NEOADJUVANT CHEMOTHERAPY WITH FLOT FOR LOCALLY ADVANCED GASTRIC CANCER: A SINGLE-CENTER EXPERIENCE FROM VIETNAM

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Neoadjuvant chemotherapy (NACT) with the FLOT regimen (5-Fluorouracil, Leucovorin, Oxaliplatin, Docetaxel) has shown promising results for locally advanced gastric cancer (LAGC). This study aimed to evaluate the initial treatment outcomes of LAGC patients receiving neoadjuvant FLOT at Hanoi Oncology Hospital. A descriptive cohort study was conducted on 35 patients with LAGC (cT3-4 and/or cN2-3, M0) treated with neoadjuvant FLOT between October 2021 and February 2024. Clinical data, radiological and histopathological responses, surgical outcomes, and adverse events were retrospectively and prospectively collected and analyzed. The median age was 62 years, with a male-to-female ratio of 4.8:1. The majority presented with epigastric pain (80%) and tumors located in the antrum (68.6%). Among all patients, 91.4% were cT4 (62.8% cT4b), and 97.1% had lymph node metastasis on imaging. Thirty patients (85.7%) completed 4 FLOT cycles. Radiologically, 50% had partial response (PR), 43.3% had stable disease (SD), and 6.7% showed progression. Of the 32 patients who underwent surgery, 29 (90.6%) had radical resection with an R0 rate of 100%. Pathologic complete response (pCR) was observed in 6.7% of cases. The postoperative lymph node-negative rate (ypN0) was 25%. Neoadjuvant chemotherapy using the FLOT regimen demonstrated favorable disease control, enabling high R0 resection rates in patients with locally advanced resect able gastric cancer. These results support the use of FLOT in carefully selected Asian populations with LAGC, although further studies with larger sample sizes and long-term follow-up are warranted.

Keywords: FLOT, neoadjuvant chemotherapy, gastric cancer, R0 resection, locally advanced cancer, Vietnam.

I. INTRODUCTION

Gastric cancer remains one of the most prevalent malignancies globally, including in Vietnam. According to the International Agency for Research on Cancer (IARC), gastric cancer ranked fifth in both incidence and cancer-related mortality worldwide in 2022, with an estimated 968,784 new cases and 660,175 deaths attributed to the disease.[1] In countries like Japan, and to a lesser extent South Korea - where nationwide screening programs are in place - early-stage detection is more feasible. However, approximately 50% of patients are still diagnosed at advanced stages, with poor prognosis and regional lymph node metastases observed in 70 - 80% of cases.[2] While curative surgery remains the cornerstone of treatment in locally advanced stages, adjuvant chemotherapy has also shown additional survival benefit. Nevertheless, upfront surgery for bulky or locally invasive tumors is often limited by high rates of positive margins and recurrence. To address these limitations, neoadjuvant chemotherapy has been evaluated in multiple clinical trials. The landmark MAGIC

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trial demonstrated improvements in overall survival (OS), progression-free survival (PFS), and 5-year survival rates using perioperative chemotherapy with ECF (epirubicin, cisplatin, and 5-FU).[2] Neoadjuvant chemotherapy has since been shown to offer additional advantages such as tumor downstaging, higher R0 resection rates, and early elimination of micrometastases, especially in patients with T3/T4 disease, bulky perigastric lymph nodes as assessed by imaging or endoscopic ultrasound, or infiltrative tumor morphology.[2]

In Vietnam, neoadjuvant chemotherapy has only recently been implemented for patients with locally advanced yet resect able gastric cancer. Doublet or triplet regimens are utilized based on patient tolerance and performance status, with triplet regimens preferred in those with good general condition. The FLOT4-AIO trial, presented at ASCO 2017, demonstrated that the FLOT regimen (docetaxel, oxaliplatin, 5-FU, leucovorin) achieved an R0 resection rate of up to 89.6% and significantly improved both PFS and OS compared to ECF/ECX.[3] Today, FLOT is widely adopted in guidelines for resect able gastric cancer from clinical stage cT2 or node-positive onward. In Vietnam, FLOT has been available since 2018 and was officially incorporated into the national gastric cancer treatment guidelines. However, due to the regimen's toxicity profile, its clinical use is mainly reserved for patients with stage T3–T4 and/or node-positive disease where R0 resection is deemed technically challenging. Despite robust global evidence, regional data remain limited - particularly within Asian populations, where tumor biology, surgical strategies, and patient demographics often differ significantly. This study aims to evaluate the initial treatment outcomes and toxicities profile of patients with locally advanced gastric cancer (LAGC) treated with neoadjuvant FLOT chemotherapy at Hanoi Oncology Hospital.

II. MATERIALS AND METHODS

1. Subjects

Eligible patients were individuals aged over 18 years with a performance status of 0-1 according to the Eastern Cooperative Oncology Group (ECOG) criteria. All patients had histologically confirmed gastric or gastroesophageal junction adenocarcinoma, staged as cT3-T4 and/or cN2-3, M0 on contrast-enhanced computed tomography (CT). Additional inclusion criteria included: no history of prior chemotherapy, receipt of at least two cycles of FLOT, preserved bone marrow, hepatic, and renal function, a baseline left ventricular ejection fraction > 50%, availability of complete clinical and pathological data, and informed consent for participation. Patients were excluded if they had hypersensitivity to any FLOT agents, concurrent malignancies, life-threatening comorbidities, acute illnesses with near-term mortality risk, were pregnant or breastfeeding, or discontinued treatment for non-clinical reasons.

2. Methods

Study design

A descriptive cohort study was conducted at Hanoi Oncology Hospital between August 2020 and February 2024, on patients diagnosed with locally advanced gastric cancer (LAGC) who received neoadjuvant chemotherapy using the FLOT regimen.

Sample size

The sample size was calculated based on an expected response rate of 70% (p = 0.7). Assuming a precision level (ε) of 0.2, and a 95% confidence level, a minimum of 31 patients was required. A total of 35 patients meeting the inclusion criteria were enrolled from October

2021 to February 2024.

Treatment schedule

Patients received the FLOT regimen every 14 days. On Day 1 of each cycle, they were administered docetaxel 50 mg/m² intravenously over 1 hour, oxaliplatin 85 mg/m² over 2 hours, leucovorin 200 mg/m² over 2 hours, and 5-fluorouracil 2600 mg/m² as a continuous 24-hour infusion. Each patient was treated with a minimum of 2 and up to 8 cycles. Supportive measures, including antiemetics and hydration, were provided routinely. Treatment was paused or discontinued in cases of severe toxicity, progression, complications such as gastric outlet obstruction or gastrointestinal bleeding, or per patient decision. Surgical evaluation was conducted after 4 cycles. Patients with adequate response and surgical feasibility were referred for curative surgery. Those with stable disease and manageable toxicity continued treatment up to 8 cycles. Patients with disease progression or unacceptable toxicity were transitioned to alternative management, including palliative care.

Assessments

Patients underwent comprehensive clinical and paraclinical evaluations at baseline, before each chemotherapy cycle, and following treatment completion. Clinical assessments included physical examination and performance status. Paraclinical evaluations comprised gastroscopy with biopsy, abdominal ultrasound, neck ultrasound, and contrast-enhanced CT scans of the thorax and abdomen. CT criteria for nodal metastasis followed ESMO 2022 guidelines, including size (short-axis ≥6 - 8mm), round morphology, central necrosis, loss of fatty hilum, and heterogeneous enhancement.[4] Additional assessments such as brain MRI or bone scintigraphy were performed when clinically indicated. Laboratory tests included complete blood count, renal and liver function, and tumor markers (CEA, CA72-4).

Study outcomes

Primary endpoints included radiological response per RECIST 1.1, pathological response based on Becker criteria (classified as complete or non-complete), surgical resectability, and R0 resection rate.[2,5]based on the original World Health Organisation guidelines first published in 1981. In 2009, revisions were made (RECIST 1.1 Secondary endpoints comprised improvement in clinical symptoms (e.g., epigastric pain, weight loss, anorexia), reduction in tumor markers, incidence and severity of adverse events, and the association between clinical or pathological factors and treatment response.

Response evaluation

Radiologic response was assessed by comparing CT scans at baseline and after 4 and 8 cycles. Lymph nodes were evaluated as target lesions, and the primary tumor as a non-target lesion. Per RECIST 1.1, responses were categorized as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). For non-target lesions, CR was defined as complete disappearance and normalization of tumor markers; PD was defined as unequivocal progression or new lesions; non-CR/non-PD indicated persistent non-target lesions.[5]based on the original World Health Organisation guidelines first published in 1981. In 2009, revisions were made (RECIST 1.1 Pathological response was evaluated postoperatively using the Becker classification.[2] Due to the retrospective nature, histopathologic response was dichotomized into complete or non-complete.

Toxicity assessment

Toxicities were monitored throughout treatment using the Common Terminology

Criteria for Adverse Events (CTCAE) version 5.0.[6] Clinical toxicities included nausea, vomiting, diarrhea, hand-foot syndrome, and peripheral neuropathy. Hematologic toxicities included anemia, leukopenia, neutropenia, and thrombocytopenia. Biochemical toxicities included elevations in AST, ALT, and creatinine. Dose modifications or treatment interruptions were recorded when toxicity met predefined severity thresholds.

Study variables

The study included both dependent and independent variables. The primary dependent variable was treatment response, classified according to RECIST 1.1 criteria as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD), and further dichotomized into disease control (CR, PR, SD) versus progression (PD) for statistical analysis. Independent variables included:

Demographic characteristics: age (continuous and categorized), gender.

Clinical characteristics: ECOG performance status (0-1 vs. 2), tumor location (antrum, body, cardia), and presenting symptoms.

Tumor staging variables: clinical T stage (cT3, cT4a, cT4b), clinical N stage (cN0 vs. cN+), and pathologic T/N stage after surgery (ypT, ypN).

Histopathologic characteristics: histologic type (well/moderately differentiated, poorly differentiated, signet ring/mucinous), presence of lymphovascular or perineural invasion, and presence of signet ring cells.

Treatment-related variables: number of FLOT cycles received, surgical resection status (R0 vs. R1/R2), and pathological complete response (pCR).

Safety variables: adverse events graded per CTCAE v5.0, including hematologic (neutropenia, anemia, thrombocytopenia) and non-hematologic (neurotoxicity, hepatotoxicity, gastrointestinal symptoms).

Statistical analysis

All data were coded and analyzed using SPSS version 20.0. Descriptive statistics were employed to summarize baseline characteristics, treatment responses, and adverse events. Categorical variables were compared using Fisher's exact test. A logistic regression model was applied to identify factors associated with the primary outcome of the study - treatment response (response vs. non-response) to the FLOT regimen. A p-value of less than 0.05 was considered statistically significant.

3. Research ethics

The study was conducted with the approval of the institutional leadership of Hanoi Oncology Hospital. Patient confidentiality was strictly maintained. Participation posed no additional risks, and all procedures conformed to standard clinical care. The research aimed solely to improve the quality of diagnosis and treatment for patients with gastric cancer.

III. RESULTS

A total of 35 LAGC patients were enrolled. The median age was 62 years (range: 35 - 71), with the majority (91.4%) under 70 years of age. Most patients were male (82.9%) and had ECOG performance status of 0 - 1. Epigastric pain was the predominant presenting symptom (80%), followed by melena (11.4%) and nausea/vomiting (8.6%). The median symptom-to-admission interval was 9 weeks. Tumors were most frequently located in the antrum (68.6%), and the majority were staged as cT4b (62.8%) with nodal involvement (97.1%). Gross morphology on endoscopy revealed that infiltrative or ulcerative-infiltrative forms predominated (51.1%). Histologically,

poorly differentiated adenocarcinoma was most common (37.2%), followed by poorly cohesive/signet ring/mucinous carcinoma (31.4%). Vascular or neural invasion was present in 60% of cases. Signet ring cells were identified in 25.7% (Table 1).

Table 1. Baseline characteristics and clinical presentation (n = 35)

Characteristics	Results
Age group (years)	
< 60	14 (40.0)
60 - 69	18 (51.4)
≥ 70	3 (8.6)
Gender	
Male	29 (82.9)
Female	6 (17.1)
ECOG performance status	
0	14 (40.0)
1	21 (60.0)
Presenting symptoms	
Epigastric pain	28 (80.0)
Melena	4 (11.4)
Nausea/vomiting	3 (8.6)
Median symptom duration (weeks)	9 (range: 3 - 16)
Tumor location	
Cardia	2 (5.7)
Body	9 (25.7)
Antrum	24 (68.6)
Clinical T stage (CT)	
cT3	3 (8.6)
cT4a	10 (28.6)
cT4b	22 (62.8)
Clinical N stage (CT)	
cN+	34 (97.1)
cN–	1 (2.9)

Characteristics	Results
Gross tumor morphology (endoscopy)	
Infiltrative or ulcerative-infiltrative	18 (51.1)
Ulcerated	8 (22.9)
Ulcerative-exophytic	8 (22.9)
Exophytic	1 (2.9)
Histology (WHO classification)	
Well/moderately differentiated AC	11 (31.4)
Poorly differentiated AC	13 (37.2)
Poorly cohesive/signet ring/mucinous	11 (31.4)
Vascular/neural invasion	
Present	21 (60.0)
Absent	9 (25.7)
Not reported	5 (14.3)
Signet ring cells	
Present	9 (25.7)
Absent	26 (74.3)

Among 35 patients, 30 (85.7%) completed 4 cycles of FLOT chemotherapy. One patient discontinued after three cycles, while four underwent surgery after two cycles due to complications. Radiologic evaluation (n = 30) showed partial response in 50%, stable disease in 43.3%, and progression in 6.7%. No complete response was observed. No significant association was found between clinical/pathological factors and response (Table 2).

Table 2. Chemotherapy completion and response (n = 35)

Characteristics	Results
FLOT cycles completed before surgery	
4 cycles	30 (85.7)
3 cycles	1 (2.9)
2 cycles	4 (11.4)
Response	
Complete response	0 (0.0)
Partial response	15 (50.0)
Stable disease	13 (43.3)
Progressive disease	2 (6.7)

In the univariate analysis, infiltrative tumor morphology showed a trend toward association with non-response to treatment (odds ratio < 1); however, this was not statistically significant, likely due to the limited sample size. Other factors, including signet ring cell histology, vascular or perineural invasion, and clinical T4b stage, also demonstrated no statistically significant association with disease progression. The multivariable model included selected variables with clinically relevant or notable univariate odds ratios; nevertheless, none retained statistical significance, as reflected by wide confidence intervals - attributable to the small number of patients who experienced disease progression (only 2 out of 30 cases) (Table 3).

Table 3. Logistic regression analysis of factors associated with treatment response

Variables	Univariate analysis OR (95% CI)	Multivariable analysis OR (95% CI)
Clinicopathologic factors		
Age (≥ 60 vs. < 60)	0.77 (0.12 - 4.89)	-
Gender (female vs. male)	-	-
ECOG (1 vs. 0)	0.93 (0.15 - 5.81)	-
Histological type (signet ring vs. others)	2.20 (0.18 - 26.1)	2.10 (0.16 - 26.7)
Vascular/neural invasion (yes vs. no)	1.50 (0.13 - 17.4)	–
Tumor morphology (infiltrative vs. others)	0.14 (0.01 - 1.64)	0.12 (0.01 - 1.95)
Staging factors		
cT4b vs. cT3–T4a	0.00 (0.00 - Inf)	-
cN+ vs. cN–	-	-

Of 35 patients, 32 underwent surgery with 29 (82.9%) received curative resection, 3 underwent palliative surgery, 2 were inoperable, and 1 patient refused further treatment. R0 resection was achieved in all curative surgeries. Pathological complete response (pCR) was seen in 2 patients (6.7%). Postoperative staging showed ypN0 in 25% and ypN3 in 28.1%. The median number of lymph nodes dissected was 20, with a median of 4 positive nodes.

Table 4. Surgical resection and pathological staging (n = 32)

Characteristics	Results
Surgical procedure	
Curative resection	29 (82.9)
Palliative surgery	3 (8.6)
Inoperable after chemo	2 (5.7)
Refused further treatment	1 (2.8)

Characteristics	Results
Resection margin status (R status)	
R0 (complete resection)	29 (100.0)
R1 or R2	0 (0.0)
Postoperative pathological T stage	
T0	2 (6.3)
T1-T2	7 (21.9)
T3	6 (18.7)
T4a–T4b	14 (43.7)
Data not available	3 (9.4)
Postoperative N stage	
N0	8 (25.0)
N1-N2	12 (37.5)
N3	9 (28.1)
Data not available	3 (9.4)
Pathological complete response (pCR)	2 (6.7)

FLOT was generally well tolerated. Grade 3-4 toxicities occurred in 14.3% of patients, primarily neutropenia (11.4%) and anemia (2.9%). Febrile neutropenia occurred in 2 patients (5.7%) requiring hospitalization. Most toxicities were grade 1-2. No renal toxicity or treatment-related mortality was observed (Table 5).

Table 5. Adverse events during neoadjuvant chemotherapy (n = 35)

Adverse event	Grade 1-2, n (%)	Grade 3-4, n (%)
Nausea/vomiting	13 (37.1)	0 (0.0)
Diarrhea	10 (28.6)	0 (0.0)
Peripheral neuropathy	6 (17.1)	0 (0.0)
Anemia	11 (31.4)	1 (2.9)
Neutropenia	18 (48.6)	4 (11.4)
Febrile neutropenia	–	2 (5.7)
Thrombocytopenia	4 (11.4)	0 (0.0)
Elevated liver enzymes	10 (27.8)	0 (0.0)
Renal toxicity	0 (0.0)	0 (0.0)
Treatment-related death	0 (0.0)	0 (0.0)

IV. DISCUSSION

This study aimed to evaluate the response rates, associated factors, and treatment-related toxicities of the perioperative FLOT regimen in patients with locally advanced gastric cancer (LAGC) at Hanoi Oncology Hospital. In our study, half of the patients completing four cycles of preoperative FLOT chemotherapy achieved partial response, and 43.3% demonstrated stable disease. The disease control rate was comparable to prior studies conducted in Asia and Europe, with reported response rates ranging from 43% to 65% using CT-based RECIST criteria.[7,8] Importantly, no significant association was found between treatment response and clinicopathologic factors such as gross tumor morphology, histological subtype, clinical T stage, or lymphovascular invasion. These findings underscore the limitations of current imaging modalities in accurately evaluating response, particularly in the context of gastric tumors where post-treatment fibrosis and edema can obscure radiologic assessment.[9]

Although CT remains the standard tool for response evaluation under RECIST, its diagnostic accuracy in restaging gastric tumors is suboptimal - especially in distinguishing residual disease from fibrosis. Moreover, the primary gastric lesion is often non-measurable, and endoscopy, though not incorporated in RECIST, may provide valuable insights into local response. Several studies have demonstrated a correlation between radiologic or endoscopic response and pathological regression, as well as overall survival.[10,11] However, conflicting results exist, highlighting the need for multi-modal assessment strategies.[12,13] The routine application of these methods in Vietnam remains limited due to cost, accessibility, and lack of insurance coverage.

Pathological evaluation after surgery showed signs of downstaging in both T and N components. Two patients (6.7%) achieved complete pathological response (pCR), which is consistent with previous studies using FLOT in advanced disease.[10,14,15] Although this pCR rate is lower than that reported in the FLOT4 trial (16%),[3] the difference may reflect the higher proportion of T4 and N+ patients in our cohort and the limited sample size. In addition, Becker's analysis suggests that complete histologic regression may be underestimated in standard pathology reporting, emphasizing the need for standardized tissue handling, slicing, and scoring protocols.[16] Nodal response is particularly relevant as ypN status is a strong independent predictor of survival.[7] In our study, 25% of patients were classified as ypN0, and all underwent D2 lymphadenectomy-now recognized as the global standard in gastric cancer surgery. Despite this, the presence of residual nodal disease after chemotherapy reflects both pre-treatment burden and treatment efficacy, and may aid in postoperative risk stratification.

Taken together, the moderate response rates observed suggest that while FLOT is an effective neoadjuvant regimen, further refinement in patient selection and response monitoring is needed. Integration of metabolic, endoscopic, and molecular tools could improve early identification of responders and non-responders, allowing treatment adaptation prior to surgery.

The safety profile of FLOT in this cohort was generally acceptable, with 11.4% of patients experiencing grade 3-4 neutropenia, lower than the 51% reported in FLOT4.[3] This difference may be partly attributed to the proactive use of primary prophylaxis with G-CSF in our setting. In contrast, liver enzyme elevations (27.8%) and thrombocytopenia (11.4%) were more frequent

than in the FLOT4 trial (1 - 2%), likely reflecting ethnic, nutritional, or environmental differences. Gastrointestinal and neurologic toxicities were mostly mild (grade 1 - 2), and no renal toxicity or treatment-related mortality was observed. Hospitalization was required in only three patients due to febrile neutropenia or severe anemia. Importantly, none of the toxicities led to surgical delays or precluded curative resection.

Despite being a three-drug combination, FLOT is not formally classified as a high-risk febrile neutropenia regimen in the NCCN guidelines. Nevertheless, given the importance of maintaining treatment intensity and avoiding delays prior to surgery, routine primary G-CSF prophylaxis appears justified in clinical practice. Our approach reflects both empirical experience and the need to preserve operability in a potentially curative context.

Notably, among the 29 patients who underwent curative surgery, no postoperative deathor re-operation occurred. This favorable perioperative safety contrasts with the 51% postoperative complication rate reported in FLOT4,[3] possibly due to differences in sample size and surgical protocols.

V. CONCLUSION

The findings from this study highlight the feasibility and safety of neoadjuvant FLOT in real-world clinical settings. However, the modest pathological response rate, particularly in high-risk T4/N+ patients, raises important questions about optimizing treatment duration and selection. Clinicians should consider integrating early response assessment strategies-such as metabolic imaging or interim endoscopy-into treatment algorithms. Additionally, developing standardized histopathological response scoring systems and consistent lymph node dissection protocols will enhance comparability across centers. Future prospective studies with larger sample sizes, molecular profiling, and long-term follow-up are needed to clarify predictive markers and define patient subgroups most likely to benefit from neoadjuvant FLOT. In the meantime, rigorous supportive care, early multidisciplinary assessment, and institutional adherence to D2 lymphadenectomy remain key pillars of optimizing outcomes in advanced gastric cancer.

DECLARATIONS

Conflicting interests

The authors declare no competing interests in preparing this article.

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Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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