



Treatment discontinuation associated with perioperative toxicity of FLOT versus XELOX chemotherapy in patients with resectable gastric cancer: prospective randomized trial (PECORINO)

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Background: Gastric cancer represents a significant global health burden, necessitating effective multimodal treatment approaches. Neoadjuvant chemotherapy has gained prominence in improving outcomes, with FLOT (5-fluorouracil, leucovorin, oxaliplatin and docetaxel) and XELOX (capecitabine and oxaliplatin) emerging as potential regimens. This study aims to compare the efficacy and safety of neoadjuvant FLOT and XELOX in resectable gastric cancer.

Methods: We conducted a prospective randomized open-label clinical trial. Sixty-nine patients with resectable gastric cancer were randomly assigned to perioperative 8 cycles of FLOT and 8 cycles of XELOX and curative surgery. The primary endpoint was the proportion of patients who fully adhered to all the allocated treatment per protocol. Secondary endpoints were pathological regression grade, progression-free survival, overall survival, chemotherapy and surgery complications rates.

Results: A total of 69 patients were included in both arms. Thirty-three of 35 (94.3%) patients in the FLOT arm and 23 of 34 (67.6%) in the XELOX arm underwent curative-intent surgery after neoadjuvant treatment. Nineteen (54.3%) and 17 (50%) patients completed the protocol-defined therapy in the FLOT and XELOX arms, respectively ($P=0.81$). The proportion alive without progression at 2 years was 18.8% [95% confidence interval (CI): 8.9–39.8%] in the XELOX group compared to 45.7% (95% CI: 31.9–65.6%) in the FLOT group. The study was prematurely terminated due to the inferiority of the XELOX regimen in preoperative settings because of the high rate of disease progression.

Conclusions: In our study, the rate of protocol completion did not statistically differ between the two groups. Perioperative FLOT chemotherapy exhibits notable efficacy in gastric cancer management, as evidenced by favorable treatment responses and surgical outcomes. The regimen's safety profile aligns with established expectations. This study supports the continued exploration of FLOT as a valuable component in the perioperative care of gastric cancer patients.

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Introduction

Gastric cancer remains one of the leading causes of cancer-related morbidity and mortality. According to the GLOBOCAN Cancer Network in 2020, the incidence of gastric cancer in Ukraine comprised 6.1–8.5 among women and ≥ 16.4 among men per 100,000 people (1). According to the data of the Cancer Registry of Ukraine, there were 7,492 newly diagnosed gastric cancer cases in 2018 (2). The trend towards increasing morbidity has been observed over the last 10 years. This is a very significant socio-economic problem that needs to be addressed, as long-term treatment outcomes remain suboptimal (3).

The MAGIC study became the evident basis for providing perioperative chemotherapy to patients with resectable locally advanced gastric cancer. This approach improves the 5-year survival rate up to 55% (4). In Ukraine, various perioperative chemotherapy regimens have been systematically employed in combination with surgery to treat locally advanced resectable gastric cancer since 2015. Chemotherapy regimens are selected according to the local protocols of each particular clinic and the patient's condition. At present, there are no nationally accepted

guidelines for treating patients with resectable gastric cancer.

According to the literature, a few studies have compared different types of perioperative chemotherapy and surgery alone (5,6). The results of two of them suggest a benefit for neoadjuvant chemotherapy in the overall survival rate. Kobayashi *et al.* [2000] compared perioperative chemotherapy with fluoropyrimidines and surgery alone (7). In those settings, perioperative chemotherapy did not show any benefits.

The 2019 NEO-CLASSIC study from China provides more information on perioperative chemotherapy for gastric cancer. According to the study design, 8 perioperative cycles of XELOX (capecitabine and oxaliplatin) chemotherapy were prescribed. In the study, complete histopathological response was 6% (8).

Clinical implementation of docetaxel, cisplatin, and fluorouracil (DCF) has an advantage in survival outcomes, although high toxicity rates have been observed (9). DCF was mainly used in metastatic gastric cancer improving progression-free survival as well as CF (cisplatin and 5-fluorouracil) regimen (10). According to another study, patients treated with FOLFOX (5-fluorouracil, leucovorin and oxaliplatin) had more metastatic lymph nodes (67.8%) compared to patients treated with EOX (epirubicin, oxaliplatin and capecitabine) (57.7%) following surgery (11). In the FOLFOX and EOX groups, 4 (4.6%) and 3 (11.5%) cases of complete tumor regression were reached, respectively. More patients in the EOX group showed 3 and 4 grades of regression according to Mandard tumor regression criteria (38.5%), in contrast to patients treated with FOLFOX (19.5%).

Recommendations of the National Comprehensive Cancer Network (NCCN) had a significant impact on the choice of the XELOX regimen in the Ukrainian medical oncology community (12). A more thorough analysis of the NCCN recommendations as the basis for the application of this regimen as a perioperative one was a study conducted in South Korea, in which XELOX in comparison with the SOX (S-1 and oxaliplatin) scheme exhibited the same

Highlight box

Key findings

- FLOT (5-fluorouracil, leucovorin, oxaliplatin and docetaxel) regimen is superior to XELOX (capecitabine and oxaliplatin) regimen in terms of clinical response.

What is known and what is new?

- Perioperative chemotherapy allows the achievement of preoperative tumor response and improvement in progression-free survival and overall survival.
- XELOX regimen leads to a higher rate of disease progression in neoadjuvant settings.

What is the implication, and what should change now?

- FLOT regimen remains the optimal modality for perioperative treatment. The XELOX regimen is available in carefully selected patients.

toxicity profile and the same time to disease progression (PD) as SOX (13) (at the time we started conducting our study). According to a randomized CLASSIC study in which XELOX was used in adjuvant settings after radical surgery, 3-year recurrence-free survival was 74% (14).

Phase II FLOT4-AIO study compared FLOT chemotherapy (5-fluorouracil, leucovorin, oxaliplatin and docetaxel; 4 preoperative cycles and 4 postoperative cycles) and a combination of epirubicin, cisplatin, and fluorouracil (15). The FLOT regimen was associated with a greater number of complete pathohistological responses (16% and 8%, respectively). The level of toxicity for FLOT was within acceptable values. The most common reported complications were neutropenia [52 (38%) of 137 patients in the ECF (epirubicin, cisplatin and 5-fluorouracil)/ECX (epirubicin, cisplatin and capecitabine) group *vs.* 67 (52%) of 128 patients in the FLOT group], leukopenia [28 (20%) *vs.* 36 (28%)], nausea [23 (17%) *vs.* 12 (9%)], infection [16 (12%) *vs.* 15 (12%)], nausea and vomiting [13 (10%) *vs.* 4 (3%)].

However, the treatment strategy for gastric cancer continued to vary depending on the region, clinic and patients' capabilities, including the fact that not all medications required for treatment are provided by the state financial support.

This study was primarily motivated by the lack of prior clinical trials and good quality data to determine the optimal perioperative treatment of gastric cancer in a Ukrainian population, and the absence of a direct comparison between the FLOT and XELOX regimens. In particular, we were concerned that the FLOT regimen might lead to dose reduction and paradoxical deterioration of treatment quality and prognosis, as well as incur greater toxicity. We present this article in accordance with the CONSORT reporting checklist (available at <https://jgo.amegroups.com/article/view/10.21037/jgo-2024-921/rc>).

Methods

Study design

This study is a prospective investigator-initiated open-labeled randomized phase II clinical trial. The primary endpoint is the proportion of patients who complete all the treatment per protocol. Completed treatment protocol is considered as 4 cycles of neoadjuvant chemotherapy followed by curative surgery and 4 cycles of adjuvant chemotherapy. Secondary endpoints were histopathological regression rate, overall survival and progression-free

survival rates, chemotherapy and surgical complications.

Ethical consideration

The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. The study was approved by the institutional ethics committee of the National Cancer Institute (No. 165). Informed consent was obtained from all individual participants.

Staging laparoscopy

Staging laparoscopy is an obligatory diagnostic procedure before randomization. It is performed to evaluate tumor extension and peritoneal carcinomatosis. During the procedure, the surgeon takes a biopsy of the parietal peritoneum and great omentum to exclude distant metastases. Furthermore, surgeons obtained peritoneal washings to exclude cyt+ status.

Inclusion criteria

- ❖ cT1b, cT2, cT3, cT4a, cT4b (except invasion of the common hepatic artery, proper hepatic artery, abdominal trunk, proximal part of the splenic artery);
- ❖ Tumor extension: esophagus, diaphragm, liver, pancreas, spleen, anterior abdominal wall, small and large intestine, distal splenic artery, spleen;
- ❖ cN0, cN1, cN2, cN3;
- ❖ M0;
- ❖ Age: 18–80 years;
- ❖ Gender: men and women;
- ❖ Eastern Cooperative Oncology Group (ECOG) status: 0–1;
- ❖ Histological type of tumor: papillary adenocarcinoma; tubular adenocarcinoma, highly differentiated or moderately differentiated; low-grade adenocarcinoma; mucinous adenocarcinoma; squamous cell adenocarcinoma; glandular squamous cell carcinoma.
- ❖ Degree of differentiation: G1–G4;
- ❖ Tumor localization: gastro-esophageal junction (Siewert II, III), cardiac stomach, gastric body, antral stomach, pyloric stomach;
- ❖ No history of cancer during the previous 5 years;
- ❖ Absence of prior chemotherapy, surgery or radiation therapy for cancer;
- ❖ Absence of severe comorbidity.

Exclusion criteria

- ❖ M1 (distant metastases);
- ❖ ECOG 2–4;
- ❖ Age >80 years or under 18 years;
- ❖ The presence of severe comorbidity;
- ❖ The patient's refusal to participate in the study.

Algorithm for patient registration and inclusion in the study

Patients with newly diagnosed gastric cancer who were admitted to or referred for a consultation to the National Cancer Institute and met all the inclusion criteria were assessed as potentially eligible for inclusion in the study.

Patients were enrolled by investigating physicians. Physicians explained all the necessary information about the clinical trial to patients and familiarized patients with informed consent. Patient's consent was confirmed with the signature. After informed consent was signed, each patient underwent staging laparoscopy. Patients who met all inclusion criteria and had no exclusion criteria after staging laparoscopy were further randomized for XELOX or FLOT chemotherapy.

After signing the informed consent, each patient was assigned a unique number, which was entered into a paper case-report form (CRF) and duplicated in electronic database. The paper form and electronic database completely duplicate each other. The electronic form and paper form were completed by the researcher as soon as the patient signed an informed consent to participate in the study. The electronic form is based on a Research Electronic Data Capture (REDCap) database.

Randomization

The randomization process was performed by the randomization module of REDCap software. We used stratified randomization in the study. Initially, the patient's data were input into the REDCap and patients were randomized into one of the two (FLOT arm and XELOX arm) groups. Patients further received preoperative chemotherapy followed by surgery and postoperative chemotherapy.

Perioperative chemotherapy

This trial included FLOT and XELOX chemotherapy

regimens. FLOT regimen included docetaxel 50 mg/m² on day 1, oxaliplatin 85 mg/m² on day 1, leucovorin 200 mg/m² on day 1 and continuous infusion of fluorouracil 2600 mg/m² on days 1 and 2; cycle each 14 days. XELOX regimen included oxaliplatin 130 mg/m² on day 1 and capecitabine 1,000 mg/m² two times per day on days 1–14; cycle each 21 days. Patients were allocated in a 1:1 ratio to receive 4 preoperative cycles and 4 postoperative cycles within each regimen.

Statistical analysis

A sample size of 328 patients (164/arm) provided 80% power using a two-sided Chi-squared test with a 5% type I error to detect a 16% increase (46% in FLOT-4 *vs.* 62% in the XELOX arm) in the proportion of patients who complete the full treatment plans between arms.

Standard descriptive statistics, including means, standard deviations, medians and interquartile ranges (IQRs) for continuous variables, and frequencies and proportions for categorical variables, were calculated separately by arm. All consented, eligible, randomized participants (intention to treat population) were included in the primary efficacy analysis on the proportion of patients who completed the protocol-defined treatment of 4 pre- and 4 post-operative cycles of FLOT or XELOX. Kruskal-Wallis tests and generalized Fisher's exact tests were used to compare differences between study arms for continuous and categorical variables, respectively. Exact two-sided 95% confidence intervals (CIs) were calculated for proportions. Overall survival was defined as the time from randomization to death or the last contact date. Individuals who were alive at last contact were censored. Progression-free survival was defined as the time from randomization to the first occurrence of a progression (peritoneal carcinomatosis, distant metastases, or local progression), recurrence, or death. Individuals who were alive and recurrence and progression free were censored at the time of last contact. Kaplan-Meier curves with log-rank tests were used to compare OS and PFS between arms. Two-year OS and PFS percentages were calculated with 95% CIs. Adverse events and toxicities are presented in a tabular form. All tests were two-sided with a 5% type I error. Analyses were conducted using R Statistical Software (v4.0; R Core Team 2024).

Quality control

Intraoperative photography was mandated. The following

steps of operation were fixed: a stomach with a tumor before the beginning of mobilization of the stomach; operating field after stomach removal and lymph nodes retrieved; stomach specimen in longitudinal section; removed lymph nodes.

Surgery

The type of surgery, date of surgery, time of starting and ending of surgery, surgical approach and blood loss were registered. Intraoperative findings, main steps and type of surgery are registered in operative notes and electronic case-report form (eCRF). In case of multivisceral resections, the extent and details of other organ resections were documented.

Pathomorphological protocol and morphological assessment

Histological examination was performed according to the adapted pathohistological protocol of the College of American Pathologists: Gastric Cancer v4.0.0.0 2017. Marking of groups of lymph nodes was not mandatory in this trial. Pathohistological regression rate was assessed according to Becker criteria.

Postoperative care

Postoperative treatment was given according to local guidelines (as adapted international guidelines) and to routine clinical practice. Key postoperative parameters were documented in the patient's eCRF: admission and discharge dates (if the discharge was postponed for any reasons, including war; date when patients were medically fit for discharge; date of abdominal drainage withdrawal, start of fluids and soft diet consumption; patients' early rehabilitation; blood transfusions. Surgical complications are registered according to Clavien-Dindo classification (16); complications of systemic chemotherapy are registered according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0 (17).

War and clinical trial

Physician and patients included in the trial faced major issues with the beginning of Russian invasion. First, patients' enrolment was temporarily unavailable from 24th February, 2022 up to the middle of May 2022 because of the impaired ability for patients to move across eastern and northern parts of Ukraine and the high risks of casualties.

The second issue is that many patients, who would potentially be included in the trial, moved to the western part of Ukraine or received treatment abroad. However, all included patients followed the study protocol after randomization. Remarkably, all patients were available for follow-up after completion of treatment.

Results

Sixty-nine patients were prospectively included in the study from July 2021 to February 2023. Thirty-five patients were randomized into the FLOT group and 34 patients were randomized into the XELOX group. Demographic characteristics were generally balanced between arms (see *Table 1*). Detailed patients' pathway is displayed in *Figure 1*.

Seventeen (50.0%, 95% CI: 32.4–67.6%) patients in the XELOX arm and 19 (54.3%, 95% CI: 36.6–71.2%) in the FLOT arm completed all cycles of protocol allocated treatment (*Figure 2*). The difference was not statistically significant between groups ($P=0.81$).

Eighty-eight-point-six percent ($n=31$) patients in the FLOT group and 91.2% ($n=31$) patients in the XELOX group completed 4 preoperative cycles of chemotherapy (*Table 2*). Patients who did not tolerate chemotherapy per protocol received fewer numbers of cycles due to severe adverse events. The most frequent severe adverse events were neutropenia (11.8% in the XELOX arm *vs.* 40.0% in the FLOT arm), leucopenia (8.8% in the XELOX arm *vs.* 31.4% in the FLOT arm) and thrombocytopenia (14.7% in the XELOX arm and 11.4% in the FLOT arm) (see *Table 3*).

The clinical response, evaluated upon completion of neoadjuvant chemotherapy, differed between groups. In the FLOT group, 8.6% ($n=3$) patients showed complete response (CR), 54.3% ($n=19$) achieved partial response (PR), 28.6% ($n=10$) had stable disease and 8.6% ($n=3$) patients experienced disease progression (PD). At the same time, 1 (2.9%) patient achieved CR in the XELOX group, 26.5% ($n=9$) patients showed PR, 38.2% ($n=13$) patients showed stable disease and 32.4% ($n=11$) patients developed PD. The main sites of PD were peritoneal carcinomatosis (4 patients) and distant metastases (5 patients) (*Table 4*).

The elevated rate of PD in the XELOX group necessitated premature study termination based on Ukraine's National Cancer Institute Ethics Committee consensus on the 1st of February 2023.

Ninety-four-point-three percent ($n=33$) of patients in the FLOT group and 67.6% ($n=23$) in the XELOX group underwent curative surgery. Median time from last cycles

Table 1 Patients' characteristics

Characteristics	FLOT	XELOX
Age, years (range)	58 [36–64]	60 [39–73]
Gender		
Men	19 (54.3)	18 (52.9)
Women	16 (45.7)	16 (47.1)
ECOG PS		
0	26 (74.3)	27 (79.4)
1	9 (25.7)	7 (20.6)
Stage of disease		
II	12 (34.3)	13 (38.2)
III	23 (65.7)	21 (61.8)
Localization of tumor		
Stomach	31 (88.6)	29 (85.3)
Gastro-esophageal junction (Siewert II/III)	4 (11.4)	5 (14.7)
T criteria		
T1b	0	0
T2	6 (17.1)	5 (14.7)
T3	21 (60.0)	19 (55.9)
T4a	8 (22.9)	10 (29.4)
N criteria		
N0	8 (22.9)	8 (23.5)
N1	16 (45.7)	19 (55.9)
N2	9 (25.7)	6 (17.6)
N3	2 (5.7)	1 (2.9)

Data are presented as median [interquartile range] or n (%). ECOG PS, Eastern Cooperative Oncology Group performance status; FLOT, 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel; XELOX, capecitabine and oxaliplatin.

of chemotherapy to surgery was 24.4 days in the XELOX group and 25.8 days in the FLOT group (*Table 5*). Most of the patients underwent total gastrectomy with D2 lymphadenectomy. Two patients in the FLOT group and 2 patients in the XELOX group underwent Ivor-Lewis procedure. R0 resection margin was established in 93.9% (n=31) patients in the FLOT group and 87.0% (n=20) in the XELOX group. ypN0 status was achieved in 43.5% in XELOX arm and 54.5% patients in FLOT arm (*Table 6*). Fifty-two-point-two percent patients in the XELOX

group and 42.4% patients in the FLOT group experienced postoperative complications. Detailed surgical morbidity is displayed in *Table 7*.

Only 17 (77.3%) patients in the XELOX group and 19 (57.6%) patients in FLOT received 4 cycles of adjuvant chemotherapy. Severe adverse events and low tolerability after neoadjuvant chemotherapy and surgery forced patients to stop systemic treatment with lesser cycles of chemotherapy. Notably, all patients received at least 2 cycles of chemotherapy (*Table 8*).

PFS and OS were evaluated for a 30-month period after randomization (up to December 2023) and is displayed in *Figures 3,4*. PFS was significantly longer in the FLOT arm than the XELOX arm (P=0.02). The 24-month PFS was 45.7% (95% CI: 31.9–65.6%) and 18.8% (95% CI: 8.9–39.8%) in the FLOT and XELOX arms, respectively.

Discussion

The PECORINO trial, a prospective investigator-initiated randomized clinical trial, sought to evaluate the rate of treatment completion of perioperative FLOT versus the XELOX regimens in patients with resectable gastric cancer. A cohort of 69 patients was enrolled, with 35 patients assigned to the FLOT group and 34 patients assigned to the XELOX group. Statistical analysis revealed that 17 (50.0%, 95% CI: 32.4–67.6%) patients in the XELOX arm and 19 (54.3%, 95% CI: 36.6–71.2%) in the FLOT arm completed all cycles of protocol allocated treatment. The difference was not statistically significant between groups (P=0.81). Therefore, our findings demonstrate the superior efficacy of the FLOT regimen as evidenced by higher rates of PRs, lower PD, and more favorable surgical outcomes compared to XELOX.

In contrast to results of our study in MAGIC trial 91% of the patients completed all cycles of ECF/ECX neoadjuvant chemotherapy and only 37% of the patients received 3 cycles of adjuvant chemotherapy (4). The proportion of patients who received two cycles of preoperative ECF chemotherapy in TOPGEAR study was 98% in chemoradiation group versus 93% in chemotherapy alone group (18). At the same time, the proportion of patients who received at least 80% of the planned treatment volume was 98% versus 92% in the chemoradiation and chemotherapy alone groups, respectively. Among patients who underwent surgery, 53% of patients in the chemoradiation group and 65% of patients in the chemotherapy group completed postoperative ECF protocol. Study ST03 also demonstrated

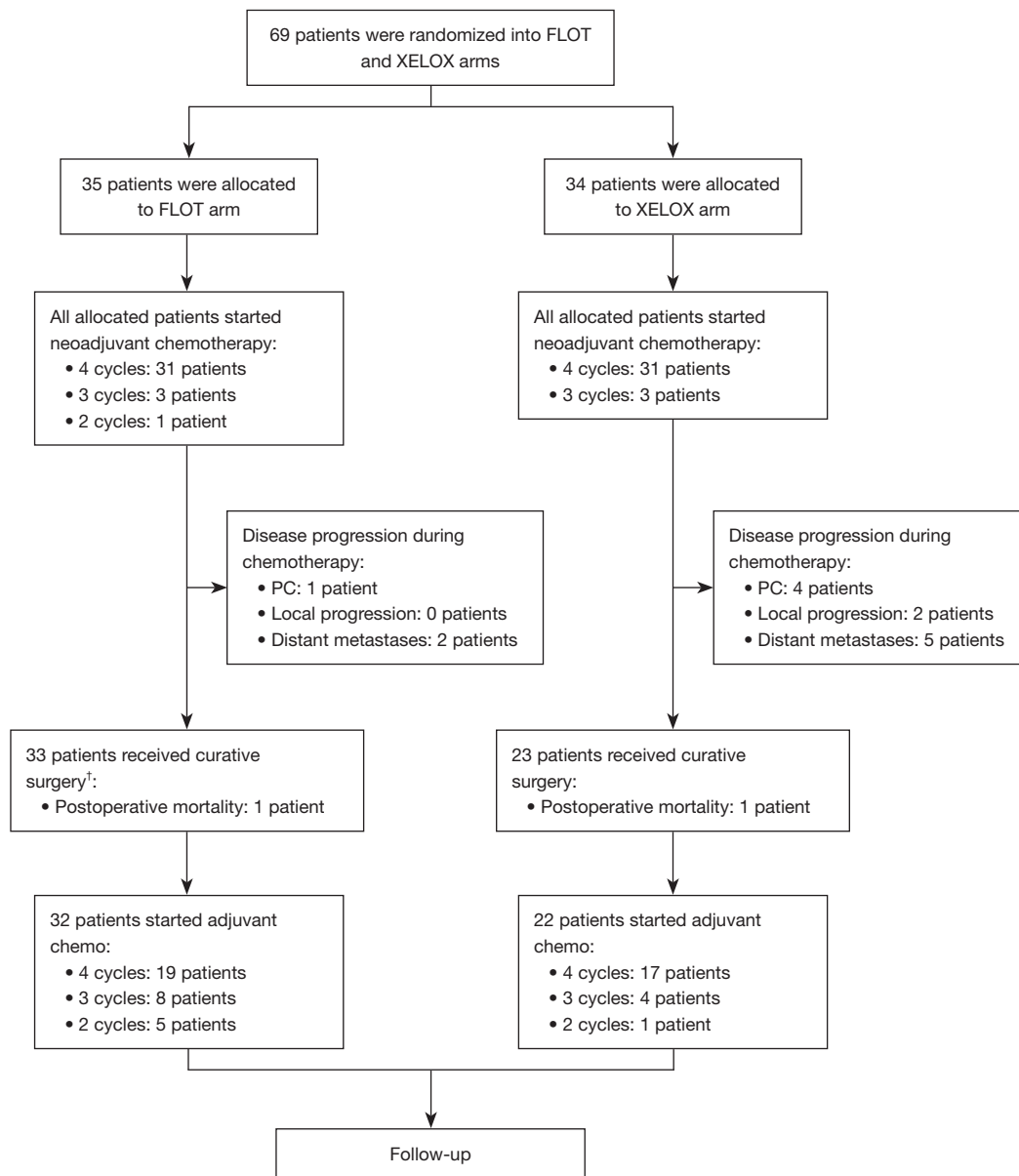


Figure 1 Flowchart of patients within the clinical trial. †, one patient received surgery even with disease progression. FLOT, 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel; PC, peritoneal carcinomatosis; XELOX, capecitabine and oxaliplatin.

that 472 (89%) of the 529 patients who were randomized to the chemotherapy-only group received all three preoperative cycles (19). Four hundred and fifty-seven (86%) of the 533 in the chemotherapy group alone received surgical treatment. Only 215 patients in the chemotherapy group received all three postoperative cycles. This data shows that protocol compliance remains one of the biggest issues in perioperative chemotherapy. Under such circumstances lesser number of adjuvant chemotherapy

cycles should be further investigated by terms of impact on PFS and OS.

The disparity in efficacy between the FLOT and XELOX regimens may be ascribed to the multi-targeted approach of FLOT, which includes docetaxel, a taxane known for its potent antitumor activity through microtubule stabilization and apoptosis induction (20). This contrasts with the XELOX regimen, where oxaliplatin acts as an alkylating agent targeting DNA, capecitabine,

a prodrug of 5-fluorouracil, primarily targets thymidylate synthase, potentially limiting its efficacy to the S-phase of the cell cycle (21). The broad-spectrum activity of FLOT could explain its superior performance, particularly in heterogenous tumors such as gastric cancer.

Comparative analysis with the prominent FLOT4-AIO trial reveals that approximately 70% of patients in both groups (FLOT and ECF/ECX) exhibited ECOG 0 status. In the aforementioned study, 91% of patients in the ECF/ECX group and 90% in the FLOT group adhered to all cycles of allocated preoperative chemotherapy (15). The incidence of serious adverse events related to treatment was comparable (27%) between the two groups. Our study corroborates these findings, demonstrating high completion rates of preoperative chemotherapy cycles in both groups, with 88.6% (31/35) in the FLOT group and 91.2% (31/34) in the XELOX group completing all four prescribed cycles. The majority of patients in both cohorts presented with ECOG 0 status [26 (74.3%) in the FLOT arm and 27 (79.4%) in the XELOX arm, respectively]. Severe treatment-related adverse events were observed in 10 (29%)

patients in the FLOT group and 8 (24%) in the XELOX group. However, the rate of PD was significantly higher in the XELOX group, resulting in a higher proportion of patients (94.3%) proceeding to curative-intent surgery in the FLOT group compared to the XELOX group (67.6%). This discrepancy underscores the differential effectiveness of the chemotherapy regimens, the impact of treatment-related toxicity, and patient tolerance on the feasibility of completing neoadjuvant therapy.

The clinical response to neoadjuvant chemotherapy markedly differentiated the two regimens. In the FLOT group, 9.1% of patients achieved a CR and 60% of patients showed PR. In contrast, no patients in the XELOX group achieved CR and a higher proportion experienced PD (32.3%). This significant difference in clinical response rates, especially the absence of CRs in the XELOX group, underscores the superior efficacy of the FLOT regimen in inducing tumor shrinkage and potentially facilitating more successful surgical resections.

The decision to prematurely terminate the study due to the elevated rate of PD in the XELOX group, as advised by the National Cancer Institute Ethics Committee, further attests to the comparative inferiority of the XELOX regimen in this setting. These findings align with the extant literature, which has increasingly favored FLOT due to its enhanced efficacy in various gastric cancer contexts. For instance, the FLOT4-AIO trial demonstrated the superiority of FLOT over epirubicin-containing regimens in terms of survival outcomes, establishing a new benchmark for neoadjuvant chemotherapy in gastric cancer (15).

Comparatively, the REAL-2 trial explored the efficacy of epirubicin-based regimens including a capecitabine and oxaliplatin combination similar to XELOX in esophagogastric cancer (22). While REAL-2 demonstrated non-inferiority of capecitabine to 5-fluorouracil, it did not include the potent combination of docetaxel and oxaliplatin found in FLOT, which may account for the differing outcomes observed in our study.

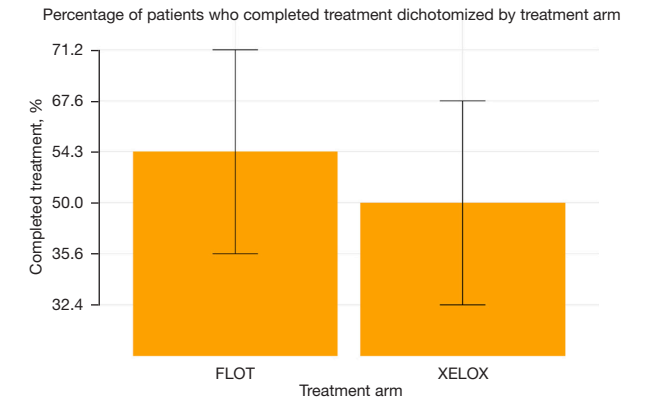


Figure 2 Percentage of patients who completed treatment dichotomized by treatment arm. FLOT, 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel; XELOX, capecitabine and oxaliplatin.

Table 2 Neoadjuvant chemotherapy completion				
Number of completed cycles	XELOX arm	FLOT arm	Total (N=69)	P value
4 cycles	31 (91.2) [76.3–98.1]	31 (88.6) [73.3–96.8]	62 (89.9) [80.2–95.8]	>0.99
Only 3 cycles	3 (8.8) [1.9–23.7]	3 (8.6) [1.8–23.1]	6 (8.7) [3.3–18]	
Only 2 cycles	0 [0–10.3]	1 (2.9) [0.1–14.9]	1 (1.4) [0–7.8]	

Data are presented as n (%) [95% CI]. CI, confidence interval; FLOT, 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel; XELOX, capecitabine and oxaliplatin.

Table 3 Toxicity rate

Adverse event	XELOX		FLOT	
	Grade 1 or 2	Grade 3 or 4	Grade 1 or 2	Grade 3 or 4
Thromboembolism	0	0	0	0
Renal toxicity	3 (8.8)	1 (2.9)	4 (11.4)	1 (2.9)
Infectious	1 (2.9)	1 (2.9)	5 (14.3)	2 (5.7)
Pain	8 (23.5)	2 (5.9)	11 (31.4)	1 (2.9)
Peripheral neuropathy	10 (29.4)	0	25 (71.4)	5 (14.3)
Fever	2 (5.9)	0	5 (14.3)	0
Plasma ALT elevation	11 (32.4)	0	5 (14.3)	0
Plasma AST elevation	9 (26.5)	0	7 (20.0)	0
Thrombocytopenia	20 (58.8)	5 (14.7)	9 (25.7)	4 (11.4)
Anemia	21 (61.8)	2 (5.9)	17 (48.6)	1 (2.9)
Neutropenia	17 (50.0)	4 (11.8)	16 (45.7)	14 (40.0)
Leukopenia	11 (32.4)	3 (8.8)	25 (71.4)	11 (31.4)
Mucositis	2 (5.9)	1 (2.9)	7 (20.0)	3 (8.6)
Constipation	1 (2.9)	0	2 (5.7)	0
Nausea	17 (50.0)	1 (2.9)	28 (80.0)	3 (8.6)
Vomiting	9 (26.5)	2 (5.9)	10 (28.6)	2 (5.7)
Diarrhea	3 (8.8)	1 (2.9)	10 (28.6)	6 (17.1)

Data are presented as n (%). ALT, alanine aminotransferase; AST, aspartate aminotransferase; FLOT, 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel; XELOX, capecitabine and oxaliplatin.

Table 4 Disease progression

Disease progression variables	XELOX arm	FLOT arm	Total (N=69)	P value
Peritoneal carcinomatosis	4 (11.8) [3.3–27.5]	1 (2.9) [0.1–15.3]	5 (7.2) [2.4–16.3]	0.36
Local progression	2 (5.9) [0.7–19.7]	0 [0–10.3]	2 (2.9) [0.4–10.2]	0.49
Distant metastases of other sites	5 (14.7) [5–31.1]	2 (5.7) [0.7–19.7]	7 (10.1) [4.2–20.1]	0.43

Data are presented as n (%) [95% CI]. CI, confidence interval; FLOT, 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel; XELOX, capecitabine and oxaliplatin.

FLOT-4-AIO clinical trial demonstrated that 90% of patients in the FLOT group completed all cycles of neoadjuvant chemotherapy, 94% of patients underwent surgery and only 46% percent of patients completed all cycles of adjuvant chemotherapy per protocol (15). Our study demonstrated 88.6% of patients in FLOT arm completed all amount of neoadjuvant chemotherapy, 94.3% of patients underwent curative surgery and 57.6% patients completed all allocated adjuvant treatment. Such results address equivocal

safety profile and tolerability of FLOT scheme.

The influence of NCCN recommendations on regimen selection, particularly XELOX, was underscored by a study conducted in South Korea, which found comparable toxicity profiles and PD times between XELOX and SOX (13). Additionally, the CLASSIC study, which utilized XELOX in adjuvant settings, reported a 3-year recurrence-free survival rate of 74%, indicating the potential of XELOX in postoperative management.

Table 5 Surgical outcomes

Surgical variables	XELOX arm	FLOT arm
Time from last chemotherapy to surgery (days)	24.4	25.8
Time from surgery to adjuvant chemotherapy (days)	33.9	30.2
Postoperative length of stay (days)	9.4	10.4
Surgical morbidity		
Clavien-Dindo 0	11 (47.8)	19 (57.6)
Clavien-Dindo I-II	8 (34.8)	10 (30.3)
Clavien-Dindo III-IV	3 (13.0)	3 (9.1)
Clavien-Dindo V	1 (4.3)	1 (3.0)

Data are presented as median or n (%). FLOT, 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel; XELOX, capecitabine and oxaliplatin.

The NEO-CLASSIC study from China, which employed a perioperative XELOX regimen, reported a complete histopathological response rate of 6% (8). This finding provides a direct point of comparison with the PECORINO trial, where the FLOT regimen demonstrated higher efficacy in terms of treatment completion, lower PD, and favorable surgical outcomes compared to XELOX. Variability in response rates between FOLFOX and EOX, as well as the distinct outcomes observed with XELOX in the CLASSIC study, highlight the heterogeneity of gastric cancer and the necessity for personalized treatment approaches (14). The PECORINO trial's findings further emphasize the need for rigorous comparative studies to refine perioperative chemotherapy strategies, ensuring they are both effective and tolerable.

The toxicity profile, an essential consideration in treatment selection, revealed that both regimens were

Table 6 Pathological findings

Pathological outcomes	XELOX arm	FLOT arm	Total	P value
pCR	0	3 (9.1)		
ypT stage				–
ypT0	1 (4.3)	4 (12.1)	–	
ypT1	2 (8.7)	8 (24.2)	–	
ypT2	5 (21.7)	11 (33.3)	–	
ypT3	10 (43.5)	6 (18.2)	–	
ypT4	5 (21.7)	4 (12.1)	–	
ypN stage				–
ypN0	10 (43.5)	18 (54.5)	–	
ypN1	8 (34.8)	10 (30.3)	–	
ypN2	3 (13.0)	4 (12.1)	–	
ypN3	2 (8.7)	1 (3.0)	–	
Pathohistological regression				0.35
1a	1 (4.3) [0.1–22]	3 (9.1) [1.9–24.3]	4 (7.1) [2–17.3]	
1b	4 (17.4) [5–38.8]	6 (18.2) [7–35.5]	10 (17.9) [8.9–30.4]	
2	5 (21.7) [7.5–43.7]	13 (39.4) [22.9–57.9]	18 (32.1) [20.3–46]	
3	13 (56.5) [34.5–76.8]	11 (33.3) [18–51.8]	24 (42.9) [29.7–56.8]	

Data are presented as n (%) or n (%) [95% CI]. CI, confidence interval; FLOT, 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel; pCR, pathological complete response; XELOX, capecitabine and oxaliplatin; ypN, pathological lymph node staging after neoadjuvant therapy; ypT, pathological tumor staging after neoadjuvant therapy.

Table 7 Surgical complications

Complication	XELOX arm	FLOT arm
Anastomotic leak	1 (4.3)	2 (6.1)
Abscess/pseudocyst	0	1 (3.0)
Bowel obstruction	1 (4.3)	0
Duodenal stump leak	1 (4.3)	1 (3.0)
Postoperative hematoma	1 (4.3)	2 (6.1)
Ischemic bowel	0	1 (3.0)
Wound infection	3 (13.0)	4 (12.1)
Splenic infarct	5 (21.7)	7 (21.2)
PE/DVT	1 (4.3)	1 (3.0)
Pleural effusion	2 (8.7)	4 (12.1)
Anemia	4 (17.4)	5 (15.2)
Pneumonia	1 (4.3)	3 (9.1)
Urinary tract infection	1 (4.3)	0

Data are presented as n (%). DVT, deep venous thrombosis; FLOT, 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel; PE, pulmonary embolism; XELOX, capecitabine and oxaliplatin.

Table 8 Adjuvant chemotherapy completion

Number of completed cycles	XELOX arm	FLOT arm	Total (N=55)	P value
4 cycles	17 (77.3) [54.2–91.7]	19 (57.6) [39.2–74.5]	36 (65.5) [51.4–77.6]	0.49
Only 3 cycles	4 (18.2) [6.2–40.4]	8 (24.2) [11.1–42.3]	12 (21.8) [11.8–34.7]	
Only 2 cycles	1 (4.5) [0.1–22.9]	5 (15.2) [5.1–31.9]	6 (10.9) [4.2–22.3]	
0 cycles	0 (0) [0–14.5]	1 (3.0) [0.1–15.8]	1 (1.8) [0–9.6]	

Data are presented as n (%) [95% CI]. CI, confidence interval; FLOT, 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel; XELOX, capecitabine and oxaliplatin.

not associated with significant toxicities that may lead to expanded dose adjustments or early treatment cessation. Notwithstanding the efficacy of FLOT, the regimen’s toxicity profile warrants careful consideration. Our study’s observation of higher rates of hematologic toxicities, particularly neutropenia, echoes findings from other trials. This necessitates a robust supportive care framework to manage potential complications, emphasizing the need for a balanced approach to treatment selection that considers both efficacy and tolerability.

Our study’s limitations include its single-center design and the relatively small sample size, which may limit the generalizability of the findings. Moreover, the premature termination of the trial underscores the need for larger, multicenter studies to confirm these results and further refine neoadjuvant treatment strategies for gastric cancer.

Results of our study highlights the ongoing need for research aimed at reducing toxicity and enhancing treatment tolerability. Future research should continue to explore the molecular underpinnings of response to perioperative regimens, with an eye towards personalized treatment

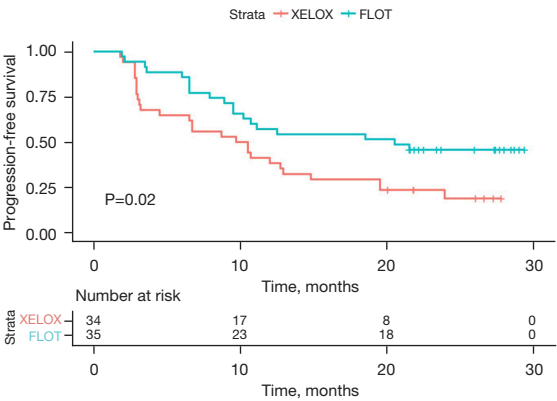


Figure 3 Kaplan-Meier plot of progression-free survival for both arms. FLOT, 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel; XELOX, capecitabine and oxaliplatin.

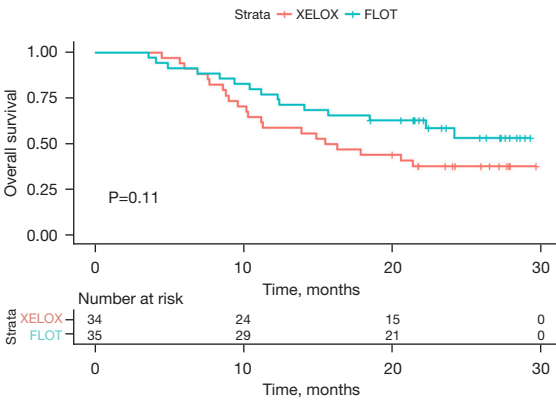


Figure 4 Kaplan-Meier plot of overall survival for both arms. FLOT, 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel; XELOX, capecitabine and oxaliplatin.

approaches that maximize efficacy while minimizing adverse effects. Thus, investigation of perioperative cytotoxic duplets and triplets may be safely conducted especially in combination with targeted and immunotherapy agents.

Conclusions

The results of PECORINO trial indicate the need for neoadjuvant treatment of resectable gastric cancer with significant implications for clinical practice. The data advocate for the adoption of FLOT as a neoadjuvant option that can be used safely in general population without compromising long term results and limits potential patients' drop out because of toxicity profile.

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Footnote

Reporting Checklist: The authors have completed the CONSORT reporting checklist. Available at <https://jgo.amegroups.com/article/view/10.21037/jgo-2024-921/rc>

Trial Protocol: Available at <https://jgo.amegroups.com/article/view/10.21037/jgo-2024-921/tp>

Data Sharing Statement: Available at <https://jgo.amegroups.com/article/view/10.21037/jgo-2024-921/dss>

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. The study was approved by the institutional ethics committee of the National Cancer Institute (No. 165). Informed consent was obtained from all individual participants.

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