Society of Medical Education & Research

2022, Volume 2, Issue 2, Page No: 32-36

Archive of International Journal of Cancer and Allied Science

Comparing Triplet and Doublet Chemotherapy Regimens for Metastatic Gastric Cancer: A Treatment Strategy Analysis

Ana Tarhan[1*], Selena Sanlier[2]

[1] Department of Medical Oncology, Faculty of Medical, Başkent University, Konya, Türkiye.
[2] Department of Medical Oncology, Bozyaka Training and Research Hospital, Izmir, Türkiye.

***E-mail** ✉ Ana.tarhan@yahoo.com

Abstract

Chemotherapy plays a central role in the management of advanced-stage gastric cancer, helping to extend survival and improve quality of life. However, there is still no consensus on whether doublet or triplet chemotherapy regimens should be used as the standard treatment for these patients. This retrospective study examines first-line chemotherapy options for metastatic gastric cancer at five medical centers in Turkey. The inclusion criteria required patients to have metastatic gastric adenocarcinoma, no prior treatment for localized gastric cancer (including surgery, chemotherapy, or radiotherapy), treatment with chemotherapy for metastatic disease (with at least two drugs), and HER-2 negative status. The analysis showed that patients treated with triplet chemotherapy had significantly longer survival compared to those who received oxaliplatin-based doublet chemotherapy (11.1 months vs. 8.1 months, P = 0.007). However, no significant survival difference was observed between the triplet chemotherapy group and those on cisplatin-based doublet chemotherapy (11.13 months vs. 10.57 months, P = 0.665). The findings suggest that triplet chemotherapy regimens should be considered as the first choice for first-line treatment in metastatic gastric cancer when possible, while cisplatin-based doublet regimens may be an appropriate alternative, especially in Turkey.

Keywords: Chemotherapy, Triplet, Doublet, Gastric cancer, Cisplatin

Introduction

Cancer is one of the leading causes of death worldwide, second only to cardiovascular diseases, and ranks as the third most common cause of death in developing countries. Gastric cancer, which sees more than one million new cases annually, is the fifth most prevalent type of cancer and the third leading cause of cancer-related mortality. It is often diagnosed at an advanced stage, making it a fatal disease, and its prognosis remains poor [1-3]. Gastric cancer is primarily found as gastric adenocarcinoma in 90% of cases, with malignant lymphoma tumors making up about 5%. Although the incidence of gastric cancer has been decreasing, the survival rate for those affected remains low, as the disease is typically asymptomatic in its early stages, making it difficult to detect early. As a result, many patients are diagnosed at a metastatic or locally advanced stage, which leads to high mortality rates [4-6].

Chemotherapy is the main treatment for patients diagnosed with advanced-stage gastric cancer. It has been shown to not only prolong survival but also enhance the quality of life for patients. Chemotherapy is typically recommended for individuals with unresectable disease, as long as they have adequate organ function and performance status. Several chemotherapy agents are effective against gastric cancer, though there is no universally accepted standard regimen. Treatment options include single-agent therapies, doublet regimens, and triplet regimens [6-8]. While adding more drugs to a regimen may improve response rates, it also increases toxicity. Some studies comparing triplet regimens to doublet regimens have suggested a survival benefit for triplet combinations, although the difference in overall

Access this article online

Website: https://smerpub.com/ **E-ISSN: 3108-4834**

Received: 24 August 2022; **Revised:** 26 November 2022; **Accepted:** 02 December 2022

How to cite this article: Tarhan A, Sanlier S. Comparing Triplet and Doublet Chemotherapy Regimens for Metastatic Gastric Cancer: A Treatment Strategy Analysis. Arch Int J Cancer Allied Sci. 2022;2(2):32-6. https://doi.org/10.51847/vOHGoT5gfM

survival was minimal. A Japanese phase 3 trial also failed to show significant differences between triplet and doublet regimens [8-10].

Despite these studies, there is no definitive consensus on whether a doublet or triplet chemotherapy regimen should be chosen as the standard first-line treatment for metastatic gastric cancer. Additionally, there is uncertainty regarding which drug combinations should be used in these regimens. To address these gaps, our study aims to evaluate first-line treatment options for metastatic gastric cancer.

Materials and Methods

This retrospective study was conducted across five medical centers in Turkey, analyzing patient data from 2015 to 2020. The study included patients who met the following criteria: diagnosis of metastatic gastric adenocarcinoma, no prior treatment for localized gastric cancer (e.g., surgery, chemotherapy, or radiotherapy), chemotherapy for metastatic disease (only those who received two or more chemotherapy agents were included, excluding those on single-agent therapy), and HER-2 negative status.

Patients were initially grouped based on the type of chemotherapy regimen received: those on a triplet chemotherapy regimen and those on a doublet chemotherapy regimen. The doublet chemotherapy group was further subdivided into cisplatin-based and oxaliplatin-based treatments. Comparisons were made between the overall survival (OS) of patients who received triplet chemotherapy and those who received doublet chemotherapy, including separate comparisons between cisplatin and oxaliplatin-based doublet regimens.

The primary endpoint of the study was overall survival, defined as the time from the initiation of chemotherapy to death or the last recorded visit. The study also examined how factors such as ECOG performance status (categorized as 0-1 or 2), age (younger or older than 65 years), and the site of metastasis (liver, lung, bone, lymph nodes, and peritoneum) influenced OS. The study was approved by the Local Ethics Committee and conducted following the Declaration of Helsinki.

Statistical analyses were performed using SPSS software (version 20.0 for Windows). Differences in clinical characteristics between groups were assessed using the chi-square test. The log-rank test was used to analyze overall survival (OS) and progression-free survival (PFS). Kaplan-Meier survival curves were generated, and Cox proportional hazards regression was applied to identify factors significantly associated with OS. A P-value of less than 0.05 was considered statistically significant.

Results and Discussion

Our study included 288 patients, divided into two groups based on the type of chemotherapy received: 132 patients in the doublet chemotherapy group and 156 patients in the triplet chemotherapy group. Within the doublet group, 99 patients received oxaliplatin-based regimens (FOLFOX and XELOX), and 33 patients received cisplatin-based regimens (cisplatin-capecitabine). **Table 1** provides an overview of the patient characteristics.

Table 1. Characteristics of study participants

Characteristic	Triplet therapy group (n = 156)	Doublet oxaliplatin-based group (n = 99)	Doublet cisplatin-based group (n = 33)
Chemotherapy regimen	mDCF (123), FLOT (25), EOX (8)	FOLFOX (30), XELOX (69)	Cisplatin-capecitabine (33)
ECOG status	0-1 (133), 2 (23)	0-1 (87), 2 (12)	0-1 (28), 2 (5)
Gender distribution	Male (106), female (50)	Male (66), female (33)	Male (23), female (10)
Metastasis sites	Liver (57), lung (25), peritoneum (118), lymph node (123), bone (17)	Liver (37), lung (15), peritoneum (71), lymph node (82), bone (13)	Liver (18), lung (6), peritoneum (24), lymph node (23), bone (9)
Mean CEA level	40.7	35.8	43.4
Overall survival (months)	11.1	8.1	10.5

In comparing overall survival between the doublet and triplet chemotherapy groups, although the triplet chemotherapy group exhibited longer survival, this difference was not statistically significant (11.13 vs. 8.4 months, P = 0.063) (**Figure 1**). When the triplet chemotherapy group was further analyzed by regimen, no

significant differences were observed in survival rates across mDCF (11.2 months), FLOT (11.1 months), and EOX (10.5 months) regimens (P = 0.391).

Within the doublet chemotherapy group, survival was slightly longer in the cisplatin-based regimen compared to the oxaliplatin-based regimen, but this difference also did not reach statistical significance (10.57 vs. 8.1 months, P = 0.086) (**Figure 2**).

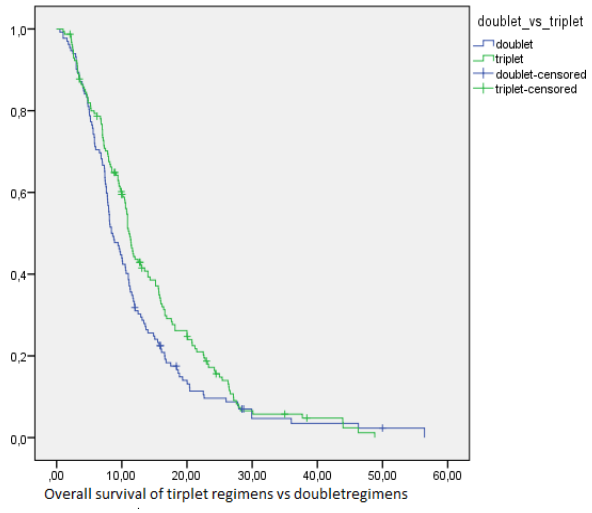

Figure 1. Overall survival curves of patients who received triplet regimens and doublet regimens

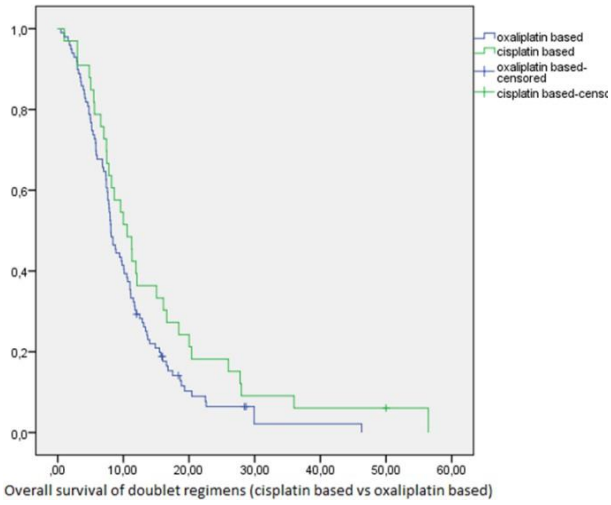

Figure 2. Overall survival curves of patients who received oxaliplatin-based doublet regimens and cisplatin-based doublet regimens

Following these results, the triplet chemotherapy group showed a significantly longer survival compared to patients who received oxaliplatin-based doublet chemotherapy (11.1 vs. 8.1 months, P = 0.007) (**Figure 3**). However, when comparing the triplet chemotherapy group to the cisplatin-based doublet chemotherapy group, no statistically significant difference in survival was observed (11.13 vs. 10.57 months, P = 0.665).

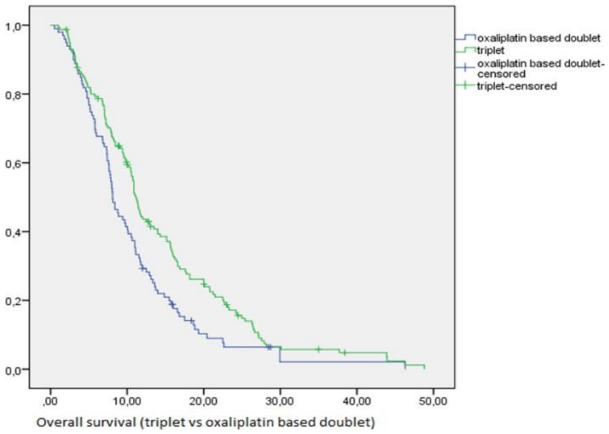

Figure 3. Overall survival (triplet vs oxaliplatin-based doublet)

In evaluating the impact of ECOG performance score, age, metastasis sites, and gender on survival, only the ECOG performance score showed a statistically significant effect on survival. No significant differences were found in the distribution of the ECOG 2 performance score among the groups (**Table 2**).

Table 2. Regression model

Variable	Sig.	Hazard ratio
Age	0.380	1.124
Gender	0.190	1.199
Liver metastasis	0.904	0.984
Lung metastasis	0.928	0.984
Bone metastasis	0.053	0.696
Peritoneal metastasis	0.363	0.870
Lymph node metastasis	0.524	0.901
ECOG	0.000	1734255.407

First-line treatment options for metastatic gastric cancer have been debated for years. Many studies have attempted to determine whether doublet or triplet chemotherapy regimens should be preferred, but the results have often been conflicting. Notably, two large randomized phase 3 trials have focused on this issue. The first trial, conducted in 2006, compared docetaxel-cisplatin-fluorouracil (5FU) with cisplatin-5FU. The results showed a statistically significant improvement in overall survival with the triplet chemotherapy, but the difference was minimal, expressed in weeks (9.2 vs. 8.6 months).

The second trial, conducted in Japan in 2019, compared doublet and triplet chemotherapies. This trial found no significant difference in overall survival between docetaxel-cisplatin-S1 triplet chemotherapy and cisplatin-S1 doublet chemotherapy. Interestingly, the doublet therapy had slightly better survival numerically (14.2 vs. 15.3 months).

In our study, although there was a numerical difference favoring triplet chemotherapy in terms of overall survival compared to doublet chemotherapy (11.1 vs. 8.4 months), the difference was not statistically significant. However, when examining the subgroups, the patients receiving triplet chemotherapy had significantly longer survival than those on oxaliplatin-based doublet therapy (11.1 vs. 8.1 months, P = 0.007). There was no statistical difference between triplet chemotherapy and cisplatin-based doublet chemotherapy.

Based on our findings, triplet therapies showed a significant survival advantage over oxaliplatin-based therapies, but their results were similar to those of cisplatin-based therapies. This outcome aligns with the results from the Japanese study, where no difference in overall survival was observed between cisplatin-based doublet chemotherapy and triplet chemotherapy. However, the Japanese study reported a survival benefit of about 4-5 months more than our study, likely due to differences in the patient populations. The Japanese study only included patients with an ECOG performance score of 0-1, while our study also included patients with an ECOG score of 2. As shown in the regression analysis, the ECOG performance score had the most significant impact on survival, which may explain the lower survival rates in our study.

In our study, cisplatin-based doublet therapies showed a superior survival rate compared to oxaliplatin-based therapies. This contrasts with the results from a 2008 phase 3 trial that found oxaliplatin-5FU-leucovorin to be statistically superior to cisplatin-5FU-leucovorin in progression-free survival, though there was no difference in overall survival. A meta-analysis published in 2011, which combined three randomized studies, found oxaliplatin to be superior to cisplatin in both overall survival and progression-free survival.

There are several factors that could explain the discrepancies between our study and previous research [10-15]. One of the most significant factors is the geographical difference. Our study was conducted in Turkey, and the population here may have a better response to cisplatin. The same geographical distinction may also apply to the Japanese trial, where patients seem to respond more favorably to cisplatin-based doublet chemotherapy.

Some limitations of our study include its retrospective design and a smaller patient sample. However, the similar distribution of patients with an ECOG performance score of 2 in both the doublet and triplet chemotherapy groups somewhat mitigates these limitations.

In summary, considering the specific characteristics of the Turkish patient population, triplet chemotherapy is likely the better option for those with good performance status. In cases where doublet chemotherapy is preferred due to potential toxicity concerns, opting for a cisplatin-based regimen may be more appropriate.

Conclusion

In cases of metastatic gastric cancer, if chemotherapy is chosen as the first-line treatment, triplet chemotherapy should be preferred when possible. If a doublet regimen is necessary for any reason, cisplatin-based therapies may be more suitable, particularly for patients in Turkey.

Acknowledgments: None

Conflict of Interest: None

Financial Support: None

Ethics Statement: None

References

1. Sahebzadeh M, Khuzani HR, Keyvanara M, Tabesh E. Explaining the Factors Shaping Two Different Beliefs about Cancer in Iran Based on Causal Layer Analysis “CLA”. Entomol Appl Sci Lett. 2021;8(2):42-50.
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-24.
3. Jiang X, Naikoo AN, Gao S. A Meta-analysis of tumor necrosis factor- α-308 G>A polymorphism in gastric cancer. Asian Biomed. 2020;14(3):91-6.
4. Zhou Y, Wang L, Lin H, Wang Y, Hou K. Bufalin inhibits the growth and epithelial to mesenchymal transition of human gastric cancer cells via

modulation of MEK/ERK pathway. Bangladesh J Pharmacol. 2021;16(1):27-33.
5. Asadi Z, Arbabi S. Evaluation of Relationship between Tissue Levels of Polycyclic Aromatic Hydrocarbon (PAHs) and History of Food Exposure to Environmental Contaminants in Patients with Gastric Cancer by Immunohistochemistry. eIJPPR 2020;10(5):210-5.
6. Jun JK, Choi KS, Lee HY, Suh M, Park B, Song SH, et al. Effectiveness of the Korean National Cancer Screening Program in reducing gastric cancer mortality. Gastroenterology. 2017;152(6):1319-28.
7. Albooq MIM, Baharoon BMM, Al-Abedi NAA, El-Hamidy SM, Shaikh AM, Alshehri KM, et al. The Possible Hepatoprotective Role of Clay Nanoparticles on the Effectiveness of Anticancer Drug in Ehrlich- induced Ascites Carcinoma in Mice. Int J Pharm Phytopharmacol Res. 2021;11(1):10-9.
8. Glimelius B, Ekström K, Hoffman K, Graf W, Sjödén PO, Haglund U, et al. Randomized comparison between chemotherapy plus best supportive care with best supportive care in advanced gastric cancer. Ann Oncol. 1997;8(2):163-8.
9. Murad AM, Santiago FF, Petroianu A, Rocha PR, Rodrigues MA, Rausch M. Modified therapy with 5-fluorouracil, doxorubicin, and methotrexate in advanced gastric cancer. Cancer. 1993;72(1):37-41.
10. Muro K, Van Cutsem E, Narita Y, Pentheroudakis G, Baba E, Li J, et al. Pan-Asian adapted ESMO Clinical Practice Guidelines for the management of patients with metastatic gastric cancer: a JSMO–ESMO initiative endorsed by CSCO, KSMO, MOS, SSO and TOS. Ann Oncol. 2019;30(1):19-33.
11. Ajani JA, D'Amico TA, Almhanna K, Bentrem DJ, Chao J, Das P, et al. Gastric cancer, version 3.2016, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2016;14(10):1286-312.
12. Van Cutsem E, Moiseyenko VM, Tjulandin S, Majlis A, Constenla M, Boni C, et al. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. J Clin Oncol. 2006;24(31):4991-7.
13. Yamada Y, Boku N, Mizusawa J, Iwasa S, Kadowaki S, Nakayama N, et al. Docetaxel plus cisplatin and S-1 versus cisplatin and S-1 in patients with advanced gastric cancer (JCOG1013): an open-label, phase 3, randomised controlled trial. Lancet Gastroenterol Hepatol. 2019;4(7):501-10.
14. Al-Batran SE, Hartmann JT, Probst S, Schmalenberg H, Hollerbach S, Hofheinz R, et al. Phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil, leucovorin plus either oxaliplatin or cisplatin: a study of the Arbeitsgemeinschaft Internistische Onkologie. J Clin Oncol. 2008;26(9):1435-42.
15. Montagnani F, Turrisi G, Marinozzi C, Aliberti C, Fiorentini G. Effectiveness and safety of oxaliplatin compared to cisplatin for advanced, unresectable gastric cancer: a systematic review and meta-analysis. Gastric Cancer. 2011;14(1):50-5.