

Triplet or Doublet Chemotherapy Regimens in Metastatic Gastric Cancer

Abstract

Chemotherapy is the most important treatment option for patients diagnosed at an advanced stage. Chemotherapy both prolongs survival and increases the quality of life. Today, there is still no definite information about whether doublet or triplet chemotherapy should be chosen in empirical therapy. Therefore, we designed our study to evaluate first-line treatment options in metastatic gastric cancer. Our study is retrospective and involves five centers in Turkey. Inclusion criteria were the presence of metastatic gastric adenocarcinoma pathology, not having received treatment for local gastric cancer (surgery, chemotherapy, or radiotherapy), having received chemotherapy (patients with two or more combinations of drugs were included in the study, and patients who received single-drug chemotherapy were not included) for metastatic disease and being HER-2 negative. The survival of the triplet chemotherapy group was significantly longer when compared with the patients who received oxaliplatin-based doublet chemotherapy (11.1 vs. 8.1 months $p=0.007$). When the patients who received triplet chemotherapy and those who received cisplatin-based doublet chemotherapy were compared, there was no statistically significant difference (11.13 vs. 10.57 months $p=0.665$). If chemotherapy will be chosen as the first-line treatment in metastatic gastric cancer, choosing triplet chemotherapy regimens if possible, and if doublet chemotherapy will be given for any reason, choosing cisplatin-based regimens may be more appropriate, especially for the patient population in Turkey.

Keywords: Gastric cancer, Triplet, Doublet, Cisplatin

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Introduction

Cancer is one of the deadliest diseases in the world after cardiovascular disease. These diseases are the second leading cause of death in developed countries and the third leading cause of death in less developed countries.^[1] Gastric cancer ranks 5th in cancer prevalence with more than one million cases per year, while it is a fatal disease when diagnosed at an advanced stage and ranks 3rd in deaths due to cancer.^[2] Gastric cancer is commonly diagnosed with malignancies and remained a considerable health problem.^[3] The current mortality rate of gastric cancer is still around 75% which makes gastric cancer one of the major contributors to the global disease burden.^[4] The most common type is gastric adenocarcinoma, which is present in 90% of cases and is approximately 5% of malignant lymphoma tumours.^[5] Although its prevalence decreases^[6] the prognosis of those who have the disease is still poor. It is difficult to detect the disease without routine screening because it is asymptomatic in the early period. Therefore, patients are detected at a metastatic or locally advanced

stage. The mortality rate of patients at this stage is also high.

Chemotherapy is the most important treatment option for patients diagnosed at an advanced stage.^[7] Chemotherapy both prolongs survival and increases the quality of life.^[8, 9] Therefore, chemotherapy is recommended for patients with unresectable disease, with adequate organ function and performance.^[10, 11] Many chemotherapy agents are active in gastric cancer and are used. However, there is no golden standard for which regime will be administered and how. Single-agent chemotherapies, doublet regimens, and triplet regimens can be used. As the number of drugs used increases, the response rates increase; however, the toxicity increases as well. There are different results in overall survival. In the first randomized phase 3 comparing triple regimens with doublet regimens, overall survival was found in favor of triplet regimens.^[12] Although statistically significant, the difference was expressed only in weeks (9.2 months vs. 8.6

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months). In the subsequent Japanese phase 3 trial study, docetaxel-cisplatin-S1 was compared with cisplatin-S1, and no difference was found between them.^[13]

Today, there is still no definite information about whether doublet or triplet chemotherapy should be chosen in empirical therapy. Besides, it is not clear which combinations this doublet or triplet regime should consist of. Therefore, we designed our study to evaluate first-line treatment options in metastatic gastric cancer.

Materials and Methods

Our study is retrospective and involves five centers in Turkey. The files of the patients admitted to these centers between 2015-2020 were examined and included in the study if they had the appropriate criteria. Inclusion criteria were the presence of metastatic gastric adenocarcinoma pathology, not having received treatment for local gastric cancer (surgery, chemotherapy, or radiotherapy), having received chemotherapy (patients with two or more combinations of drugs were included in the study, and patients who received single-drug chemotherapy were not included) for metastatic disease and being HER-2 negative.

According to the chemotherapy they underwent, the patients were first divided into two groups: Those who received a triplet chemotherapy regimen and a doublet chemotherapy regimen. Those who had doublet chemotherapy were divided into two subgroups those receiving cisplatin-based doublet therapy and oxaliplatin-based doublet therapy. Those who underwent triple chemotherapy were evaluated in terms of overall survival, firstly with those who received doublet chemotherapy and then with cisplatin or oxaliplatin-based

doublet therapy. Also, patients who had triplet and doublet chemotherapy were re-evaluated according to the chemotherapy regimen they received. Overall survival differences between groups were examined in our study. Overall survival was calculated as the time from the onset of chemotherapy to the date of death or last visit. Regardless of which treatment the patient received, the effects of ECOG performance score (ECOG classified as 0-1 to 2), age (classified as over 65 and under), and metastasis sites on overall survival were investigated. Sites of metastasis were liver, lung, bone, lymph node, and peritoneum. Our study was performed as per the Declaration of Helsinki. The study was reviewed with the approval of the Local Ethics Committee.

All of the analyses were performed using the SPSS statistical software program package (SPSS version 20.0 for windows). The chi-square test analyzed the differences in the clinical characteristics between the two groups. OS and PFS were calculated with the log-rank test. The Kaplan–Meier method was used to draw survival curves. The Cox proportional hazards regression model was used to determine statistically significant variables related to OS. Differences were considered significant when the p-value was less than 0.05.

Results and Discussion

A total of 288 patients were included in our study. 132 of these patients were in the doublet chemotherapy group, and 156 in the triplet chemotherapy group (123 mDCF, 25 FLOT, 8 EOX patients). In the doublet chemotherapy group, 99 patients received oxaliplatin-based (FOLFOX and XELOX), and 33 patients received cisplatin-based (all cisplatin-capecitabine) chemotherapy. The general characteristics of the patients are presented in **Table 1**.

Table 1. General characteristics of the patients

	Triplet Therapy Group N=156	Doublet Oxaliplatin Based Group N=99	Doublet Cisplatin Based Group N=33
Chemotherapy regimen	mDCF (n=123) FLOT (n=25) EOX (n= 8)	FOLFOX (n=30) XELOX (n=69)	Cisplatin-Capecitabine (n=33)
ECOG			
0-1	133	87	28
2	23	12	5
Gender			
Male	106	66	23
Female	50	33	10
Metastatic Site			
Liver	57	37	18
Lung	25	15	6
Peritoneum	118	71	24
Lymph node	123	82	23
Bone	17	13	9
CEA (mean)	40.7	35.8	43.4
Overall Survival (month)	11.1	8.1	10.5

First, doublet and triplet chemotherapy were compared in terms of overall survival. Although the survival of the patients who received triplet chemotherapy was longer numerically,

there was no statistical significance (11.13 vs. 8.4 months $p=0.063$) (**Figure 1**). When the patients who received triplet chemotherapy were evaluated according to the chemotherapy

regimen they received, there was no statistically significant difference between them (mDCF 11.2, FLOT 11.1, EOX 10.5 months $p = 0.391$). Doublet chemotherapies were examined in two groups cisplatin-based and oxaliplatin-based. Although cisplatin-based chemotherapies had more prolonged survival numerically, there was no statistically significant difference (10.57 vs. 8.1 months $p=0.086$) (**Figure 2**).

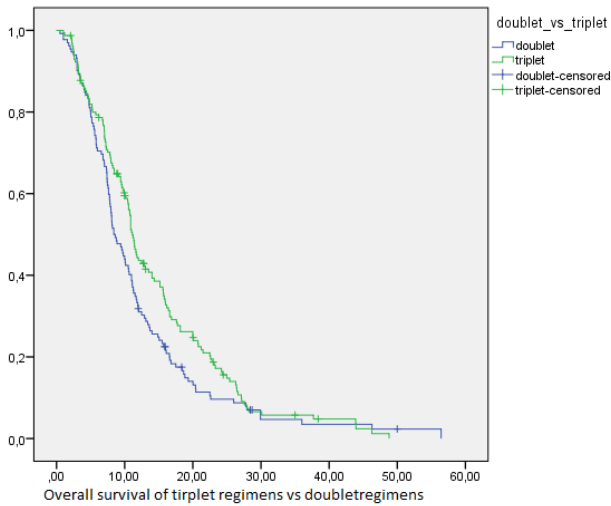


Figure 1. Overall survival curves of patients who received triplet regimens and doublet regimens

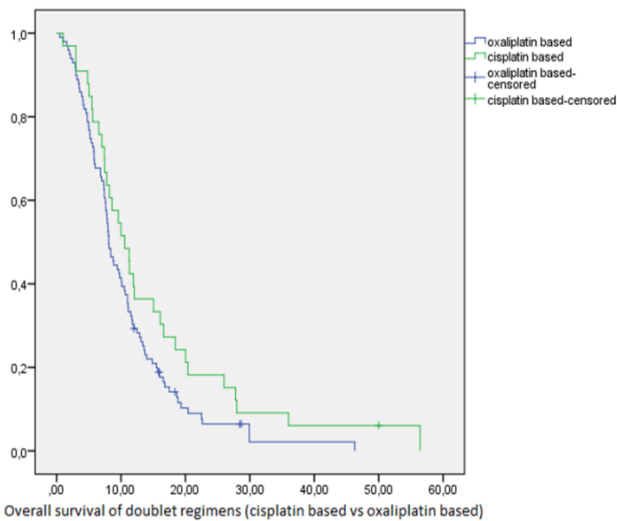


Figure 2. Overall survival curves of patients received oxaliplatin based doublet regimens and cisplatin based doublet regimens.

Following these results, the survival of the triplet chemotherapy group was significantly longer when compared with the patients who received oxaliplatin-based doublet chemotherapy (11.1 vs. 8.1 months $p=0.007$) (**Figure 3**). When the patients who received triplet chemotherapy and those who received cisplatin-based doublet chemotherapy were compared, there was no statistically significant difference (11.13 vs. 10.57 months $p=0.665$).

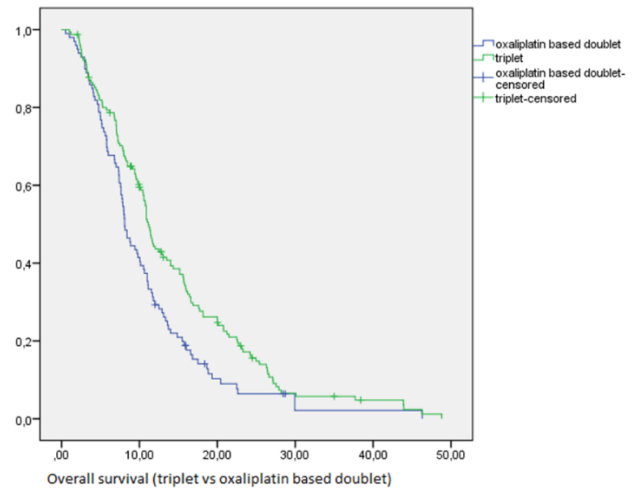


Figure 3. Overall survival curve of triplet chemotherapy group and who received oxaliplatin based doublet therapy

When the effects of patients' ECOG performance score, age distribution, metastasis sites, and gender variables on survival were evaluated, no parameter had a statistically significant effect on survival, except for the ECOG performance score (**Table 2**). The distribution of the ECOG 2 performance score among the groups was not statistically significantly different.

Table 2. Regression model

	Sig.	Hazard ratio
Age	,380	1,124
Gender	,190	1,199
Liver metastasis	,904	,984
Lung metastasis	,928	,984
Bone metastasis	,053	,696
Peritoneal metastasis	,363	,870
Lymphnode_metastasis	,524	,901
ECOG	,000	1734255,407

First-line treatment in metastatic gastric cancer has been controversial for a long time. Although many studies have been conducted on whether doublet chemotherapies or triplet chemotherapies are preferred, these studies have revealed many conflicting results. Two large randomized phase 3 trials have been conducted, particularly on whether the treatment is doublet or triplet. The first of these is a study conducted in 2006, in which docetaxel-cisplatin-fluorouracil (5Fu) was compared with cisplatin-5Fu, and overall survival was statistically significantly superior in favor of triplet chemotherapy.^[12] However, when the overall survival figures were examined, there was a difference between the two groups that could only be expressed in weeks (9.2 vs. 8.6 months).

The second phase 3 trial conducted is a Japanese study carried out in 2019.^[13] In this trial, doublet chemotherapies and triplet chemotherapies were compared. In the study comparing docetaxel-cisplatin-S1 triplet chemotherapy and cisplatin-S1

doublet chemotherapy, no statistically significant difference was found between the groups in overall survival. It even came out numerically in favor of doublet therapy (14.2 vs. 15.3 months).

In our study, although there was a numerical difference in overall survival between triplet chemotherapies and doublet chemotherapies in favor of triplet chemotherapies, this difference did not reach statistical significance (11.1 vs. 8.4 months). When the subgroups were examined in our study, patients who had doublet chemotherapy were divided into two groups: those receiving cisplatin-based therapy and oxaliplatin-based therapy. The group receiving triplet therapy and the group receiving oxaliplatin-based therapy were compared, and overall survival was found to be statistically significantly longer in the triplet therapy group (11.1 vs. 8.1 months $p=0.007$). However, no statistical difference was found between patients receiving triplet chemotherapy and cisplatin-based therapy.

According to our study results, triplet therapies are better than oxaliplatin-based therapies in overall survival but are similar to cisplatin-based therapies. This result is remarkably consistent with the Japanese trial we have described above. In that study, cisplatin-based doublet chemotherapy and triplet chemotherapy were no different in terms of overall survival. However, in this study, overall survival was approximately 4-5 months higher than in our study. This result was thought to be due to the difference in the patient population. In that study, patients with an ECOG performance score of 0-1 were included in the study, while patients with ECOG 2 were also included in our study. As shown in the regression analysis, the ECOG performance score is the most effective parameter for survival. This may be the reason why survival rates were lower in our study.

In our study, it can be concluded that cisplatin-based doublet therapies are superior to oxaliplatin-based therapies. In the phase 3 trial comparing cisplatin with oxaliplatin, an opposite result was obtained. In that study conducted in 2008, oxaliplatin-5 Fu-leucovorin was found to be statistically significantly superior to cisplatin-5Fu-leucovorin in progression-free survival.^[14] However, this difference was not reflected in overall survival. Besides, a meta-analysis of 3 randomized studies was published in 2011, and in this meta-analysis, oxaliplatin was found to be superior to cisplatin in both overall survival and progression-free survival.^[15]

There may be many reasons why these results conflict with our study. The most important of these are the geographical differences. Our study was conducted in Turkey, and the population in our country may respond better to cisplatin. The same geographic difference applies to the Japanese trial. It can be said that Japanese patients also respond well to cisplatin-based doublet chemotherapy.

The limitations of our study are its retrospective nature and the low number of patients. However, the fact that the number of patients with an ECOG performance score of 2 in the doublet

and triplet chemotherapy groups is similar partially reduces this deficiency.

In conclusion, considering the patient population in Turkey, it may be more appropriate to prefer triplet therapy in cases with good performance status. If doublet chemotherapy would be preferred due to the risk of toxicity, it may be more appropriate to choose a cisplatin-based treatment.

Conclusion

If chemotherapy will be chosen as the first-line treatment in metastatic gastric cancer, choosing triplet chemotherapy regimens if possible, and if doublet chemotherapy will be given for any reason, choosing cisplatin-based regimens may be more appropriate, especially for the patient population in Turkey.

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Conflict of interest

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Ethics statement

None.

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