ORIGINAL RESEARCH

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Benefits and Toxicity of Taxane Addition to Platinum-Fluoropyrimidine Combination in Gastric Cancer Patients with Peritoneal Metastasis

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ABSTRACT Objective: In advanced gastric cancer (AGC), peritoneal metastasis (PM) is associated with poor prognosis and worse performance status (PS), which makes chemotherapy administration difficult. However, PM can present with many different clinical pictures. The aim of this study was to investigate the benefits and toxicity of taxane addition to platinum-fluoropyrimidine combination in clinically poor (CPPG) and good prognostic groups (CGPG) of AGC patients with PM. **Material and Methods:** A total of 172 AGC patients with PM who were treated with taxane plus platinum plus fluoropyrimidine (TPF) or platinum plus fluoropyrimidine (PF) were included in the study. The patients with massive ascites or PS 2-3 or inadequate oral intake were included in the CPPG group, while those with an absence of these clinical factors were included in the CGPG group. The efficacy and toxicity of dose intensity on survival were evaluated separately for each group using the Kaplan-Meier method. **Results:** At the baseline, 16.9% of all patients had massive ascites, 30.2% had PS of ≥2, and 33.7% had inadequate oral intake. Accordingly, 50.6% of the patients were in CPPG. The overall survival times were found to be similar in patients treated with TPF as well as those treated with PF. Moreover, the addition of taxane treatment did not have any effect on either the poor prognostic group or the good prognostic group. However, as the dose intensity was increased, the grade 3/4 toxicity, dose delay, and reduction rates also increased. **Conclusion:** Addition of taxane to PF did not contribute to survival in AGC patients with peritoneal metastasis, independent of the clinical prognostic group.

Keywords: Gastric cancer; peritoneal metastasis; dose intensity; prognosis

Peritoneal involvement seems to be the most common pattern of metastasis or recurrence and is associated with a poor prognosis in advanced gastric cancer (AGC).[1] More importantly, peritoneal metastasis is associated with several serious clinical complications such as massive ascites, bowel obstruction, hydronephrosis, poor oral intake, and poor performance status (PS), which worsen the quality of life. As a result of these complications, patients with peritoneal metastasis are often too frail to be administered chemotherapy (CT) and have a poor survival rate as compared to those without peritoneal metastasis.[2-5] In previous studies, it was shown that triplet regimens containing taxanes, platinum, and fluoropyrimidine (TPF; F) offer better survival and response rates than doublet regimens such as platinum plus F (PF) derivatives. Thus triplet regimens are highly recommended for those AGC patients who are fit for treatment.[6] The use of oxaliplatin in place of cisplatin and capecitabine in place of 5-fluoropyrimidine in doublet treatment regimens did not affect the survival of patients.[7] As most of the studies had been conducted

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to demonstrate the effect of CT for all types of AGC, and patients suffering from severe peritoneal carcinomatosis were sometimes excluded from studies due to heavy tumor burden with poor PS. Hence, the effects of systemic CT on peritoneal metastatic disease still remains unclear.[2,6] AGP patients with poor PS, poor oral intake, or massive ascites along with peritoneal metastasis have been evaluated separately in a few retrospective studies. However, studies for those without severe peritoneal involvement are lacking. Some patients with peritoneal metastasis who have better PS status may benefit from more intensive CT regimens as well as those without peritoneal metastasis.

In the presence of peritoneal metastasis in AGC, the efficacy and safety of treatment intensity should be clarified according to the clinical prognostic classification based on PS, ascites severity, and oral intake. In this regard, we have aimed to compare the benefit and toxicity of taxane addition to the platinum-fluoropyrimidine combination in the clinically poor prognostic group (CPPG) and clinically good prognostic group (CGPG) as a real-life study.

MATERIAL AND METHODS

STUDY DESIGN

The current multicenter retrospective observational study was conducted on 172 AGC patients with peritoneal metastasis. This study was approved by the Kahramanmaraş Sütçü İmam University Faculty of Medicine Clinical Research Ethics Committee and conducted in compliance with the ethical principles in the Declaration of Helsinki.

The aim of the study was to compare the benefits and toxicity of taxane addition to PF combination on CPPG and CGPG patients having AGC with peritoneal metastasis.

PATIENTS AND TREATMENTS

This retrospective analysis screened data of AGC patients from multiple centers who had undergone CT between January 2006-January 2020 were screened. Patients without any follow-up data were excluded. Patients with de novo peritoneal metastasis or recurrence with peritoneal involvement who could receive CT were included. The presence of ascites, positive peritoneal washing, and peritoneal nodules as seen upon imaging by computed tomography (CT) or positron emission tomography scanning was counted as peritoneal metastasis. Only patients treated with at least one cycle of CT at different dose intensities according to the primary physician's discretion were enrolled for the study. The following information of patients were noted: age, gender, tumor pathological type, human epidermal growth factor receptor 2 (her 2) status, histopathological differentiation, de novo or recurrent disease, presence of only peritoneal metastasis or together with other sites, history of palliative gastrectomy, Eastern Cooperative Oncology Group (ECOG) PS (0-1 vs. 2-3), ascites levels (grade 0-3 versus massive), the status of oral intake (enough or inadequate), creatinine levels (<1.2 mg/dL or over), and urea levels (<40 mg/dL or over).[8] Inadequate oral intake was defined as the inability to take the estimated food and fluid intake via oral diet or nutrition support, according to the European Society for Clinical and Metabolism Guideline.

All patients had been treated with either a taxane plus platinum plus fluoropyrimidine (TPF) regimen or a platinum plus fluoropyrimidine (PF) regimen according to the physician's discretion. Trastuzumab was added to the treatment if there were 2-3 positive her-2 staining results with immunohistochemistry and in situ hybridization. Taxanes were administered every 2 weeks at 50 mg/m^2 or every 3 weeks at 40-75 mg/m^2. We divided the whole patient cohort into 2 groups; (i) patients treated with triplet regimes and (ii) those treated with doublet regimes. The patients received up to 6 cycles of treatment with PF/TPF, followed by maintenance with fluoropyrimidine in the absence of progression or toxicity.

We investigated the clinicopathological characteristics and the effects of dose intensities on progression-free survival (PFS) and overall survival (OS) of the patients.

In the presence of any one of either massive ascites, ECOG PS 2-3, or inadequate oral intake, the patient was placed in the CPPG group, and in the absence of all three parameters, the patient was placed under the CGPG group. We compared the efficacy and tolerability of treatment dose intensity be-

tween CPPG and CGPG patients. Patients were monitored every three cycles of CT to assess response rate, survival, and toxicities according to Common Terminology Criteria for Adverse Event, version 4.0.

STATISTICS

Based on the multinational V325 phase II/III trial, 23% of risk reduction on OS was expected upon the addition of taxane treatment for 80% power. Accordingly, 176 patients were required to be recruited in each arm, but this could not be achieved. Quantitative variables were described as means with standard deviation and median with range, while qualitative variables were presented as frequencies with proportions. To detect significant differences between the qualitative variables, chi-square and/or fischer-exact tests for rates were performed. OS was calculated from the date of diagnosis of metastasis to either the time of death or the date of the last follow-up visit. PFS was calculated from the date of diagnosis of metastasis to either disease progression or death. PFS and OS were estimated using the Kaplan-Meier method, while the Log-rank test was used to compare the effects of various clinicopathological parameters and the treatment dose intensity on survival for univariate analysis. A p-value of less than or equal to 0.05 was considered statistically significant, and statistical analyses were carried out using the statistical software package SPSS 22.0 (SPSS, Chicago, IL, USA).

RESULTS

PATIENTS

A total of 172 patients from 6 centers were included in this retrospective study. 62.2% patients had received TPF treatment, while 65 (37.8%) patients had received PF treatment.

The mean age was 50.9±12.4 years, and as many as 46.5 percent of the patients were female. 56.4% of the patients had intestinal adenocarcinoma, 40.1% had ring cell adenocarcinoma, and 2.3% had mucinous carcinoma. 51.7% of the patients had only peritoneal metastasis, and the remaining had peritoneal metastasis along with other metastases. 65.4% and 69.2% of the patients had the her-2 negative disease in the TPF and PF groups, respectively. 31.8% of the TPF group patients and 16.9% of the PF group patients had unknown her-2 expression status since antiher2 treatments were not yet approved at the time of their diagnosis. Ninety-six (55.8%) patients had de novo metastatic disease. Adjuvant treatment data of 35 (20.3%) patients could not be reached. Twenty-three (13.4%) of the patients had received chemo-radiotherapy, and only 1 (0.6%) patient had received radiotherapy alone. All the remaining patients had received either adjuvant or perioperative CT.

At the baseline, 16.9% of all patients had massive ascites, 30.2% had an ECOG PS score of 2 or above, 33.7% had an inadequate oral intake, and 4.1% of the patients had deteriorated renal function.

48.3% of patients had received second-line CT, while 16.3% had received third-line therapy.

EFFICACY ANALYSIS ACCORDING TO CLINICOPATHOLOGICAL FACTORS

The median PFS was 5.0 (4.08-5.92) months, and the OS was 9.0 (7.70-10.29) months. The OS was 9.0 months in both groups of patients treated with TPF or PF.

As far as treatment options of clinicians are concerned in terms of dose intensity, the choice of dose intensity increased when the patients were younger or had a better PS and had received CT for the first-line or presented with de novo peritoneal metastasis (Table 1).

Factors such as age, gender, tumor differentiation and histological type, peritoneal involvement alone or more, line of CT, her-2 status, history of palliative gastrectomy, de novo, or recurrent disease did not affect PFS and OS (Table 2). On the other hand, the presence of massive ascites, inadequate oral intake, ECOG PS score of ≥2, and renal dysfunction were associated with poor survival (Table 2).

EFFICACY ANALYSIS ACCORDING TO TREATMENT DOSE INTENSITY IN PATIENTS WITH CLINICALLY POOR AND CLINICALLY GOOD PROGNOSTIC GROUPS

As many as 50.6% of the patients were in the clinically poor prognostic group. Firstly, the dose inten-

TABLE 1: Patients and cancer baseline characteristics according to dose intensity.

	TCF	CF	p value
Characteristic	n (%)	n (%)	
Gender			
Female	56 (52.3)	24 (36.9)	0.049
Male	51 (47.7)	41 (63.1)	
Age, years			
<65	97 (90.7)	49 (75.4)	0.007
≥65	10 (9.3)	16 (24.6)	
Palliative gastrectomy	24 (22.6)	19 (29.7)	0.306
None	82 (77.4)	45 (70.3)	
ECOG PS			
0-1	73 (73.7)	33 (55.9)	0.021
2-3	26 (26.3)	26 (44.1)	
Ascites grade			
Grade 0-3	85 (85.0)	47 (77.0)	0.203
Massive	15 (15.0)	14 (23.0)	
Oral intake			
Poor	41 (55.4)	17 (42.5)	0.18
Enough	33 (44.6)	23 (57.5)	
Only peritoneal metastasis	56 (52.3)	33 (50.8)	0.84
Peritoneal with other sites	51 (47.7)	32 (49.2)	
Histology			
Intestinal adenocarcinoma	55 (51.4)	42 (64.6)	0.184
Ring cell carcinoma	47 (43.9)	22 (33.8)	
Mucinous adenocarcinoma	4 (3.7)	-	
Other	2 (0.9)	1 (1.5)	
Differentiation			
Well	5 (5.5)	2 (4.3)	0.252
Moderately	9 (9.9)	10 (21.3)	
Poor	66 (72.5)	32 (68.1)	
Undifferentiated	11 (12.1)	3 (6.4)	
Creatinine			
≤1.2 mg/dL	89 (97.8)	56 (91.8)	0.084
>1.2 mg/dL	2 (2.2)	5 (8.2)	
Urea			
≤40 mg/dL	78 (88.6)	53 (89.8)	0.82
>40 mg/dL	10 (11.4)	6 (10.2)	
Second-line treatment;			
Received	54 (52.9)	29 (48.3)	0.57
Was not eligible	48 (47.1)	31 (51.7)	

ECOG PS: Eastern Cooperative Oncology Group Performance Status; TCF: Taxane plus CF; CF: Platinum plus fluoropyrimidine.

sity of treatment was evaluated for all these patients. Numerically the PF regimen resulted in a better PFS than the TPF regimen, while the OS was similar for both the TPF and PF regimes (Table 2). Additionally, the overall response rate and disease control rate of TCF and CF regimens were also comparable (Table 3).

When the patients were divided into 2 subgroups based on clinical prognosis, the difference in OS could not be demonstrated with the addition of taxane to the PF regimen in the clinically poor group [7.0 (5.4-8.6) vs. 8.0 (5.3-10.8) months for TPF and PF, respectively; p=0.94] (Figure 1). Similarly, for the good prognostic group, no additional survival advantage was demonstrated with TPF [15.0 (11.1-18.9) vs. 16.0 (3.9-23.7) months for TCF and CF, respectively; p:0.99] (Figure 2).

TOXICITY ANALYSIS OF THE PATIENTS ACCORDING TO TREATMENT DOSE INTENSITY

The median number of CT cycles was 5 (1-9) and 6 (1-9) in the TPF and PF groups, respectively. At least anyone out of dose reduction, grade 3/4 cytopenia, all grade 3/4 toxicity, and renal dysfunction were higher in patients treated with TPF (Table 4). However, these differences were not statistically significant (Table 4).

DISCUSSION

The presence of peritoneal metastasis, which is known to be an indicator of poor prognosis, was considered to be a separate clinical entity for many types of cancer and was evaluated separately in terms of different treatment strategies in this context.[9,10] This may be due to the clinical fragility of the patients as well as possible differences in the pharmacokinetic/pharmacodynamic properties of the administered drugs that reach the peritoneal surfaces. Consistent with the large randomized trials, the present study also demonstrated that AGC patients with peritoneal metastasis who had received CT had median PFS and OS of 5.0 and 9.0 months, respectively. The triplet regimen did not produce a better median PFS compared to the doublet regimen for these patients. Moreover, there was no difference in median OS between the 2 groups, even if more dose-intensive treatments were preferred in the younger patients with better ECOG PS. On the other hand, as expected, the presence of massive ascites, ECOG PS 2-3, inadequate oral intake, renal dysfunction, and the condition of being unsuitable for second-line CT were associated with poor survival. Therefore, poor clinical factors proved to be more determinative prognostic markers than the treatment dose intensity.

TABLE 2: Efficacy analysis according to clinicopathological factors and treatment dose intensity.

	PFS, months			OS, months		
	Median	**95% CI**	**p value**	**Median**	**95% CI**	**p value**
CT intensity TCF CF	4.0 6.0	3.03-4.97 4.48-7.51	0.23	9.0 9.0	7.45-10.6 7.32-10.7	0.98
Age <65 ≥65	5.0 6.0	4.1-5.9 2.6-9.4	0.47	10.0 9.0	8.4-11.7 7.3-10.6	0.65
Gender Female Male	5.0 5.0	3.8-6.2 3.7-6.3	0.82	10.0 9.0	8.6-11.4 6.7-11.3	0.77
Differentiation Well Moderately Poor Undifferentiated	2.0 7.0 5.0 6.0	0.4-3.6 5.6-8.3 3.6-6.4 3.2-8.7	0.17	11.0 13.0 11.0 10.0	0.7-21,3 7.4-18.6 9.4-12.6 8.3-11.6	0.46
Histology Intestinal adenocarcinoma Ring cell carcinoma Mucinous adenocarcinoma	5.0 5.0 2.0	3.8-6.2 3,7-6.3 0.0-6.91	0.55	10.0 9.0 3.0	7.9-12.1 6.7-11.3 1.2-7.9	0.159
Her-2 status Positive Negative Unknown	7.0 5.0 6.0	3.3-10.6 4.1-5.9 4.2-7.8	0.58	8.0 9.0 10.0	4.6-11.4 7.3-10.7 7.8-12.2	0.44
Only peritoneal metastasis Peritoneal with other sites	5.0 5.0	3.6-6.3 3.7-6.3	0.93	9.0 9.0	7.5-10.5 6.5-11.4	0.91
Disease status De novo metastatic Recurrent	5.0 5.0	3.9-6.1 3.5-6.5	0.83	9.0 9.0	7.6-10.4 6.5-11.5	0.92
Palliative gastrectomy None	6.0 4.0	4.5-7.4 2.9-5.0	0.10	11.0 9.0	7.4-14.6 7.1-10.9	0.07
ECOG performance status 0-1 2-3	6.0 3.0	4.9-7.0 2.4-3.6	<0.001	11.0 5.0	9.1-12.9 2.6-7.4	<0.001
Ascites grade Grade1-3 Massive	5.0 3.0	3.9-6.2 2.2-3.7	0.004	10.0 6.0	8.7-11.3 4.3-7.7	0.007
Oral intake Poor Enough	4.0 7.0	2.9-5.1 5.5-8.4	0.002	7.0 13.0	4.9-9.1 7.9-18.1	0.001
Creatinin <1.2 ≥1.2	5.0 2.0	4.1-5.9 0.0-4.5	0.095	9.0 3.0	7.42-10.6 0.4-5.6	0.018
Urea <40 ≥40	5.0 2.0	4.1-5.9 0.5-3.5	0.051	10.0 4.0	8.6-11.4 1.39-6.6	<0.001
Second-line treatment Did not received Received				6.0 13.0	4.1-7.8 10.5-15.5	0.001
Clinical prognostic groups Poor Good	4.0 7.0	3.1-4.8 4.5-9.2	<0.001	7.0 15.0	5.6-8.4 11.2-18.8	<0.001

CT: Chemotherapy; PFS: Progression-free survival; OS: Overall survival; CI: Confidence interval; TCF: Taxane plus CF; CF: Platinum plus fluoropyrimidine.

TABLE 3: Overall response rate according to treatment intensity.

Parameters	Triplet therapy %	Doublet therapy %	p value
Overall response rate	28. 3	27.4	1.00
Stable disease	36.4	35.5	
Progression	35.4	37.1	
Overall response rate	14.1	16.1	0.93
Stable disease	47.5	48.4	
Progression	38.4	35.5	

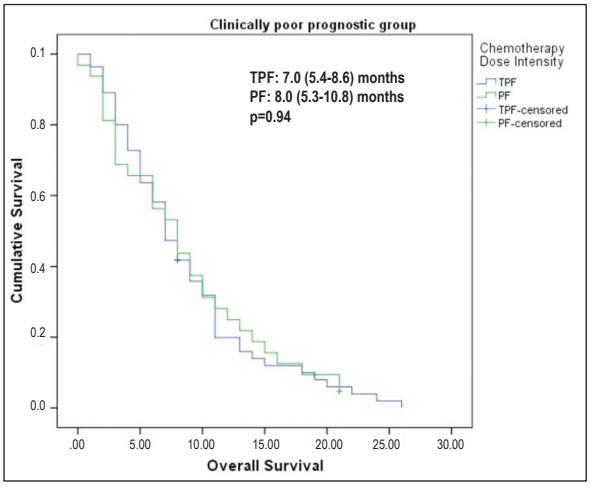

FIGURE 1: Kaplan-Meier curve showing the contribution of taxane addition to PF regimen in the clinically poor prognosis group (CPPG).

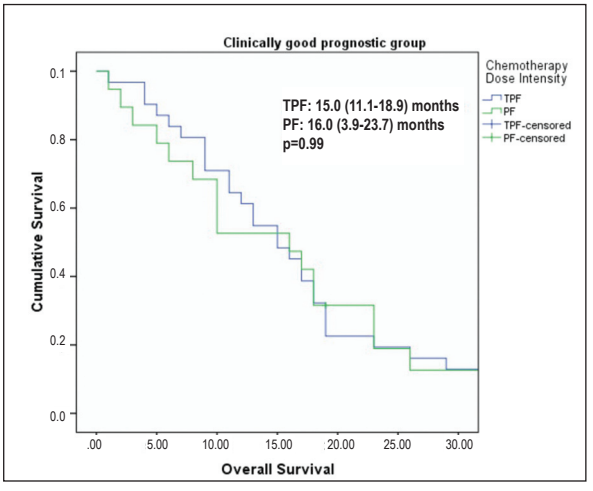

FIGURE 2: Kaplan-Meier curve showing the contribution of taxane addition to PF regimen in the clinically good prognosis group (CGPG).

TABLE 4: Treatment exposure, discontinuation, and toxicity.

	Treatment group		p value
Parameters	TCF	CF	
At least 1 dose reduction, %	33.7	28.7	0.54
At least 1 cycle delay, %	34.5	38.8	0.62
Adverse events, grade 3/4, in total	42.7	31.0	0.17
Cytopenia, grade 3/4	26.8	19.0	0.15
Liver function deteriorations, grade 3/4	4.9	7.7	0.48
Renal function deteriorations, grade 3/4	8.7	5.7	0.56
Cycles number, median (range)	5 (1-9)	6 (1-9)	
Rate of completion of first three cycles	86.0	82.3	0.77

TCF: Taxane plus CF; CF: Platinum and fluoropyrimidine.

In our study, better survival could not be achieved by increasing the intensity of the treatment alone, but it was seen that these regimens could be superior to each other in different clinical scenarios. In this regard, the effect of treatment intensity was evaluated separately in the CPPG and CGPG groups. For the CGPG, there was no positive effect of increasing the dose intensity on survival. The TPF regimen failed to show its superiority in the CGPG group, as was seen in a previous Phase III study conducted for all types of AGC.[6] This situation may be explained by the worse clinical course of patients with peritoneal metastasis as compared to the general population.

When the studies available in the literature on AGC patients with peritoneal metastases are reviewed, it is seen that there is a search for an ideal treatment regimen with bearable toxicity and survival advantage for the group of patients with clinically poor prognosis and with peritoneal involvement, often with massive peritoneal effusion and/or inadequate oral intake. The regimens of methotrexate (MTX)/5-Fluorourasil (5-FU) have been analyzed in patients with massive ascites and patients with insufficient oral intake requiring intravenous drip infusion due to peritoneal spread, but the efficacy reported was not sufficient, with an OS time

of just 4.6 (95% CI 3.9-5.3) months.[11] Monotherapy with a 5-FU plus leucovorin regimen was evaluated for patients with massive ascites and/or inadequate oral intake showing a mild OS advantage—of 6.0 months (95% CI, 2.1-9.9).[12] A randomized Phase III Study compared the efficacy of 5-FU monotherapy with methotrexate plus 5-FU therapy in AGC patients with severe peritoneal metastasis and found no difference between the arms (hazard ratio: 0.94; 95% confidence interval: 0.72-1.22; p=0.31). However, compared to the aforementioned studies above, a better median survival time of 9.4 months in the 5-FU arm and 10.6 months in the MTX plus 5-FU arm were obtained, possibly due to the better clinical status of the patients included in the study. Therefore, MTX was not a suitable partner for enhancing the effect of 5-FU in patients with severe peritoneal metastasis.[13] In our study, a median OS of 8 months (5.3-10.8) could be achieved with PF in patients who were in the poor prognostic group. Although the combination of platinum as an agent created drawbacks for the patient group with massive ascites, insufficient oral intake, and low-performance scores, we have shown that the platinum combination doublet regimen has provided numerically better PFS in total. Moreover, if patients with poor clinical prognosis can tolerate platinum, then platinum-based double regimens can be considered a more appropriate treatment considering the other supporting studies available in the literature.[14-16] In the study by Ohnuma et al. that evaluated the efficacy and toxicity of a triple regimen in patients with peritoneal metastasis based on the severity of peritoneal metastasis, a shorter survival time was obtained in patients with massive effusion consistent with our study, and the effectiveness of the triple regimen decreased.[17] Taken together, all these results indicate that the combination of platinum with fluoropyrimidine seems to be a reasonable option for AGC patients with clinically poor prognostic parameters, while adding taxane to PF did not demonstrate a better survival.

Although disease control rates were similar in both groups, at least 1 dose reduction and grade 3-4 adverse events and cytopenia were higher in patients treated with TCF. Dose reduction with increased toxicity may be the reason why the addition of taxane did not improve survival even in the good clinical prognostic group. Therefore, the choice of triplet regimens does not seem to be rational for patients with both clinically good as well as poor prognostic groups of AGC patients with peritoneal metastasis.

One main limitation of our study is that the data analysis was performed retrospectively and that the number of patients was limited. Yet another important limitation of this study is the subjective evaluation of the nutritional status of patients. We understand that the presence of peritoneal metastasis can present different clinical pictures and standard treatment regimens need further confirmation in terms of efficacy/toxicity in this group of patients. These data shed light on providing a basis for randomized clinical studies with a larger number of patients. Importantly, in the present study, triplet regimens that were known to be superior for the total population were not-found to be superior in AGC patients with peritoneal metastasis of the CPPG group, and platinum-based double regimens proved to be effective and reasonable treatment options for both the CGPG and CPPG groups.

CONCLUSION

In the presence of peritoneal metastasis, the main clinical factors causing poor prognosis are the presence of massive ascites, an ECOG PS of 2 and above, inadequate oral intake, renal dysfunction, and not being suitable for second-line treatment regardless of treatment intensity. The addition of taxane to PF did not affect survival in AGC patients with peritoneal metastasis, independent of which clinical prognostic group they belonged to.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the

potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Tülay Kuş, Gökmen Aktaş, Nuriye Yıldırım Özdemir;* ***Design:*** *Tülay Kuş, Gökmen Aktaş, Nuriye Yıldırım Özdemir, Fatih Köse, Ahmet Özet;* ***Control/Supervision:*** *Tülay Kuş, Gökmen Aktaş, Fatih Köse, Ahmet Özet;* ***Data Collection and/or Processing:*** *Tülay Kuş, Gökmen Aktaş, Nuriye Yıldırım Özdemir, Osman Sütçüoğlu, Ülkü Yalçıntaş Arslan, Merve Dirikaç, Gülsüm Akkuş, Havva Yeşil Çıngır;* ***Analysis and/or Interpretation:*** *Tülay Kuş, Gökmen Aktaş;* ***Literature Review:*** *Tülay Kuş, Gökmen Aktaş, Nuriye Yıldırım Özdemir;* ***Writing the Article:*** *Gökmen Aktaş, Tülay Kuş;* ***Critical Review:*** *Fatih Köse, Ahmet Özet;* ***References and Fundings:*** *Tülay Kuş, Gökmen Aktaş;* ***Materials:*** *Tülay Kuş, Gökmen Aktaş.*

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