Clinical Research

Comparison of Cisplatin and Oxaliplatin-Based Therapies in HER2-Positive Metastatic Gastric Cancer Patients

İzzet DOĞAN[1,a], Senem KARABULUT[1]

[1]*İstanbul University Institute of Oncology, Medical Oncology, İstanbul, Türkiye*

ABSTRACT

Objective: We aimed to compare cisplatin and oxaliplatin-based therapies in patients with HER2-positive gastric cancer.
Material and Method: We evaluated clinicopathological and treatment data of the patients who used cisplatin, fluoropyrimidine, trastuzumab (CFT) or oxaliplatin, capecitabine, trastuzumab (OCT) retrospectively. The clinicopathological characteristics of the two groups were assessed, as well as their survival results.
Results: Twenty-three (57.5%) patients received CFT regimen, and seventeen (42.5%) patients OCT regimen. Clinicopathological features and ECOG performance status were similar in between groups. Median progression-free survival was 12 (CI 95%, 10.8-13.1) months in the CFT group and 8.6 (CI 95%, 5.9-11.3) months in the OCT group (p =0.39). Median overall survival (OS) was 21.7 (95% CI 16.9-26.4) months in the CFT group and 13.6 (CI 95%, 6.7-20.5) months in the OFT group. In univariate analysis, the change in OS between the two groups was statistically significant; however, the findings were not confirmed in multivariate analysis.
Conclusion: There was a trend in the study that patients treated with CFT had better OS compared to OCT. This situation did not reach statistical significance. Treatment-related toxicities were similar between the two groups.

Keywords: *Gastric Cancer, HER2/Neu, Oxaliplatin, Cisplatin, Prognosis.*

ÖZ

HER2-Pozitif Metastatik Mide Kanserli Hastalarda Sisplatin Ve Oksaliplatin Bazlı Tedavilerin Karşılaştırılması
Amaç: HER2 pozitif mide kanserli hastalarda sisplatin ve oksaliplatin bazlı tedavileri karşılaştırmayı amaçladık.
Gereç ve Yöntem: Sisplatin, floropirimidin, trastuzumab (CFT) veya oksaliplatin, kapesitabin, trastuzumab (OKT) tedavi rejimlerini alan hastaların klinikopatolojik ve tedavi verilerini retrospektif olarak değerlendirdik. İki grubun klinikopatolojik özellikleri ve sağkalım sonuçlarını karşılaştırdık.
Bulgular: Yirmi üç (%57,5) hasta CFT rejimi ve on yedi (%42,5) hasta OKT rejimi aldı. Klinikopatolojik özellikler ve ECOG performans durumu gruplar arasında benzerdi. Medyan progresyonsuz sağkalım CFT grubunda 12 (%95 GA, 10,8-13,1) ay ve OKT grubunda ise 8,6 (%95 GA, 5,9-11,3) aydı (p =0,39). Medyan genel sağkalım (OS) CFT grubunda 21,7 (%95 GA 16,9-26,4) ay ve OFT grubunda ise 13,6 (%95 GA, 6,7-20,5) aydı. Tek değişkenli analizde, iki grup arasındaki genel sağkalım farkı istatistiksel olarak anlamlıydı; ancak bulgular çok değişkenli analizde doğrulanmadı.
Sonuç: Çalışmada CFT ile tedavi edilen hastaların, OKT ile tedavi edilen hastalara kıyasla daha iyi genel sağkalıma sahip olduğu yönünde bir trend vardı. Fakat bu durum istatistiksel anlamlılığa ulaşmadı. Tedaviye bağlı toksisiteler iki tedavi grubu arasında benzerdi.
Anahtar Sözcükler: *Mide Kanseri, HER2/Neu, Oksaliplatin, Sisplatin, Prognoz.*

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ORCID IDs: İ.D. 0000-0003-1018-1119, S.K. 0000-0003-4740-9973.

Gastric cancer is one of the most diagnosed cancer globally, and the mortality rates are high. Smoking, alcohol consumption, obesity, genetic mutations, and dietary characteristics have been identified as risk factors for gastric cancer. A significant proportion of gastric cancer patients are symptomatic at diagnosis and present with locally advanced or metastatic disease. Fluoroprimidine, platinum, and taxane-based treatments are used to treat metastatic gastric cancer patients. Fluorouracil and capecitabine have similar efficacy in gastric cancer patients (1).

HER2 receptor positivity rate in gastric cancer may vary according to ethnicity. Studies have generally shown positivity between 10% and 20% in metastatic gastric cancer (2, 3). In resectable gastric cancer, HER2 expression is less frequent than in metastatic gastric cancer (4). HER2 amplification is more prevalent in gastroesophageal junction (GEJ) adenocarcinomas than in gastric adenocarcinomas and in intestinal subtype adenocarcinomas than in diffuse subtype adenocarcinomas (5). Trastuzumab's mechanism of action in cancer therapy is not entirely known. Trastuzumab is a humanized monoclonal antibody (mAb) that targets the extracellular region of the HER2 tyrosine kinase recep-

[a]Yazışma Adresi: İzzet DOĞAN, İstanbul University Institute of Oncology, Medical Oncology, İstanbul, Türkiye
Tel: 0212 414 2434 e-mail: dr.izzetdogan@gmail.com
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tor (6).

In HER2-positive advanced gastric cancer, the TOGA trial showed that adding trastuzumab to chemotherapy improved overall survival (OS) (5). The TOGA study showed that the patients whose HER2 positivity was detected with together immunohistochemistry (score 3+) and in-situ hybridization method benefited most from trastuzumab-based treatment. The efficacy and safety of different treatment regimens with trastuzumab have been investigated. Studies comparing the effectiveness of chemotherapy combinations used with trastuzumab are rare in the literature. This study aimed to compare the efficacy of cisplatin and oxaliplatin using with trastuzumab in metastatic HER2-positive gastric cancer patients.

MATERIAL AND METHOD

Patients and data collection

HER2-positive metastatic gastric cancer patients who were diagnosed and treated in the outpatient clinic of a single tertiary oncology center between 2014 and 2019 were included in the study. The study was planned retrospectively. The local ethics commission approved the study (Number:2021/229154). The patients included in the study were identified through the hospital data processing system. All the patients who received trastuzumab with oxaliplatin or cisplatin were included in the study. Patients who did not have enough data to analyze were not included in the research. The clinical (age, gender, performance status, number of metastasis sites), pathological (tumor type, tumor region), and treatment data (surgery, adjuvant treatments, treatment types, and doses) of the patients were recorded from the hospital registry system. Immunohistochemistry and in-situ hybridization methods were used to determine the presence of the HER2 receptor. The patient's performance status was assessed using the Eastern Cooperative Oncology Group (ECOG) performance scale. The eighth TNM tumor staging system was used to determine the tumor staging. The clinical and pathological features of the treatment groups were compared. The patients were separated into two groups as those receiving trastuzumab and fluoropyrimidine together with oxaliplatin or cisplatin. In the cisplatin-based therapy group (CFT), the patients received trastuzumab (every three weeks, at a dose of 8mg/kg in the first cycle and 6mg/kg in subsequent cycles), cisplatin (75mg/m2 in every three weeks), and a fluoropyrimidine (600 mg/m2 5-fluorouracil for five days in every three weeks or 1000 mg/m2 capecitabine for 14 days in every three weeks). In the oxaliplatin-based therapy group (OCT), the patients received trastuzumab (every three weeks, at a dose of 8mg/kg in the first cycle and 6mg/kg in subsequent cycles), oxaliplatin (130 mg/m2 in every three weeks), and capecitabine (1000 mg/m2 for 14 days in every three weeks). To assess therapy responses, we employed the Response Evaluation Criteria in Solid Tumors (RECIST). All adverse events related to chemotherapy were recorded. The CTCAE (Common Terminology Criteria for Adverse Events) Version 5.0 was used to measure treatment-related toxicity.

The patients' death status was checked using the Ministry of Health's death notification system. The period from diagnosis to death was defined as OS (due to any cause). From the beginning of therapy to the progression period was used to define progression-free survival (PFS). OS and PFS were compared between two groups. All clinicopathological variables of the patients were assessed in univariate analysis for survival impact. Prognostic factors that were statistically significant in univariate analysis or in the literature were subjected to multivariate analysis.

Statistical analysis

SPSS version 25 (IBM, USA) was done for all analyses. Continuous data were reported as median (minimum-maximum) values, whereas categorical variables were provided as numbers and percentages. To check whether continuous variables have a normal distribution, the Kolmogorov-Smirnov test was utilized. To compare categorical variables, the Chi-square technique and Fisher's exact test were utilized. Using the Kaplan Meier approach, the log-rank test was applied to assess OS and PFS. Univariate and multivariate analyses were conducted using the Cox regression model. To establish statistical significance, a p-value of less than 0.05 was accepted.

RESULTS

A total of 53 patients were identified who received oxaliplatin or cisplatin with trastuzumab. Thirteen patients were excluded because they did not meet the inclusion criteria. The research comprised a total of 40 patients, including 23 individuals in the CFT group and 17 in the OCT group. The median age was 61 years (38-91). Thirty (75%) of the patients were male, and 10 (25%) of them were female. Primary tumor localizations were GEJ-15%, cardia-25%, corpus-22.5%, antrum-30% and unknown-7.5%. Twenty-five (62.5%) patients had liver metastasis, and 11 (27.5%) patients lung metastasis. Twelve (30%) patients had undergone surgery. Three (7.5%) patients had received adjuvant radiotherapy. Compared to the two therapy groups, denovo metastatic disease was more common in the OCT group. Second-line chemotherapy was used more commonly in patients who were treated with CFT regimen. Other clinicopathological features were similar in between two groups. Clinicopathological features of the two therapy groups were compared in table 1.

Table 1. *Patients characteristic.*

Characteristics	CFT group Total number:23(%)	OCT group Total number:17 (%)	p-value
Age			
<60	12 (52.2)	4 (23.5)	
60>	11 (47.8)	13 (76.5)	0.06
Gender			
Male	18 (78.3)	12 (70.6)	0.71
Female	5 (21.7)	5 (29.4)	
ECOG performance status			
0-1	21 (91.3)	16 (94.1)	0.65
2	2 (8.7)	1 (5.9)	
Primary tumor location			
GEJ	4 (17.5)	2 (11.7)	
Non-GEJ	17 (73.8)	14 (82.4)	0.68
Unknown	2 (8.7)	1 (5.9)	
De novo metastatic disease			
Yes	13 (56.5)	15 (88.2)	**0.03**
No	10 (43.5)	2 (11.8)	
Prior Surgery			
Yes	10 (43.4)	2 (11.8)	
No	12 (52.2)	13 (76.4)	0.07
Unknown	1 (4.4)	2 (11.8)	
Prior Chemotherapy			
Yes	9 (39.2)	3 (17.6)	
No	13 (56.4)	14 (82.4)	0.11
Unknown	1 (4.4)		
Number of metastatic sites			
1-2	14 (60.8)	14 (82.3)	
>2	6 (26)	2 (11.8)	0.25
Unknown	3 (13.2)	1 (5.9)	
Tumor responses			
Complete response	1 (4.3)	0 (0)	
Partial response	14 (60.9)	6 (35.3)	
Stable response	1 (4.3)	4 (23.5)	0.15
Progression	7 (30.5)	7 (41.2)	
Treatment-related toxicity			
Yes	17 (73.9)	16 (94.1)	0.20
No	6 (26.1)	1 (5.9)	
Second-line treatment			
Yes	11 (47.9)	2 (11.8)	
No	10 (43.4)	15 (88.2)	**0.009**
Unknown	2 (8.7)		

Prognostic factors and survival outcome

The Median follow-up time was 13.7 (2.57-55.6) months. Thirty-five (87.5%) patients died during the study period. Median PFS was 12 (CI 95%, 10.8-13.1) months in the CFT group and 8.6 (CI 95%, 5.9-11.3) months in the OCT group (Figure 1).

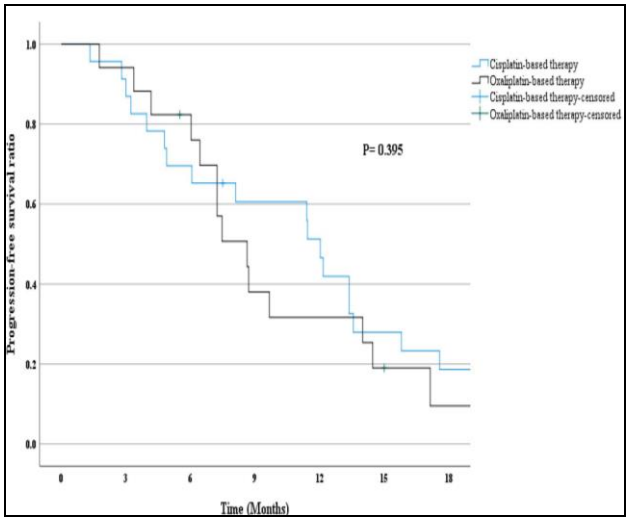

Figure 1. *Kaplan-Meier curves for PFS in the treatment groups.*

Median OS was 21.7 (95% CI 16.9-26.4) months in the CFT group and 13.6 (CI 95%, 6.7-20.5) months in the OCT group (Figure 2).

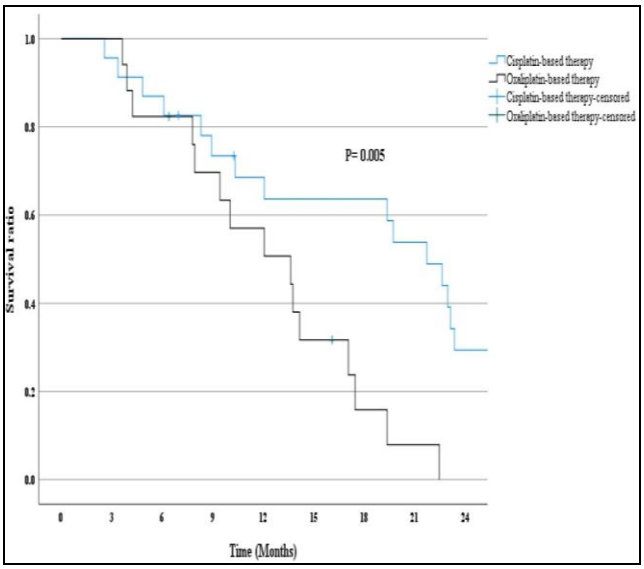

Figure 2. *Kaplan-Meier curves for OS in the treatment groups.*

Although there was no statistically major difference in terms of PFS, the CFT group was superior in terms of OS from the OCT group in univariate analysis. However, although there was a trend regarding the superiority of CFT in multivariate analysis, the p-value did not reach significance. Performance status and the number of metastatic locations at diagnosis were statistically meaningful prognostic factors for OS in multivariate analysis (Table 2).

Table 2. *Univariate and multivariate analysis for OS.*

	Univariate analysis p-value	Multivariate analysis p-value
Age (<60 vs. ≥60)	0.352	0.676
Gender (Male vs. Female)	0.758	0.795
ECOG PS (0-1 vs. 2)	**<0.001**	**0.011**
Primary tumor location (EGJ vs. Gastric)	0.996	
De novo metastatic (Yes vs. No)	0.603	
Prior Surgery (Yes vs. No)	0.523	
Prior Chemotherapy (Yes vs. No)	0.586	
Number of metastatic sites (1-2 vs. >2)	**0.019**	**0.005**
First-line CTx regimens CFT vs. OCT	**0.005**	0.099
Second-line treatment (Yes vs. No)	**0.005**	0.054

Presents multivariate analyses results. In all grades, hematological and non-hematological toxicities were similar in between groups.

DISCUSSION

Limited data are available regarding the optimal regimen to add to trastuzumab-based therapy in metastatic patients with HER2-positive gastric cancer. In our study, we found that CFT and OCT therapies had similar efficacy and safety. Trastuzumab-based therapies are used as standard in the first series in HER2-positive metastatic gastric cancer. Cisplatin-based therapies have been used to treat metastatic gastric cancer for a long time. A multicenter randomized phase 3 study by Lee et al. showed that oxaliplatin was non-inferior to cisplatin (7). Yamada et al. (8) found that oxaliplatin and cisplatin had similar efficacy when used in combination with S1 in patients with metastatic gastric cancer, but that oxaliplatin-based therapy was relatively less toxic.

Similarly, in a phase 2 study, Kim et al. detected that cisplatin and oxaliplatin-based treatments had similar efficacy and safety when used weekly with docetaxel in advanced gastric cancer patients (9). However, in a phase 2 study published by Hironaka et al. (10), has been found that oxaliplatin combined with S1 was more effective than cisplatin in metastatic gastric cancer. In this research, the median OS was 18.4 months in the S-1 plus leucovorin and oxaliplatin group and 12.6 months in the S-1 plus cisplatin group. These results were supported in a phase 3 study recently published by Kang et al. (11) the researchers have been found that using oxaliplatin in combination with S1 in the Asian population significantly improved survival to cisplatin and the response ratio from 50% to 73%. In the literature, different results were obtained in studies comparing oxaliplatin and cisplatin in advanced gastric cancer patients. In our results, although cisplatin-based therapy had similar efficacy to oxaliplatin-based therapy in HER2-positive gastric cancer patients, a non-significant survival-enhancing trend was observed in cisplatin-based therapy. Our study's small number of patients may have caused a bias effect. But, these contradictory results in the literature can also be explained by the different efficacy levels of drugs in different races. In addition, HER2-positive gastric cancer may have different properties in terms of platinum sensitivity. An article that investigated the cell growth inhibitory effect of trastuzumab in HER2-positive gastric SNU-216 cancer line discovered to a synergistic effect when using together trastuzumab with cisplatin (12).

In a meta-analysis published by Zhang et al. (13), oxaliplatin was found to have a better profile in terms of safety, together with it was superior to cisplatin in patients with metastatic gastric cancer. Furthermore, compared to cisplatin-based treatment, oxaliplatin-based therapy has been detected that minimized grades 3-4 of anemia, leukopenia, and febrile neutropenia. However, oxaliplatin-based treatment significantly had been increased tiredness, sensory neuropathy, diarrhea, and thrombocytopenia. Another meta-analysis found that oxaliplatin-based therapy had lower toxicity and better tolerance, particularly in older patients and when administered in two-drug, bi-weekly regimens in metastatic gastric cancer (14). In another meta-analysis published by Huang et al. (15), although oxaliplatin-based treatment has similar efficacy with cisplatin-based treatment, toxicities other than sensorineural neuropathy and thrombocytopenia were less detected. In our study, hematological and non-hematological toxicities were observed at similar rates in the patients of the two treatment groups. Due to a low number of patients, the toxicity difference between the treatment groups may not have emerged.

Our research has a few limitations. Because this was an uncommon tumor, the number of patients in our research was modest. Some data were missing due to the study's retrospective nature. There was a heterogeneous distribution for some characteristics in the treatment groups.

Conclusions

Although there was a trend in this study that cisplatin-based therapy compared to oxaliplatin-based therapy was improved to OS in metastatic patients with HER2-positive gastric cancer, this situation did not reach statistical significance. Treatment-related toxicities were similar at all grades in both treatment groups. Data on the most appropriate treatment regimen for use with trastuzumab in HER2-positive metastatic gastric cancer patients are limited in the literature. To the best of our knowledge, this is the first study in the literature to compare the efficacy of cisplatin and oxaliplatin in HER2-positive gastric cancer patients. In this respect, our study contains essential information. Our results need to be confirmed by other studies. Prospective multicenter studies that included larger patient groups are required to find the most appropriate treatment regimens to use with trastuzumab in metastatic HER2-positive gastric cancer patients.

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None

Statement of Ethics

The local ethics committee approved this study (2021/229154).

Informed Consent

For this type of research, informed consent is not required.

Conflict of Interest

The authors declared that there are no potential conflicts of interest**.**

Financial Disclosure
Neither financial nor of other natüre.

REFERENCES

1. Kang YK, Kang WK, Shin DB et al. Capecitabine/cisplatin versus 5-fluorouracil/cisplatin as first-line therapy in patients with advanced gastric cancer: a randomised phase III noninferiority trial. Ann Oncol 2009; 20: 666-73.
2. Shan L, Ying J, Lu N. HER2 expression and relevant clinicopathological features in gastric and gastroesophageal junction adenocarcinoma in a Chinese population. Diagn Pathol 2013; 8: 76.
3. Abrahao-Machado LF, Scapulatempo-Neto C. HER2 testing in gastric cancer: An update. World J Gastroenterol 2016; 22: 4619-25.
4. Kataoka Y, Okabe H, Yoshizawa A et al. HER2 expression and its clinicopathological features in resectable gastric cancer. Gastric Cancer 2013; 16: 84-93.
5. Bang YJ, Van Cutsem E, Feyereislova A et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet 2010; 376: 687-97.
6. Valabrega G, Montemurro F, Aglietta M. Trastuzumab: mechanism of action, resistance and future perspectives in HER2-overexpressing breast cancer. Ann Oncol 2007; 18: 977-84.
7. Lee KW, Chung IJ, Ryu MH, et al. Multicenter phase III trial of S-1 and cisplatin versus S-1 and oxaliplatin combination chemotherapy for first-line treatment of advanced gastric cancer (SOPP trial). Gastric Cancer 2021; 24: 156-67.
8. Yamada Y, Higuchi K, Nishikawa K et al. Phase III study comparing oxaliplatin plus S-1 with cisplatin plus S-1 in chemotherapy-naive patients with advanced gastric cancer. Ann Oncol 2015; 26: 141-8.
9. Kim YS, Sym SJ, Park SH et al. A randomized phase II study of weekly docetaxel/cisplatin versus weekly docetaxel/oxaliplatin as first-line therapy for patients with advanced gastric cancer. Cancer Chemother Pharmacol 2014; 73: 163-9.
10. Hironaka S, Sugimoto N, Yamaguchi K et al. S-1 plus leucovorin versus S-1 plus leucovorin and oxaliplatin versus S-1 plus cisplatin in patients with advanced gastric cancer: a randomised, multicentre, open-label, phase 2 trial. Lancet Oncol 2016; 17: 99-108.
11. Kang YK, Chin K, Chung HC et al. S-1 plus leucovorin and oxaliplatin versus S-1 plus cisplatin as first-line therapy in patients with advanced gastric cancer (SOLAR): a randomised, open-label, phase 3 trial. Lancet Oncol 2020; 21: 1045-56.
12. Kim SY, Kim HP, Kim YJ et al. Trastuzumab inhibits the growth of human gastric cancer cell lines with HER2 amplification synergistically with cisplatin. Int J Oncol 2008; 32: 89-95.
13. Zhang F, Zhang Y, Jia Z, Wu H, Gu K. Oxaliplatin-Based regimen is superior to cisplatin-based regimen in tumour remission as first-line chemotherapy for advanced gastric cancer: A meta-analysis. J Cancer 2019; 10: 1923-9.
14. 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: 50-5.
15. Huang J, Zhao Y, Xu Y et al. Comparative effectiveness and safety between oxaliplatin-based and cisplatin-based therapy in advanced gastric cancer: A meta-analysis of randomized controlled trials. Oncotarget 2016; 7: 34824-31.