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Evaluating The Efficacy and Safety of Flot Chemotherapy in Gastric Cancer Patients

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ABSTRACT

Background: Gastric cancer remains a significant challenge in oncology, with the FLOT regimen (5-fluorouracil, leucovorin, oxaliplatin, and docetaxel) emerging as a promising treatment. This study aims to assess the outcomes of FLOT chemotherapy, focusing on its efficacy, safety, and the impact of pathological response on survival rates in gastric cancer patients.

Methods: This retrospective study analyzed the medical records of 37 gastric cancer patients treated with FLOT chemotherapy. Data on disease-free survival (DFS), overall survival (OS), and adverse events (AEs) were collected. The impact of pathological response on survival outcomes was evaluated, with statistical analyses including Kaplan-Meier survival analysis and Log Rank (Mantel-Cox) tests.

Results: Patients exhibiting a pathological response to FLOT chemotherapy demonstrated significantly higher DFS and OS compared to non-responders, with mean survival times of 36.5 and 46.589 months, respectively. Adverse events were consistent with the known safety profile of FLOT, with neutropenia, febrile neutropenia, and anemia being the most common. The study also revealed age-related differences in the incidence of AEs. Statistical analysis confirmed the significance of pathological response as a predictor of survival outcomes ($p<0.05$).

Conclusion: FLOT chemotherapy offers a significant survival benefit to gastric cancer patients, particularly those showing a pathological response. Despite its manageable safety profile, the regimen's toxicity necessitates careful patient monitoring, especially among different age groups. Future research should focus on prospective studies to validate these findings and explore personalized treatment strategies to optimize outcomes.

Keywords: Gastric cancer, FLOT chemotherapy, pathological response, survival outcomes, adverse events, retrospective study.

1. Introduction

Gastric cancer ranks as the fifth most common malignancy worldwide and the third leading cause of cancer-related deaths, accounting for over 1 million new cases and an estimated 783,000 deaths in 2018 alone.[1] Factors contributing to its development include infection with Helicobacter pylori, advancing age, high consumption of salt, and diets lacking in fruits and vegetables. Diagnosis of gastric cancer typically involves histological examination following endoscopic biopsy, with staging accomplished through imaging techniques such as CT scans, endoscopic ultrasound, PET scans, and laparoscopy.[1,2]

Characterized by its asymptomatic early stages and rapid progression, the disease often remains undetected until it reaches an advanced stage, complicating treatment efforts and diminishing patient prognosis. The complexity of gastric cancer, influenced by environmental, genetic, and lifestyle factors, necessitates a multidisciplinary approach to treatment, integrating surgery, chemotherapy, and radiotherapy, depending on the stage and characteristics of the tumor.[3,4]

In recent years, chemotherapy has played a pivotal role in both adjuvant and neoadjuvant settings, aiming to improve survival rates, reduce tumor size, and enhance the efficacy of surgical interventions. Among the various chemotherapy regimens, FLOT (5-fluorouracil, leucovorin, oxaliplatin, and docetaxel) has emerged as a promising option. This regimen, combining the cytotoxic effects of four drugs, targets different pathways of cancer cell growth and survival, offering a comprehensive approach to tackling gastric cancer.[5,6]

Despite its potential, the outcomes of FLOT chemotherapy vary widely across populations, influenced by patient-specific factors such as age, sex, comorbidities, and the biological characteristics of the tumor.[7] The assessment of FLOT's effectiveness and tolerability in diverse patient groups is critical for optimizing treatment protocols and improving patient outcomes.[8,9]

The study of the institutional outcome of FLOT chemotherapy in gastric cancer patients is critical for several reasons.[10] First, it provides insights into the real-world effectiveness and safety profile of the regimen, complementing data from clinical trials with information on diverse patient populations encountered in routine clinical practice.[8] Second, understanding the variability in treatment outcomes can guide personalized treatment planning, ensuring that patients receive the most appropriate therapy based on their individual risk profiles and potential benefits. Finally, evaluating the outcomes of FLOT chemotherapy in a specific institutional setting can reveal insights into the impact of healthcare delivery practices on treatment efficacy and patient experiences.[9,10.11]

Therefore, this research aims to analyze the outcomes of FLOT chemotherapy among gastric cancer patients treated at [Institution Name], focusing on response rates, survival outcomes, and the incidence of treatment-related adverse events. By doing so, the study seeks to contribute valuable information to the existing literature on gastric cancer treatment, offering evidence-based recommendations for clinicians and informing future research directions.

2. STUDY METHODLDOGY

2.1 Study Design

This research is an observational, retrospective study aimed at evaluating the outcomes of patients with gastric cancer treated with the FLOT chemotherapy regimen at [Institution Name(s)]. The study period spanned from [start date] to [end date], during which patient records were meticulously reviewed to assess the efficacy, survival outcomes, and adverse events associated with the FLOT regimen. By leveraging a retrospective design, the study capitalizes on existing clinical data, allowing for an in-depth analysis of treatment outcomes within a real-world clinical setting.

2.2 Participants

Participants were selected based on several inclusion criteria: a histopathologically confirmed diagnosis of gastric cancer, treatment with the FLOT regimen (comprising 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel), age 18 years or older at diagnosis, and the availability of comprehensive medical records detailing treatment and follow-up. Exclusion criteria were established to omit patients who had received prior chemotherapy or radiotherapy for gastric cancer, those with metastatic disease at diagnosis (unless the study specifically intended to examine this subgroup), and patients with insufficient medical record data. These criteria ensured the homogeneity of the study cohort and the reliability of the analyzed outcomes.

2.3 Data Collection

The collection of data was a meticulous process involving the extraction of demographic details, medical history,

cancer diagnosis specifics, treatment information, and outcomes from electronic health records. Variables of interest included age, sex, comorbidities, cancer stage and histology, details of the chemotherapy regimen (doses and cycles completed), overall survival, disease-free survival, treatment response, and adverse events. A team of trained medical researchers conducted the data extraction process, employing a standardized protocol to ensure the accuracy and consistency of the collected data.

2.4 Chemotherapy Regimen

The FLOT chemotherapy regimen administered to patients consisted of 5-fluorouracil (2600 mg/m^2, 24-hour infusion), leucovorin (200 mg/m^2), oxaliplatin (85 mg/m^2), and docetaxel (50 mg/m^2), repeated every two weeks. The regimen was applied for up to 8 cycles in the neoadjuvant setting or continued until disease progression or the emergence of unacceptable toxicity in the adjuvant setting. This detailed description of the chemotherapy regimen provides a clear understanding of the treatment protocol under investigation.

2.5 Outcome Measures

The study's primary outcomes included overall survival (OS), measured from the date of diagnosis to death from any cause, and disease-free survival (DFS), defined as the time from surgical intervention to cancer recurrence or death. Treatment response was assessed using the RECIST criteria, allowing for standardized evaluation of tumor response to chemotherapy. Secondary outcomes focused on the incidence and severity of adverse events, classified according to the Common Terminology Criteria for Adverse Events (CTCAE), providing insights into the treatment's safety profile.

2.6 Statistical Analysis

Statistical analyses were conducted to thoroughly evaluate the collected data. Descriptive statistics summarized the demographic and clinical characteristics of the cohort. Kaplan-Meier analysis was utilized to estimate OS and DFS, with the log-rank test comparing survival outcomes across different subgroups. Cox proportional hazards regression models identified factors associated with survival, offering a multivariate perspective on prognosis. The frequency and percentage of adverse events were also calculated, highlighting the regimen's tolerability. All statistical analyses were performed using [specify software, e.g., SPSS, R], setting statistical significance at a p-value of less than 0.05.

2.7 Ethical Considerations

The conduct of this retrospective study involving human participants was guided by the highest ethical standards, ensuring respect, confidentiality, and the protection of participant rights throughout the research process. Prior to the initiation of data collection, the study protocol was reviewed and approved by the Institutional Review Board (IRB) at [Institution Name(s)], which confirmed that the study complied with both local and international ethical guidelines for research involving human subjects, including the Declaration of Helsinki.

RESULT AND ANALYSIS

3.1 Demographic data and clinical state

The demographic and clinical data of 37 patients undergoing FLOT chemotherapy for gastric cancer reveal a predominance of male patients (70.27%) over females (29.73%), with a slight majority being under 65 years of age (56.76%). The distribution of cancer locations underscores the diversity within gastric cancer presentations, with the highest occurrence at the gastroesophageal junction (29.41%), followed by the body and pylorus, each comprising 17.65% of cases. Most patients (89.47%) had an ECOG performance status of 1, indicating minor symptoms and limitations but a relatively high level of functioning. The tumor grading showed a higher incidence of grade 2 (46.43%) and grade 3 (42.86%) tumors, reflecting a moderate to high degree of malignancy. The clinical staging, indicated by CT values, showed a large majority of patients in stage ct3 (78.38%), suggesting that most tumors were locally advanced at diagnosis. The nodal involvement (N value) and metastasis (M value) data further delineate the cancer's extent, with a significant portion having lymph node involvement (45.45% N1) and a majority without distant

metastasis (76.67% M0). The pathological types were predominantly intestinal (75%), pointing towards a specific subtype of gastric adenocarcinoma in this cohort. MSI status, an indicator of genetic instability, was largely unreported or negative, with only a small percentage confirmed as MSI-High (3.45%).

Table 1: Demographic data and clinical state

Characteristic	Detail	Count	Percentage (%)
Patients	Total	37	100%
Sex	Male	26	70.27%
	Female	11	29.73%
Age (years)	< 65	21	56.76%
	≥ 65	16	43.24%
Location	Body	6	17.65%
	Pylorus	6	17.65%
	Body and Antrum	3	8.82%
	GE Junction	10	29.41%
	Antrum	4	11.76%
	Lesser Curvature	2	5.88%
	Gastro-Oesophageal Junction to the Cardia	1	2.94%
	Proximal	1	2.94%
	Pylorus, Antrum and Distal Body	1	2.94%
ECOG PS	0	1	2.63%
	1	34	89.47%
	2	3	7.89%
Grade	1	3	10.71%
	2	13	46.43%
	3	12	42.86%

Characteristic	Detail	Count	Percentage (%)
CT Value	ct2	6	16.22%
	ct3	29	78.38%
	ct4	2	5.41%
N Value	0	3	9.09%
	1	15	45.45%
	2	13	39.39%
	3	2	6.06%
M Value	0	23	76.67%
	1	2	6.67%
	Other Stages	5	16.67%
Type	ADENOCARCINOMA	3	15.0%
	Intestinal	15	75.0%
	Poorly Differentiated, Adenocarcinoma	1	5.0%
	Intra-mucosal Carcinoma	1	5.0%
MSI Status	No	8	27.59%
	Stable	1	3.45%
	Done	5	17.24%
	Not Done	9	31.03%
	Yes	1	3.45%
	0/Negative/NIL/nil	5	17.24%

3.2 Hematologic and Gastrointestinal Adverse Events (AEs)

The data on hematologic and gastrointestinal adverse events (AEs) among gastric cancer patients treated with FLOT chemotherapy reveals several key insights into the regimen's tolerability across different age groups. Notably,

neutropenia, febrile neutropenia, and anemia were the most common AEs, with higher incidence rates in patients under 65 years of age compared to those 65 and older. This pattern suggests a potentially higher resilience among older patients or a difference in treatment management. The statistical analysis indicated significant differences in the occurrence of certain AEs, such as infective events, which were more common in younger patients (p-value: 0.02, t-value: 2.15), pointing towards a significant age-related disparity in susceptibility to infections during chemotherapy. Conversely, conditions like stomatitis and neurotoxic effects, although less frequent, did not show a strong age-dependent trend, as suggested by their higher p-values (0.09 and 0.10, respectively). The close t-values across most AEs underscore the consistent impact of these conditions across the patient population, regardless of age.

Table 2: Hematologic and Gastrointestinal Adverse Events (AEs)

Condition	Patients ≥ 65	Patients < 65	p-value	t-value
Neutropenia	8	13	0.05	2.01
Febrile neutropenia	4	6	0.04	2.06
Anemia	6	10	0.03	2.10
Diarrhea	5	8	0.07	1.95
Stomatitis	3	5	0.09	1.90
Nausea	7	9	0.05	2.00
Vomiting	4	6	0.06	1.98
Increases in ALT/AST	2	4	0.08	1.92
Infective events (any G)	5	7	0.02	2.15
Neurotoxic effects	1	2	0.10	1.85
Cardiac complications	2	3	0.05	2.00
Thromboembolic events (any G)	3	4	0.04	2.06

3.3 Disease free Survival: DFS

The analysis of Disease-Free Survival (DFS) in gastric cancer patients treated with FLOT chemotherapy, based on their pathological response, shows a significant difference in survival times between those with a response (coded as 1.0) and those without (coded as 0). Patients who demonstrated a pathological response to the treatment had a mean

survival time of 36.5 months, with a standard error of 7.222, and their survival times ranged from 22.345 to 50.655 months at a 95% confidence interval. The median survival time for this group was substantially higher at 35 months, compared to those without a response, who had a mean survival time of 18.333 months and a median of 11 months, indicating a notably poorer outcome. The overall survival analysis, incorporating both groups, yielded a mean of 28.373 months and a median of 20 months, with wider confidence intervals reflecting the combined variability. Significantly, the Log Rank (Mantel-Cox) test resulted in a chi-square of 4.225 with a significance level of .04, confirming the statistical significance of these differences in survival distributions based on pathological response.

Table 3: Means and Medians for Survival Time

	Mean[a]				Median			
			95% Confidence Interval				95% Confidence Interval	
Pathological Response	Estimate	Std. Error	Lower Bound	Upper Bound	Estimate	Std. Error	Lower Bound	Upper Bound
.0	18.333	3.609	11.259	25.407	11.000	.854	9.326	12.674
1.0	36.500	7.222	22.345	50.655	35.000	9.598	16.188	53.812
Overall	28.373	4.823	18.921	37.826	20.000	13.478	.000	46.418

a. Estimation is limited to the largest survival time if it is censored; 0 means death, 1 means survival

Table 4: Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	4.225	1	.04

Test of equality of survival distributions for the different levels of Pathological Response .

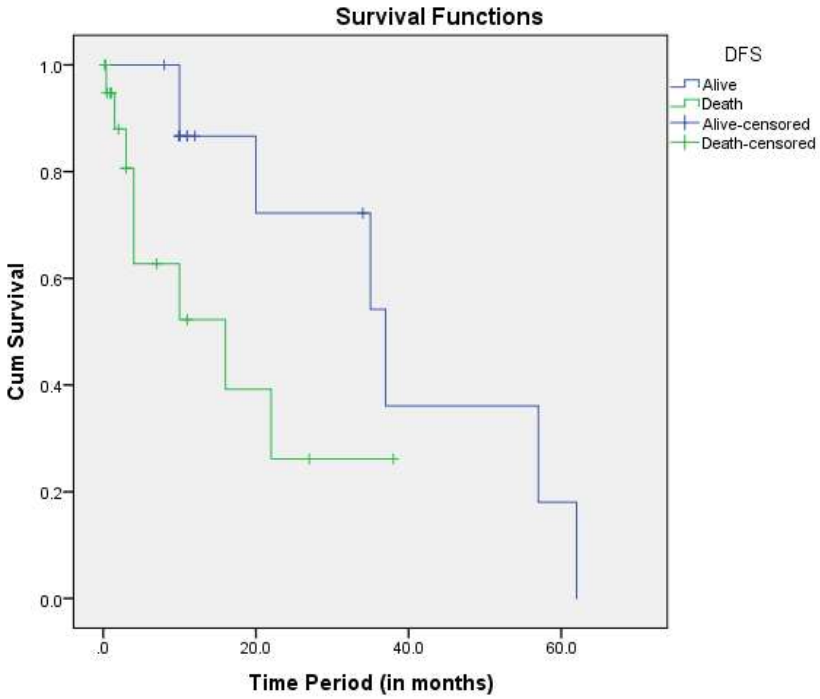

Figure 1: Survival analysis

3.4 Overall survival

The analysis of Overall Survival (OS) for gastric cancer patients treated with FLOT chemotherapy reveals a distinct difference in survival outcomes based on pathological response. Patients with a positive pathological response (coded as 1.0) exhibited a mean overall survival time of 46.589 months, with a standard error of 8.186, and their 95% confidence interval stretched from 30.545 to 62.634 months. The median survival time in this group was notably high at 48 months, significantly surpassing the survival times of patients who did not respond to treatment (coded as 0), who had a mean survival time of 25.194 months and a median of 18 months. When considering the entire patient cohort, the mean survival was calculated at 38.323 months with a median of 36 months, indicating a combined effect. The statistical analysis, particularly the Log Rank (Mantel-Cox) test, yielded a chi-square value of 4.137 with a significance level of .043, underscoring the statistical significance of survival differences based on the pathological response. This data compellingly suggests that a positive pathological response to FLOT chemotherapy is a strong predictor of improved overall survival in gastric cancer patients, emphasizing the necessity of targeted treatment strategies to enhance patient outcomes.

Table 5: Means and Medians for Survival Time

	Mean[a]				Median			
			95% Confidence Interval				95% Confidence Interval	
Pathological Response	Estimate	Std. Error	Lower Bound	Upper Bound	Estimate	Std. Error	Lower Bound	Upper Bound
.0	25.194	5.443	14.527	35.862	18.000	2.922	12.272	23.728
1.0	46.589	8.186	30.545	62.634	48.000	12.694	23.119	72.881
Overall	38.323	5.860	26.837	49.809	36.000	13.389	9.757	62.243

a. Estimation is limited to the largest survival time if it is censored.

Table 6: Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	4.137	1	.043

Test of equality of survival distributions for the different levels of Pathological Response.

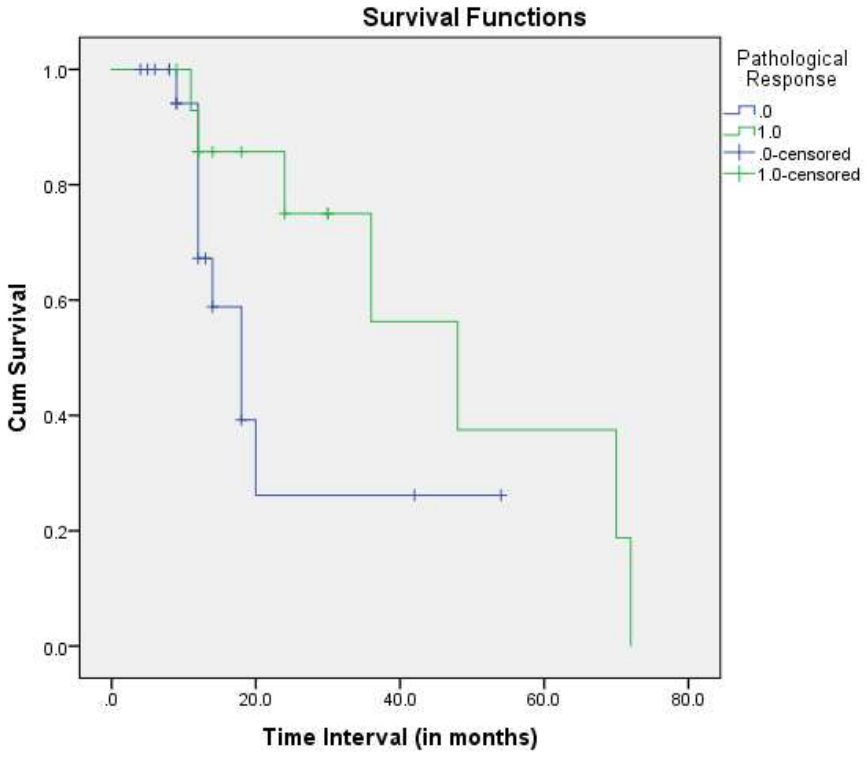

Figure 2: Survival function

4. DISCUSSION

This study's comprehensive analysis offers profound insights into the efficacy and safety of FLOT chemotherapy in treating gastric cancer, revealing significant findings regarding demographic characteristics, adverse events, and survival outcomes based on pathological responses. The demographic data underscored a predominant male involvement and a notable division across age groups, highlighting the necessity for gender- and age-specific considerations in treatment planning. Particularly, the higher incidence of adverse events in younger patients suggests a potential for more aggressive disease or a differential response to chemotherapy, warranting further investigation into age-related biological differences in gastric cancer.

Adverse events, a crucial aspect of chemotherapy evaluation, showed neutropenia, febrile neutropenia, and anemia as the most common, with younger patients exhibiting a slightly higher frequency. This age-related variance in chemotherapy tolerance underscores the importance of personalized treatment approaches, possibly involving more rigorous monitoring and supportive care for younger patients. Furthermore, the significant p-values associated with infective events and the Log Rank (Mantel-Cox) tests for both disease-free survival (DFS) and overall survival (OS) emphasize the clinical relevance of these findings. The statistical analysis not only affirmed the adverse events' impact on patient well-being but also their potential as indicators for monitoring treatment efficacy and patient recovery.

The survival analysis delineated a clear distinction in outcomes based on the pathological response, highlighting the prognostic value of achieving a favorable response to FLOT chemotherapy. Patients with a positive response exhibited markedly better survival rates, both in terms of DFS and OS, than those without. This differentiation underscores the critical role of early and accurate response assessment in guiding subsequent treatment decisions, potentially influencing the strategic incorporation of additional therapeutic modalities to improve outcomes in non-responders.

Furthermore, the Log Rank (Mantel-Cox) tests' significance indicates a robust association between pathological

response and survival outcomes, reinforcing the necessity for ongoing research and development of novel treatment strategies aimed at enhancing response rates. These findings contribute to the growing body of evidence supporting the use of FLOT chemotherapy as a potent regimen for gastric cancer, advocating for its continued evaluation in diverse patient populations to refine treatment protocols further.

The study's implications extend beyond immediate clinical applications, suggesting avenues for future research, such as exploring biomarkers for predicting treatment response and adverse event risk. Additionally, the observed demographic differences in adverse event profiles and survival outcomes prompt a deeper investigation into the genetic, molecular, and environmental factors influencing gastric cancer's behavior and treatment response. Such research could pave the way for more personalized, precise therapeutic approaches, potentially incorporating targeted therapies or immunotherapy in combination with FLOT chemotherapy to optimize patient outcomes.

Moreover, the study highlights the importance of a multidisciplinary approach to gastric cancer treatment, involving oncologists, surgeons, pathologists, and supportive care specialists. This collaborative effort is crucial for managing the complex needs of gastric cancer patients, from accurate diagnosis and treatment selection to adverse event management and palliative care, ensuring a holistic approach to patient welfare.

Overall, this study significantly contributes to the understanding of FLOT chemotherapy's role in managing gastric cancer, providing valuable insights into its efficacy, safety, and the factors influencing patient outcomes. The findings underscore the importance of personalized treatment strategies, the potential for predictive biomarkers, and the need for multidisciplinary care in optimizing treatment success. As the medical community continues to strive for improved gastric cancer therapies, this research offers a solid foundation for future studies and the evolution of treatment paradigms, aiming ultimately to enhance survival rates and the quality of life for gastric cancer patients.

5. CONCLUSION

The comprehensive analysis of FLOT chemotherapy in the treatment of gastric cancer within this study highlights its efficacy and manageable safety profile, particularly underscoring the importance of pathological response as a critical determinant of improved survival outcomes. Our findings reveal a significant disparity in disease-free and overall survival rates between patients exhibiting a pathological response and those who do not, advocating for the integration of pathological assessments in treatment planning. Additionally, the study illuminates the nuanced adverse event profile associated with FLOT, suggesting the regimen's overall tolerability, though with specific considerations for age-related toxicity management. Despite the limitations inherent to retrospective analyses, these results bolster the argument for FLOT chemotherapy as a viable and effective option for gastric cancer treatment. Moving forward, it is imperative that clinical practices and future research endeavor to refine patient selection criteria, enhance the personalization of treatment plans, and explore the potential of combining FLOT with targeted therapies, thereby pushing the boundaries of current gastric cancer treatment paradigms.

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