Eskisehir Medical Journal
Eskişehir Tıp Dergisi

Eskisehir Med J. 2025; 6(2):75-80
doi: 10.48176/esmj.2025.185

Original Article / Araştırma Makalesi

COMPARISON OF DOUBLET AND TRIPLET CHEMOTHERAPY REGIMENS IN GERIATRIC PATIENTS WITH METASTATIC GASTRIC CANCER

METASTATİK MİDE KANSERLİ GERİATRİK HASTALARDA İKİLİ VE ÜÇLÜ KEMOTERAPİ REJİMLERİNİN KARŞILAŞTIRILMASI

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ABSTRACT

Introduction: There is a lack of guidelines for managing elderly metastatic gastric cancer patients. This study aimed to compare the efficacy and adverse events of doublet and triplet chemotherapy regimens in the first-line treatment of elderly patients with metastatic gastric cancer.

Methods: We retrospectively evaluated geriatric metastatic gastric cancer patients who were treated at the Van Yüzüncü Yıl University Medical Faculty between 2011 and 2021. Demographic characteristics, treatment regimens and responses, grade 3-4 toxicity, progression-free survival (PFS), and overall survival (OS) were analyzed with appropriate statistical methods.

Results: The mean age of the 224 patients was 73.8±3.6 years and 56 (25%) were female. Double-agent chemotherapy was administered to 99 (44.2%) patients, whereas 125 (55.8%) received triple-agent chemotherapy. The median OS was 9.8 months in the doublet group and 10.1 months in the triplet group (p=0.954). The median PFS was 5.8 months in the doublet group and 6.2 months in the triplet group, respectively (p=0.935). No statistically significant difference was found in terms of adverse events rates between groups.

Conclusions: In this study, triplet chemotherapy had no additional toxicity, but also did not have a significant improvement in survival. Therefore, dual regimens, which may have lower toxicity in the geriatric population, may be considered preferable.

Keywords: Chemotherapy, gastric cancer, elderly, first-line treatment

ÖZET

Giriş: Yaşlı metastatik mide kanseri hastalarının yönetimi için kılavuz eksikliği bulunmaktadır. Bu çalışmanın amacı, metastatik mide kanserli yaşlı hastaların birinci basamak tedavisinde ikili ve üçlü kemoterapi rejimlerinin etkinliğini ve yan etkilerini karşılaştırmaktır.

Yöntemler: Van Yüzüncü Yıl Üniversitesi Tıp Fakültesi'nde 2011-2021 yılları arasında tedavi edilen geriatrik metastatik mide kanseri hastaları retrospektif olarak değerlendirildi. Demografik özellikler, tedavi rejimleri ve yanıtlar, grade 3-4 toksisite, progresyonsuz sağkalım (PFS) ve genel sağkalım (OS) uygun istatistiksel yöntemlerle analiz edildi.

Bulgular: Hastaların ortalama yaşı 73,8±3,6 idi. Çalışmaya dahil edilen 224 hastanın 56'sı (%25) kadındı. Hastaların 99'una (%44,2) ikili kemoterapi rejimi uygulanırken, 125'ine (%55,8) üçlü kemoterapi rejimi uygulandı. Ortanca OS, ikili grupta 9,8 ay ve üçlü grupta 10,1 aydı (p=0,954). Ortanca PFS sırasıyla ikili grubunda 5,8 ay ve üçlü grupta 6,2 aydı (p=0,935). Advers olay oranları açısından gruplar arasında istatistiksel olarak anlamlı bir fark bulunmamıştır.

Sonuç: Bu çalışmada, üçlü kemoterapinin ek toksisiteye neden olmadığı ancak sağkalımı da önemli ölçüde iyileştirmediği bulunmuştur. Bu nedenle, geriatrik popülasyonda daha düşük toksisiteye sahip olabilecek ikili rejimler tercih edilebilir.

Anahtar Kelimeler: Kemoterapi, mide kanseri, geriatri, birinci basamak tedavi

INTRODUCTION

Gastric cancer (GC) is a major health problem worldwide. According to Global Cancer Statistics, an estimated 1089103 new cases of GC (5.6% of all newly diagnosed cancers) and 768793 deaths from GC (7.7% of cancer-related deaths) will occur worldwide in 2020 (1). In the United

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Submission Date: 28.12.2024 **Acception Date:** 17.03.2025
Cite as: Yilmaz Urun Y, Dirik Y, Duzen Oflas N, et al. Comparison of Doublet and Triplet Chemotherapy Regimens in Geriatric Patients with Metastatic Gastric Cancer. Eskisehir Med J. 2025; 6(2): 75-80. doi: 10.48176/esmj.2025.185

States, it is estimated that there will be 26890 newly diagnosed GC and 10880 deaths due to GC in 2024 (2).

Chemotherapy is the mainstay treatment for metastatic GC, and the median overall survival (OS) of patients treated with chemotherapy is approximately 12 months. Chemotherapy provides a statistically significant survival benefit compared to best supportive care (3). The European Society for Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN) guidelines recommend palliative chemotherapy for patients with HER-2-negative locally advanced or metastatic GC and immunotherapy in addition to chemotherapy for patients with accessibility (4,5).

Age is the largest non-modifiable risk factor for cancer. The incidence of most solid organ tumors increases with age. More than a third of new cancer diagnoses in the United Kingdom each year are in people aged 75 and older, and the number of older individuals living with cancer is expected to triple from 2010 to 2040 (6). Aging is associated with a progressive decline in functional reserves, an increase in the prevalence of chronic diseases, and an increase in the incidence of cancer. Increased age is also associated with changes in the pharmacokinetics and pharmacodynamics of cancer treatment and increased susceptibility to systemic side effects (7). Therefore, appropriate patient selection is crucial for the effective and safe delivery of cancer treatment.

Although chemotherapy is a fundamental component in the treatment of metastatic GC, there is a lack of guidelines for managing elderly metastatic GC patients. Current guidelines for the treatment of GC are mainly based on evidence from clinical trials in younger patients; however, geriatric cancer patients have a worse OS than younger patients (8). In a retrospective study, 306 patients who received chemotherapy were divided into two categories: under and over 70 years of age, and no statistically significant difference was found in progression-free survival (PFS) and OS between the two groups (9). In a meta-analysis of 23 trials and 4540 patients published in 2019, compared with doublet chemotherapy regimen, triplet chemotherapy regimen improved OS, PFS, and objective response rate (ORR) in patients with advanced GC, but OS improved only in western patients and not in Asian patients (10). Many chemotherapeutic agents are effective and used in the treatment of GC. Although, there is no standard treatment of GC, double-agent, or triple-agent chemotherapy regimens can also be used.

The aim of our study was to compare the efficacy and side effects of doublet chemotherapy regimens with triplet chemotherapy regimens in the first-line treatment of patients aged ≥ 70 years with HER-2 negative metastatic GC, which has become an important part of our routine practice.

METHODS

Patients with recurrent or metastatic GC who were treated at the Van Yüzüncü Yıl University Medical Faculty Hospital between January 2011 and December 2021 were evaluated. Our inclusion criteria were as follows: (1) age ≥ 70 years, (2) cytologically or histologically proven recurrent or metastatic GC, (3) HER-2 negative disease, (4) no prior treatment for recurrent metastatic disease, (5) treatment with one of the doublet or triplet regimens as chemotherapy, and (6) completeness of at least two cycles of chemotherapy. The exclusion criteria were as follows: (1) age < 70 years, (2) no pathologic or cytologic diagnosis, (3) HER-2 positive disease, and (4) any previous treatment for metastatic recurrent disease.

Demographic characteristics, treatment regimens and responses, prognostic factors, grade 3-4 toxicity, PFS, and OS were analyzed. PFS was assessed by calculating the time relapsed from the start of the initial treatment until the occurrence of disease progression, death, or the final documented visit in patients who did not experience progression. OS was determined by measuring the time from the initiation of first-line treatment to the occurrence of death or last follow-up. The patients were divided into two groups: double- and triple-agent chemotherapy. The double-agent chemotherapy regimens were FOLFOX (oxaliplatin, folinic acid, and fluorouracil); FOLFIRI (irinotecan, folinic acid, and fluorouracil) CAPOX, (capecitabine, and oxaliplatin); CX (cisplatin, and capecitabine); and CF (cisplatin, and fluorouracil). Triple-agent chemotherapy regimens were DCF (docetaxel, cisplatin, and fluorouracil), ECF (epirubicin, cisplatin, and fluorouracil), ECX (epirubicin, cisplatin, and capecitabine), and EOX (epirubicin, oxaliplatin, and capecitabine). Radiological evaluations were performed every 8 weeks with computed tomography scans of the thorax and abdomen or Positron Emission Tomography-Computed Tomography (PET-CT). Treatment response was evaluated according to RECIST 1.1. The toxicity assessment was performed according to the common criteria of the National Cancer Institute. It was graded as follows: 1=mild, 2=moderate, 3=severe, and 4=very severe.

Ethics Committee Approval:

This study was conducted in accordance with the principles of the Declaration of Helsinki. The study was approved by the Ethics Committee of Van Yüzüncü Yıl University Medical Faculty (date: 16.02.2024, decision no: 2024/02-07). Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Statistical Analysis:

Statistical analyses were performed using IBM SPSS Statistics for Windows version 25 (IBM Corp., Armonk, N.Y., USA). Categorical variables are presented as numbers (percentages), while continuous variables with normal distribution are presented as mean ± standard deviation (SD); non-normal variables are reported as median (minimum-maximum). Comparisons between groups were performed using Chi-square and Fisher's exact tests for

categorical variables. Survival analyses were conducted using the Kaplan-Meier method. Statistical significance was set at $p < 0.05$.

RESULTS

A total of 224 patients (168 men (75%) and 56 women (25%)) were included. The mean age was 73.8 ± 3.6 years. Liver metastases were present in 68.3%, lung metastases in 21.4 %, peritoneal metastases in 36.6 %, and bone metastases in 9.8% of patients, respectively. The mean carcinoembryonic antigen (CEA) value of the patients at the beginning of treatment was 147.7 ng/mL and carbohydrate antigen 19-9 (CA-19-9) was 3020 U/mL, whereas CEA was 290 ng/mL and CA-19-9 was 3247 U/mL at the end of treatment. The demographic and clinical characteristics of patients are presented in Table 1.

Table 1. Demographic and clinical characteristics of the patients

All patients (n = 224)	
Age (mean±sd) (years)	73.8 ± 3.6
n (%)	
Gender	
Female	56 (25)
Male	168 (75)
Hypertension	59 (26.3)
Diabetes Mellitus	19 (8.5)
ECOG PS*	
0	37 (16.5)
1	119 (53.1)
2	67 (29.9)
3	1 (0.4)
History of surgery	
No	170 (75.9)
Yes	54 (24.1)
Surgery type	
Curative	33 (61.1)
Palliative	21 (38.9)
Tumor Localization	
Cardia	86 (39.1)
Corpus	52 (23.6)
Antrum	63 (28.6)
Diffuse	19 (8.6)
Metastatic organ site	
Liver	153 (68.3)
Lung	48 (21.4)
Bone	22 (9.8)
Peritoneum	82 (36.6)
Brain	2 (0.9)
Other	9 (16.1)
Progression	193 (86.2)
Final situation	
Alive	44 (19.5)
Dead	180 (80.4)

*ECOG PS, Eastern Cooperative Oncology Group performance status

99 (44.2%) patients received double-agent chemotherapy and 125 (55.8%) patients received triple-agent chemotherapy. In all patients, median OS was 9.9 months (7.8-11.9) and median PFS was 6.1 months (5.1-7.2). In analyses of OS with double-agent chemotherapy versus triple-agent chemotherapy, OS was similar between these treatment groups, 9.8 months (95% CI 7.2-12.3) with double-agent chemotherapy vs 10.1 months (95% CI 6.9-13.2) with triple-agent chemotherapy; (p = 0.954) (Figure 1).

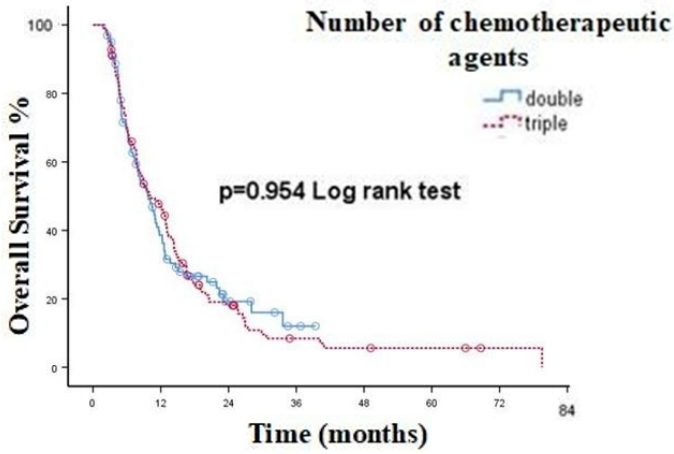

Figure 1. Survival curve for overall survival comparison between chemotherapy regimens

In analyses of PFS with double-agent chemotherapy versus triple-agent chemotherapy, PFS was similar between these treatment groups, 5.8 months (95% CI 4.1-7.4) with double-agent chemotherapy versus 6.2 months (95% CI 5.2-7.1) with triple-agent chemotherapy; (p = 0.935) (Figure 2).

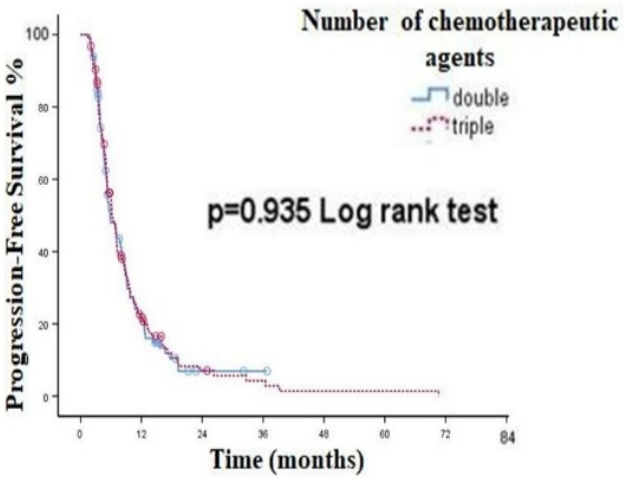

Figure 2. Survival curve for progression-free survival comparison between chemotherapy regimens

Grade 3-4 neutropenia developed in 24.5% of the patients receiving double-agent chemotherapy and 28.5% of the patients receiving triple-agent chemotherapy. There was no statistically significant difference between the groups in terms of grade 3-4 neutropenia (p = 0.508). There were also no significant differences between the groups in terms of other side effects (p > 0.05). The side effects are summarized in Table 2.

Table 1. Demographic and clinical characteristics of the patients

Adverse event	Double-agent Chemotherapy n=99	Triple-agent Chemotherapy n=125	p
	n (%)	n (%)	
Grade 3-4 neutropenia	24 (24.5)	35 (28.5)	0.508
Grade 3-4 anemia	15 (15.3)	25 (20.5)	0.322
Grade 3-4 thrombocytopenia	5 (5.1)	8 (6.6)	0.649
Febrile neutropenia	6 (6.1)	13 (10.7)	0.234
Grade 3-4 mucositis	5 (5.1)	10 (8.1)	0.374
Grade 3-4 diarrhea	4 (4.1)	7 (5.7)	0.759
Grade 3-4 nausea-vomiting	17 (17.2)	18 (14.5)	0.588
Grade 3-4 peripheral sensory neuropathy	5 (5.1)	2 (1.6)	0.246
Grade 3-4 allergic reaction	2 (2)	1 (0.8)	0.588
Grade 3-4 thrombosis	6 (6.1)	9 (7.3)	0.711
Grade 3-4 hepatotoxicity	0	1 (0.8)	1
Grade 3-4 nephrotoxicity	7 (7.1)	5 (4.1)	0.316
Grade 3-4 cardiotoxicity	3 (3.1)	1 (0.8)	0.325

DISCUSSION

In our study, we found that there was no statistically significant difference between doublet and triplet chemotherapy regimens in terms of PFS, OS and grade 3-4 side effects in the first-line treatment of patients aged ≥ 70 years with HER-2 negative metastatic or recurrent GC.

In a study comparing chemotherapy and best supportive care, patients with metastatic GC who received chemotherapy in addition to best supportive care had a longer OS of 8 months versus 5 months and a longer time to progression of 5 months versus 2 months (11). In a meta-analysis by Wagner et al., there was a one-month difference in OS in patients receiving combination therapy for metastatic disease compared to those receiving monotherapy, and this difference was statistically significant. As expected, the frequency of side effects was higher in patients receiving combination therapy than in monotherapy (12). The first-line treatment for metastatic HER-2 negative GC is controversial. In the literature, there are many studies on doublet or triplet chemotherapies in GC, but these studies have revealed conflicting results. In a retrospective study, patients with metastatic GC who received a triplet chemotherapy regimen had significantly longer survival than those who received an oxaliplatin-based doublet chemotherapy regimen (11.1 versus 8.1 months, p = 0.007). There was no statistically significant difference between patients receiving triplet chemotherapy regimen and patients receiving cisplatin-based doublet chemotherapy regimen (11.13 versus 10.57 months, p = 0.665) (13). In particular, two large randomized phase 3 trials have been conducted on doublet or triplet treatments. The first of these studies was conducted in 2006, comparing docetaxel-cisplatin-fluorouracil with cisplatin-fluorouracil. The OS was statistically significant, although there was a small difference in favor of triplet chemotherapy (9.2 months versus 8.6 months; p = 0.02) (14). In a phase 3 study conducted in Japan in 2019, the addition of docetaxel to cisplatin plus S-1 did not improve OS. In fact, the study numerically favored doublet therapy (14.2 versus 15.3 months) (15).

Our study included patients older than 70 years, and there was no significant difference between the doublet and triplet regimens in terms of OS and PFS. There is no clear evidence on palliative chemotherapy in geriatric patients. In geriatric patients with cancer, the choice of appropriate chemotherapy can be challenging due to diminished organ function, reduced functional status, comorbidities and other biological problems associated with aging (16,17). The ESMO GC guidelines recommend dose-reduced oxaliplatin-based chemotherapy for elderly and/or frail patients based on results from the phase III GO-2 trial, which showed lower toxicity and comparable survival outcomes compared to the

standard dose (18). In a phase III study in Korea in patients aged ≥ 70 years, adding oxaliplatin to capecitabine showed a survival benefit with acceptable toxicity (19).

In a retrospective analysis of three large randomized trials, the benefits of chemotherapy for gastroesophageal cancer in patients aged 70 years and above were evaluated and compared with those in younger patients. 257 of the 1080 patients with gastroesophageal cancer, 257 were aged > 70 years. Response rates, OS, and incidence of grade 3 or 4 toxicities were similar between the two groups, suggesting that patients over 70 years of age derive a similar benefit from treatment as younger patients. Patients older than 70 years received lower doses of chemotherapy; therefore, results showing no increase in toxicity with age should be interpreted with caution (20). In a meta-analysis of 21 studies including 3475 patients, an improvement in OS (HR 0.90, 95% CI 0.83-0.97) and PFS (HR 0.80, 95% CI 0.69-0.93) was observed in favor of the triplet chemotherapy regimen. Furthermore, triplet chemotherapy was associated with better ORR than doublet chemotherapy. However, as expected, grade 3-4 thrombocytopenia (6.2% vs. 3.8%), infection (10.2% versus 6.4%), and mucositis (9.7% versus 4.7%) significantly increased with the triplet regimen compared to the doublet regimen (21). Chemotherapy-related toxicity has a significant impact on treatment decisions. In our study, there was no significant difference in grade 3-4 hematological and non-hematological side effects between doublet and triplet chemotherapy regimens, and chemotherapy-related side effects were consistent with those reported in the literature.

Study Limitations:

Although our study has limitations, such as being single-center and retrospective design, it represents the first investigation conducted in this disease group when reviewing the literature. In addition, our patient group was very homogeneous, as we excluded patients under 70 years of age, patients with HER-2 positivity and those receiving treatment other than chemotherapy. The other limitation of our study is that treatment adherence was not assessed. Although no statically significant difference in OS and PFS was observed between doublet and triplet chemotherapy regimens, this may be due to the small sample size. Thus, larger-scale, prospective, randomized, well-designed studies in this patient group are needed to clarify differences in outcomes.

CONCLUSION

In conclusion, this study contributes to the understanding of treatment strategies for metastatic GC, suggesting that double-agent chemotherapy may be as effective as triple-agent chemotherapy in geriatric patient aged ≥70 years without the added toxicity. These findings advocate for a personalized approach to treatment, where decisions are tailored to individual patient profiles, taking into account factors such as age, comorbidities, and potential side effects.

* This study was presented as oral presentation at the 17th East-Southeast Anatolia Hepato-gastroenterology Days Symposium in Gaziantep on September 6, 2024 and 14th International Hippocrates Congress on Medical and Health Sciences , online on 15-16 March 2024

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Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Authorship Contributions: Idea/Concept:MÜ,YYÜ Design:GG,YYÜ Supervision:MÜ,GG, Data Collection and Processing:NDO, YD, Analysis or Interpretation:YYÜ, NDO Literature Search:SC, YD, NDO, Writing:YYÜ, SC, YD, Critical Review: MÜ,GG, References and Fundings:- Materials: -.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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