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Neoadjuvant chemotherapy outcome with taxane-based versus non-taxane protocols in gastric cancer

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Abstract:

BACKGROUND: Gastric cancer is the fifth most common cancer worldwide. One of the chemotherapy agents, taxanes is important in increasing patients' survival. The purpose of this study is to assess the efficacy of taxane-based drugs versus non-taxanes in neoadjuvant chemotherapy in non-metastatic gastric adenocarcinoma (GA) in Iranian patients.

MATERIALS AND METHODS: In a historical cohort method, 65 patients between 18 and 75 years old who suffered from non-metastatic GA were included. Nineteen and 21 and 25 patients, had undergone DCF (docetaxel, cisplatin, 5fluorouracil) and FLOT (5fluorouracil, leucovorin, oxaliplatin, docetaxel) and FOLFOX6 (oxaliplatin, leucovorin, 5fluorouracil) regimens, respectively, between 2018 and 2021. Survival criteria consisting of progression-free survival (PFS), overall survival (OS), progression rate, and mortality rate were evaluated using the Kaplan–Meier method, in a three-year follow-up period.

RESULTS: The majority of patients were male (72.3%), with a median age of 65 years. Most of the patients had lesions with tumor, node, metastasis (TNM) stage IIIb (27.7%) and poor differentiated pathological grade (49.2%). OS time had a significant correlation with the low TNM stage ($P = 0.01$), well-differentiated pathological grade ($P = 0.005$), and FLOT vs. FOLFOX protocol (20.3 vs. 12.2 months, respectively. $P = 0.04$). FLOT regimen had significantly better OS survival vs. DCF regimen (20.3 vs. 15.4 months, respectively, $P = 0.03$). No significant correlation was observed between survival criteria and other factors like gender, age, past medical history, Karnofsky scale, and tumor location in the stomach. The taxane-based arm (sum of DSF and FLOT) had no superiority over the non-taxane arm in survival criteria.

CONCLUSION: FLOT protocol, as a taxane-based regimen had better survival compared to FOLFOX protocol in neoadjuvant chemotherapy in gastric non-metastatic adenocarcinoma.

Keywords:

Folfox protocol, gastric cancer, neoadjuvant chemotherapy, taxanes

Background

Gastric cancer is a major worldwide problem in both developed and developing countries. GLOBOCAN 2020 estimates of cancer incidence and mortality, produced by the International Agency for Research on Cancer, states that gastric cancer represents the fifth most common tumor and the fourth cause of cancer-related death worldwide.[1] Gastric cancer can be treated if detected in the early stages. The main treatment for gastric cancer is surgery, and chemotherapy and radiotherapy are given along with it if needed.[2,3]

Many researchers have accepted the role of neoadjuvant chemotherapy for advanced gastric cancer.

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(MAGIC)[4] and The Federation Nationale des Centres de Lutte Contre Le Cancer and the Federation Francophone de Cancerologie Digestive (FNCLCC/FFCD ACCORD)[5] studies are two important trials in this field; and both trials have shown a significant improvement in survival criteria in patients treated with perioperative chemotherapy with drugs epirubicin, cisplatin, and 5-fluorouracil. Subsequent studies showed that a taxane-containing chemotherapy regimen is effective and tolerable.[6]

In several types of research, taxane classes consisting of paclitaxel and docetaxel have been used in systemic chemotherapy regimens for gastric cancer.[7] Different chemotherapy regimens have been introduced and this study aims to compare the outcomes of neoadjuvant chemotherapy with taxane-based regimens including DCF (docetaxel, cisplatin, 5fluorouracil) and FLOT (5fluorouracil, leucovorin, oxaliplatin, docetaxel) versus a non-taxane-based regimen FOLFOX6 (oxaliplatin, leucovorin, 5fluorouracil), in non-metastatic gastric adenocarcinoma (GA) in Iranian patients. Due to the fact that many different drugs and protocols have been introduced for cancer chemotherapy, conducting such comparative studies will help researchers in choosing appropriate treatments.

Materials and Methods

Study design and setting

This historical cohort study was conducted in two academic hospitals (Taleqani and Firoozgar), by the hematology and oncology departments of two universities, between 2018 and 2021 in Iran.

Study participants and sampling

Sixty-five adult patients aged 18 to 75 years, diagnosed with non-metastatic GA who were candidates for neoadjuvant treatment were included. The students evaluated the patients and did data collection and analysis. All steps were under the supervision of academic professors.

Data collection tool and technique

The disease diagnosis was based on radiologic and endoscopic studies. Initial evaluations included patients' history, physical examination, laboratory and radiologic examinations, demographic characteristics and tumor clinicopathological characteristics, tumor, node, metastasis (TNM) stage, and pathological grade. All are in accordance with standard guidelines.

We considered DCF and FLOT as taxane-containing protocols and FOLFOX6 as a well-established non-taxane-based protocol for comparison. The components of these regimens are similar except for the taxane drug, specifically about FLOT with FOLFOX6. As a result, their comparison determines the effect of adding Texan drugs to the survival criteria.

The selection process of the type of chemotherapy protocol was according to the physician's decision. Nineteen and 21 and 25 patients, had undergone DCF and FLOT and FOLFOX regimens, respectively, according to Table 1.[8-11]

The patients were operated on and received post-operative care. The follow-up matters have been based on serial examinations and endoscopic and radiologic evaluations. Clinical and radiological response and survival results were retrieved from patients' records.

Progression-free survival (PFS) is defined as the duration from the start time of chemotherapy to the first clinical or radiological evidence of disease progression or death occurrence from any reason. Disease-free survival (DFS) means the rate of patients who have been cured and had not shown any sign of disease in the follow-up period. Overall survival (OS) is defined as the duration from the start time of chemotherapy to follow-up discontinuation or death from any cause. Progression rate (PR) and mortality rate (MR) are the percentages of patients who show tumor progression or die during the follow-up period, respectively. For statistical analysis, IBM SPSS Statistics for Windows 10, Version 26.0. (IBM Corp) and Intel Core i7-11th Generation were used. The baseline characteristics were compared by the Chi-square or two-sample *t*-test tests. Survival criteria were analyzed using the Kaplan–Meier method and survival curves were drawn accordingly. The log-rank test was used for univariate analysis, and Cox regression for multivariate analysis. The value of $P < 0.05$ was considered significant.

Ethical consideration

The patients were included in the study with informed consent. Each patient was assigned a code and the patients' secrets were kept.

Results

Of 65 assigned patients, the majority were male (72.3%) and the mean age at the time of diagnosis was 65 years. 58.5% had a previous history of disease and comorbidity. 13.8% had tobacco use and 9.2% were addicted to opium. Karnofsky performance status scale (KPS) was 80 before treatment, and this average did not differ significantly during the chemotherapy period. The most common location of tumors was the mid-to-upper stomach, referring to the middle and upper thirds of the stomach corpus, which include the cardia and fundus (46.2%). The most common The size and the extent of the main tumor

Table 1: Chemotherapy regimens details[8-11]

Regimen	Drug	Dose	Prescribing Method	Interval
DCF	Docetaxel	75 mg/m^2	IV infusion over 2 h on day 1	Every 3 weeks
	Cisplatin	75 mg/m^2	IV infusion over 2 h on day 1	
	5Fluorouracil	750 mg/m^2	Continuous iv infusion on days 1 to 5	
FLOT	5Fluorouracil	2600 mg/m^2	Continuous iv infusion on day 1	Every 2 weeks
	Leucovorin	200 mg/m^2	IV infusion over 2 h on day 1	
	oxaliplatin	85 mg/m^2	IV infusion over 2 h on day 1	
	Docetaxel	50 mg/m^2	IV infusion over 2 h on day 1	
FOLFOX6	Oxaliplatin	85 mg/m^2	IV over 2 h on day 1	Every 2 weeks
	Leucovorin	350 mg/m^2	IV over 2 h on day 1	
	5Fluorouracil	400 mg/m^2	Bolus infusion over 2 h on day 1	
	5Fluorouracil	2400 mg/m^2	Continuous iv infusion over 46 h on days 1 and 2	

and The number of nearby lymph nodes (T and N) stages were T3 and N3 (69.2% and 38.5%, respectively), and the most common TNM stage was IIIb (27.7%) followed by IIIa. 50.8% of the patients had well or moderate and 49.2% had poor differentiated pathological tumor grades.

Generally, values of survival criteria in patients were as follows: PFS: 12.3 months, DFS: 21.5%, OS: 15.7 months, 1-year OS: 58.4%, 2-year OS: 26.1%, PR: 61.5%, and MR: 47.7%.

PFS, DFS, 1-year OS, 2-year OS, OS, PR, and MR did not have any significant correlation with sex, age, past medical history, smoking, and location of the tumor in the stomach. Some of these criteria correlated with the age and TNM stage and pathological grade of the tumor.

PFS had a significant correlation with FLOT vs. FOLFOX group (16.8 vs. 10 months, P = 0.03, Chart 1) and was confirmed in multivariate analysis.

OS had correlation with FLOT vs. DCF (20.3 vs. 15.4 months, P = 0.03, Chart 2) but was not confirmed in multivariate analysis (%95 CI = 0.13-1.2, P = 0.08). OS correlated with FLOT vs. FOLFOX regimen (20.3 vs. 12.2 months, P = 0.04, Chart 3), which was also confirmed in multivariate analysis. Other than the above, no other correlation was detected between survival criteria and drug regimens.

There was no correlation between survival criteria and taxane group (sum of DSF and FLOT) vs. FOLFOX regimen, whereas this correlation was detected regarding FLOT vs. FOLFOX protocol.

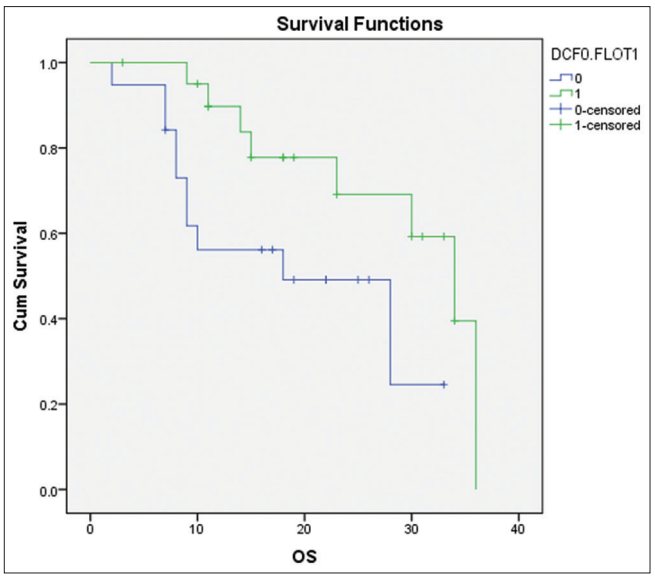

Chart 1: Comparison of PFS between FOLFOX and FLOT protocols

Discussion

Gastric cancer is the fifth most common tumor and the fourth cause of cancer-related death worldwide.[1] It contributes to a major economic medical burden and population mortality. GLOBOCAN 2020 estimates of cancer incidence and mortality show an estimated 19.3 million new cancer cases and 10 million cancer-related deaths worldwide in 2020. Breast cancer has a first place with an estimated 2.3 million new cases (11.7%), followed by lung, colorectal, prostate, and stomach (5.6%) cancers. Lung cancer remained the most common cause of cancer death, with an estimated 1.8 million (18%), followed by colorectal, liver, and then stomach (7.7%).[1] More than 50% of patients are neglected and diagnosed with a locally advanced stage because of a lack of effective screening programs.[12] The main treatment for gastric cancer is surgery, with chemotherapy and radiotherapy given if needed.[2,13] Many clinicians agree that neoadjuvant chemotherapy for operable GA provides the survival benefit over surgery alone and should be considered.[4]

The landmark trials in this context are MAGIC[4] and FNCLCC/FFCD ACCORD[5] studies, both showing a significant improvement in OS in patients treated with perioperative chemotherapy with drugs epirubicin, cisplatin, and 5-fluorouracil. The German FLOT-4 study is the more recent clinical trial in this field that compared the MAGIC regimen with a taxane-containing triplet (FLOT protocol) and demonstrated an improvement in median

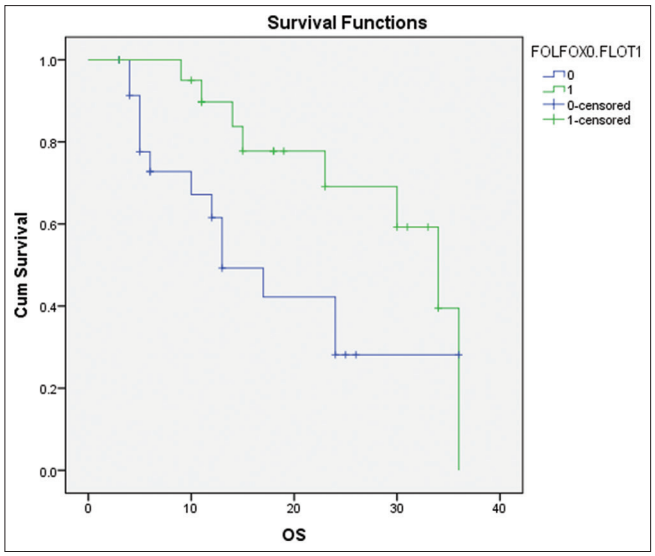

Chart 2: Comparison of OS between DCF and FLOT protocols

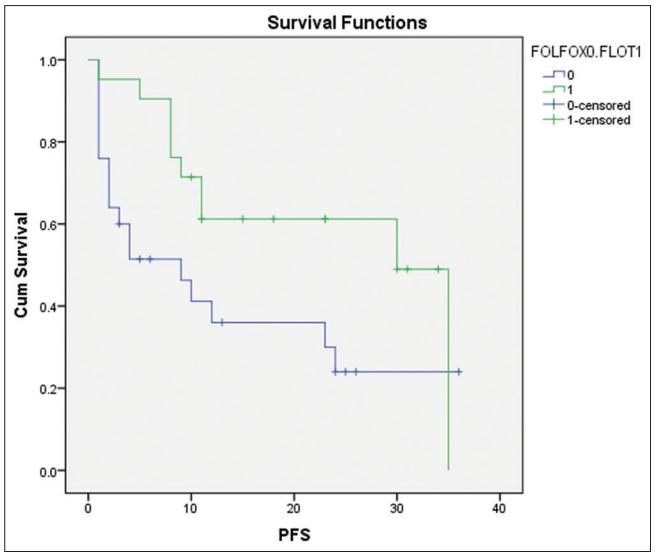

Chart 3: Comparison of OS between FOLFOX and FLOT protocols

PFS in the FLOT arm.[14] The other studies could demonstrate that a taxane-containing chemotherapy regimen is effective and well-tolerated.[6] Comparative studies of various chemotherapy drugs for gastric cancer indicate that docetaxel, oxaliplatin, and 5-FU are acceptable treatment options.[13]

Numerous studies showed that taxanes, a class of antitumor and antileukemic agents consisting of paclitaxel and docetaxel, have been used in various systemic chemotherapy regimens for gastric cancer.[7] Paclitaxel was derived from the bark of the Pacific yew tree Taxus brevifolia[15] and docetaxel was isolated from the needle leaves of the European Taxus baccata. It has been shown that these extracts have an assembly-promoting effect on microtubule proteins, which interrupts cell proliferation and division.[16-18]

The number of chemotherapy drugs approved each year has been growing progressively, which makes it difficult for clinicians to select suitable medicine.[3] Therefore, further studies and scientific points of view in this field are of great help to the treatment and survival of patients.

In an extensive meta-analysis study, Anna Dorothea Wagner *et al*.[13] in Switzerland reviewed 64 randomized controlled trials (RCTs) that had compared systemic, intravenous, and oral chemotherapy with the best basic supportive care for advanced gastric cancer. The following results were obtained: Combination chemotherapy improves survival compared to 5-FU monotherapy. Docetaxel, 5-FU, or oxaliplatin are valid options and the treatment decision could be based on side effects. Irinotecan and docetaxel-containing protocols show survival benefits in the studies. Docetaxel-containing three-drug protocols (DCF, FLOT) show better results, but both advantages and toxicity of such combinations should be considered.

Zheng *et al*.[19] in China compared oxaliplatin and taxane drugs in GA chemotherapy and concluded that in diffuse-type cancer, the oxaliplatin arm had better DFS and OS results than with the taxane-based arm; whereas there was no statistical difference observed in the intestinal type.

In a study by Borges *et al*.[20] in Portugal, the primary treatment outcomes of taxane-based triplets (DCF and FLOT) were compared with anthracycline-based triplets (FOLFOX, XP [Capecitabine and Cisplatin]) in inoperable advanced GA. The second group indicated better PFS and OS criteria.

Shi *et al*.[21] in China performed a systematic review and meta-analysis and assessed the effect of taxanes as the first-line treatment of GA. They concluded that adding taxanes to current first-line treatments improves OS and PFS criteria. Similar to that of conventional chemotherapy drugs (oxaliplatin and epirubicin, etc.), it should be considered that these treatments also increase the risk of toxicity and complications.

In a study by Van Den Ende *et al*.[22] in the Netherlands, it was shown that the use of surgery alone reduced OS in patients with GA by 58% compared to adding taxane-based perioperative chemotherapy, and therefore, it was recommended.

Kim *et al*.[23] in France showed that using taxane-based chemotherapy resulted in more successful tumor resection and increased OS up to 41 months.

In a study by Atarian *et al*.[24] in Iran, adding docetaxel to a common regimen and prescribing the DCF protocol in inoperable GA, improved PFS and OS significantly, with a brief increase in toxicity. Researchers recommended the DCF regimen as one of the standard options in untreated advanced GA.

In another study by Samiei F *et al*.[25] in Iran, epirubicin, oxaliplatin, and capecitabine (EOX) were prescribed in patients with advanced gastric cancer and downstaging of tumors and an acceptable answer was obtained.

The present historical cohort study was conducted in two academic hospitals in Iran. Of 65 assigned patients, the majority were male and the mean age at the time of diagnosis was 65 years. KPS scale was 80 before treatment and this average did not differ significantly during the chemotherapy period.

The most common location of tumors was the mid-to-upper stomach.

The most common T and N stage was T3 and N3 and the most common TNM stage was IIIb followed by IIIa. 50.8% of patients had well or moderate and 49.2% had poorly differentiated tumor grades. Generally, the mentioned demographic characteristics and results are consistent with other studies.[20,24]

We considered DCF and FLOT as taxane-containing protocols and FOLFOX6 as a non-taxane-based well-established protocol for comparison. The components of these regimens are similar except for the taxane drug, specifically about FLOT with FOLFOX. Therefore, their comparison determines the effect of adding taxane drugs to the survival criteria.

The survival criteria were analyzed using the Kaplan–Meier method and survival curves were obtained. The log-rank test was used for univariate analysis, and Cox regression for multivariate analysis.

Values of survival criteria in patients were as follows: PFS: 12.3 months, DFS: 21.5%, OS: 15.7 months, 1-year OS: 58.4%, 2-year OS: 26.1%, PR: 61.5%, and MR: 47.7%.

These criteria had correlations with some of the tumor characteristics like the age and TNM stage and pathological grade of the tumor.

PFS had a significant correlation with FLOT vs. FOLFOX group (16.8 vs. 10 months, $P = 0.03$, Chart 1) and was confirmed in multivariate analysis.

OS had correlation with FLOT vs. DCF (20.3 vs. 15.4 months, $P = 0.03$, Chart 2) but was not verified in multivariate analysis (%95 CI = 0.13-1.2, $P = 0.08$). OS correlated with FLOT vs. FOLFOX regimen (20.3 vs. 12.2 months, $P = 0.04$, Chart 3) which was also confirmed in multivariate analysis. Other than the above, no other correlation was detected between survival criteria and drug regimens.

There was no correlation between survival criteria and taxanes group (sum of DSF and FLOT) vs. FOLFOX regimen, whereas this correlation was detected about FLOT vs. FOLFOX protocol.

The superiority of the FLOT regimen over DCF is in the addition of the fourth drug (leucovorin), where, of course, the resulting side effects should be considered. As the mentioned studies show, and confirmed in the present study, as the first research about this issue in Iran, the taxane-based protocols have superiority over other protocols in the neoadjuvant chemotherapy in GA. In particular, the FLOT protocol shows better results and its use can therefore be recommended. Evaluation of the complications of chemotherapy drugs was not investigated in this study and should be considered in the selection of medication. All the discussed regimens have been approved in different studies and may be chosen based on the patient's conditions and the physician's experience.

Limitations and recommendations

The sample size was small and the results should be examined in larger studies. Also, the patients' follow-up duration should be increased. The side effects of chemotherapy drugs should be investigated in additional studies. Randomized clinical trials can confirm the results.

Conclusion

FLOT protocol as a taxane-based regimen was correlated with better survival criteria compared to FOLFOX protocol in neoadjuvant chemotherapy in gastric non-metastatic adenocarcinoma. Larger studies are ultimately necessary.

List of abbreviations

GA: gastric adenocarcinoma; KPS: Karnofsky performance status scale; TNM: tumor, node, metastasis staging classification; DCF: docetaxel, cisplatin, 5fluorouracil; FLOT: 5fluorouracil, leucovorin, oxaliplatin, docetaxel; FOLFOX: oxaliplatin, leucovorin, 5fluorouracil; PFS: progression-free survival; DFS: disease-free survival; OS: overall survival; PR: progression rate; MR: mortality rate.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

Authors ' contributions

ShK is the first author, Concept and design: ShK, SS, HR; SS is the Corresponding author; Data collection, implementation: MF, MA, ASH; Manuscript writing: ShK, MF, SS; Data Analysis: ShK, MF, MA, Ash, MDGh; All authors read and approved the final manuscript.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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