (13,3%) in FLOT group and 3 patients (11,1%) in mDCF group. 5 patients (11,1%) reached near complete remission in FLOT group and 4 patients (14,8%) reached near complete remission in mDCF group. Partial response was obtained in 15 patients (33,3%) in FLOT group ana 8 patients (29,6%) in mDCF group. 18 patients (40%) had poor response in FLOT group and 12 patients (40,7%) had poor response in mDCF group. Progression was seen in 1 patients (2,2%) in FLOT group and 1 patients (3,7%) in mDCF group. There was no significantly difference in terms of treatment response between 2 groups (p>0,05). All other demographic features are shown in Table 1.

Treatment

Total gastrectomy was performed in 81.4% of the patients. The rate of D1 and D2 lymph node dissection was 61.4% and 38.6%, respectively. The distribution of patients by TRG after NACt were as follows; grade 1; 12.5%, grade 1b; 12.5%, grade 2; 31.9%, grade 3; 40.3%.

Rate of patients, who had disease progression was 2,8% after NACt. Following surgery, 23.8% of the patients received adjuvant chemoradiation, while 86.1% received adjuvant chemotherapy. 79.2% of the patients were able to complete the treatment. 26.4% of the patients relapsed at follow-up (Table 1).

Survival Analysis

While median DFS could not be reached in the mDCF arm, it was 19.0 months in the FLOT arm; however, there was no significant difference between the groups (long rank p=0.218) (Fig. 1). Median OS was not reached in both groups and no significant difference was found between the groups (long rank p=0.514) (Fig. 2).

In univariate analysis, DFS was statistically and significantly better in those who could complete treatment compared to those who did not [HR=0.270 (0.108-0.674), p=0.005] (Table 2). Neither lynph node dissection type nor positive margins of the specimens affected DFS (p>0,05). Moreover, TNM classification, type of surgery (total or subtotal gastrectomy), localization of the tumor (upper, mid or lower), histologic features (signet-ring cell, adenocancer or mucinous), grade of the tumor, clinical stage of the patient (stage 2 or 3), treatment regimen (mDCF ır FLOT), Her-2 status, response of the NACt or receiving adjuvant chemotherapy or chemoradiation did not affected DCF (p>0,05).

In the multivariate analysis, being able to complete the treatment was found to be the only factor affecting DFS [HR=0.270 (0.108-0.674), p=0.005] (Table 3). Rate of DFS in 6, 12,18 and 24 months were 95,4%, 80,9%, 63% and 42% in FLOT group, respectively. In mDCF group, rate of DFS in 6, 12, 18 and 24 months were 100%, 88%, 71,2% and 62,2%, respectively.

Table 1. Data of the patients by treatment groups

Characteristics	All patients (n=72)		FLOT (n=45)		mDCF (n=27)		p
	n	%	n	%	n	%	
Gender							
Female	28	38.9	18	40.0	10	37.0	0.803
Male	44	61.1	27	60.0	17	63.0	
Age (year)							
Median (min-max)	55 -39-72		56-39*69		55-42*71		0.807
Hypertension	11	15.3	7	15.6	4	14.8	0.607
Diabetes Mellitus	6	8.3	3	6.7	3	11.1	0.665
Smoking							
No	39	54.2	26	57.8	13	48.1	0.427
Yes	33	45.8	19	42.2	14	51.9	
ECOG							
0	71	98.6	45	100.0	26	96.3	0.375
1	1	1.4	0	0.0	1	3.7	
CEA							
ng/mL	24.7- 84.5		9.3-12.7		41.1-120.4		0.244
CA19-9							
U/mL	126.0- 332.1		164.7-394.3		84.9-256.6		0.800
Clinical Stage							
II	5	6.9	3	6.7	2	7.4	0.635
III	67	93.1	42	93.3	25	92.6	
NACt, number of cycles							
Median (min-max)	4.3*8		4-3*8		4-3*8		0.995
Lauren classification							
intestinal	62	86.1	38	84.4	24	88.9	0.733
diffuse	10	13.9	7	15.6	3	11.1	
Localization							
upper	48	66.7	33	73.3	15	55.6	0.049
mid	21	29.2	9	20.0	12	44.4	
lower	3	4.2	3	6.7	0	0.0	
Histology							
Signet-ring cell	7	9.7	4	8.9	3	11.1	0.113
adenocancer	56	77.8	38	84.4	18	66.7	
mucinous	9	12.5	3	6.7	6	22.2	
grade							
2	51	70.8	31	68.9	20	74.1	0.772
3	19	26.4	13	28.9	6	22.2	
4	2	2.8	1	2.2	1	3.7	
Type of surgery							
subtotal	13	18.6	9	20.5	4	15.4	0.754
total	57	81.4	35	79.5	22	84.6	
Lymph node dissection							
D1	43	61.4	24	54.5	19	73.1	0.124
D2	27	38.6	20	45.5	7	26.9	
Number of LN dissected							
Median (min-max)	27-10*57		32-11-57		24-10*40		
Number of LN involved							
Median (min-max)	1-0*24		1-0*11		0.5-0*24		

Table 1. CONT.

Characteristics	All patients (n=72)		FLOT (n=45)		mDCF (n=27)		p
	n	%	n	%	n	%	
Margin positivity	3	4.3	3	6.8	0	0.0	0.289
PNI positivity	35	48.6	21	46.7	14	51.9	0.670
LVI positivity	33	45.8	21	46.7	12	44.4	0.855
ypTNM							
0	9	12.9	6	13.6	3	11.5	0.967
1	5	7.1	2	4.5	3	11.5	
2	20	28.6	14	31.8	6	23.1	
3	36	51.4	22	50.0	14	53.8	
ypT							
0	10	14.3	7	15.9	3	11.5	0.906
1	5	7.1	3	6.8	2	7.7	
2	4	5.7	2	4.5	2	7.7	
3	40	57.1	26	59.1	14	53.8	
4	11	15.7	6	13.6	5	19.2	
ypN							
0	30	42.9	18	40.9	12	46.2	0.591
1	12	17.1	7	15.9	5	19.2	
2	14	20.0	11	25.0	3	11.5	
3	14	20.0	8	18.2	6	23.1	
Her-2 status							
0	61	84.7	38	84.4	23	85.2	0.977
1	3	4.2	2	4.4	1	3.7	
2	2	2.8	1	2.2	1	3.7	
3	6	8.3	4	8.9	2	7.4	
Pathological response to NACt							
CR	9	12.5	6	13.3	3	11.1	0.992
Near CR	9	12.5	5	11.1	4	14.8	
Partial	23	31.9	15	33.3	8	29.6	
Poor	29	40.3	18	40.0	11	40.7	
Progression	2	2.8	1	2.2	1	3.7	
Adjuvant chemotherapy	17	23.6	9	20.0	8	29.6	0.352
Yes	62	86.1	42	93.3	20	74.1	0.034
FLOT	42	68.9	42	100.0			
mDCF	19	31.1			19	100.0	
Number of adjuvant cycle							
Median (min-max)	4 --1-6		4-1*4		3-2*6		0.039
Completion of treatment							
Yes	57	79.2	37	82.2	20	74.1	0.410
Recurrence status and localization							
Yes	19	26.4	10	22.2	9	33.3	0.300
local	2	8.7	1	9.1	1	8.3	0.364
Liver	4	17.4	0	0.0	4	33.3	
peritoneum	11	47.8	6	54.5	5	41.7	
Lymph node	3	13.0	2	18.2	1	8.3	
Brain	1	4.3	1	9.1	0	0.0	
Bone	2	8.7	1	9.1	1	8.3	
1. line chemotherapy	16	69.6	7	63.6	9	75.0	0.667
Final status							
ex	5	6.9	1	2.2	4	14.8	0.062
alive	67	93.1	44	97.8	23	85.2	

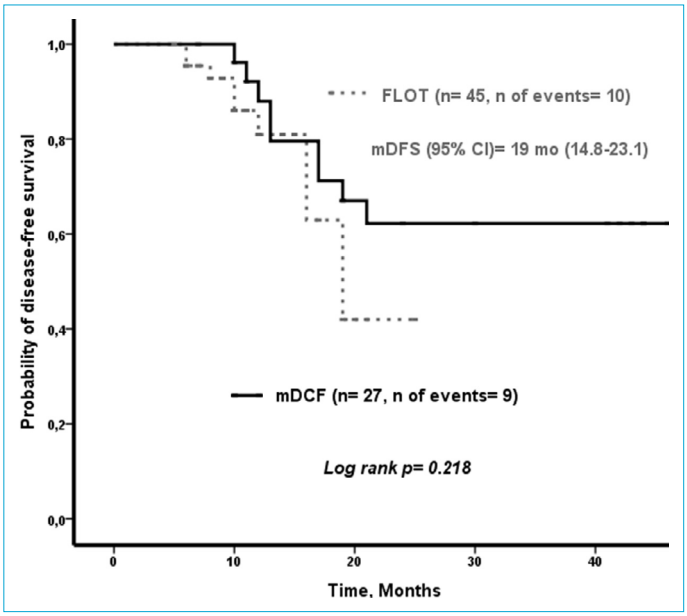

Figure 1. Disease-free survival between treatment groups.

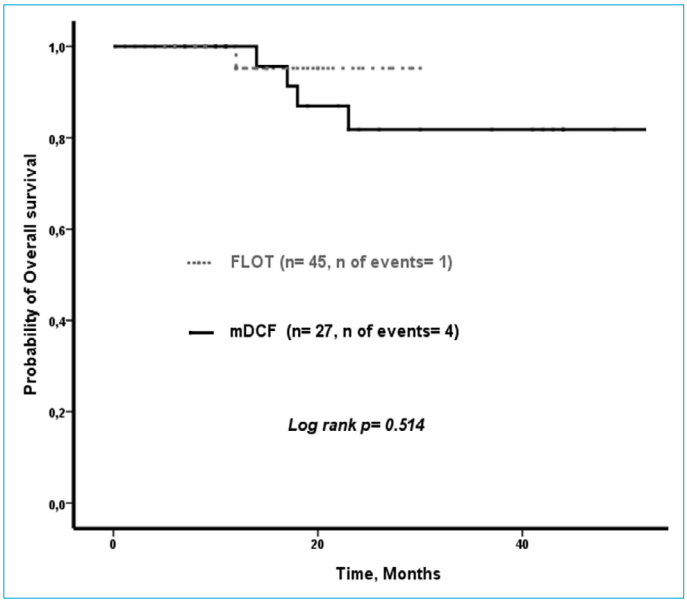

Figure 2. Overall survival between treatment groups.

Discussion

This study aimed to compare the effects of mDCF vs. FLOT regimens on survival and treatment response in patients with locally-advanced GC and found no significant difference between the regimens in terms of both DFS and OS. In addition, there was no significant difference between the treatment arms in regards to treatment response.

Despite new advances in surgical techniques and novel drugs in the oncological field, GC continues to be an important cause of cancer-related deaths all over the world.[13] In patients with non-metastatic GC, although cure can be

Table 2. Univariate analyses for DFS

Characteristic	HR	95 % CI for HR		P
Gender				
Male vs. female	1.623	0.584	4.508	0.353
Age				
Year	1.010	0.952	1.071	0.745
HT				
Yes vs. no	1.053	0.349	3.180	0.927
DM				
Yes vs. no	0.610	0.081	4.579	0.631
Smoking				
Yes vs. no	0.890	0.358	2.211	0.802
ECOG				
0 vs. 1	2.047	0.603	8.585	0.621
CEA				
Ng/mL	1.004	0.999	1.008	0.120
CA19.9				
U/mL	1.001	0.999	1.003	0.305
Clinical stage				
III vs. II	2.468	0.328	18.584	0.380
NACt regimen				
mDCF vs. FLOT	0.526	0.195	1.423	0.206
Lauren classification				
Diffuse vs. intestinal	1.229	0.407	3.710	0.715
Localization				
upper (ref)				0.689
Mid	0.885	0.334	2.346	0.806
Lower	1.766	0.382	8.161	0.466
Histology				
Signet-ring cell (ref)				0.365
Adenocancer	2.333	0.308	17.675	0.412
mucinous	0.926	0.084	10.226	0.950
Grade				
I				0.240
II	2.273	0.874	5.913	0.092
III	1.155	0.148	8.990	0.891
Type of surgery				
Total vs. subtotal	1.143	0.328	3.981	0.834
LN dissection				
D2 vs. D1	0.635	0.206	1.955	0.429
Number of LN dissected	0.981	0.934	1.029	0.429
Number of LN involved	1.024	0.974	1.076	0.360
Margin				
Positive vs. negative	2.404	0.548	10.546	0.245
NI				
Positive vs. negative	1.514	0.608	3.769	0.373
VI				
Positive vs. negative	1.471	0.597	3.625	0.402
TNM				
ypTNM 0 (ref.)				0.429
ypTNM I	0.000	0.000		0.983
ypTNM II	1.772	0.184	17.059	0.621
ypTNM III	3.808	0.498	29.123	0.198

Table 2. CONT.

Characteristic	HR	95 % CI for HR		P
T				
ypT0 (Ref.)				0.692
ypT1	0.000	0.000		0.990
ypT2	0.000	0.000		0.991
ypT3	2.972	0.384	23.035	0.297
ypT4	4.812	0.561	41.240	0.152
N ypN0(Ref.)				0.043
ypN1	1.160	0.212	6.340	0.864
ypN2	3.576	0.884	14.474	0.074
ypN3	5.046	1.459	17.449	0.011
Her-2 status				
3 vs. 0-2	1.574	0.207	11.989	0.661
Response to NACt				
no response (Ref.)				0.214
partial response	0.284	0.062	1.298	0.105
complete-near complete	0.551	0.173	1.760	0.315
Adj chemotherapy				
Yes vs. no	0.449	0.170	1.187	0.106
Adj chemoradiation				
Yes vs. no	0.764	0.253	2.311	0.634
Completion of Treatment				
Yes vs. no	0.270	0.108	0.674	0.005

Table 3. Multivariate analyses for DFS

Characteristic	HR	95% CI for HR		p
CEA	1.005	1.000	1.010	0.038
Completion of treatment				
Yes vs. No	0.140	0.031	0.643	0.011

achieved in some patient groups by multimodality treatments, some patients eventually relapse and the chance of cure in this recurrent group is very low. With various strategies, it is aimed to prevent disease relapses and thus related deaths. A meta-analysis published in 1999 showed the survival benefit of adding adjuvant chemotherapy to surgery, leading to adjuvant therapies to be used more frequently.[14]

In the CLASSIC study, which included 1035 gastric cancer patients with stage II, IIIA or IIIB disease, patients were randomized after curative surgery with D2 lymph-node dissection to receive up to 8 cycles of CAPEOX regimen (capecitabine 2x1000 mg/m^2, 1-14 days, oxaliplatin 130 mg/m^2 on day 1, cycled every 21 days) to the observation arm. The study was conducted in South Korea, China, and Taiwan. Only 67% of patients were able to complete the planned 8 cycles of chemotherapy, with 90% of them requiring dose modification due to adverse events. At a median follow-up of 34 months, chemotherapy was found to be associated with a significant improvement in 3-year disease-free survival (DFS; 59%-74%), with 5-year OS of 78%-69%, HR 0.66.[15]

In a study evaluating the benefit of neoadjuvant chemoradiotherapy, patients with T3-T4 tumors with adenocarcinoma of the lower esophagus, esophagogastric junction, or gastric cardia were randomly assigned to induction chemotherapy followed by surgery or induction chemotherapy followed by chemoradiotherapy and then surgery. The primary endpoint was overall survival time. A total of 354 patients were needed to detect a 10% increase in 3-year survival (from 25% to 35%) with the addition of radiotherapy, but the study was closed prematurely after recruiting 119 patients. The median follow-up period was 46 months. The number of patients achieving complete tumor resection was not different between the treatment groups (69.5% vs. 71.5%). The rates of pathological complete response (15.6% vs 2.0%) and N0(64.4% vs. 37.7%) at resection were higher in the chemoradiotherapy arm. Adding radiotherapy increased the 3-year survival rate from 27.7% to 47.4% (log-rank p=0.07). Despite the increase in postoperative mortality in the chemoradiotherapy arm (10.2% vs. 3.8%; p=0.26), it was not statistically significant. Although the study was closed early and statistical significance was not met, the results suggested a survival advantage of preoperative chemoradiotherapy over preoperative chemotherapy in esophagogastric junction adenocarcinomas.[16] The region where the study was conducted was an epidemic region in terms of gastric cancer incidence; intestinal type gastric cancer was more frequent and the incidence of signet-ring cell cancer was relatively lower.

Some of the patients with GC treated with upfront surgery who had to receive adjuvant chemotherapy could not receive or complete the treatment due to postoperative complications, hence the expected benefit of adjuvant therapy had been limited before the advent of NACt.[4,5]

Neoadjuvant chemotherapy in GC began with the landmark phase III MAGIC trial which compared perioperative chemotherapy with epirubicin, cisplatin, and fluorouracil to surgery alone in patients with locally-advanced GC, demonstrating a survival benefit of NACt over surgery. An important aspect of this study was that only 42% of the patients were able to complete the postoperative adjuvant treatment, hence emphasizing once again that NACt should be preferred due to its tolerability.[4] In our study, the rate of completion of adjuvant treatment in the FLOT arm was 82.2% vs. 74.1% in the mDCF, which was quite high compared to literature.

The subsequent FLOT4 study showed that the periopera-

tive chemotherapy with FLOT regimen was shown to be superior to ECF/ECX regimen (epirubicin+cisplatin+5-fluorouracil or capecitabine) in patients with locally-advanced GC, demonstrating a significantly greater OS in the FLOT group than in the ECF/ECX group (50 months vs. 35 months; HR, 0.77; 95% CI, 0.63–0.94), with pathological complete response rates of 37% in FLOT arm compared to 23% in ECF/ECX arm.[17]

In our study, approximately 25% of the patients achieved a pathologically complete or nearly complete response after NACt and 25% had partial response to treatment, showing consistent finding with the literature. DFS was found to be 19 months in the FLOT group compared to not reached the DCF arm. The treatment completion rate in the DCF arm was, although not significant, relatively lower than in the FLOT arm. However, DFS was longer in the DCF arm than in the FLOT arm, although it was not statistically significant.

In PRODIGY study evaluating the effectiveness of NACt, 484 Korean patients with stage II or III gastric and/or EGJ adenocarcinoma were divided into 2 groups as follows; dosataksel+oksaliplatin+S-1 as neoadjuvant treatment followed by surgery and then 48 weeks of adjuvant S-1 treatment or surgery followed by 48 weeks of S-1 treatment.

The rate of N0 disease was higher (55% vs. 22%) and T4 tumor was lower (19% vs. 40%) in the patients receiving neoadjuvant treatment, providing a significant benefit in 3-year DFS, (66% vs. 60%, HR 0,70), with no significant advantage in OS (74% vs. 73%, HR 0,84).[18]

The major limitations of our study were as follows; first, it had a retrospective nature; second, small number of patients were included compared to the literature; third and the most important one, the side effects profile could not be reported due to the retrospective design of the study. However, our study consisted of patients with homogeneous characteristics, with sufficient follow-up times. In addition, to the best of our knowledge, it is the first study comparing FLOT vs. mDCF regimen in this patient group.

In conclusion, we found that mDCF and FLOT regimens both provided similar response rates and survival durations in patients with locally-advanced GC in the neoadjuvant setting. In the light of these results, we think that cisplatin can be preferred instead of oxaliplatin in the elderly patient population such as patients with DM or those with high risk of neuropathy. However, the results of our study need to be supported by large prospective studies, especially involving elderly patients, particularly those at high risk of neuropathy.

Disclosures

Ethics Committee Approval: This study and all relevant procedures were performed in accordance with the Helsinki Declaration after obtaining the ethical board approval from the Yüzüncü Yıl University Ethics Committee: 10.07.2020; Number 2020/04-04.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – M.U., A.S., S.S.; Design – A.S., Y.Y.U.; Supervision – M.U., S.S., A.S.; Resources – M.U., A.S., Y.Y.U.; Materials – M.U., Y.Y.U., A.S.; Data Collection and/or Processing – M.U., A.S.; Analysis and/or Interpretation – M.U., Y.Y.U.; Literature Search – S.S., A.S., Y.Y.U.; Writing Manuscript – M.U., A.S., S.S.; Critical Review – Y.Y.U., S.S., A.S.; Other – M.U., A.S.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68(6):394–424.
2. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011;61(2):69–90.
3. Zhu AL, Sonnenberg A. Is gastric cancer again rising? J Clin Gastroenterol 2012;46(9):804–6.
4. Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 2006;355(1):11–20.
5. Schuhmacher C, Gretschel S, Lordick F, Reichardt P, Hohenberger W, Eisenberger CF, et al. Neoadjuvant chemotherapy compared with surgery alone for locally advanced cancer of the stomach and cardia: European Organisation for Research and Treatment of Cancer randomized trial 40954. J Clin Oncol 2010;28:5210–8.
6. Xiong BH, Cheng Y, Ma L, Zhang CQ. An updated meta-analysis of randomized controlled trial assessing the effect of neoadjuvant chemotherapy in advanced gastric cancer. Cancer Invest 2014;32:272–84.
7. Ajani JA, D'Amico TA, Bentrem DJ, Chao J, Cooke D, Corvera C, et al. Gastric Cancer, Version 2.2022, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2022;20(2):167–92.
8. Lordick F, Carneiro F, Cascinu S, Fleitas T, Haustermans K, Piessen G, et al. Gastric cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol 2022;33(10):1005–20.
9. Katayama H, Tsuburaya A, Mizusawa J, Nakamura K, Katai H, Imamura H, et al. An integrated analysis of two phase II trials (JCOG0001 and JCOG0405) of preoperative chemotherapy followed by D3 gastrectomy for gastric cancer with extensive lymph node metastasis. Gastric Cancer 2019;22:1301–07.
10. Sakin A, Sahin S, Sakin A, Aldemir MN, Bayram I, Kotan C.

The Effect of Obesity on Response to Neoadjuvant Therapy in Locally Advanced Gastric Cancer. Asian Pac J Cancer Prev 2020;21:2723–31.
11. Tomasello G, Petrelli F, Ghidini M, Pezzica E, Passalacqua R, Steccanella F, et al. Tumor regression grade and survival after neoadjuvant treatment in gastro-esophageal cancer: A meta-analysis of 17 published studies. Eur J Surg Oncol 2017;43(9):1607–16.
12. Becker K, Mueller JD, Schulmacher C, Ott K, Fink U, Busch R, et al. Histomorphology and grading of regression in gastric carcinoma treated with neoadjuvant chemotherapy. Cancer 2003;98:1521–30.
13. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin 2014;64(1):9–29.
14. Earle CC, Maroun JA. Adjuvant chemotherapy after curative resection for gastric cancer in non-Asian patients: revisiting a meta-analysis of randomised trials. Eur J Cancer 1999;35(7):1059–64.
15. Bang YJ, Kim YW, Yang HK, Chung HC, Park YK, Lee KH, et al. Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. Lancet 2012;379(9813):315–21.
16. Stahl M, Walz MK, Riera-Knorrenschild J, Stuschke M, Sandermann A, Bitzer M, et al. Preoperative chemotherapy versus chemoradiotherapy in locally advanced adenocarcinomas of the oesophagogastric junction (POET): Long-term results of a controlled randomised trial. Eur J Cancer 2017;81:183–90.
17. Al-Batran SE, Hofheinz RD, Pauligk C, Kopp HG, Haag GM, Luley KB, et al. Histopathological regression after neoadjuvant docetaxel, oxaliplatin, fluorouracil, and leucovorin versus epirubicin, cisplatin, and fluorouracil or capecitabine in patients with resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4-AIO): results from the phase 2 part of a multicentre, open-label, randomised phase 2/3 trial. Lancet Oncol 2016;17(12):1697–708.
18. Kang YK, Yook JH, Park YK, Lee JS, Kim YW, Kim JY, et al. PRODIGY: A Phase III Study of Neoadjuvant Docetaxel, Oxaliplatin, and S-1 Plus Surgery and Adjuvant S-1 Versus Surgery and Adjuvant S-1 for Resectable Advanced Gastric Cancer. J Clin Oncol 2021;39(26):2903–13.