



# Second-line chemotherapy using taxane in patients with advanced gastric cancer who presented with severe peritoneal metastasis: a multicenter retrospective study

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## Abstract

**Background** Individuals with advanced gastric cancer (AGC) who present with severe peritoneal metastasis (SPM) have poor prognosis. This study aimed to evaluate efficacy and safety of second-line treatment for patients with such condition.

**Methods** This retrospective study included patients receiving taxane-based second-line chemotherapy at three Japanese institutions between 2010 and 2016. Patients with AGC who present with SPM were included if they had massive ascites and/or inadequate oral intake requiring intravenous nutritional support.

**Results** In this study, 43 (40%) of 108 patients had an Eastern Cooperative Oncology Group Performance Status score  $\geq 2$ , and the median serum albumin level of the patients was 3.3 g/dL. Ramucirumab was used in combination with paclitaxel in 21 patients. The median overall survival (OS) and progression-free survival (PFS) were 5.1 and 2.8 months, respectively. Inadequate oral intake was considered a negative prognostic factor of both OS and PFS in the multivariate analysis. Three treatment-related deaths were observed, which include those attributed to febrile neutropenia, gastrointestinal perforation, and pneumonitis. Common grade  $\geq 3$  adverse events were neutropenia (35%), leukopenia (30%), anemia (24%), and anorexia (16%). We observed febrile neutropenia in 8% and gastrointestinal perforation in 4% of patients, and such conditions were dominantly observed in patients with inadequate oral intake.

**Conclusion** Taxane-based second-line chemotherapy was effective and safe for patients with AGC who present with SPM. Attention must be provided when treating patients with inadequate oral intake as they are likely to have short prognosis and serious toxicities.

**Keywords** Gastric cancer · Severe peritoneal metastasis · Second-line chemotherapy · Massive ascites · Inadequate oral intake

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## Abbreviations

AGC	Advanced gastric cancer
GC	Gastric cancer
SPM	Severe peritoneal metastasis
BSC	Best supportive care
OS	Overall survival
PFS	Progression-free survival
PM	Peritoneal metastasis
SPM	Severe PM
JCOG	Japan clinical oncology group
CR	Complete response
PR	Partial response
SD	Stable disease
TTF	Time to treatment failure
PDT	Post-discontinuation therapy

## Introduction

Gastric cancer (GC) is the fifth most common cancer and the third leading cause of cancer-related deaths worldwide [1]. The standard chemotherapy for advanced GC (AGC) is the combination of fluoropyrimidine and platinum, with trastuzumab if the patient with HER-2 positive GC, in the first-line setting [2–4] and paclitaxel plus ramucirumab in the second-line setting [5]. Although these chemotherapy treatments have survival benefits, AGC is not curable, and best supportive care (BSC) is recommended in patients with generally poor condition who cannot tolerate chemotherapy.

Peritoneal metastasis (PM) is common in individuals with AGC, and it causes serious clinical complications, such as massive ascites, bowel obstruction, jaundice, and hydro-nephrosis [6, 7]. These complications can rapidly worsen a patient's general condition, making them ineligible for chemotherapy. PM is associated with poor prognosis, and the survival time of patients with severe PM (SPM) who present with massive ascites and/or bowel obstruction is extremely short even with chemotherapy [8–11]. Unfortunately, most pivotal phase III trials have not included patients with AGC who present with SPM; hence, the standard first- and second-line chemotherapy for such patients has not been established to date [2–5, 12]. Some retrospective studies have shown the efficacy and safety of fluoropyrimidine-based regimen as first-line chemotherapy for patients with AGC who present with SPM [9, 10, 13]. Recently, the first randomized phase II/III trial (JCOG1108/WJOG7312G trial: UMIN000010949) for this particular subset of AGC has been reported. In this trial, first-line 5-FU//leucovorin (*l*-LV) plus paclitaxel did not confer a significant survival benefit but might be preferred because of longer PFS and acceptable toxicity compared to 5-FU//LV [14].

Second-line chemotherapy for AGC is provided more frequently in Japan than in other countries, as shown by a high proportion of patients (approximately 75%–80%) receiving second-line chemotherapy in several Japanese phase III trials [2, 4, 12]. Second-line chemotherapy is effective in prolonging the survival time of patients [15]. As shown in the RAINBOW trial, the combination therapy of paclitaxel and ramucirumab, which targets vascular endothelial growth factor receptor-2, has been established as a new standard second-line treatment for AGC [5]. In patients with mild to moderate PM, the administration of paclitaxel weekly is considered a promising treatment that results in longer PFS compared with the best available 5-FU regimen in the JCOG0407 trial [16]. However, to date, there are only few data about the use of second-line chemotherapy in patients with SPM. Therefore, this study aimed to investigate the efficacy and safety of taxane-based second-line chemotherapy for patients with AGC who present with SPM.

## Patients and methods

### Patients

We retrospectively reviewed the records of patients with AGC who presented with SPM and received taxane-based second-line chemotherapy between July 2010 and June 2016 at three institutions in Japan. All patient data were extracted from a database at each center. In this study, SPM was defined as PM associated with massive ascites and/or inadequate oral intake. This definition was based on previous retrospective studies [9, 10, 13] and the JCOG1108/WJOG7312G trial [14]. Inadequate oral intake was defined as the need for intravenous nutritional support. The degree of ascites was evaluated via computed tomography and was classified as follows: none, undetectable; mild, localized to the pelvic cavity or upper abdominal cavity; moderate, inconsistent with either mild or massive ascites; and massive, extending continuously between the pelvic cavity and upper abdominal cavity. The eligibility criteria for this study were as follows: (1) histologically proven adenocarcinoma of the stomach or gastroesophageal junction, (2) with SPM during the initiation of second-line chemotherapy, (3) absence of concomitant advanced malignant disease, (4) refractory or intolerance to fluoropyrimidine (and trastuzumab if a patient has HER-2 positive disease), and (5) receiving taxane-based second-line chemotherapy after disease progression during first-line chemotherapy or recurrence within 6 months after the last adjuvant chemotherapy dose. We excluded patients with a history of taxane treatment and/or those with serious complications, such as active infection, renal failure (serum creatinine level  $\geq 3.0$  mg/dL), and hepatic failure or obstructive jaundice (serum total bilirubin level  $\geq 2.0$  mg/dL).

### Assessments

We compared the degree of ascites between baseline and during treatment and determined the best responses in ascites, which were as follows: complete response (CR), the ascites completely disappeared; partial response (PR), there was a decrease by at least 1° from baseline; stable disease (SD), there was no change from baseline; progressive disease, there was an increase by at least one degree from baseline; and not evaluated, it was impossible to evaluate because fluid was drained before assessment or because there are no available records of the assessment results. We defined the response rate and disease control rate in ascites as the proportion of patients with the best CR or PR and the best CR, PR, or SD, respectively, among

patients with ascites at baseline. The improvement rate of oral intake was defined as the proportion of patients whose oral intake improved and who did not require nutritional support for at least 7 days among the patients who had inadequate oral intake at baseline.

### Statistical analysis

OS was defined as the time from treatment initiation to death from any cause, and PFS was defined as the time from treatment initiation to disease progression or death from any cause. Time to treatment failure (TTF) was defined as the time from the initiation of treatment to the last dose of second-line chemotherapy. Both OS and PFS were estimated using the Kaplan–Meier method. Prognostic factors were evaluated in the univariate and multivariate analyses using Cox proportional hazards models. Covariates with a  $p$ -value  $< 0.20$  in the univariate analysis were included in the multivariate analysis. Fisher's exact test was used for the test of independence between two categorical groups. All analyses were two-sided, and a  $p$ -value  $< 0.05$  was considered statistically significant. All statistical analyses were performed using StatView software version 5.0 (SAS Institute, Cary, NC, the USA).

### Human rights statement and informed consent

All procedures were in accordance with the ethical standards of the responsible committees on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later revisions. Informed consent for chemotherapy was obtained from all patients before treatment. This study was approved by the institutional review board of each center.

## Results

### Patients

In total, 115 patients with AGC who presented with SPM received taxane-based second-line chemotherapy. Seven patients (four with serum total bilirubin level  $\geq 2.0$  mg/dL, two with a history of receiving taxane, and one with serious infection) were excluded; thus, 108 patients were finally included. The characteristics of the patients are shown in Table 1. Forty-three (40%) patients had an Eastern Cooperative Oncology Group Performance Status (PS) score  $\geq 2$  (including one patient with a PS score of 3), and the median serum albumin level of the patients was 3.3 (range 1.8–4.3) g/dL. Thirty (34%) patients already had SPM before the initiation of first-line treatment. The detailed information about the number of patients receiving chemotherapy is as follows:

paclitaxel ( $n = 80$ ), paclitaxel plus ramucirumab ( $n = 21$ ), nanoparticle albumin-bound paclitaxel ( $n = 3$ ), 5-FU//leucovorin plus paclitaxel ( $n = 3$ ), and docetaxel ( $n = 1$ ). The following characteristics are more commonly observed in patients receiving paclitaxel plus ramucirumab ( $n = 21$ ) than in those receiving treatment without ramucirumab ( $n = 87$ ): intestinal histological type (33% vs 10%), PS score of 0 or 1 (76% vs 56%), metastatic sites  $\geq 2$  (81% vs 44%), and adequate oral intake (71% vs 44%). The details are shown in Online Resource 1.

### Reasons for discontinuation of treatment

The median TTF was 2.2 months. The reasons for treatment discontinuation were as follows: disease progression [ $n = 90$  (83%)], adverse events [ $n = 11$  (10%)], patient refusal [ $n = 3$  (3%)], and other reasons [ $n = 4$  (4%)]. The adverse events leading to treatment discontinuation were peripheral neuropathy ( $n = 4$ , including three grade 3 and one grade 2 cases), gastrointestinal perforation ( $n = 2$ , including one grade 5 and one grade 3 cases), pneumonitis ( $n = 2$ , including one grade 5 and one grade 3 cases), febrile neutropenia ( $n = 1$ , grade 5 case), fatigue ( $n = 1$ , grade 2 case), and allergic reaction ( $n = 1$ , grade 3 case).

### Efficacy

In total, 105 (97%) patients had died. The median OS and PFS were 5.1 and 2.8 months, respectively (Fig. 1a). In the analysis according to the subtype of SPM, the median OS of patients with massive ascites only, inadequate oral intake only, and both were 6.0, 4.4, and 3.2 months, respectively. The median PFS were 3.5, 2.5, and 2.1 months, respectively (Fig. 1b–c). The univariate analysis of OS identified two prognostic factors: presence of massive ascites and inadequate oral intake. The multivariate analysis showed that inadequate oral intake was the only independent prognostic factor [hazard ratio (HR) = 2.41; 95% confidence interval (CI) 1.47–3.97;  $p < 0.01$ ]. Similarly, in the analysis of PFS, inadequate oral intake was the only independent prognostic factor in the multivariate analysis (HR = 1.88; 95% CI 1.15–3.08;  $p = 0.01$ ) (Table 2).

The response rate and disease control rate in ascites were 27% (28/102) and 78% (80/102), respectively. The improvement rate of oral intake was 31% (17/55) (Table 3).

### Safety

Data about toxicity are shown in Table 4. Three (3%) treatment-related deaths were recorded, which include those attributed to febrile neutropenia in a patient receiving paclitaxel plus ramucirumab, gastrointestinal perforation in a patient receiving paclitaxel plus ramucirumab,

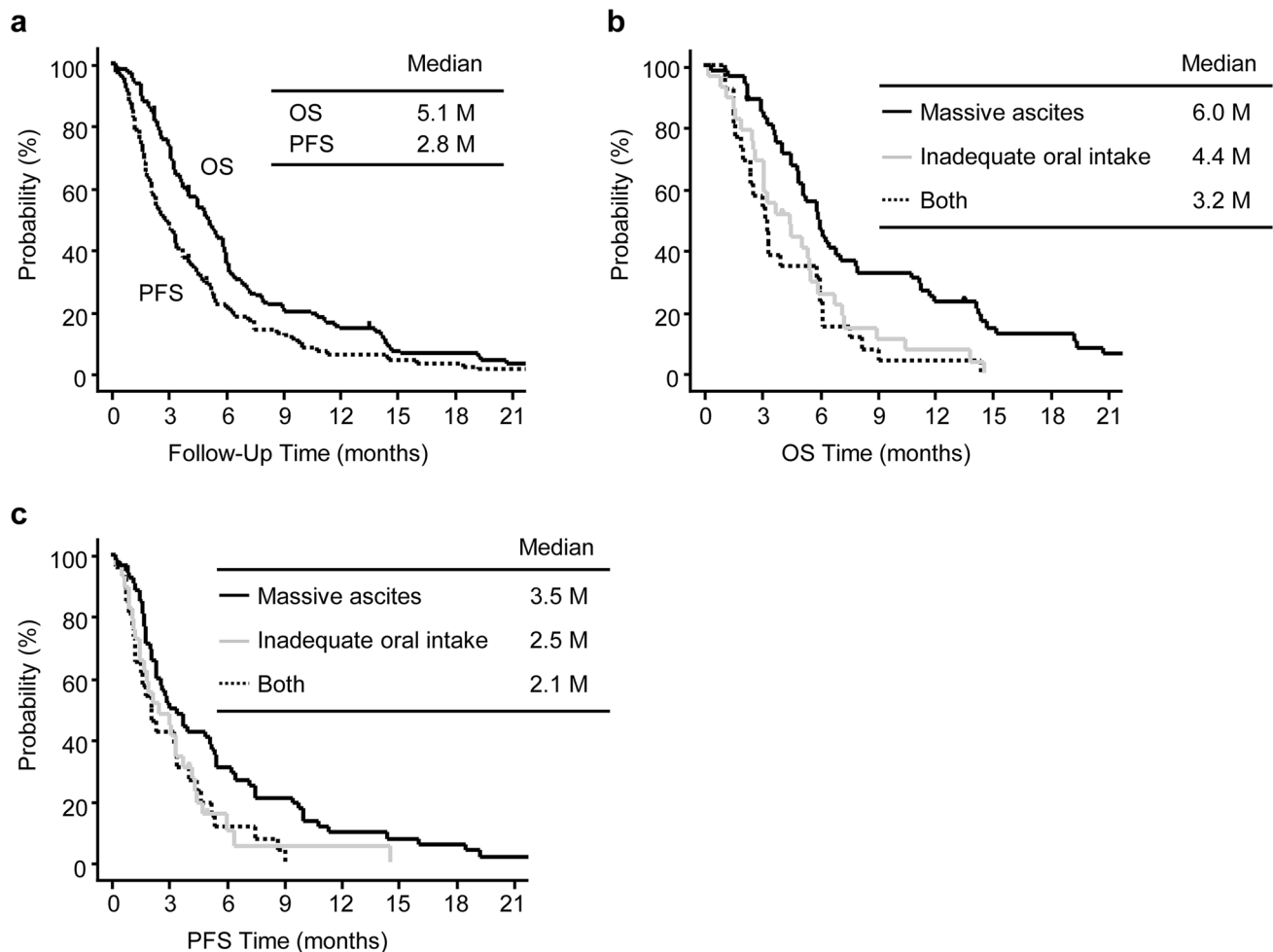
**Table 1** Characteristics of the patients

	Characteristics	(N = 108) (%)	
Age	Median (range)	63	(25–83)
Sex	Male	62	(57)
	Female	46	(43)
ECOG PS	0	10	(9)
	1	55	(51)
	2	42	(39)
	3	1	(1)
Histology	Intestinal	16	(15)
	Diffuse	92	(85)
Primary tumor	Presence	66	(61)
	Absence	42	(39)
Disease status	Advanced	76	(70)
	Recurrent	32	(30)
Number of metastatic sites	1 (only PM)	53	(49)
	≥2	55	(51)
Amount of ascites	None	6	(6)
	Mild	16	(15)
	Moderate	7	(6)
	Massive	79	(73)
Oral intake	Adequate	53	(49)
	Inadequate	55	(51)
Subtype of SPM	Only massive ascites	53	(49)
	Only inadequate oral intake	29	(27)
	Both	26	(24)
Presence of SPM at the initiation of firstline treatment	Yes	37	(34)
	No	71	(66)
Serum albumin level (g/dL)	Median (range)	3.3	(1.8–4.3)
Serum CRP level (mg/dL)	Median (range)	1.1	(0.0–19.6)
Agents used during the first-line treatment	Fluoropyrimidine	108	(100)
	Platinum	66	(61)
	CDDP	44	(41)
	OHP	22	(20)
	PTX	80	(74)
Regimen of the Second-line treatment	PTX + RAM	21	(19)
	Nab-PTX	3	(3)
	FLTAX	3	(3)
	DTX	1	(1)

*CDDP* cisplatin, *CRP* C-reactive protein, *DTX* docetaxel, *ECOG PS* Eastern Cooperative Oncology Group performance status, *Nab-PTX* nanoparticle albumin-bound paclitaxel, *OHP* oxaliplatin, *PM* peritoneal metastasis, *PTX* paclitaxel, *RAM* ramucirumab, *SPM* severe peritoneal metastasis

and pneumonitis in a patient receiving paclitaxel. In all patients, common grade  $\geq 3$  adverse events were neutropenia [ $n = 38$  (35%)], leukopenia [ $n = 32$  (30%)], anemia [ $n = 26$  (24%)], and anorexia [ $n = 16$  (15%)]. Febrile neutropenia occurred in nine (8%) patients, which included six patients with a PS score of 2 and seven patients whose oral intake were inadequate, and gastrointestinal

perforation occurred in four (4%) patients, which included two patients with a PS score of 2 and three patients whose oral intake were inadequate. The details of each case are shown in Online Resource 2. Both febrile neutropenia and gastrointestinal perforation were more commonly observed in patients with inadequate oral intake than in those with adequate oral intake [13% (7/55) vs 4% (2/53)



**Fig. 1** Kaplan–Meier analysis of overall survival (OS) and progression-free survival (PFS). **a** Overall survival and progression-free survival of all patients ( $N=108$ ). **b** Overall survival of patients with massive ascites only ( $N=53$ ), inadequate oral intake only ( $N=29$ ),

and both ( $N=26$ ). **c** Progression-free survival of patients with massive ascites only ( $N=53$ ), inadequate oral intake only ( $N=29$ ), and both ( $N=26$ )

and 5% (3/55) vs 2% (1/53), respectively]. Meanwhile, higher incidence of febrile neutropenia and gastrointestinal perforation was not observed in patients with massive ascites, compared to those without massive ascites [5% (4/79) vs 17% (5/29) and 4% (3/79) vs 3% (1/29), respectively]. Also, both febrile neutropenia and gastrointestinal perforation were more commonly observed in patients receiving paclitaxel plus ramucirumab than in those receiving taxane only [14% (3/21) vs 7% (6/87) and 10% (2/21) vs 2% (2/87), respectively]. In patients with massive ascites, the incidence of febrile neutropenia and gastrointestinal perforation were almost similar between patients receiving paclitaxel plus ramucirumab and those receiving taxane only [6% (1/16) vs 5% (3/63),  $p > 0.99$  and 6% (1/16) vs 3% (2/63),  $p = 0.50$ , respectively]. Meanwhile, in patients with inadequate oral

intake, the incidence of febrile neutropenia tended to be higher, and that of gastrointestinal perforation was significantly higher in patients receiving paclitaxel plus ramucirumab than in those receiving taxane only [33% (2/6) vs 10% (5/49),  $p = 0.16$  and 33% (2/6) vs 2% (1/49),  $p = 0.03$ , respectively] (Table 5). Gastrointestinal bleeding occurred only in two (2%) patients, and both patients received taxane only.

### Post-discontinuation therapy (PDT)

In total, 28 (26%) patients received PDT. The regimens of PDT were as follows: irinotecan plus cisplatin ( $n=6$ ), irinotecan ( $n=6$ ), FOLFOX ( $n=6$ ), 5-FU/l-LV ( $n=3$ ), ramucirumab ( $n=2$ ), S-1 plus oxaliplatin ( $n=1$ ), S-1 plus cisplatin ( $n=1$ ), and others ( $n=3$ ).

**Table 2** Univariate and multivariate analyses of the prognostic factors of OS and PFS (*N* = 108)

Variables	OS						PFS						
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis			
	HR	[95% CI]	<i>p</i> -value	HR	[95% CI]	<i>p</i> -value	HR	[95% CI]	<i>p</i> -value	HR	[95% CI]	<i>p</i> -value	
Age	≥ 65 (vs. < 65)	0.96	[0.65–1.42]	0.85	1.00	[0.68–1.47]	0.99						
Sex	Female (vs. male)	1.21	[0.81–1.78]	0.35	1.14	[0.77–1.70]	0.51						
ECOG PS	2–3 (vs. 0–1)	1.29	[0.87–1.91]	0.20	1.18	[0.80–1.75]	0.41						
Histology	Diffuse (vs. intestinal)	1.17	[0.66–2.06]	0.60	1.03	[0.59–1.78]	0.92						
Disease status	Recurrent (vs. advanced)	0.83	[0.55–1.27]	0.40	0.81	[0.53–1.24]	0.34						
Number of metastatic sites	≥ 2 (vs. 1)	0.92	[0.63–1.36]	0.68	0.84	[0.57–1.24]	0.38						
SPM at 1st-line treatment start	Presence (vs. absence)	1.08	[0.71–1.63]	0.72	1.19	[0.79–1.79]	0.40						
Massive ascites	Presence (vs. absence)	0.65	[0.42–1.02]	0.06	1.20	[0.71–2.06]	0.50	0.72	[0.46–1.12]	0.14	1.11	[0.64–1.90]	0.71
Oral intake	Presence (vs. absence)	2.18	[1.45–3.29]	< 0.01	2.41	[1.47–3.97]	< 0.01	1.79	[1.19–2.68]	< 0.01	1.88	[1.15–3.08]	0.01
Serum albumin level	< 3.3 g/dL (vs. ≥ 3.3 g/dL)	1.07	[0.73–1.58]	0.72	1.07	[0.72–1.58]	0.74						

*CI* confidence interval, *ECOG PS* Eastern Cooperative Oncology Group performance status, *HR* hazard ratio, *OS* overall survival, *SPM* severe peritoneal metastasis, *PFS* progression-free survival

**Table 3** Response rate in individuals with ascites and improvement rate of oral intake

		Patients with ascites at baseline (N=102)		
		N	(%)	
Complete response	11	(11)	RR in	individuals with ascites: 27% DCR in individuals with ascites: 78%
Partial response	17	(17)		
Stable response	52	(51)		
Progressive disease	2	(2)		
Not evaluated	20	(20)		
<b>Patients with inadequate oral intake at baseline (N = 55)</b>				
		N	(%)	
Improvement	17	(31)	Improvement rate of oral intake: 31%	
No improvement	38	(69)		

DCR disease control rate, RR response rate

### Discussion

This study first investigated second-line treatment specifically for patients with AGC who presented with SPM. Herein, we reveal the efficacy and safety of taxane-based

chemotherapy using real-world clinical data.

In contrast with previous clinical trials in the second-line setting, patients with SPM had a poorer general condition. The high proportion of patients with a poor PS score ( $\geq 2$ , 40%) and low serum albumin level (with a median of 3.3 g/dL) were significant characteristics, which were presented in the current study. These characteristics are similar to those of patients with AGC who presented with SPM and who received first-line chemotherapy, as reported in another retrospective study. That is, 40% had a PS score  $> 2$ , and the median serum albumin level was 3.1 g/dL in the first-line setting [13]. This may lead to poor prognosis: median OS of 5.1 months and median PFS of 2.8 months in the present study. Although this result was worse than survival times in second-line chemotherapy for generally advanced GC, with a median OS of 7.7–9.6 months and median PFS of 3.6–4.4 months [5, 16–18], taxane-based second-line chemotherapy may have more survival benefits than BSC in patients with SPM, considering the reported median survival time of 2.4–3.8 months in patients with AGC receiving BSC [19–22]. Importantly, we showed the difference in prognosis between the subtypes of SPM. That is, longer OS and PFS were observed in the subtype with massive ascites alone compared with the other two subtypes. Similarly, the multivariate analysis showed that inadequate oral intake was the only adverse prognostic factor of both OS and PFS. These findings indicated that patients with inadequate oral intake may have more aggressive state of disease than others; therefore, we should be cautious in terms of treatment.

**Table 4** Adverse events

Adverse Event	All patients (N = 108)				PTX+RAM (N = 21)				Taxane only (N = 87)			
	All Gr.		Gr. 3-4		All Gr.		Gr. 3-4		All Gr.		Gr. 3-4	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Leukopenia	82	(76)	32	(30)	14	(67)	6	(29)	68	(78)	26	(30)
Neutropenia	72	(67)	38	(35)	14	(67)	7	(33)	58	(67)	31	(36)
Anemia	75	(69)	26	(24)	11	(52)	1	(5)	64	(74)	25	(29)
Thrombocytopenia	11	(10)	2	(2)	3	(14)	1	(5)	8	(9)	1	(1)
Febrile neutropenia	9	(8)	9	(8)	3	(14)	3	(14)	6	(7)	6	(7)
Anorexia	57	(53)	16	(15)	13	(62)	0	(0)	44	(51)	16	(18)
Nausea	47	(44)	5	(5)	8	(38)	0	(0)	39	(45)	5	(6)
Vomiting	29	(27)	3	(3)	4	(19)	0	(0)	25	(29)	3	(3)
Diarrhea	26	(24)	1	(1)	5	(24)	0	(0)	21	(24)	1	(1)
Stomatitis	8	(7)	0	(0)	1	(5)	0	(0)	7	(8)	0	(0)
Fatigue	76	(70)	8	(7)	17	(81)	0	(0)	59	(68)	8	(9)
Sensory neuropathy	44	(41)	6	(6)	10	(48)	0	(0)	34	(39)	6	(7)
Gastrointestinal Perforation	4	(4)	3	(3)	2	(10)	2	(10)	2	(2)	1	(1)
Gastrointestinal bleeding	2	(2)	2	(2)	0	(0)	0	(0)	2	(2)	2	(2)
TRD	3 (3)				2 (10)				1 (1)			

PTX paclitaxel, RAM ramucirumab, TRD treatment-related death

**Table 5** Comparison of the incidence of febrile neutropenia and gastrointestinal perforation according to the subtype of SPM between patients who received PTX + RAM and taxane only

	Febrile neutropenia			Gastrointestinal perforation		
	PTX + RAM	Taxane only	<i>p</i> -value	PTX + RAM	Taxane only	<i>p</i> -value
(a) Only massive ascites	7% (1/15)	3% (1/38)	0.49	0% (0/15)	3% (1/38)	> 0.99
(b) Only inadequate oral intake	40% (2/5)	13% (3/24)	0.19	20% (1/5)	0% (0/24)	0/17
(c) Both	0% (0/1)	8% (2/25)	> 0.99	100% (1/1)	4% (1/25)	0.08
(d) With massive ascites	6% (1/16)	5% (3/63)	> 0.99	6% (1/16)	3% (2/63)	0.50
(e) Without massive ascites	40% (2/5)	13% (3/24)	0.19	20% (1/5)	0% (0/24)	0.17
(f) Adequate oral intake	7% (1/15)	3% (1/38)	0.49	0% (0/15)	3% (1/38)	> 0.99
(g) Inadequate oral intake	33% (2/6)	10% (5/49)	0.16	33% (2/6)	2% (1/49)	0.03

PTX paclitaxel, RAM ramucirumab, SPM severe peritoneal metastasis

Patients included in the (d) subgroup consist of (a) and (c)

Patients included in the (e) subgroup are equal to (b)

Patients included in the (f) subgroup are equal to (a)

Patients included in the (g) subgroup consist of (b) and (c)

The incidence of common adverse events was almost comparable to that of the effects of paclitaxel-based treatment, as reported in the RAINBOW and WJOG4007 trials in the second-line setting [5, 17]. However, febrile neutropenia and gastrointestinal perforation were more commonly observed in the present study compared to RAINBOW trial: the frequency of febrile neutropenia was 8%, 3%, and 2% in the present trial, the paclitaxel plus ramucirumab arm in RAINBOW trial, and the paclitaxel plus placebo arm in RAINBOW trial, respectively. Of note, these serious toxicities were dominantly observed in patients with inadequate oral intake in the present study. In addition, a higher incidence of febrile neutropenia was observed in patients receiving paclitaxel plus ramucirumab (14%) than in patients receiving taxane only (7%). Similarly, gastrointestinal perforation was more commonly observed in patients receiving paclitaxel plus ramucirumab (10%) than in those receiving taxane only (2%). Interestingly, the higher incidence of febrile neutropenia and gastrointestinal perforation after paclitaxel plus ramucirumab compared to after taxane only was observed in the subgroup with inadequate oral intake, but not in the subgroup with massive ascites. This may be caused by patient's poor systemic conditions, particularly in the subgroup with inadequate oral intake. Of note, approximately 33% of patients who have inadequate oral intake and who were receiving paclitaxel plus ramucirumab presented with gastrointestinal perforation. This finding indicated that gastrointestinal perforation during anti-angiogenesis treatment is significantly correlated to severe peritoneal metastasis involving in the intestinal

tract stenosis. A previous report has shown that tumor infiltration in the intestinal tract and stenosis due to PM might be the risk factors of gastrointestinal perforation [23]. These findings can serve as a warning to observe caution when providing treatment with paclitaxel plus ramucirumab particularly in patients with inadequate oral intake due to SPM.

This study had some limitations. First, this was a retrospective study. Second, the limited sample size made it challenging to obtain a clear conclusion. Thus, further studies must be conducted to validate the actual efficacy and safety of second-line chemotherapy in patients with AGC who presented with SPM in prospective clinical trials.

In conclusion, taxane-based second-line chemotherapy was effective and safe in patients with AGC who presented with SPM. Attention must be provided when treating patients with inadequate oral intake as they are likely to have poor prognosis and serious toxicities.

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### Compliance with ethical standards

**Conflicts of interest** TM reports honoraria from Taiho, Lilly Japan, Yakult Honsha, and Sanofi. KM reports honoraria from Bristol Myers-Squibb, Taiho, and Eli Lilly, and research funding from Bristol Myers Squibb and Taiho. TEN reports honoraria from Bristol Myers-Squibb, Sawai, Nippon Kayaku, Yakult, Taiho, and Eli Lilly, and research



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