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Comparison of the Efficacy of FOLFIRI and Paclitaxel Chemotherapy Regimens in the Second Line Treatment of Metastatic Gastric Cancer

Metastatik Mide Kanseri İkinci Seri Tedavide FOLFIRI ve Paklitaksel Kemoterapi Rejimlerinin Etkinliğinin Karşılaştırılması

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ABSTRACT

Objective: Although the incidence of gastric cancer has shown a significant decrease over the years, it remains the fourth leading cause of cancer-related deaths, resulting in more than 700,000 annual deaths worldwide. The main goal of metastatic gastric cancer treatment is to alleviate symptoms and, if feasible, improve survival. The purpose of our study was to compare the effectiveness of two chemotherapy regimens, FOLFIRI, and paclitaxel, which are commonly used in the second-line treatment of metastatic gastric cancer.

Material and Method: Patients over the age of 18 with a diagnosis of metastatic gastric carcinoma who were treated with either FOLFIRI or paclitaxel as second-line therapy were enrolled in our study. These two treatment groups were compared in terms of overall and progression-free survival.

Results: A total of 99 patients were included. 56 (56.6%) patients had received FOLFIRI and 43 (43.3%) had received paclitaxel. The median overall survival for the entire cohort was 9 months: 10 months for FOLFIRI and 8 months for paclitaxel, with no statistically significant difference between them. In multivariate analysis, Eastern Cooperative Oncology Group (ECOG) performance status, body mass index, and number of chemotherapy cycles were identified as independent prognostic factors.

Conclusion: In our study, no statistically significant difference was found in terms of overall and progression-free survival between FOLFIRI and paclitaxel chemotherapy regimens in second-line treatment for metastatic gastric cancer. Both regimens can be considered reasonable second-line treatment options. According to the results of our study, the choice of chemotherapy for second-line treatment should be made on an individual basis, considering factors such as the treatment received in the first-line, side effects, medication cost, and accessibility.

Keywords: *Metastatic gastric cancer, Second-line chemotherapy, Prognostic factor*

ÖZET

Giriş: Mide kanseri insidansı yıllar içinde önemli ölçüde azalmış olsa da hala dünya çapında yıllık 700.000'den fazla ölüme neden olmaktadır. Kansere bağlı ölümlerin dördüncü en yaygın nedenidir. Metastatik mide kanseri tedavisinin temel amacı semptomları iyileştirmek ve mümkünse sağkalımı artırmaktır. Çalışmamızın amacı, metastatic mide kanserinde ikinci basamak tedavide kullanılan FOLFIRI ve paklitaksel kemoterapi rejimlerinin etkinliklerini karşılaştırmaktır.

Materyal ve Metot: Çalışmaya 18 yaş üstü, metastatic mide kanseri tanısı olup ikinci basamak tedavi olarak FOLFIRI veya paklitaksel alan hastalar dahil edildi. Bu iki grup, genel sağ kalım ve progresyonsuz sağ kalım açısından karşılaştırıldı.

Bulgular: Çalışmaya toplam 99 hasta alındı. 56 (%56.6) hasta FOLFIRI, 43 (%43.3) hasta paklitaksel kemoterapisi almıştı. Tüm kohort için medyan genel sağkalım 9 ay, FOLFIRI rejimi için 10 ay, paklitaksel rejimi içinise 8 ay idi ve aralarında istatistiksel olarak anlamlıbir fark yoktu. Çok değişkenli analizde Eastern Cooperative Oncology Group performans skoru, vücut kitle indeksi ve kemoterapi siklusu sayısı bağımsız prognostic faktörler olarak bulundu.

Sonuç: Metastatik mide kanserinde ikinci basamak tedavide FOLFIRI ve paklitaksel kemoterapi rejimleri arasında genel ve progresyonsuz sağ kalım açısından istatistiksel olarak anlamlı bir fark saptanmadı. Her iki rejim de makul ikinci basamak tedavi seçenekleri olarak Kabul edilebilir. Çalışmamızın sonuçlarına gore ikinci basamak tedavi de verilecek kemoterapiye birinci basamakta aldığı tedavi, yan etkiler, maliyet ve ilaca ulaşılabilirlik gözönünde bulundurularak hasta bazlı olarak karar verilmelidir.

Anahtar kelimeler: *Metastatik mide kanseri, İkinci basamak kemoterapi, Prognostik faktör*

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INTRODUCTION

Although the incidence of gastric cancer has shown a significant decrease over the years, it remains the fourth leading cause of cancer-related deaths worldwide, with over 700,000 deaths reported annually (Sung et al., 2021). In the United States, approximately 26,500 new cases are diagnosed each year, with an estimated 11,130 patients succumbing to the disease (Siegel et al., 2023). The prognosis for gastric cancer heavily relies on early-stage diagnosis and the possibility of curative surgery. However, despite undergoing curative surgery, nearly half of the patients experience disease recurrence (D'Angelica et al., 2004). Although surgery serves as the main treatment, these patients frequently require adjuvant treatment due to the high risk of recurrence and metastasis (Karaman et al., 2022).

The main objective of second-line treatment in metastatic gastric cancer is to improve symptoms and, if possible, enhance survival, similar to the first-line treatment. In the context of second-line treatment, several options have demonstrated improved survival in phase 3 studies, including irinotecan (Thuss-Patience et al., 2011), docetaxel (Ford et al., 2014), ramicuramab (Fuchs et al., 2014), and ramicuramab in combination with paclitaxel (Wilke et al., 2014). Furthermore, a meta-analysis conducted to evaluate the benefits of second-line treatment in patients initially treated with platinum and fluoropyrimidine-containing regimens in the first line, which subsequently progressed, showed that both chemotherapies and immunotherapies significantly enhanced survival compared to placebo (Tomita et al., 2020). Nevertheless, there is still no gold standard treatment in the second-line treatment. Clinicians make a treatment plan by taking into account various factors, including the overall health status of the patients, comorbidities, the treatment regimen administered in the first-line, drug costs, potential toxicities, and drug accessibility.

Our study aimed to compare the effectiveness of two commonly used chemotherapy regimens, FOLFIRI (Folinic acid, fluorouracil, and irinotecan) and paclitaxel, in the second-line treatment of metastatic gastric cancer in our country.

MATERIAL and METHOD

We retrospectively reviewed the files of patients who were treated in our center between 2016 and 2020. Patients over the age of 18, diagnosed with stage 4 gastric carcinoma, who had received only one line of chemotherapy for metastatic disease, experienced disease progression, possessed sufficient organ function for second-line chemotherapy and had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-2 were included in the study. Patients with an ECOG PS score of 3-4, patients who received more than one line of chemotherapy, patients with inadequate organ function for chemotherapy, and patients with central nervous system metastases were excluded from the study.

Patients were divided into two groups FOLFIRI and paclitaxel according to the second-line chemotherapy regimen. These two groups were compared in terms of overall and progression-free survival. We defined overall survival (OS) as the time from the start of second-line treatment until the patient's death or the last follow-up examination. We defined progression-free survival (PFS) as the time from the start of second-line treatment until the date of disease progression, patient death, or the last follow-up examination. Tumor progression was evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria.

In addition, patients were also classified by gender, body mass index (BMI) (<22, ≥22), histology (adenocarcinoma, signet ring cell carcinoma), grade (well differentiated, moderately differentiated, poorly differentiated), HER-2 status (negative-positive), site of the primary tumor (proximal, distal, fundus), Lauren classification (intestinal, diffuse), palliative surgery (present, absent), metastasis site (liver, peritoneum, distal lymph nodes, lung, bone, ovary), ECOG PS (0-1-2), first-line chemotherapy regimen (singlet-doublet-triplet).

Treatment regimens

FOLFIRI (irinotecan 180 mg/m2 day one, leucovorin 400 mg/m2 as a two-hour infusion, and 5-fluorouracil 400 mg/m2 as bolus, day one and day two followed with 1,200 mg/m2/day as 22-h continuous infusion), paclitaxel 80 mg/m2 intravenously on days 1, 8, and 15 of every 28-day cycle.

Statistical analysis

Categorical variables were presented as numbers (percentages), while continuous variables were presented as median (range). The compliance of the numerical values with the normal distribution was assessed through histograms and the Kolmogorov-Smirnov test. As the quantitative variables did not follow a normal distribution, the Mann-Whitney U test was employed to compare two independent groups. To compare proportions in different groups, the Chi-square test was used. Survival analyses were conducted using the Kaplan-Meier method, starting from the initiation of second-line chemotherapy, and compared using the Log-Rank test. Prognostic factors for survival were investigated through Cox regression analysis. Variables that were found to be statistically significant in the univariate analysis were included in the multivariate regression model. A p-value of less than 0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, N.Y., USA).

RESULTS

A total of 99 patients were included in the study. Table 1 presents a summary of the baseline characteristics of the patients. Median age was 60 (range: 25-85) years, 26 patients (26.3%) were women and 73 patients (73.7%) were men. All patients had a good performance status (ECOG 0-2). FOLFIRI was initiated in 56 (56.6%) patients, while paclitaxel was

started in 43 (43.4%) patients as second-line chemotherapy (CT), with a median time of 11 months after the initial diagnosis as shown in Table 2.

The median OS from the initiation of second-line chemotherapy for the entire cohort was 9 months (95% CI, 7.75-10.24). There was no statistically significant difference observed between FOLFIRI (median OS: 10 months, 95% CI, 7.18-12.82) and paclitaxel (median OS: 8 months, 95% CI, 6.66-9.34) (p=0.162) as shown in Figure 1. The median PFS from the start of second-line chemotherapy for the entire cohort was 6 months (95% CI, 7.75-10.25). Similarly, no statistically significant difference was found between FOLFIRI (median PFS: 6 months, 95% CI, 3.87-8.13) and paclitaxel (median PFS: 6 months, 95% CI, 3.94-8.06) (p=0.793) as illustrated in Figure 2.

In the univariate analysis for OS, ECOG PS, BMI, number of CT cycles, response to CT, and peritoneal metastasis were identified as statistically significant factors. However, in the multivariate analysis, ECOG PS, BMI, and number of CT cycles were determined to be independent prognostic factors as shown in Table 3.

Table 1. Baseline characteristics of patients

Characteristics	All patients n=99 (100%)	FOLFIRI n=56 (56.6%)	Paclitaxel n=43 (43.4%)	P
Age (median, range)	60 (25-85)	59.5 (37-81)	63 (25-85)	0.008
Gender				
Female	26 (26.3%)	16 (28.6%)	10 (23.3%)	0.551
Male	73 (73.7%)	40 (71.4%)	33 (76.7%)	
BMI (kg/m^2)	24.4 (16.8-48.7)	23.7 (16.8-48.7)	24.7 (17.9-34.2)	0.577
<22	24	13	11	0.945
≥22	60	33	27	
Unknown	15	10	5	
Histology				
Adenocarcinoma	86 (86.9%)	50 (89.3%)	36 (83.7%)	0.416
Signet ring cell carcinoma	13 (13.1%)	6 (10.7%)	7 (16.3%)	
Grade				
Well differentiated	2 (2%)	1 (1.8%)	1 (2.3%)	0.975
Moderately differentiated	63 (63.6%)	36 (64.3%)	27 (62.8%)	
Poorly differentiated	34 (34.3%)	19 (33.9%)	15 (34.9%)	
HER2 status				0.029
Negative	86 (86.9%)	45 (80.4%)	41 (95.3%)	
Positive (FISH)	13 (13.1%)	11 (19.6%)	2 (4.7%)	
Site of the primary tumor				0.060
Proximal	61 (61.6%)	39 (69.6%)	22 (51.2%)	
Distal	36 (36.4%)	17 (30.4%)	19 (44.2%)	
Fundus	2 (2%)	0	2 (4.7%)	
Lauren classification				0.464
Intestinal	92 (92.9%)	53 (94.6%)	39 (90.7%)	
Diffuse	7 (7.1%)	3 (5.4%)	4 (9.3%)	
Palliative surgery	37 (37.4%)	14 (25%)	23 (53.5%)	0.004
Metastasis sites				
Liver	44 (44.4%)	27 (48.2%)	17 (39.5%)	0.389
Peritoneum	36 (36.4%)	22 (39.3%)	14 (32.6%)	0.490
Distant lymph nodes	23 (23.2%)	14 (25%)	9 (20.9%)	0.635
Lung	14 (14.1%)	8 (14.3%)	6 (14%)	0.962
Bone	6 (6.1%)	5 (8.9%)	1 (2.3%)	0.172
Over	3 (3%)	2 (3.6%)	1 (2.3%)	0.720
ECOG PS				0.362
0	39 (39.4%)	25 (44.6%)	14 (32.6%)	
1	40 (40.4%)	22 (39.3%)	18 (41.9%)	
2	20 (20.2%)	9 (16.1%)	11 (26.6%)	

FOLFIRI = Folinic acid, fluorouracil, and irinotecan; BMI = Body mass index; HER2 = human epidermal growth factor receptor 2; ECOG PS: Eastern Cooperative Oncology Group Performance Status

Table 2. Treatment patterns and responses of patients

Characteristics	All patients n=99 (100%)	FOLFIRI n=56 (56.6%)	Paclitaxel n=43 (43.4%)	P
First treatment type				1
CT	98 (99%)	55 (98.2%)	43 (100%)	
CRT	1 (1%)	1 (1.8%)	0	
First-line CT regimen				0.103
Singlet (5-FU)	22 (22.2%)	10 (17.9%)	12 (27.9%)	
Doublet	35 (35.4%)	17 (30.4%)	18 (41.9%)	
Triplet	41 (42.4%)	29 (51.8%)	13 (30.2%)	
Trastuzumab	10 (10.1%)	8 (14.3%)	2 (4.7%)	0.179
Second-line CT number (median, range)	6 (1-12)	6 (1-12)	6 (2-8)	0.754
Second-line CT response				0.937
Complete	2 (2%)	1 (2.6%)	1 (2.8%)	
Partial	26 (26.3%)	13 (33.3%)	13 (36.1%)	
Stable	26 (26.3%)	13 (33.3%)	13 (36.1%)	
Progression	21 (21.2%)	12 (30.8%)	9 (25%)	
Unknown	24 (24.2%)			
Progression	69 (69.7%)	39 (69.6%)	30 (69.8%)	0.989
Third-line CT	32 (32.3%)			
Final situation				0.005
Alive	41 (41.4%)	30 (53.6%)	11 (25.6%)	
Dead	58 (58.6%)	26 (46.4%)	32 (74.4%)	

FOLFIRI = Folinic acid, fluorouracil, and irinotecan; CT = Chemotherapy; CRT = Chemoradiotherapy; 5-FU = 5-fluorouracil

Table 3. Univariate analysis and multivariate analysis

Characteristics	Univariate analysis			Multivariate analysis		
	P	OR	CI 95%	P	OR	CI 95%
ECOG PS						
0	0.004			0.045		
1	0.463	0.79	0.43 - 1.47	0.085	0.49	0.21 - 1.10
2	0.009	2.45	1.25 - 4.79	0.356	1.60	0.59 - 4.34
BMI						
<22	ref			ref		
≥22	0.015	2.55	1.20 - 5.42	0.002	4.81	1.81 - 12.78
Second CT regimen						
FOLFIRI	ref			ref		
Paclitaxel	0.179	1.44	0.85 - 2.45	0.670	0.86	0.42 - 1.75
Second CT number	<0.001	0.72	0.60 - 0.86	0.004	0.72	0.58 - 0.90
Second CT response						
Complete	0.020			0.638		
Partial	0.760	1.37	0.18 - 10.43	0.799	1.33	0.15 - 11.72
Stable	0.281	3.06	0.40 - 23.34	0.533	2.04	0.22 - 19.25
Progression	0.181	3.99	0.53 - 30.38	0.457	2.46	0.23 - 16.19
Liver metastasis	0.100	1.56	0.92 - 2.67	0.385	1.43	0.64 - 3.22
Peritoneum metastasis	0.035	1.77	1.04 - 3.0	0.852	1.07	0.52 - 2.20

* Multivariate analysis was performed on 62 patients, as there were missing data for BMI in 15 patients, CT cures in 23 patients, and CT response in 24 patients.

OR = Odds ratio; CI = Confidence interval; ECOG PS: Eastern Cooperative Oncology Group Performance Status; BMI = Body mass index; CT = Chemotherapy; FOLFIRI = Folinic acid, fluorouracil, and irinotecan.

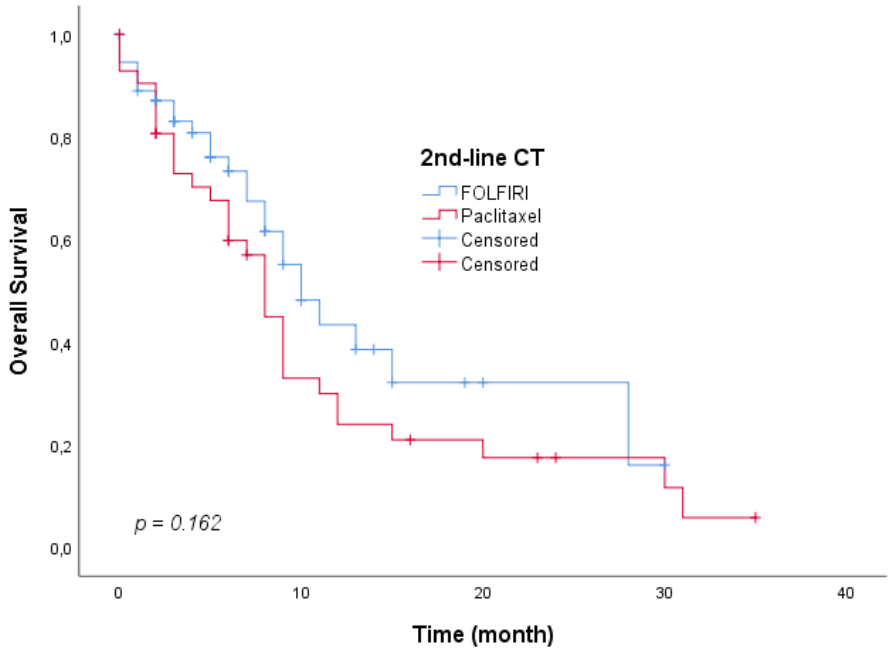

Figure 1. Survival curve for OS comparison between FOLFIRI and paclitaxel
OS = Overal survival; FOLFIRI = Folinic acid, fluorouracil, and irinotecan; CT = Chemotherapy.

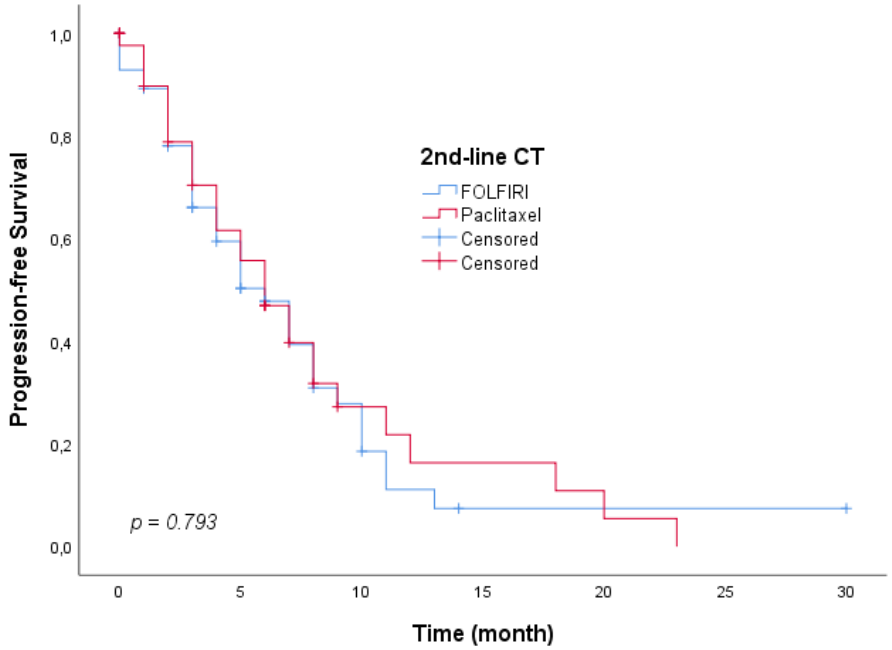

Figure 2. Survival curve for PFS comparison between FOLFIRI and paclitaxel
PFS = Progression-free survival; FOLFIRI = Folinic acid, fluorouracil, and irinotecan; CT = Chemotherapy.

DISCUSSION

Studies have demonstrated that irinotecan and taxanes, which are commonly used conventional chemotherapies in the second-line treatment of metastatic gastric cancer, have shown improved survival outcomes compared to the best supportive treatment (Thuss-Patience et al., 2011; Ford et al., 2014). In addition, a phase 3 study comparing the addition of ramucirumab, an antiangiogenic agent, to paclitaxel versus single-agent paclitaxel demonstrated a statistically significant difference in survival outcomes. The addition of ramicurumab to paclitaxel resulted in a median overall survival (mOS) of 9.6 months compared to 7.4 months in the paclitaxel-only group (p=0.017) (Wilke et al., 2014). Following the aforementioned study, the combination of paclitaxel and ramucirumab started to be recommended for patients who had access to ramucirumab. However, the high cost of this drug has limited its availability, resulting in many centers continuing to use conventional chemotherapies alone in clinical practice.

The choice of second-line chemotherapy varies among specialists and centers. Clinicians take various factors into account, including the overall health of the patients, the chemotherapy regimen administered in the first line, the cost and accessibility of the drug, potential side effects, and their expertise, to determine the most appropriate treatment plan.

In the most recent edition of the European Society for Medical Oncology (ESMO) gastric cancer guidelines published in 2022, the recommendations for second-line treatment in HER-2 negative metastatic gastric cancer are as follows: paclitaxel and ramucirumab combination is recommended for patients who are eligible for both chemotherapy and antiangiogenic therapy; fragile patients who are not eligible for chemotherapy can be treated with ramucirumab alone; for patients who are not eligible for antiangiogenic agents or face challenges in accessing the drug, taxanes or irinotecan can be considered as second-line treatments; and patients with deficient mismatch repair (dMMR) may be treated with pembrolizumab (Lordick et al., 2022).

In our study, PFS was 6 months in both groups. The median OS for the entire population was 9 months. Specifically, the FOLFIRI group had a median OS of 10 months, while the paclitaxel group had a median OS of 8 months. Although the FOLFIRI group showed a numerical advantage in terms of survival, this difference did not reach statistical significance (p=0.162). In the study in which irinotecan was used as a single agent, mOS was 4 months (Thuss-Patience et al., 2011). In a phase 3 study involving 219 patients comparing single-agent irinotecan and paclitaxel, the median OS was 9.5 months for paclitaxel and 8.4 months for irinotecan, but this difference did not reach statistical significance (p=0.38). The median PFS was 3.6 months for paclitaxel and 2.3 months for irinotecan (p=0.33). The response rate was 20.9% for paclitaxel and 13.6% for irinotecan (p=0.24) (Hironaka et al., 2013). In a retrospective study evaluating second-line chemotherapies, no statistically significant difference was observed in survival between FOLFIRI, taxane, and platinum-based chemotherapies. The median survival for FOLFIRI, taxane, and platinum-based chemotherapies was 5 months, 5.6 months, and 6.5 months, respectively (p=0.554) (Yildirim and Özveren, 2023).

Patient selection criteria for second-line systemic therapy have not yet been firmly established. However, in one study, five independent factors were identified that were associated with poor overall survival. These factors include performance status 2, hemoglobin levels below 11.5 g/dL, serum carcinoembryonic antigen (CEA) levels above 50 ng/mL, presence of three or more metastatic sites, and progression occurring within six months or less after completion of first-line treatment. Based on these risk factors, patients were categorized into three risk groups: low, medium, and high. The overall survival of patients categorized as low risk (no risk factors) was 12.7 months, while patients classified as medium risk (one or two risk factors) had an OS of 7.1 months. Patients with high risk (three or more risk factors) had an OS of 3.3 months (Catalano et al., 2008). In another retrospective study, it was identified that a high-performance score and low hemoglobin levels were poor risk factors for second-line chemotherapy (Ji et al., 2009).

Since our study was retrospective, the groups were not homogenous. ECOG PS, BMI, number of chemotherapy cycles, response to chemotherapy, and peritoneal metastasis were statistically significant in univariate analysis for OS. However, due to missing data, the multivariate analysis was conducted on a subset of 64 patients. In this analysis, ECOG PS, BMI, and number of chemotherapy cycles were identified as independent prognostic factors for overall survival. No statistically significant differences were found in the distribution of these parameters with independent effects on overall survival between the groups. The results suggested that a good performance score, high BMI, positive response to chemotherapy, receiving more chemotherapy cycles, and the presence of peritoneal metastasis were associated with increased survival.

According to the results of our study, we did not find evidence of superiority between these two conventional chemotherapy regimens in terms of progression-free and overall survival for second-line treatment of metastatic gastric cancer. Therefore, the choice of second-line treatment may be more appropriate based on the quality and side effects of the drugs used in the first-line treatment. In cases where access to ramucirumab is not available, taxanes and irinotecan-based chemotherapy can be considered reasonable options. In our center, if the patient did not receive taxanes in the first-line treatment, taxanes are generally preferred for second-line treatment. On the other hand, patients who received taxanes in the first-line treatment are often administered irinotecan-based chemotherapy as the second-line treatment.

Although our study has several limitations, including a relatively small number of patients, being conducted at a single center, having a retrospective design, and not evaluating the side effects, it is considered one of the few studies that have assessed these commonly used chemotherapy regimens. Despite these limitations, our study provides valuable insights into the efficacy and comparison of these chemotherapy regimens in the second-line treatment of gastric cancer. However, further larger-scale, multicenter studies with prospective designs and comprehensive evaluation of side effects are warranted to further validate our findings and provide more robust evidence.

Conclusion

We compared two commonly used second-line regimens for the treatment of metastatic gastric cancer, FOLFIRI, and paclitaxel, in terms of overall and progression-free survival. The results showed no statistically significant difference between these two regimens, suggesting that both can be considered reasonable options for second-line treatment. Based on the findings of our study, the choice of

chemotherapy in second-line treatment should be individualized, taking into account factors such as the specific treatment received in the first-line, potential side effects, cost considerations, and drug accessibility. However, larger prospective studies are necessary to further explore this issue and provide more robust evidence for treatment decision-making in second-line therapy for metastatic gastric cancer.

Conflict of Interest

No conflict of interest.

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Ethical Approval

The required approval for conducting the study was obtained from the Ethics Committee of the Faculty of Medicine, Van Yuzuncu Yil University (Date 10.07.2020/ Number 2020/04-29)).

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