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Pathologic Response Rates in Patients with Gastric Cancer Following FLOT Neoadjuvant Chemotherapy

Samaneh Sajjadi [1], Mostafa Kamandi [1], Abolghasem Allahyari [1], Sajjad Ataei Azimi [1], Alireza Baari [1], Niloufar Valizadeh [2], Farbod Hatami [2,*]

[1] Department of Internal Medicine, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[2] Network of Immunity in Infection, Malignancy and Autoimmunity (NIIMA), Universal Scientific Education and Research Network (USERN), Tehran, Iran

[*] *Corresponding author:* Network of Immunity in Infection, Malignancy and Autoimmunity (NIIMA), Universal Scientific Education and Research Network (USERN), Tehran, Iran. Email: f.hatami.md@gmail.com

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Abstract

Background: Gastric adenocarcinoma is among the most prevalent cancers associated with a high mortality rate. The multidrug neoadjuvant chemotherapy administered before and after surgery has attracted attention as a beneficial standard of care for managing this malignancy.

Objectives: This study assessed the pathologic response of patients with gastric cancer who were treated with fluorouracil plus leucovorin, oxaliplatin, and docetaxel (FLOT).

Methods: Patients with pathologically confirmed gastric adenocarcinoma without distant metastases were enrolled in this retrospective cohort study conducted at Imam Reza and Ghaem hospitals in Mashhad. Data regarding demographics, tumor status, treatment toxicity, and pathology results were collected using a predesigned questionnaire after four cycles of FLOT neoadjuvant chemotherapy. SPSS-26.0 was utilized to analyze the data, and a significance level of $P < 0.05$ was applied.

Results: We evaluated data from 53 cases with a mean age of 51.1 ± 9.7 years. Diffuse adenocarcinoma was the most common finding in histology (54.7%). Pathologic complete response was observed in 16 (30.2%) patients. Most (69.8%) patients received only 7 out of 8 planned cycles. Concerning surgical margin, 46 (86.8%) patients achieved R0 tumor resection. Pathologic complete response was not significantly linked with age ($P = 0.91$), sex ($P = 0.65$), performance status ($P = 0.2$), tumor histology ($P = 0.14$), tumor grading ($P = 0.07$), tumor location ($P = 0.8$), and the number of neoadjuvant chemotherapy cycles ($P = 0.9$).

Conclusions: Our findings demonstrated the relative clinical efficacy of neoadjuvant chemotherapy with the FLOT regimen administered before and after surgery. However, due to chemotherapy-related side effects, patients may not adhere to all eight prescribed cycles of chemotherapy.

Keywords: Gastric Cancer, Neoadjuvant Chemotherapy, FLOT Treatment Regimen

1. Background

Gastric cancer is the fifth most prevalent cancer and the fourth leading cause of cancer-related mortality worldwide (1). Although the prevalence has decreased in developed countries over the past few decades, gastric cancer remains notably common in Asia and Iran. Hence, it is classified as a common malignancy. Gastric cancer accounts for 11.5% and 15.5% of all malignancies and cancer-related mortality, respectively (2, 3).

The high mortality rate from gastric cancer reflects the high prevalence of late-stage disease at presentation. Radical surgery is currently recognized as the only treatment that might cure a patient with advanced disease. However, more than 50% of patients undergoing surgery for locally advanced gastric malignancy develop recurrent disease, and only 40% survive for three years (4, 5).

Considering that most patients are already in a late stage of the disease when they are diagnosed and that survival rates are low, extensive radical surgery with

resection of metastatic lymphatic nodes, either on its own or in combination with post-surgical adjuvant chemotherapy, cannot achieve the goal of cure. Therefore, presurgical or neoadjuvant chemotherapy is required to control micrometastases before surgery and improve radical resection outcomes.

Recent meta-analyses of randomized clinical trials have demonstrated the efficacy of neoadjuvant chemotherapy in resectable tumor patients. Neoadjuvant chemotherapy has been linked to a significant reduction in nodal stage, disease relapse, and mortality rate, leading to an increase in overall survival rate. Despite this, there is no consensus regarding the optimal neoadjuvant therapy regimen, as different studies have used different regimens (6, 7).

5-fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) is one of the neoadjuvant chemotherapy regimens that has recently been evaluated in clinical trials and has exhibited significantly better overall survival results than triplet neoadjuvant therapy with cytotoxic agents, including epirubicin and cisplatin plus either fluorouracil or capecitabine (ECF/ECX). FLOT tends to be more well-accepted by experts and is considered the standard regimen in many countries (8-10). Nevertheless, pathologic response is one of the key determinants of patient survival and prognosis that has not been assessed yet in neoadjuvant therapy with FLOT.

A pilot study confirmed that preoperative neoadjuvant chemotherapy with 5-fluorouracil in patients with resectable gastric cancer resulted in complete and significant pathologic response rates of 11% and 63%, respectively (11). In another study examining 480 patients with gastric cancer, neoadjuvant chemotherapy with a cisplatin-based regimen was associated with complete and partial pathologic responses in 21% and 25% of cases, respectively. In addition, there was a significant correlation between pathologic response and tumor type, lymph node, lymphatic invasion, and resection status (12).

2. Objectives

This study was conducted to assess the pathologic response of patients with gastric cancer to neoadjuvant therapy with FLOT.

3. Methods

A retrospective cohort study was carried out in the Ghaem and Imam Reza hospitals affiliated with Mashhad University of Medical Sciences. Using purposive sampling, we enrolled patients with gastric cancer who were candidates for neoadjuvant chemotherapy. Patients signed consent forms for participation after an explanation of the aim, design, and protocol of the study. The institutional ethics committee approved the study protocol (IR.MUMS.MEDICAL.REC.1400.272)

The sample size was determined in accordance with the degree of tumor downgrading. Using the formula for estimating qualitative traits in the community, $\alpha = 0.05$, and $d = 0.135$, we estimated a sample size of 53 cases based on the study by Becker et al., which indicated that 45% of patients had tumor downgrading following neoadjuvant treatment. Given a 10% attrition rate, the required sample size was 59 individuals (12).

Our inclusion criteria comprised confirmed diagnosis of gastric cancer based on biopsy and pathology results, age younger than 70 years, Eastern Cooperative Oncology Group (ECOG) score ≤ 2, absence of metastasis in imaging and laparoscopy, absence of neuropathy based on history taking and physical examination, and clinical staging status of T2, N1, or higher. Patients with evidence of metastasis, serum creatinine level > 1.5 mg/dL, liver enzymes more than twice normal, serum alkaline phosphatase level > 1.5 times normal, serum bilirubin level > 2 mg/dL, and patients who refused surgery were excluded. At baseline, diagnostic biopsies obtained following an upper gastrointestinal endoscopy were collected and documented for initial pathologic evaluation. In addition, patients' demographics were collected using questionnaires developed for this study.

Patients were administered four cycles of neoadjuvant chemotherapy with the FLOT regimen following a standard physical examination to ensure that they were clinically fit for systemic chemotherapy. On the first day, 5-fluorouracil (2,600 mg/m^2 over 24 hours), leucovorin (200 mg/m^2 over 2 hours), oxaliplatin (85 mg/m^2 over 2 hours), and docetaxel (50 mg/m^2 over 2 hours) were administered via parenteral route. Before each course, patients were examined for complications based on common terminology criteria for adverse events (CTCAE) version 5.0 and a complete blood count concerning bone marrow toxicity. Courses were repeated every two weeks. The malignant tumor was then surgically excised, followed by four cycles of adjuvant chemotherapy using the same regimen.

Statistical analyses were performed in SPSS version 26.0 software (SPSS, Inc., Chicago, IL, USA). Continuous and categorical data are presented as mean ± standard deviation and frequency and median (interquartile range), respectively. The Shapiro-Wilk test was performed to determine whether continuous variables follow a normal distribution. Moreover, we used the independent T-test or Mann-Whitney to compare variables between the two groups, as appropriate. χ^2 test was applied for categorical data. A P-value of less than .05 was considered to be significant.

4. Results

We analyzed data from 53 cases of gastric cancer that were candidates for FLOT neoadjuvant chemotherapy treatment. Our sample had a mean age of 51.1 ± 9.7 years and was predominantly male (77.4%). Most patients (67.9%) had an ECOG 1 performance status. The most common histology finding was diffuse adenocarcinoma (54.7%), and the majority of tumors (45.9%) were grade II. Tumors were primarily found in the antrum/pylorus (45.3%) and the cardia (30.2%). The data are displayed in Table 1.

Table 1. Patients Demographics (N = 53)

Parameters	Values
Age	51.1 ± 9.7
Sex	
Male	41 (77.4)
Female	12 (22.6)
Performance status	
ECOG I	36 (67.9)
ECOG II	17(32.1)
Histological classification	
Intestinal type	24(45.3)
Diffuse type	29(54.7)
Tumor grade	
0	10 (18.9)
1	24 (45.3)
3	19 (35)
Tumor site	
Cardia	16 (30.2)
Body	13 (24.5)
Antrum/pylorus	24 (45.3)

Pathologic complete response was observed in 16 (30.2%) patients. Moreover, 16 (30.2%) and 14 (26.4%) patients had a residual tumor in the area of the primary lesion and the area of the primary lesion with lymphatic nodes, respectively. Regarding surgical margin, 46 (86.8%) patients had R0 tumor resection (Table 2).

Table 2. Resection Status and Pathological Response Rate After Neoadjuvant Chemotherapy (N = 53)

Parameters	Values
Pathological response rate	
Complete	16 (30.2)
Residual tumor in stomach	23 (43.4)
Residual tumor in lymphatic nodes	0
Residual tumor in stomach.lymphatic nodes	14 (26.4)
Surgical margin	
R0	46 (86.8)
R1	7 (13.2)

Only two (3.8%) patients completed all eight cycles of chemotherapy in our treatment plan, while the majority (69.8%) received seven cycles. The completion rate of four preoperative courses of neoadjuvant chemotherapy was significantly higher than that of adjuvant chemotherapy (94.3% versus 3.8%). We also investigated adherence to the treatment plan and complications following chemotherapy, finding that most patients (90.6%) had a delay of at least three weeks and that the majority had mild hematologic side effects (Table 3).

Table 3. Complications and Patients' Adherence to Treatment Plan (N = 53)

Parameters	Values
Neutropenia	
Grade 0	38 (71.7)
Grade 1	13 (24.5)
Grade 2	1 (1.9)
Grade 3	1 (1.9)
Grade 4	0
Febrile neutropenia	
Yes	1 (1.9)
No	52 (98.1)
Thrombocytopenia	
Grade 0	1 (9. 1)
Grade 1	52 (98.1)
Treatment delays	
No delay	2 (3.8)
One week	2 (3.8)
Two weeks	1 (1.9)
Three weeks and more	48 (90.6)
Neoadjuvant chemotherapy cycles	
2	3 (5.7)
4	50 (94.3)
Adjuvant chemotherapy cycles	
0	10 (18.9)
1	1 (1.9)

Parameters	Values
2	3 (5.7)
3	37 (69.8)
4	2 (3.8)
Total chemotherapy cycles with FLOT regimen	
2	3 (5.7)
4	7 (13.2)
5	1 (1.9)
6	3 (5.7)
7	37 (69.8)
8	2 (3.8)

We categorized patients into two groups to find potential factors contributing to pathologic complete response. However, we did not find a significant difference between the groups regarding age (P = 0.91), sex (P = 0.65), performance status (P = 0.2), tumor histology (P = 0.14), tumor grading (P = 0.07), tumor location (P = 0.8), and the number of neoadjuvant chemotherapy cycles (P = 0.9). The data are presented at Table 4.

Table 4. Comparison of Patients' Characteristics Between Cases with and Without Pathologic Complete Response

Parameters	Non-PCR (N = 37)	PCR (N = 16)	P-Value
Age	51.4 ± 9.3	51.2 ± 12	0.91 [a]
Sex			0.65 [b]
Male	28 (75.7)	13 (81.3)	
Female	9 (24.3)	3 (18.8)	
Performance status			0.20 [b]
ECOG I	29 (78.4)	7 (43.8)	
ECOG II	8 (21.6)	9 (56.3)	
Histological classification			0.14 [b]
Intestinal type	15 (40.5)	9 (56.3)	
Diffuse type	22 (59.5)	7 (43.7)	
Tumor grade			0.07 [b]
0	5 (13.5)	5 (31.3)	
1	14 (37.8)	10 (62.5)	
3	18 (48.6)	1 (3.6)	
Tumor site			0.800 [b]
Cardia	11(29.7)	5 (31.3)	
Body	10 (27)	3 (18.8)	
Antrum/pylorus	16 (43.2)	8 (50)	
Neoadjuvant chemotherapy cycles			0.90 [b]
2	2 (5.4)	1 (6.3)	
4	35 (94.6)	15 (93.8)	

Abbreviation: PCR, pathologic complete response.

[a] Independent T-test.

[b] χ^2 test.

5. Discussion

More than one-fifth of patients in this study exhibited pathologic complete responses. We did not observe a significant difference between potential factors associated with pathologic complete responses, such as age, gender, level of functioning, tumor histology, tumor grading, tumor location, or the number of neoadjuvant chemotherapy cycles. In addition, the majority of patients who underwent surgery had R0 resection. In a clinical trial conducted in China in 2021, Sah et al. examined ten patients with gastric cancer (CT3-4bN1-3M0) who received four cycles of neoadjuvant chemotherapy using the FLOT regimen. All patients underwent radical gastric surgery. Nine patients achieved R0 resection, while three experienced complete/subtotal pathological regression. With a median follow-up period of 23.13 months, the two-year overall survival rate was 80%, and the two-year relapse-free survival rate was 70%. Two patients were deceased because of disease progression. In agreement with our findings, Sah et al. have concluded that neoadjuvant chemotherapy with the FLOT regimen is a safe and effective treatment for patients with gastric cancer (13).

In a 2021 observational study by Villanueva et al., 59 patients with gastric cancer (cT3-4 and/or N + M0) were treated with eight cycles of the FLOT regimen with a two-week interval and given the moniker total neoadjuvant chemotherapy. Of the 39 patients who underwent surgery, 18.2% had a pathologic complete response, and the overall survival time was 21.32 months on average (14). Garcia Grove et al.'s retrospective study evaluated the pathological response and survival of patients with resectable gastric adenocarcinoma or gastroesophageal junction adenocarcinoma treated with perioperative chemotherapy of the FLOT regimen. Five (14.7%) patients exhibited a pathologic complete response out of a total of 34 cases (15). Similarly, Zhang et al. reported that in 23 cases of gastric cancer (cT3-4 and/or N + M0) treated with four cycles of FLOT neoadjuvant chemotherapy with a two-week interval, R0 resection was achieved in 94.3% of patients, and pathologic complete response was confirmed in 13% of patients (16).

In 2019, Wang et al. compared the efficacy of FLOT neoadjuvant chemotherapy in treating 47 patients with gastric cancer (T3-4) to 269 patients who underwent primary surgery. They reported that R0 resection was performed in 88.4% and 86.4% of the FLOT and surgery

groups, respectively, without a significant difference ($P > 0.05$). After surgery, however, there were significantly more cases without lymph node metastasis in the FLOT group than in the surgery group (40.5% versus 7.7%). With a median follow-up of 41 months, survival analysis revealed significantly greater overall and three-year survival in the FLOT group versus the surgery group [(44 vs. 23 months, $P = 0.01$) and (58.7% vs. 30.9%, $P < 0.001$)] (9). Al-Batran et al. conducted a phase II/III clinical trial in which 300 patients with gastric or gastroesophageal adenocarcinoma clinically staged T2 or higher and N positive were randomly assigned to one of two treatment groups: Perioperative ECF/ECX (3 courses before surgery and three courses after surgery with a 3-week interval) or FLOT (4 courses before and four courses after surgery with a 2-week interval). The completion rates of planned chemotherapy in the FLOT and ECF/ECX groups were 93% and 92%, respectively. Patients treated with FLOT had a significantly higher pathologic complete response than those treated with ECF/ECX (16% vs. 6%, $P = 0.02$). Forty percent of the ECF/ECX group and 25 percent of the FLOT group reported at least one serious adverse effect (8).

Overall, our findings and previous reports have suggested that four-cycle neoadjuvant chemotherapy with FLOT before surgery is associated with pathologic complete response in 15 - 30% of patients with gastric cancer, which is significantly higher than the response rate observed in other chemotherapy regimens. Despite this, it is evident that a significant proportion of patients have not responded adequately to neoadjuvant chemotherapy, regardless of the regimen employed. This highlights the importance of future research into the prognostic and treatment-predictive effects of background genetic/molecular factors, as well as the development of novel targeted therapies based on these factors.

In this study, the majority (63.1%) of patients only received seven of the eight planned chemotherapy cycles. In addition, our findings revealed that complications were limited to mild hematological side effects, although a significant proportion of patients reported treatment delays of more than three weeks. Sah et al. demonstrated that all ten patients enrolled in the trial completed four courses of neoadjuvant FLOT chemotherapy with no serious hematologic adverse events (grade 3 or higher), with the exception of one case of grade 3 anemia. Nine patients completed four courses of adjuvant chemotherapy following surgery, but only one patient completed the full dose. In other patients, the adjuvant chemotherapy dose was reduced by 25% or less (13). Villanueva et al. reported that 65.5% of patients who completed eight courses of total neoadjuvant chemotherapy experienced major adverse effects (14). In addition, 20 of the 23 cases enrolled in the study by Zhang et al. completed the four planned courses of neoadjuvant chemotherapy. Following chemotherapy, leukopenia (17.4%), neutropenia (30.4%), anemia (13%), anorexia (13%), and nausea (14.7%) were the most common adverse events of grades 3 and 4 (16). Likewise, the most common non-surgical grade 3 and 4 adverse events in Al-Batran et al.'s trial were neutropenia (38% ECF/ECX vs. 52% FLOT), leukopenia (20% ECF/ECX vs. 28% FLOT), nausea (17% ECF/ECX vs. 9% FLOT), and infection (12% ECF/ECX vs. 12% FLOT) (8).

Theoretically, the number of FLOT cycles seems to be a prognostic factor of response to neoadjuvant chemotherapy. However, this study demonstrated it as a nonsignificant factor. This finding might stem from the small number of patients who completed the predefined chemotherapy cycles. In interpreting the results of our study, it is important to keep in mind that the majority of our patients completed neoadjuvant chemotherapy prior to surgery, while the majority of patients left the treatment plan in adjuvant chemotherapy. This is significant because it indicates that patients' tolerance to chemotherapy decreases following surgery. Consequently, it is reasonable to employ new techniques, such as total neoadjuvant chemotherapy, whose role in the treatment of rectal adenocarcinoma was recently highlighted.

This study had several limitations. First, we did not measure the expression levels of the HER2/neu, programmed death-ligand 1, and MSI genes in our patients. Given the importance of personalized medicine in treating patients with locally advanced gastric cancer, it is crucial to determine the prognostic significance of these genes. Second, we did not design a control group to compare with our regimen. Third, there was no analysis of survival. Fourth, the interference of the COVID-19 pandemic with appropriate patient care and treatment accommodation (17). We suggest that future research employ a prospective design with a control group and report both overall and disease-free survival. In addition, we recommend evaluating the prognostic and predictive significance of HER2/neu, programmed death-ligand 1, and MSI genes in patients with gastric cancer.

5.1. Conclusions

In conclusion, our findings demonstrated that pre- and postoperative neoadjuvant chemotherapy with the FLOT regimen is an appropriate method for treating patients with gastric cancer. This protocol produces a higher pathologic response rate, making it a good standard of care, especially for locally advanced gastric adenocarcinoma. Concerning a high incidence of adverse effects associated with the FLOT regimen, we recommend that the attending physician promptly calculate/adjust the therapeutic dose, consider the weight change, monitor bone marrow reserve, and examine the liver and renal function.

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Footnotes

Authors' Contribution: Study concept and design: M. K. and A. A.; acquisition of data: S. S.; analysis and interpretation of data: A. B. and S. A. A.; drafting of the manuscript: F. H.; critical revision of the manuscript for important intellectual content: M. K.; statistical analysis: Biostatician.

Conflict of Interests Statement: The authors report no conflicts of interest.

Data Availability: All data generated and analyzed during this study can be accessed through direct communication with the corresponding author and the agreement of all research team members.

Ethical Approval: The study protocol was approved by the Research Ethics Committee of Mashhad University of Medical Sciences (IR.MUMS.MEDICAL.REC.1400.272).

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Informed Consent: Patients signed consent forms for participation after an explanation of the aim, design, and protocol of the study.

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