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ANTICANCER ORIGINAL RESEARCH PAPER

Real life experience of patients with locally advanced gastric and gastroesophageal junction adenocarcinoma treated with neoadjuvant chemotherapy: a Turkish oncology group study

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ABSTRACT

Neoadjuvant chemotherapy (NACT) in gastroesophageal junction (GEJ) and gastric cancer (GC) was shown to improve survival in recent studies. We aimed to share our real-life experience of patients who received NACT to compare the efficacy and toxicity profile of different chemotherapy regimens in our country. This retrospective multicentre study included locally advanced GC and GEJ cancer patients who received NACT between 2007 and 2021. Relation between CT regimens and pathological evaluation were analysed. A total of 794 patients from 45 oncology centers in Turkey were included. Median age at the time of diagnosis was 60 (range: 18–86). Most frequent NACT regimens used were FLOT (65.4%), DCF (17.4%) and ECF (8.1%), respectively. In the total study group, pathological complete remission (pCR) rate was 7.2%, R0 resection rate 86.4%, and D2 dissection rate was 66.8%. Rate of pCR and near-CR (24%), and R0 resection (84%) were numerically higher in FLOT arm ($p > 0.05$). Patients who received FLOT had also higher chemotherapy-related toxicity rate compared to patients who received other regimens ($p > 0.05$). Median follow-up time was 16 months (range: 1–154 months). Estimated median overall survival (OS) was 58.4months (95% CI: 35.2–85.7) and disease-free survival (DFS) was 50.7 months (95% CI: 25.4–75.9). The highest 3-year estimated OS rate was also shown in FLOT arm (68%). We still do not know which NACT regimen is the best choice for daily practice. Clinicians should tailor treatment regimens according to patients' multifactorial status and comorbidities for to obtain best outcomes. Longer follow-up period needs to validate our results.

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Introduction

Gastric cancer (GC) is an important health problem in Turkey. GC is the fifth common cancer, and the third common cause of cancer related death after lung cancer in our country [1]. In addition GC is also a global problem, as it is the third common cause of cancer-related death in the world [2]. It is usually diagnosed in an advanced stage [3]. While 5-year survival rates for stage I patients with curative resection are between 70% and 75%, it decreases to 25–30% in the locally advanced stage [4]. Therefore, instead of complete resection and lymph node dissection which is known as the only curative treatment in earlier stages, multimodal treatment is a better option for the treatment of locally advanced disease.

Goals of perioperative treatments are to observe the response rates which also gives us hints of the biology of the disease, to eliminate possible micrometastatic disease, to down-stage the primary tumor to increase the chance of R0 resection, and finally to improve survival [5–7].

The United Kingdom Medical Research Council (MAGIC) trial was the first large randomized controlled trial to demonstrate significant benefit of perioperative chemotherapy in GC and gastroesophageal junction (GEJ) cancer. In this study patients who received epirubicin, cisplatin and 5-fluorouracil (ECF) regimen before surgery survived longer than the ones who were only operated [5]. Subsequent study of 'Federation Nationale des Centres de Lutte contre le Cancer' (FLNCC) also demonstrated that cisplatin and 5-fluorouracil (CF) regimen in perioperative setting improved survival compared to surgery alone [6]. Finally, perioperative docetaxel, oxaliplatin, 5-Fluorouracil (FLOT) regimen was shown to be superior for survival when it was compared to ECF in the FLOT4-AIO trial [7].

Still best regimen in neoadjuvant setting needs to be tailored for each patient. Many factors are taken into consideration when choosing neoadjuvant chemotherapy (NACT) regimens in our daily practice such as age, performance status and comorbidities of patients. Our aim is to share the real-life experiences of patients with gastric and GEJ carcinomas who received different NACT regimens in our country and to compare efficacy and toxicity profile of different regimens.

Patients and methods

We retrospectively evaluated 797 patients with locally advanced (clinical T2 or higher, and/or node positive stage with using computer tomography and endoscopic ultrasound for clinical staging) GC and GEJ adenocarcinoma who were treated with NACT between October 2007–March 2021. The study included 728 patients from 45 different oncology centers in Turkey, who were older than 18 years, were received NACT. Five patients who received neoadjuvant chemoradiotherapy (NACRT), and one patient whose tumor was squamous cell histology were excluded.

Demographic, clinicopathologic, efficacy and side effect data of different NACTs were recorded from their files. Clinical staging at presentation was performed according to American Joint of Committee on Cancer (AJCC) staging 7th edition [8]. Collage of American Pathologists (CAP) -Tumor Regression Grading (TRG) were used for pathological evaluation after surgery [9].

- TRG0: Pathological complete response (pCR): no viable cancer cells;
- TRG1: Near complete response (near CR): single cells or small groups of cancer cells;
- TRG2: Partial response (PR): residual cancer outgrown by fibrosis;
- TRG3: Poor response/no response: minimal or no tumor was killed or extensive residual cancer.

Chemotherapy related toxicities were graded according to Common Terminology Criteria for Adverse Event Version 4.03. Different chemotherapy regimens were compared in terms of efficacy, safety and toxicity.

The primary end point, real-life differences in survival of patients who received different chemotherapy regimens was defined as follows: overall survival (OS) was defined as the time interval in months between the diagnosis of disease to death or last outpatient visit if the patient was still alive. Disease free survival (DFS) was defined as the time interval in months between the diagnosis of disease to relapse, or last follow-up if patient was not relapsed.

The secondary end point, toxicity profile of different regimens was defined as a comparison of the rates of different adverse events, discontinuation or dose modification seen throughout the entire treatment course.

Statistical analysis

All categorical variables were presented as frequencies and group percentages, ranges were denoted for parameters with a median value. Chi-square test was

used to compare categorical variables. Univariate and multivariate cox/logistic regression models were conducted to assess factors that predicting survival and pathological response. OS and DFS were estimated with Kaplan–Meier method and log-rank test. Confidence interval (CI) was selected as 95% and a 2-sided p value less than .05 was accepted as statistically significant. Statistical analyses were performed using SPSS 20.0 software.

Protocols of chemotherapy regimens

FLOT: 5-Fluorouracil, leucovorin, oxaliplatin, docetaxel

Fluorouracil 2600 mg/m^2 IV continuous infusion over 24 h on Day 1

Leucovorin 200 mg/m^2 IV on Day 1

Oxaliplatin 85 mg/m^2 IV on Day 1

Docetaxel 50 mg/m^2 IV on Day 1

Cycled every 14 days

FOLFOX: 5-Fluorouracil, leucovorin, oxaliplatin

Fluorouracil 2400 mg/m^2 IV continuous infusion over 48 h on Days 1 and 2

Fluorouracil 400 mg/m^2 IV on Day 1

Leucovorin 400 mg/m^2 IV on Day 1

Oxaliplatin 85 mg/m^2 IV on Day 1

Cycled every 14 days

CAPEOX: capecitabine and oxaliplatin

Capecitabine 1000 mg/m^2 PO BID on Days 1–14

Oxaliplatin 130 mg/m^2 IV on Day 1

Cycled every 21 days

CF: cisplatin and 5-Fluorouracil

Cisplatin 50 mg/m^2 on Day 1

Fluorouracil 2000 mg/m^2 IV continuous infusion over 48 h on Days 1 and 2

Cycled every 14 days

DCF: docetaxel, cisplatin and 5-Fluorouracil

Docetaxel 75 mg/m^2 IV on Day 1

Cisplatin 75 mg/m^2 on Day 1

Fluorouracil 750 mg/m^2 daily IV continuous infusion on Days 1–5

Cycled every 21 days

DCX: docetaxel, cisplatin and capecitabine

Docetaxel 60 mg/m^2 IV on Day 1

Cisplatin 60 mg/m^2 on Day 1

Capecitabine 1650 mg/m^2 PO on Days 1–14

Cycled every 21 days

ECF: epirubicin, cisplatin and 5-fluorouracil,

Epirubicin 50 mg/m^2 IV on Day 1

Cisplatin 60 mg/m^2 IV on Day 1

Fluorouracil 200 mg/m^2 daily IV continuous infusion on Days 1–21

Cycled every 21 days

ECX: epirubicin, cisplatin and capecitabine

Epirubicin 50 mg/m^2 IV on Day 1

Cisplatin 60 mg/m^2 IV on Day 1

Capecitabine 825 mg/m^2 PO BID on Days 1–14

Cycled every 21 days

*CAPEOX/FOLFOX, DCF/DCX and ECF/ECX were combined and evaluated as a single group.

Results

Total of 794 patients with GC/GEJ were included in this study, with a male predominance (72.5%). Median age at the time of diagnosis was 60 (range: 18–86). Histology was adenocarcinoma in all, and 52.5% of patients had gastric primary. Sixty-six patients were not operated after NACT for various reasons (disease progression, poor performance, etc.) had no pathological evaluation. Patient and tumor characteristics were described in Table 1.

Mostly used NACT regimens were FLOT (65.4%), DCF (17.4%) and ECF (8.1%), respectively. Patients received median of four cycles of NACT (range: 1–10). Adjuvant chemotherapy was given to 617 (77.7%) patients, and 58 of them received additional adjuvant radiotherapy.

Forty-three patients (8.2%) had pCR. Rate of pCR and near-CR (24%), and R0 resection (84%) were higher in FLOT arm numerically ($p = .14$ and .5). Comparison of most common preferred chemotherapy regimens according to pathological response were presented in Table 2.

Conversely, patients who received FLOT had higher chemotherapy-related toxicity rate compared to patients who received other regimens ($p > .05$). Febrile neutropenia was observed in 18 patients after FLOT regimen despite of granulocyte colony-stimulating factor (GCSF) prophylaxis. Comparison of chemotherapy regimens according to toxicity profiles are presented in Table 3. Total of 794 patients, 211 (26.6%) patients had disease progression. Conversely, 48(72.7%) of 66 non-operated patients, could not be operated due to progression. Moreover, progressions preventing surgery accepted as measure of the low efficacy of a treatment. These results were also presented in Table 3.

Median follow-up time was 16 months (range: 1–154 months). During follow-up, 206 (25.9%) patients were deceased, and 211 (26.6%) relapsed. Estimated three-year OS rate was 59%. Estimated median OS was 58.4 months (95% CI: 35.2–85.7) and DFS was 50.7 months (95% CI: 25.4–75.9). Although

it was not statistically significant, the highest 2- and 3-year estimated OS rate was shown in FLOT arm (80% and 68%). As we presented in Figures 1 and 2 Kaplan–Meier survival curves overlapping with each other. There is no difference between chemotherapy regimens in terms of OS and DFS. Three most common relapse sites were peritoneal carcinomatosis (11.1%), liver metastasis (6.2%) and loco-regional relapses (2.9%). Results of survival analysis according to chemotherapy regimens is presented in Table 4.

As we presented in Table 5, positive surgical margins in surgery and no pathological response to NACT were determined as independent poor prognostic factors for both OS and DFS in multivariate analysis. We also presented results of pivotal trials comparing with our study in Table 6.

Table 1. Characteristics of patients and tumors.

Descriptives	$n = 794$, n(%)
Gender	
Female	226(28.5)
Male	568(71.5)
ECOG-PS	
0	440(55.4)
1	317(39.9)
2	37(4.7)
Age at diagnosis	
<65	554(69.8)
≥65	240(30.2)
Smoking history	
Current/Past	329(41.4)
Location of tumor	
GEJ	377(47.5)
Gastric	417(52.5)
Fundus	50(6.2)
Corpus	17(2.1)
Antrum	10(1.2)
Clinical stage	
cT1-2N+	36(4.5)
cT3-4N0	351(44.2)
cT3-4N+	407(51.3)
Type of surgery	
Total gastrectomy	511(64.4)
Subtotal gastrectomy	208(26.2)
Palliative surgery/not operated	75(9.4)
Lymph node dissection	
D1	242(33.2)
D2	486(66.8)
missing	66(8.3)
Resection	
R0	641(80.7)
R1	55(6.9)
R2	98(12.3)
LVI	404(50.9)
PNI	342(43.1)
Grade groups	
Grade 1	53(6.7)
Grade 2	395(49.7)
Grade 3	319(40.2)
Grade 4	27(3.4)

ECOG-PS: Eastern Cooperative Oncology Group Performance Status; GEJ: gastroesophageal junction; LVI: lymphovascular invasion; PNI: perineural invasion; CR: complete response; PR: Partial response of Pivotal Trials Using Perioperative Treatment.

Discussion

In recent years, multimodal approach has been preferred in the treatment of GC and GEJ carcinomas which have aggressive biology and poor prognosis. NACT had valuable advantages such as downstaging of tumor, possibly preventing micrometastatic disease, increasing R0 resection rate and as a result of all improving survival.

In randomized controlled trials, it has been shown that higher rate of R0 resection and D2 dissection improved survival via improving pathological responses [10]. While MAGIC and French FNCLCC/FFCD trials did not include a proper extended lymphadenectomy in the majority of cases, FLOT-AIU trial had mostly D2 dissection. In all these three landmark studies R0 resection rates were higher in selected arms. We observed that 61.2% of our patients had D2 dissection, and R0 resection rates according to NACT were 84% with FLOT, 81% with DCF, 78% with CF, 67% with ECF and 64% with FOLFOX, which were consistent with the literature.

In our pathological evaluation, we observed higher pCR rates with FLOT regimen (8.2%), but this was lower than 16% of pCR seen in FLOT4-AIO trial . CR and Near-CR (response rate) rate was also higher in FLOT4-AIO trial (37%) than our study (24%).

In FLOT4-AIO trial, distribution of diagnostic age and ECOG-PS were similar with our study. Conversely, 3.2% of patients in FLOT4-AIO trial could not be

Table 2. Comparison of most common preferred chemotherapy regimens according to pathological evaluation.

		Pathological response			Resection rate	
Chemotherapy regimens	n (%)	CR, n (%)	CR+ nearCR, n (%)	PR+ poor/no response, n (%)	R0, n (%)	R1 + R2, n (%)
FLOT	519(100)	43(8.2)	125(24)	394(75)	436(84)	49(9.4)
FOLFOX/CAPEOX	39(100)	2(5.1)	5(12.8)	34(87)	25(64)	9(23)
DCF/DCX	138(100)	7(5.0)	21(12.8)	117(84.7)	112(81)	19(13.7)
CF/CX	19(100)	1(5.2)	3(15.7)	16(84.2)	15(78)	3(15.7)
ECF/ECX	64(100)	3(4.6)	12(18.7)	52(81.2)	43(67)	16(25)
Total	794(100)	57(7.2)	169(21.3)	625(78.7)	641(86.4)	101(13.6)

FLOT: 5-Fluorouracil, leucovorin, oxaliplatin, docetaxel; FOLFOX: 5-fluorouracil, leucovorin, oxaliplatin; CAPEOX: capecitabine and oxaliplatin; CF: cisplatin and 5-fluorouracil; DCF: docetaxel, cisplatin and 5-fluorouracil; DCX: docetaxel, cisplatin and capecitabine; ECF: epirubicin, cisplatin and 5-fluorouracil; ECX: epirubicin, cisplatin and capecitabine; GEJ: gastroesophageal junction; CR: complete response; PR: partial response; R0: microscopically margin-negative resection; R1: microscopically margin-positive resection; R2: macroscopically margin-positive resection.

Table 3. Comparison of chemotherapy regimens according to toxicity profiles.

Chemotherapy regimens	*n* (%)	Adverse events, *n* (%)		Most common adverse events		FN, *n* (%)	Stop/interrupt treatment, *n* (%)	Progression rates in non-operated patients, *n* (%)
		Grade 1 or 2	Grade 3 or 4	Grade 1 or 2	Grade 3 or 4			
FLOT	519(100)	249(47.9)	157(30.2)	Anemia	Neutropenia	18 (3.4)	34 (6.5)	38(7.3)
FOLFOX/CAPEOX	39(100)	13(33.3)	6(15.3)	Neuropathy	Neutropenia	0	0 (0)	4(10.2)
DCF/DCX	138(100)	48(34.7)	32(23.1)	Neutropenia	Neutropenia	0	5 (3.6)	2(1.4)
CF/CX	19(100)	4(21.0)	5(26.3)	Trombositopenia	Anemia	0	0 (0)	0
ECF/ECX	64(100)	28(43.2)	5(7.8)	Neutropenia, Nausea	Nausea	2(3.1)	1 (1.5)	4(6.2)

FLOT: 5-Fluorouracil, leucovorin, oxaliplatin, docetaxel; FOLFOX: 5-fluorouracil, leucovorin, oxaliplatin; CAPEOX: capecitabine and oxaliplatin; CF: cisplatin and 5-fluorouracil; DCF: docetaxel, cisplatin and 5-fluorouracil; DCX: docetaxel, cisplatin and capecitabine; ECF: epirubicin, cisplatin and 5-fluorouracil; ECX: epirubicin, cisplatin and capecitabine; FN: febrile neutropenia.

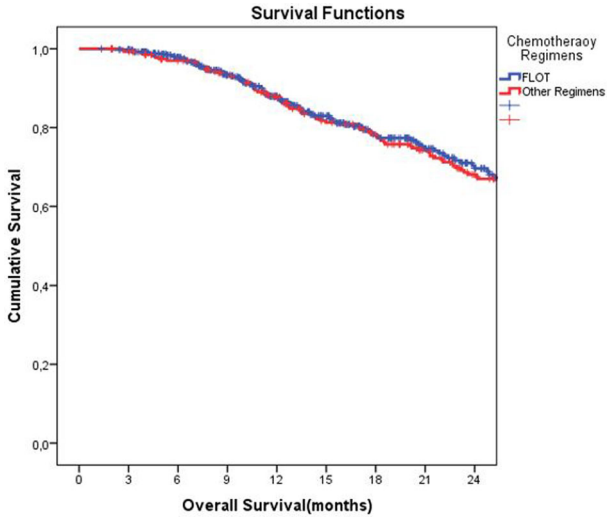

Figure 1. Kaplan-Meier Curve Presenting Overall Survival According to FLOT vs Other Chemotherapy.

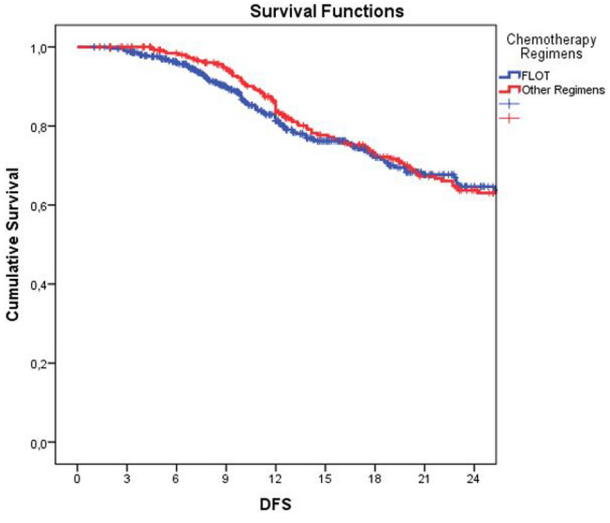

Figure 2. Kaplan Meier Curve Presenting Disease Free Survival According to FLOT vs Other Chemotherapy Regimens.

operated due to various reasons, this rate was 8.8% in our study. These poor prognostic patient group may have adversely affected our results. Nevertheless, 90% patients in FLOT4-AIO trial completed all cycles of allocated chemotherapy, while this rate was only 77.4% in our study. We believe that failure to complete all cycles of chemotherapy is the most important factor affecting our lower pathological response rate.

Perioperative chemotherapy for GE and GEJ adenocarcinoma was shown to improve survival in the literature. First, study was reported in 2006, the MAGIC [5] trial showed significant improvement in 5-year OS rate with perioperative ECF treatment over surgery alone (36% vs. 23%). Second study came out on 2011, French FNCLCC/FFCD trial [6], reported patients who received CF before and after surgery resulting in a significant improvement of 5-year DFS and OS over surgery alone (DFS: 34% vs. 19%, and OS: 38% vs. 24%, respectively). Finally, the FLOT4-AIO trial compared FLOT and ECF/ECX regimens as perioperative treatment in advanced GC and GEJ cancer with clinical resectable tumors, stage cT2 or higher or nodal positive stage or both, with no evidence of distant metastases. Results of this landmark study published in 2016 and updated in 2019, showed a 5-year OS rate improvement with FLOT regimen (45% vs. 36%, respectively) [7,11]. Besides these randomized trials, Li et al. demonstrated perioperative FOLFOX regimen improved survival [12]. In this prospective non-randomized study, locally advanced GC patients received a total of 6 cycles of FOLFOX chemotherapy perioperatively vs. postoperatively with a 4-year OS rate of 78% vs. 51%, respectively. DCF regimen usually investigated on advanced GC and GEJ tumors. V325 Phase II/III trial demonstrated significantly improved OS, time to progression and quality of life over CF regimen [13]. Two-year survival rate was 18% with DCF and 9% with CF. All these pivotal trials summarized in Table 6.

Our study is different from other studies, as we compared five different NACT regimens frequently used in daily practice. In our study population, 1-, 2- and 3-year estimated survival rates were 88%, 70% and 59%, respectively. According to NACT regimens, estimated 3-year OS rates were 68% with FLOT, 61% with DCF, 57% for FOLFOX, 55% with CF and 52%

Table 4. Survival analysis.

Chemotherapy regimen	Median DFS (months) (95% CI)	3-year DFS rate (%)	Median OS (months) (95% CI)	3-year OS rate (%)
All patients	50.7 (25.4–75.9)	58	58.4 (35.2–85.7)	59
FLOT	NR(NR)	68	NR(NR)	68
FOLFOX/CAPEOX	NR(NR)	60	NR(NR)	57
DCF/DCX	85.7 (32.0–133.5)	64	107.9 (24.1–191.8)	61
CF/CX	NR(NR)	43	NR(NR)	55
ECF/ECX	34.6 (19.8–49.5)	44	36.3 (30.2–42.3)	52

FLOT: 5-Fluorouracil, leucovorin, oxaliplatin, docetaxel; FOLFOX: 5-fluorouracil, leucovorin, oxaliplatin; CAPEOX: capecitabine and oxaliplatin; CF: cisplatin and 5-fluorouracil; DCF: docetaxel, cisplatin and 5-fluorouracil; DCX: docetaxel, cisplatin and capecitabine; ECF: epirubicin, cisplatin and 5-fluorouracil; ECX: epirubicin, cisplatin and capecitabine; OS: overall survival; DFS: disease free survival; NR: non-reached; CI: confidence interval; NR: non reached.

Table 5. Univariate and multivariate analyses of factors that predicting survival.

	Univariate analysis for OS		Univariate analysis for DFS		Multivariate analysis for OS		Multivariate analysis for DFS	
Factor	**HR (95% CI)**	***p* value**	**HR (95% CI)**	***p* value**	**HR (95% CI)**	***p* value**	**HR (95% CI)**	***p* value**
Gender (male vs. female)	1.16 (0.85–1.56)	.33	1.25(0.93–1.68)	.13	–	–	–	–
Age at Diagnosis (≥60 vs. <60)	1.23 (0.57–1.01)	.07	1.03(0.77–1.39)	.80	–	–	–	–
Clinical Stage (lymph nodes positive vs. negative)	1.06 (0.80–1.39)	.67	1.37(1.04–1.82)	**.02**	–	–	1.27(0.95–1.68)	.09
Location (Gastric vs. GEJ)	1.24(0.72–1.25)	.73	1.10(0.83–1.45)	.48	–	–	–	–
Surgical margin (positive vs. negative)	2.08(1.43–2.93)	**<.001**	1.57(1.08–2.29)	**.01**	2.03(1.42–2.91)	**<.001**	1.54(1.06–2.25)	**.02**
Lymph Nodes Dissection Type (D1 vs. D2)	1.13(0.84–1.51)	.39	1.24(0.94–1.63)	.12			–	–
Perineural invasion (yes vs. no)	1.67(1.27–2.20)	**<.001**	1.47(1.12–1.92)	**.005**	1.62(1.20–2.18)	**.001**	1.10(0.79–1.52)	.55
Lymphovascular invasion (yes vs. no)	1.63(1.23–2.16)	**<.001**	1.52(1.14–2.01)	**.003**	1.27(0.90–1.81)	.16	1.28(0.96–1.72)	.80
Receiving Adjuvant Treatment (no vs. yes)	2.27(1.68–3.07)	**<.001**	1.26(0.88–1.80)	.20	2.45(1.73–3.45)	**<.001**	–	–
Pathological Response								
(No response vs. others)	2.16(1.63–2.85)	**<.001**	1.73(1.32–2.27)	**<.001**	0.56(0.42–0.76)	**<.001**	**1.63(1.23–3.15)**	**.001**
(Others vs. Complete response)	2.10(1.03–4.26)	**.02**	1.22(0.71–2.10)	.45	1.26(0.60–2.63)	.53		

HR: hazard ratio; CI: confidence interval; GEJ: gastroesophageal junction.

Table 6. Comparison of pivotal trials using perioperative treatment.

Trial	Chemotherapy regimen	*n*(%)	pCR rate (%)	D2 dissection rate (%)	R0 resection rate (%)	Median DFS (months); HR (%95CI) (*p*)	Median OS (months); HR (%95CI)
MAGIC(5)	ECF + Surgery	250	Not reported	42.5	81.9	Estimated surival rate was given	Estimated surival was given
	Surgery	253		40.4	66.7	HR 0.66 (0.53 to 0.81) $p < .001$	HR 0.75 (0.60 to 0.93) $p = .009$
French FNCLCC/ FFCD [6]	CF + Surgery	113	Not	Not	84	HR 0.65 (0.48 to 0.89)	HR 0.69 (0.50 to 0.95)
	Surgery	111	Reported	reported	74	$p = .003$	$p = .02$
FLOT4/AIO [7]	FLOT	356	16	57	85	30 months	50 months
	ECF/ECX	360	6	53	78	18 months HR 0.75 (0.62 to 0.91) $p = .003$	35 months HR 0·77 (0.63 to 0·94) $p = .012$
Li et al [12]	Perioperative FOLFOX	36	6.1		86	Survival rate was given	Survival rates were given
	Adjuvant FOLFOX	37	–	Not reported	55	$p = .031$	$p = .022$
Basoglu et al	FLOT	519	8.2	64.3	84	NR(NR)	NR(NR)
	Others	275	5.1	55.2	74.5	50.7 months (22.7 to 78.6) HR 0.93 $p = .71$	59.4 months (32.7 to 86.7) HR 1.0 $p = .99$

FLOT: 5-Fluorouracil, leucovorin, oxaliplatin, docetaxel; FOLFOX: 5-fluorouracil, leucovorin, oxaliplatin; CAPEOX: capecitabine and oxaliplatin; CF: cisplatin and 5-fluorouracil; DCF: docetaxel, cisplatin and 5-fluorouracil; DCX: docetaxel, cisplatin and capecitabine; ECF: epirubicin, cisplatin and 5-fluorouracil; ECX: epirubicin, cisplatin and capecitabine; pCR: pathological complete response; HR: hazard ratio; CI: confidence interval.

with ECF. Since the follow-up period was shorter in our study, we presented the estimated 3-year survival rates. Therefore, we do not consider it appropriate to compare these results. We plan to update our study results after a longer follow-up period.

We observed higher survival rates compared to the literature. In our opinion, there could be several reasons for this. First, patients having clinical positive lymph nodes (cN+) who were expected to have poor prognosis were lower in our study population. In addition, our patient cohort had higher D2 dissection rate (66.8%) that effected higher survival rates.

However, since patients with complete retrospective data were included in the study, patients with possibly had poor prognosis and had incomplete data (such as the group of patients who were died possibilly and have been gone out of control, changed centers due to poor prognosis and complications) were excluded due to investigator's bias.

In the literature, it has been shown that completion of planned chemotherapy is as important as selected regimen on efficacy. Dose modifications or interrupt treatment and failure to continue with adjuvant chemotherapy adversely affected on survival outcomes.

Although perioperative FLOT is considered as standard-of-care for locally advanced resectable GC and GEJ adenocarcinomas, its' toxicity profile and intolerance jeopardize completion of the planned 8 cycles. Only 58% of patients completed preoperative FLOT and 46% of patients completed all cycles (pre and post-operative treatment) in the initial phase 2/3 trial (FLOT-AIO) . 50% of patients completed preoperative FLOT and 41% of patients completed all planned cycles in our study, consistent with the literature.

Good performance patients were carefully selected for these trials. It was demonstrated that grade 3 or 4 neutropenia was 52%, and febrile neutropenia was 2% in FLOT-AIU trial. Despite higher primary GCSF prophylaxis in our study (34% in FLOT-AIU trial, 92% in ours), we observed higher grade 3 or 4 neutropenia (62%) and febrile neutropenia (3.4%). It may be due to low socioeconomical level and lack off self-care in our country. In our study, we also observed grade 3 or 4 chemotherapy-related adverse events and interruption of treatment most frequently with FLOT regimen (30.2% and 6.5%).

Conversely, the least grade 3 or 4 chemotherapy-related adverse events and interruption of treatment was observed with ECF (3.1% and 1.5%). Most common grade 3 or 4 adverse event was nausea (6.7%). It was 6.4% in MAGIC study and 16% in FLOT-AIU study. Most common toxicity being nausea consistent with the literature, might have been induced by cisplatin.

Adding docetaxel to CF resulted increasing toxicity as well as adding epirubicin to CF has been described in the literature (especially leukopenia for all) [13]. Hence, CF replaces ECF and DCF in guidelines as neoadjuvant setting. Higher CF toxicity results compared to both ECF and DCF may be due to the small number of patients in that arm in our study.

Enzinger et al. [14] confirmed in the CALGB 80403/E1206 study, that the FOLFOX regimen had similar effectiveness and better tolerance than the ECF regimen. Efficacy of FOLFOX regimen on neoadjuvant setting was also determined in other recent studies [15–18]. Al-Batran et al. [16] and De Vita et al. [18] showed that FOLFOX regimen did not lead more grade 3 or 4 toxicities.

In our study we observed that FOLFOX/CAPEOX regimens are well-tolerated. In this arm, grade 3 or 4 adverse events occurred 15.3% of patients, most common side effect was neutropenia (5.1%) and none of these patients stopped or interrupted the treatment. In FOLFOX group, patients older than 65 years was 50% of the group, and it was higher than other chemotherapy arms. It was striking that FOLFOX was a more tolerable regimen.

The limitations of our study are its' retrospective design and shorter follow-up period. Despite the pathological evaluation was demonstrated one by one ypT and ypN in the landmark trials, we only have combined ypTN data in patients' files. It is difficult for us to compare pathological results in detail. Our survival rates were estimation, and with longer follow-up period, survival results can be altered.

Conclusion

Here, we investigated perioperative chemotherapy preferences in locally advanced GC and GEJ tumors in our country, and aimed to share the real-life experience in efficacy and tolerability of different regimens. We still do not know which NACT regimen is the best choice for daily practice. Clinicians should be aware of potential side-effects of the regimens and tailor it wisely for the patient. We believe that better results will be obtained with determining correct patient-treatment pairs.

Disclosure statement

No potential conflict of interest was reported by the authors.

Ethics approval

All procedures performed were in accordance with ethical standards of institutional and/or national research

committee, and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Ethical committee approval was obtained from our institute with a number of: 09.2020.1108.

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