

Gastrointestinal Cancer

An Analysis of Tolerance and Early Survival Outcomes with Perioperative Modified FLOT in Gastric Cancers

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Abstract



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Purpose Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel (FLOT) is a current standard of care for locoregionally advanced gastric adenocarcinomas. There is limited real world data with regard to the tolerance and efficacy of this regimen.

Materials and Methods This is a retrospective analysis of gastric cancer patients who were offered neoadjuvant perioperative modified FLOT regimen between December 2016 and October 2018, at the Tata Memorial Hospital, Mumbai. Chemotherapy-related side-effects are reported along with overall survival (OS), as calculated by Kaplan-Meier method.

Results Three hundred and forty-three consecutive patients were started on neoadjuvant chemotherapy (NACT) with mFLOT of which 298 patients (87%) completed the planned treatment. A total of 294 patients (86%) underwent curative resection of gastric cancer. Common grade 3 and grade 4 toxicities during NACT were diarrhea in 42 patients (12%) and febrile neutropenia in 27 patients (8%). Toxic death was seen in nine (2.6%) patients. A total of 264 patients (77%) completed planned adjuvant chemotherapy. Common grade 3 and grade 4 toxicities during adjuvant therapy were diarrhea in 42 patients (12%) and febrile neutropenia in 16 patients (6%). With a median follow-up of 19 months, the estimated 2-year median OS was 69.4%.

Conclusion Administration of modified FLOT regimen in locoregionally advanced gastric cancers is feasible in clinical practice with high completion rates, though requiring dose modifications due to the incidence of clinically relevant grade 3 to 5 toxicities. Early outcomes with the regimen are on par with survivals from the FLOT-AIO study.

Keywords

- ▶ FLOT
- ▶ gastric cancer
- ▶ tolerance
- ▶ toxicity
- ▶ neoadjuvant
- ▶ adjuvant

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Introduction

Perioperative chemotherapy/chemoradiotherapy has become the standard of care for loco-regionally advanced gastric adenocarcinomas. Except early GC (T \geq T1b, node negative), it is recommended to offer perioperative therapy to all GCs in view of the significant survival advantage compared with surgery alone.^{1,2} While there are ongoing studies examining the relative benefits of different strategies (neoadjuvant chemoradiation vs. perioperative chemotherapy, etc.), different approaches are used across the globe with varying outcomes.^{3,4}

Perioperative fluorouracil plus leucovorin, oxaliplatin, and docetaxel (FLOT) has become one of the preferred choices of treatment in this scenario based on the results from the FLOT4 trial, where the regimen showed survival benefits compared with standard of care epirubicin, cisplatin, and capecitabine or fluorouracil.⁵ Importantly, there were no significant differences in chemotherapy-related adverse events and hospitalization rates. This lack of increased chemotherapy-related toxicity is surprising, given the high rates seen in prior studies evaluating docetaxel-based triplet regimens in advanced GC.^{6,7} Given the selected nature of patients in clinical trials, it becomes imperative to assess whether the trial results translate directly into clinical practice in terms of tolerance and outcomes. Factors like nutritional deficiencies, dysphagia, borderline Eastern Cooperative Oncology group (ECOG) performance status (PS), and comorbidities may impair tolerance in a nontrial cohort.⁸

With this background, the authors evaluated a large cohort of patients with GC who received modified FLOT and report a detailed analysis of chemotherapy-related side-effects. We also comment on patterns of relapse and early survival outcomes.

Methods

The study is a retrospective analysis of a prospectively maintained database of patients with resectable LA-GC who were started on the neoadjuvant FLOT regimen from December 2016 to October 2018 in the Department of GI Medical Oncology, at Tata Memorial Hospital. Patients included in the analysis satisfied the following criteria:

1. \geq T2 and/or node (N) positive, based on upper GI endoscopy, contrast-enhanced CT scan (thorax, abdomen, and pelvis) or contrast enhanced FDG-18 PET CT.
2. Absence of visceral organ metastases based on CT or PET-CT scans.
3. Absence of peritoneal metastases on staging laparoscopy (SL). Patients with peritoneal cytology positive disease were included in the patient population. All patients in the study cohort underwent SL as part of institutional policy.

Patients received a modified version of FLOT regimen, every 2 weeks, in the following doses:

- Docetaxel 50 mg/m² D1,

- Oxaliplatin 85 mg/m² D1
- Leucovorin 200 mg/m² D1
- 5-Fluorouracil 2,400 mg/m² D1 and D2 continuous intravenous infusion over 46 hours (as opposed to 2,600 mg/m² on D1 over 24 hours in the original FLOT4 AIO study).

Patients were planned for four cycles preoperatively (neoadjuvant chemotherapy or NACT) and four cycles postoperatively (ACT). Dose modifications at baseline were allowed and were performed during chemotherapy based on assessments by the treating medical oncology team. NCI-CTCAE version 4.03 was used for assessment and recording of toxicity.

Patients who did not have clinical and radiological disease progression after NACT were evaluated for resection with D2 lymphadenectomy. A few patients underwent D3 lymphadenectomy as part of an ongoing clinical trial in our institution. Patients undergoing radical resection were assessed for completion of ACT with FLOT post recovery from surgery.

Relapses were noted and recorded as

- Locoregional: recurrences in regional nodes 1 to 16, anastomotic site, remnant stomach, duodenal stump or tumor bed.
- Distant: all recurrences beyond those mentioned as locoregional. Patients with locoregional and distant metastases were included in the category of distant metastases.

Statistical Analysis

Baseline clinical and demographic variables, pathological indicators, toxicities during chemotherapy, and pattern of relapses were collected retrospectively from the database and entered in SPSS software version 25. Toxicities were reported separately for NACT and ACT chemotherapy. Descriptive statistics were used to compute these variables. Objective tumor responses were defined as the proportion of patients who had complete response (CR) or partial response (PR); disease control, defined as the proportion of patients who had the best response of CR, PR, or stable disease (SD). Disease progression and tumor response were reported as per Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, where feasible. Disease-free survival (DFS) was calculated from date of starting therapy to date of disease recurrence, progression, cessation of treatment due to adverse events, loss to follow-up or death (in case of no documented progression). Overall survival (OS) was calculated from date of starting therapy to date of death. Median DFS and OS were calculated using Kaplan-Meier estimates.

Baseline Characteristics

Between December 2016 and October 2018, 343 patients were started on mFLOT regimen. Baseline characteristics of the study cohort as well as the FLOT cohort from FLOT4-AIO study for purposes of comparison are reported in [Table 1](#).

Table 1 Baseline clinical characteristics

Characteristic	Current study (n = 343)	FLOT-AIO (FLOT cohort) (n = 356)
Median age (years)	55 (22–78)	62 (54–69)
Gender		
• Female	96 (28)	88 (25%)
• Male	247 (72)	268 (75%)
ECOG PS		
• 0	15 (4)	246 (69%)
• 1	308 (90)	109 (31%)
• 2	20 (6)	1 (<1%)
Location		
• Proximal (including GE junction)	136 (40)	208 (56%)
• Body	66 (19)	158 (44%) ^a
• Distal	141 (41)	
Presence of obstruction		
• Yes	89 (26)	–
• No	256 (74)	–
Signet ring		
• Yes	96 (28)	100 (28%)
• No	349 (72)	245 (69%)
• Missing	0	11 (3)
Degree of differentiation ^b		
• Well differentiated	11 (3)	12 (3)
• Moderately differentiated	115 (34)	123 (35%)
• Poorly differentiated	198 (58)	177 (50%)
• Not specified/Missing	19 (6)	32 (9%)

Abbreviations: AIO, Arbeitsgemeinschaft Internistische Onkologie; ECOG, Eastern Cooperative Oncology group; FLOT, fluorouracil plus leucovorin, oxaliplatin, and docetaxel; PS, performance status. Note: Data are median or n (%). Percentages might not add up to 100 because of rounding.

^aReported as Siewert types and gastric only.

^bReported as Grade 1, Grade 2, and Grade 3 in FLOT4 trial.

Patients in the current study were younger (median age: 55 vs. 62 years); there were significantly increased number of patients with ECOG PS 1 and a numerically lesser proportion of proximal tumors. Clinical or endoscopic evidence of gastric outlet obstruction was present in 74 (26%) patients.

NACT and Response Rates

Of the 343 patients starting NACT, 298 (87%) completed the planned four cycles of chemotherapy. The most common reasons for discontinuing or early cessation of NACT were grade three-fourths toxicity, deaths due to toxicity, and early disease progression in 23 (7%), nine (3%), and four (1%) patients, respectively. Nine (3%) patients defaulted during NACT.

Radiological response assessments were available in 306 (89%) patients. CR and PR were seen in two (1%) and 164 (48%) patients, while SD was observed in 125 (36%) patients. Response rates were 48% while disease control was noted in 85% of patients.

Surgical Aspects

A total of 299 (87%) patients proceeded to curative intent resection after NACT (→ **Supplementary Table 1**, available in the online version only), of whom 294 (86%) patients underwent tumor resection. The remaining five patients were considered as inoperable on exploration. Twenty patients (6%; n = 343) underwent attempted resection prior to completion of four cycles of NACT, due to poor tolerance to NACT in 10 patients, upper gastrointestinal hemorrhage in six patients, perforation in three patients, and worsening gastric outlet obstruction in one patient. The most common cancer-directed surgeries performed were distal subtotal gastrectomy in 139 (40%) patients and total gastrectomy in 126 (37%) patients. A total of 258 patients (75%) underwent a D2 lymphadenectomy and median retrieval of nodes was 26 (range: 0–65). The median nodal retrieval in the FLOT-AIO study was similar (24 nodes). 281 (82%) patients underwent R0 resections. Pathological CR was seen in 22 (7%) patients, while it was 15% in the FLOT-AIO study. There were five (2%) deaths due to postoperative complications (→ **Supplementary Table 1**, available in the online version only).

Adjuvant Chemotherapy

Two hundred and eighty-four patients (83%) of the entire cohort were started on adjuvant chemotherapy. These regimens included triplet regimens (FLOT or docetaxel-oxaliplatin-capecitabine) in 247 patients (72%), doublet regimens in 30 patients (9%), and single agent docetaxel in six patients (2%). Ten patients (3%) were not started on adjuvant chemotherapy post-surgery. A majority of patients (72%) were able to start adjuvant chemotherapy within 4 weeks of surgery. Of 343 patients, 264 (77%) were able to complete the planned adjuvant therapy.

Chemotherapy-Related Toxicities

Chemotherapy-related toxicities are reported separately for NACT and adjuvant chemotherapy. In patients receiving NACT, common grade 1 and grade 2 toxicities included diarrhea in 186 patients (54%), vomiting in 162 patients (47%), and fatigue in 159 patients (46%). Common grade 3 and grade 4 toxicities seen were febrile neutropenia in 27 patients (8%), and diarrhea in 42 patients (12%).

In patients on adjuvant therapy, common grade 1 and grade 2 toxicities were fatigue in 101 patients (36%), diarrhea in 98 patients (35%), and vomiting in 69 patients (24%). Common grade 3 and grade 4 toxicities noted were neutropenia in 48 patients (17%), febrile neutropenia in 16 patients (6%), and diarrhea in 17 patients (6%) (→ **Table 2**).

Relapse Patterns and Survival

With a median follow-up of 19.2 months, of the 294 patients who had undergone tumor surgery, 61 patients (21%) had

Table 2 Potentially chemotherapy-related adverse events

Toxicity	Neoadjuvant chemotherapy (n = 343)			Adjuvant chemotherapy (n = 284)			Cumulative toxicities
	Grade 1 or 2	Grade 3 or 4	All grades	Grade 1 or 2	Grade 3 or 4	All grades	All grades
Neutropenia	29 (9)	60 (18)	84 (25)	26 (9)	48 (17)	70 (25)	124 (42)
Febrile neutropenia	–	27 (8)	27 (8)		16 (6)	16 (6)	43 (15)
Thrombocytopenia	18 (5)	3 (1)	20 (6)	9 (3)	3 (1)	11 (3)	28 (10)
Anemia	96 (28)	15 (4)	108 (32)	39 (14)	3 (1)	42 (15)	121 (40)
Mucositis	95 (28)	7 (2)	101 (29)	39 (14)	3 (1)	42 (15)	124 (42)
Vomiting	162 (47)	10 (3)	170 (50)	69 (24)	2 (1)	71 (25)	191 (61)
Diarrhea	186 (54)	42 (12)	214 (62)	98 (35)	17 (6)	108 (38)	211 (74)
Neuropathy	52 (15)	3 (1)	55 (16)	53 (19)	2 (1)	55 (19)	96 (33)
Fatigue	159 (46)	22 (6)	174 (51)	101 (36)	5 (2)	103 (36)	206 (65)
HFS	6 (2)	2 (1)	7(2)	8 (3)	3 (1)	11 (4)	17 (6)
Toxic deaths			9 (2.6)			0	9 (3)
Dose modification	67 (20)			90 (31)			111 (38)

Abbreviation: HFS, Hand-foot-syndrome.
 Note: Data are n (%).

recurrent disease. The sites of recurrence were locoregional in seven patients (2%) and distant in 54 patients (18%). Amongst patients with distant recurrences, common sites of recurrence were peritoneal, liver, and retroperitoneal nodes.

As of cut-off date for analysis, median DFS and median OS were not reached. One-hundred and two patients (30%) had events satisfying criteria for estimation of DFS. The estimated 2-year median DFS was 61.4%. Seventy-eight patients (23%) had died at the time of data censoring and the estimated 2-year median OS was 69.4% (→ Fig. 1).

Discussion

The FLOT regimen was developed based on the efficacy of docetaxel-based regimens in advanced gastric cancers and the supposition that it would improve survival in locoregionally advanced gastric cancers as well. The improved survival outcomes as well as the surprisingly well tolerated nature of the regimen in the FLOT4-AIO trial has ensured that it is now considered a standard in this scenario. Besides the CROSS trial, no other trial in the recent past has shown such significant differences in survival as the FLOT4-AIO study.^{2,5} It is therefore necessary to evaluate the regimen in nontrial routine clinical practice to observe for any nuances that may alter or require change before widespread applicability.

The current study identified 343 patients who received a modification of the FLOT regimen as perioperative chemotherapy in our institution. We used a modification of the original regimen because of an unacceptably high rate of grade 3 to 5 (CTCAE 4.03) toxicities initially seen in our patients when we used doses as per the trial. The investigators modified the doses based on the tolerability seen with the commonly used modified FOLFOX-7 regimens, which use 5-fluorouracil as a 46-hour infusion.⁹ Additionally, there is prospective data to suggest equivalence of regimens using

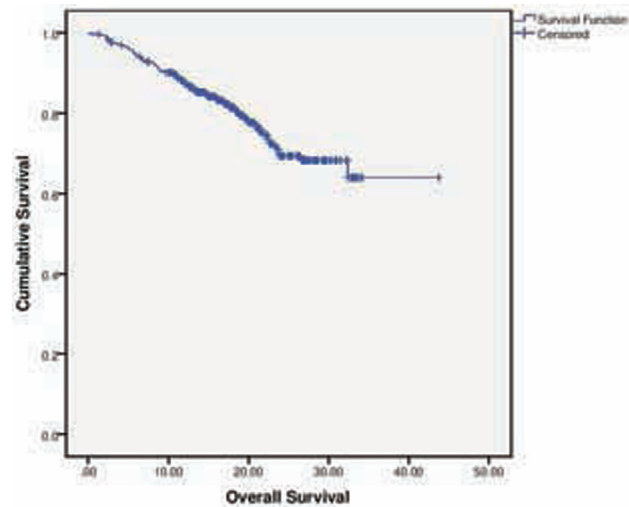


Fig. 1 Overall survival mFLOT 4. mFLOT, modified fluorouracil plus leucovorin, oxaliplatin, and docetaxel.

24-hour or 48-hour infusion in terms of side-effects and efficacy.¹⁰ The characteristics of the FLOT cohort from the seminal study as well as this study are comparable in terms of numbers and are placed side by side for the purposes of comparison. It is clearly visible that the current study cohort is markedly different from the seminal study cohort in terms of proportion of patients with varying ECOG (PS 0–4 vs. 69%; PS 1–90 vs. 31%; PS 2–6% vs. <1%), location of primary (proximal: 40 vs. 56%), and proportion of patients with T4 disease (ypT4: 19 vs. 10%). ECOG PS, especially beyond ECOG PS 1, has a significant bearing on outcomes as well as potential tolerance, though not unequivocally.¹¹ More importantly, the higher incidence of T4 in the current study is an indicator of greater disease bulk, delayed presentation of disease in the cohort, and potentially lesser downstaging

with NACT in terms of response achievement. T4 gastric cancers also predict for an increased margin positive resection rate, increased peritoneal recurrences, and lesser outcomes.^{12,13}

A lesser proportion of patients proceeded to radical resection in the study as compared with the trial (87 vs. 94%) and this is reflective of the real-world nature of data of the study. Reasons for this include a 3% loss to follow-up rate during NACT as well as an increased incidence of deaths during NACT (2.6%) in the current study. However, reassuringly, the R0 resection rates (82 vs. 78%) are comparable between the studies. Another difference between the groups is the lesser percentage of patients achieving pathological CR in the study (7 vs. 15%). We could identify an increased proportion of T4 cancers in this cohort as one possible reason for this difference. The correlation between pathological CR and outcomes in gastric cancer is well known; however, as discussed later, the similar early survival outcomes in this study as compared with the FLOT-4 AIO trial do not bear this out.^{14,15}

Eighty-seven percent of patients were able to complete planned NACT, which is similar to the 90% seen in the FLOT AIO trial. Eighty-two percent of patients in the current study were able to start adjuvant therapy, which is markedly more than the 60% in the trial. It is well known that compliance and completion rates of adjuvant therapy are lesser compared with neoadjuvant therapy due to delayed recovery from major surgery, postoperative complications, patient fatigue, and significant toxicities in neoadjuvant setting precluding administration in the adjuvant scenario.^{1,16–18} One of the reasons for a higher rate of adjuvant administration in our study is the dose modification used by the physicians—adjuvant was modified according to tolerance during neoadjuvant so as to minimize toxicity. These modifications included dose reductions, as well as using two-drug or monotherapy regimens. Such modifications may not be allowed in trials due to prespecified protocols but can be used in clinical practice as seen in this study. The benefits of such an approach are evident—barring the incidence of neuropathy, every chemotherapy-related side-effect is lesser in the adjuvant setting as compared with the neoadjuvant setting in this study. This is important as attempts should be made to ensure completion of planned therapy to the extent possible.

On comparing toxicities between the FLOT4 AIO FLOT cohort and the current study, the number of toxic deaths in the current study is increased as compared with the original study (2.6 vs. 1%) (→ **Supplementary Table 2**, available in the online version only). There is an increased incidence of febrile neutropenia and grade 3 and grade 4 diarrhea in this dataset while a majority of the other side-effects appear similar or less. Reasons for this include a greater proportion of patients receiving adjuvant in the current study and thereby have an increased possibility of having toxicities. Other reasons include an increased proportion of patients with higher ECOG PS (PS 1–31 vs. 90%; PS 2–6% vs. <1%), who are prone to greater toxicities, a high proportion of patients presenting with gastric outlet obstruction (26%), and possi-

ble differences in 5 FU metabolism by dihydro pyrimidine dehydrogenase deficiency in Indians causing an increased incidence of diarrhea.^{19,20} The requirement for dose modifications is significant in both studies, specifically during adjuvant therapy (FLOT—46%; mFLOT—31%) and this is essential to ensure safe administration of chemotherapy.

While the focus of this study was tolerance, the median follow-up of 19 months allows a glimpse into the relapse patterns as well as survival outcomes. The early relapses are predominantly distant (89%), with locoregional relapses (11%) being a minority. The increased number of peritoneal recurrences is also reflective of the high proportion of T4 cancers in the current cohort. The incidence of locoregional relapses is as expected in the current era. Most contemporary studies have locoregional relapse ranges in the range of 10 to 15%.^{21–23} The estimated median 2-year OS, within the confines of the limited number of events is encouraging and appears to be similar to the data from the FLOT-AIO study (69.4 vs. 68%). These early outcomes hint at the similar efficacy of the modified FLOT regimen as compared with the standard FLOT regimen in the real world, though long-term outcomes are required before firm conclusions can be reached.

The strength of this study is an attempt to identify nuances in the usage of perioperative modified FLOT in gastric cancers in a large nontrial cohort. However, the retrospective nature of this study means there is a lost follow-up cohort whose outcomes we cannot comment upon. The modification of FLOT by using a 46-hour infusion as opposed to a 24-hour infusion has a biological basis and was a change made to ameliorate toxicities. An increased rate of toxic deaths during neoadjuvant therapy is a reminder of the intensive nature of the FLOT regimen and bears caution when the regimen is used in routine clinical practice. Reassuringly, the early OS outcomes appear on par with the data from the seminal study.

In conclusion, administration of modified FLOT regimen in locoregionally advanced gastric cancers is feasible in clinical practice with high completion rates, though requiring dose modifications due to the incidence of clinically relevant grade 3 to 5 toxicities. Early outcomes with the regimen are on par with survivals from the FLOT-AIO study.

Note

The study was approved by Institutional Ethics Committee III, ACTREC, Tata Memorial Centre, Kharghar, Navi Mumbai, India (900711).

Study was performed in accordance with the ethical principles for Medical Research Involving Human Subjects, outlined in the Declaration of Helsinki.

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None.

Conflict of Interest

None declared.

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