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Original Research

Randomised phase II trial comparing four front-line doublets in Asian patients with metastatic gastric cancer

Chan Kim [a,1], Hong Jae Chon [a,1], Joo Hoon Kim [a,1], Minkyu Jung [b], Chung Mo Nam [c], Hyo Song Kim [b], Beodeul Kang [b], Hyun Cheol Chung [b,d,e], Sun Young Rha [b,d,e,*]

[a] *Medical Oncology, CHA Bundang Medical Center, CHA University, Seongnam, South Korea*
[b] *Department of Medical Oncology, Yonsei Cancer Center, Yonsei University Health System, South Korea*
[c] *Department of Preventive Medicine, Yonsei University College of Medicine, Seoul, South Korea*
[d] *Songdang Institute for Cancer Research, Yonsei University College of Medicine, Seoul, South Korea*
[e] *Brain Korea 21 PLUS Project for Medical Science, Yonsei University College of Medicine, Seoul, South Korea*

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KEYWORDS
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Abstract ***Introduction:*** Consensus has not been reached regarding the standard regimen for front-line chemotherapy of recurrent/metastatic gastric cancer. In this randomised phase II study, we compared four doublet regimens: S-1 and cisplatin (SP); oxaliplatin and 5-FU (FOLFOX); docetaxel and 5-FU (DF) and paclitaxel and 5-FU (PF).

Patients and methods: Patients without prior history of chemotherapy for recurrent/metastatic gastric cancer were randomised evenly to each regimen. The primary end-point was progression-free survival (PFS). The secondary end-points were overall survival (OS), response rate (RR) and safety profile.

Results: A total of 179 Korean patients were enrolled from March 2010 to May 2015. The study was prematurely terminated because of slow accrual. At data cut-off, the median PFS was 8.4 months for SP, 5.8 months for FOLFOX, 5.7 months for DF and 4.2 months for PF ($P = 0.023$). The median OS was 14.7 months for SP, 11.3 months for FOLFOX, 11.7 months for DF and 10.8 months for PF ($P = 0.143$). RR was 18%, 23%, 16% and 32% for SP, FOLFOX, DF and PF, respectively. The platinum group displayed a longer PFS trend than the taxane group (7.2 versus 4.9 months, $P = 0.058$), but no significant difference in OS was found. Notably, 105 patients were exposed to all three drugs (platinum, taxane and fluoropyrimidine) throughout the treatment course, and OS was identical whether starting with platinum or taxane (13.3 versus 13.3 months, $P = 0.997$). All regimens were well tolerated.

* *Corresponding author:* Department of Internal Medicine, Yonsei University College of Medicine, 50 Yonsei-ro, Seodaemun-Ku, Seoul, 03722, South Korea. Fax: +82 2 362 5592.
E-mail address: rha7655@yuhs.ac (S.Y. Rha).
[1] These authors equally contribute to this work.

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Conclusion: SP showed the most favourable results in PFS, whereas a significant difference in OS was not observed among the four regimens.

1. Introduction

Although many randomised trials have been performed over the last two decades, there is no international consensus on the optimal front-line combination regimen for metastatic gastric cancer (GC). Though platinum and fluoropyrimidine containing doublets are standard treatments, the preferred regimen varies between country and institution [1–3]. After the introduction of oral fluoropyrimidines (capecitabine and S-1) and the new platinum compound oxaliplatin, the diversity of combination regimens was further strengthened, and various regimens have been used in different parts of the world [2,4,5].

Taxanes are another active anticancer agent against GC. The first-line triplet combination chemotherapy comprising docetaxel in addition to cisplatin and 5-fluorouracil (DCF) results in a higher response rate (RR) and a moderate increase in overall survival (OS) compared with a doublet regimen [6]. However, the DCF regimen was not easily tolerated and resulted in more severe toxicities. New alternative taxane-containing triplets, such as fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) or docetaxal, oxaliplatin, and fluorouracil (TEF), are being developed to balance efficacy and toxicity [7–9].

Recently, another combinations have been attempted in several phase II studies to explore the potential of first-line taxane as a doublet [10–14]. In these reports, even after the removal of platinum or fluoropyrimidine from the triplet regimen, the remaining doublet had almost comparable OS to the triplet regimen. In particular, the doublet of fluoropyrimidine and taxane, either docetaxel or paclitaxel, was well-tolerated with acceptable efficacy [11,12]. Based on these results, we hypothesise that taxane-containing doublet regimens could be an acceptable front-line therapy with favourable OS and tolerable toxicity. Furthermore, we expect that when patients are exposed to all three drugs (platinum, taxane and fluoropyrimidine) throughout the course of disease treatment, they would have similar OS regardless of the starting regimen. This is currently more likely the case than in the past because a considerable number of patients receive multiple lines of salvage chemotherapy and most are inevitably exposed to all three drugs, not simultaneously but sequentially.

Here, we conducted a randomised phase II study to compare four different first-line regimens, namely S-1 and cisplatin (SP), oxaliplatin and 5-FU (FOLFOX), docetaxel and 5-FU (DF) and paclitaxel and 5-FU (PF), in patients with metastatic GC.

2. Materials and methods

2.1. Patients

The main eligibility criteria were as follows: histologically or cytologically confirmed metastatic or recurrent gastric adenocarcinoma; age $\geq$20 years; an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; presence of measurable or non-measurable lesions confirmed by computed tomography; adequate organ function: haemoglobin $\geq$9.0 g/dL, absolute neutrophil count $\geq$ 1500/μL, platelet $\geq 75 \times 10^3$/μL, serum creatinine: $\leq 1.5 \times$ upper normal limit (UNL), creatinine clearance $\geq$ 50 mL/min, aspartate aminotransferase/alanine aminotransferase $\leq 5.0 \times$ UNL and written informed consent of the patient. The major exclusion criteria were prior palliative chemotherapy for GC and significant comorbidities. Prior adjuvant chemotherapy was allowed if recurrence occurred >6 months after the end of adjuvant chemotherapy. A period of $\geq$2 weeks should have passed since the end of palliative radiotherapy. After the protocol amendment on October 2010, HER2+ GC patients were excluded from this study. HER2 status in tumour specimens was analysed using the HercepTest Kit (DAKO, Denmark) for immunohistochemical (IHC) staining and the Vysis HER2/CEP2 probe kit (Abbott, USA) for fluorescent *in situ* hybridisation. HER2 positivity was defined as either 3 + IHC staining or 2 + IHC staining and HER2 amplification (HER2/CEP17 ratio $\geq$ 2), as previously described [15]. The trial was performed in accordance with the Declaration of Helsinki, and the protocol was approved by the Institutional Review Board of Severance Hospital, Yonsei University Health System, Seoul, Korea (IRB 4-2009-0596).

2.2. Study design and treatment

This trial was a prospective, open-label, randomised, single centre, phase II study comparing four regimens: SP, FOLFOX, DF and PF (ClinicalTrials.gov identifier: NCT01283204). Eligible patients were randomly assigned to each treatment group at a ratio of 1:1:1:1. Patients were stratified according to ECOG performance status (0 or 1 *versus* 2) and the history of adjuvant therapy after curative gastrectomy (yes *versus* no). The randomisation sequence was generated by an independent team of statisticians using the

permuted block method. The allocated treatments were not masked from the investigator and patients.

2.3. Treatment

In the SP group, S-1 was administered orally, twice daily, for the first 2 weeks of a 3-week cycle. The dose of S-1 was 80 mg/m^2 twice daily. Cisplatin was administered at 60 mg/m^2 as an intravenous infusion with adequate hydration on day 1 of each cycle. In the FOLFOX group, the patients were administered a modified FOLFOX-6 regimen comprising a 2-h infusion of oxaliplatin (100 mg/m^2) and folinic acid (200 mg/m^2), followed by a 400 mg/m^2 bolus 5-FU and continuous infusion of 5-FU (1200 mg/m^2) on days 1 and 2 every 2 weeks. The PF regimen consisted of a 3-h infusion of paclitaxel (175 mg/m^2) on day 1, followed by continuous infusion of 5-FU (1000 mg/m^2) for 3 days every 3 weeks. The DF regimen substituted paclitaxel with docetaxel (75 mg/m^2) on day 1. The treatment was continued until progression of disease (PD), the appearance of unacceptable toxicity or withdrawal of consent. Patients in the SP arm received prophylactic aprepitant from their first cycle because cisplatin is a highly emetogenic chemotherapeutic drug, whereas patients in the other arms received aprepitant when they suffered from grade 3/4 nausea or vomiting after previous cycles.

2.4. Assessments

The primary end-point was progression-free survival (PFS), defined as the time from the randomisation to PD or death from any cause. Patients who were alive without progression were regarded as censored at the date of last assessment. The secondary end-points were OS, overall response rate (ORR), best overall response and safety profile. OS was measured as the time from the date of randomisation to the date of death from any cause or the last follow-up. Tumour response was evaluated every 6 weeks using the Response Evaluation Criteria in Solid Tumours, version 1.1. The ORR included partial and complete responses. Best overall response was defined as the best response recorded from the start of treatment until PD. Adverse events (AEs) were evaluated according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 3.0.

2.5. Statistical analysis

Because conventional parallel design requires a massive sample size when PFS is a primary end-point and this study was a pilot phase II trial for picking the winner for future confirmatory phase III trials, we employed the selection design proposed by Liu *et al.* [16]. With this approach, we were able to select the best regimen for further studies regardless of how small the survival advantage was over other regimens. The selection design generated a realistic sample size by calculating the possibility of selecting the best arm among the various arms rather than statistically comparing each arm individually. In this design, ordinary values of alpha and beta cannot be determined nor applied [16,17]. Sample sizes for a correct selection probability of 90% were produced for Weibull survival distribution, $S(t) = \exp\{-(\lambda t)^p\}$, with the following parameters: the median PFS of the best arm is 6 months, the median PFS of other arms is 4.5 months, 6–12 months accrual, a total 6 months of follow-up after the last accrual and a hazard ratio (HR) of 1.3. Finally, a total of 228 samples (57 patients per treatment group) were determined, assuming a 10% follow-up loss. We performed analyses in the intention-to-treat population, excluding patients who did not receive study medication. PFS was determined by Kaplan–Meier estimates of the survival function in each treatment group. HRs and confidence intervals (CIs) were calculated using a Cox proportional hazards model. The frequencies of haematologic or non-haematologic AEs among groups were compared using generalised estimating equation [18]. A post hoc analysis was performed to compare platinum- or taxane-based regimens for PFS and OS. In explorative analyses, subgroup analyses were performed on demographic factors in the Cox proportional hazard model. The safety data were presented descriptively. Statistical analyses were carried out using SPSS, version 18 (IBM SPSS, Chicago, IL).

3. Results

3.1. Patients and treatments

From March 2010 through May 2015, a total of 179 Korean patients were randomly allocated to one of the four treatment arms. The study was terminated before its target enrolment of 228 patients because of slow accrual in the latter half of the study period. A total of 177 patients received the study treatment and were included in the efficacy and safety evaluation (Fig. S1). Patient demographics and disease characteristics are shown in Table 1. Briefly, the male-to-female ratio was 2.3 and median age 57 years (range: 26–78 years). Most of the baseline characteristics were similar across the four treatment arms, However, there were slightly more intestinal-type GCs in the taxane arms than in the platinum arms. Because this trial was designed and initiated before the approval of trastuzumab for HER2+ GC in Korea, two HER2+ patients (1%) were included in early 2010, and, after the protocol amendment in late 2010, there were no additional HER2+ patients thereafter. The median follow-up duration was 12.4 months (range 0.3–76.8 months).

The median number of treatment cycles administered was seven (range 1–29) in the SP arm, six (range 1–23)

Table 1
Patient demographics and baseline disease characteristics.

Variables	Total (N = 177)	SP (N = 45)	FOLFOX (N = 44)	DF (N = 45)	PF (N = 43)
Age, years					
Median (range)	57 (26–78)	63 (36–78)	56 (35–74)	55 (26–78)	57 (31–74)
Sex					
Male	123 (69%)	32 (71%)	28 (64%)	29 (64%)	34 (79%)
Female	54 (31%)	13 (29%)	16 (36%)	16 (36%)	9 (21%)
ECOG					
0	108 (61%)	29 (64%)	25 (57%)	28 (62%)	26 (61%)
1	65 (37%)	15 (33%)	18 (41%)	16 (36%)	16 (37%)
2	4 (2%)	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Histology (Lauren)					
Intestinal	50 (28%)	11 (24%)	10 (23%)	16 (36%)	13 (30%)
Diffuse	105 (59%)	28 (62%)	28 (64%)	24 (53%)	25 (58%)
Mixed	22 (12%)	6 (13%)	6 (14%)	5 (11%)	5 (12%)
HER2					
Negative	175 (99%)	44 (98%)	44 (100%)	45 (100%)	42 (98%)
Positive	2 (1%)	1 (2%)	0 (0%)	0 (0%)	1 (2%)
Previous gastrectomy					
No	107 (60%)	23 (51%)	29 (66%)	24 (53%)	31 (72%)
Yes	70 (40%)	22 (49%)	15 (34%)	21 (47%)	12 (28%)
Use of adjuvant platinum					
No	145 (82%)	37 (82%)	36 (82%)	37 (82%)	35 (81%)
Yes	32 (18%)	8 (18%)	8 (18%)	8 (18%)	8 (19%)

SP, S-1 and cisplatin; FOLFOX, oxaliplatin and 5-FU; DF, docetaxel and 5-FU; PF, paclitaxel and 5-FU; ECOG, Eastern Cooperative Oncology Group.

in the FOLFOX arm, six (range 1–34) in the DF arm and eight (range 1–17) in the PF arm. The relative dose intensity was 86.1% for S-1 and 80.3% for cisplatin in the SP arm; 80.5% for 5-FU and 79.9% for oxaliplatin in the FOLFOX arm; 92.5% for 5-FU and 89.9% for docetaxel in the DF arm and 96.3% for 5-FU and 96.3% for paclitaxel in the PF arm. At the time of the data analysis, all patients discontinued the treatment. The most common reasons for discontinuation were PD (66%), AEs (16%) and patient withdrawal from treatment (8%).

3.2. Efficacy

The median PFS was significantly longer with SP than with FOLFOX, DF or PF (PFS: 8.4 months [95% CI: 3.2–13.6] *versus* 5.8 [2.9–8.7], 5.7 [3.3–8.2] and 4.2 [3.6–4.8] months, $P = 0.023$, respectively; Fig. 1A). The median OS was not significantly different among the four regimens. The median OS with SP, FOLFOX, DF and PF was 14.7 [95% CI 10.9–18.5], 11.3 [7.1–15.5], 11.7 [9.1–14.3] and 10.8 [7.5–14.] months, respectively (Fig. 1B). The RR and disease control rate were 18% and 91% in SP; 25% and 84% in FOLFOX; 16% and 89% in DF and 32.6% and 79.1% in PF, respectively (Table 2).

3.3. Safety

Table 3 summarises the most common haematological and non-haematological AEs in the four groups. Grade 3/4 AEs were reported in 71%, 72%, 70% and 34% of patients in the SP, FOLFOX, DF and PF arms, respectively. Grade 3/4 haematological AEs were lower in the PF arm than in the other treatment arms. Neutropenia was reported in 60% of patients in the DF group, 50% in the FOLFOX group, 38% in the SP group and 7% in the PF group. Grade 3/4 anaemia and thrombocytopaenia were more common in the SP arm than in other arms. Febrile neutropenia was reported in two patients (4%) in the SP arm and five patients (11%) in the DF arm. Among grade 3/4 non-haematological AEs, anorexia and fatigue were reported in 11% of patients in the SP arm. Nausea was reported in 16% of patients in the FOLFOX arm. AEs leading to discontinuation of treatment occurred in 27% of patients in the SP arm, 11% in the FOLFOX arm, 13% in the DF arm and 12% in the PF arm (Fig. S1). There were two treatment-related deaths because of septic shock, one each in the SP arm and DF arm.

3.4. Comparison of first-line platinum- and taxane-based regimens

Poststudy chemotherapy was received in 117 (66%) patients (Fig. S2). To compare first-line platinum- and taxane-based regimens, the four regimens were grouped as platinum (SP and FOLFOX, n = 89) and taxane (DF and PF, n = 88) groups. In the platinum group, 54 patients received at least one subsequent salvage chemotherapies; among them, 47 were exposed to taxane-based chemotherapy. In the taxane group, 63 patients received at least one subsequent salvage chemotherapies; among them, 58 were exposed to platinum-based

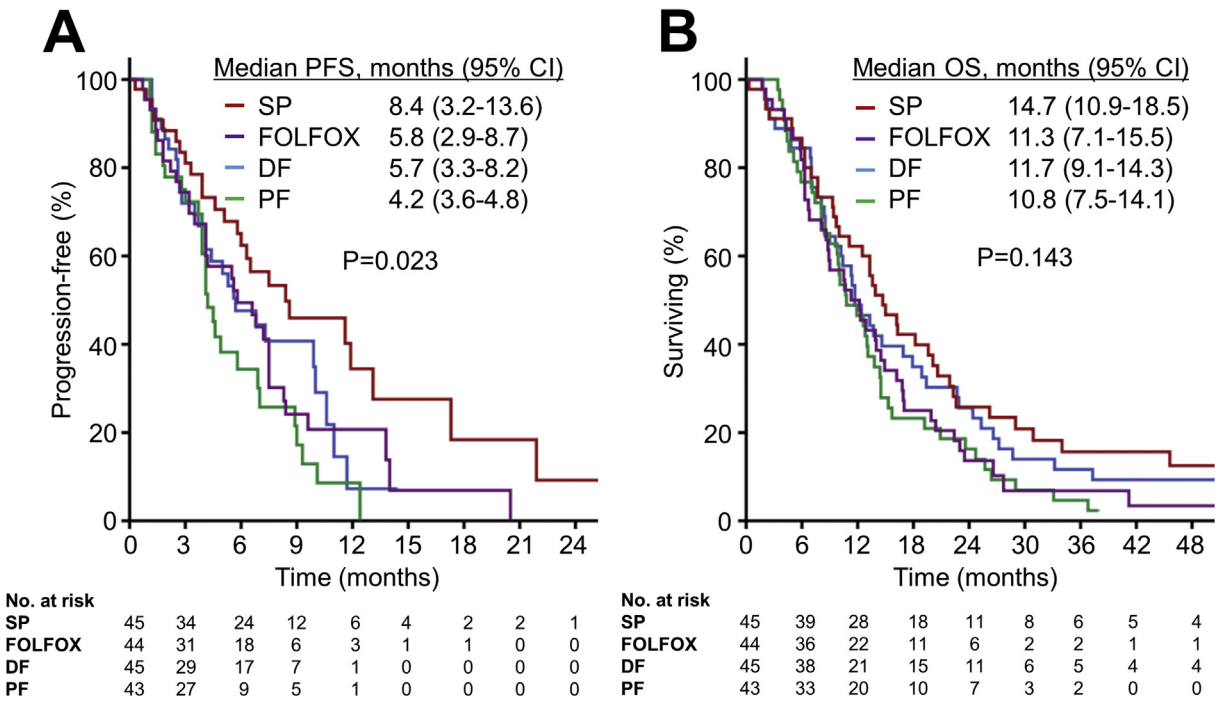

Fig. 1. Progression-free survival (PFS) (A) and overall survival (OS) (B). SP, S-1 and cisplatin; FOLFOX, oxaliplatin and 5-FU; DF, docetaxel and 5-FU; PF, paclitaxel and 5-FU; CI, confidence interval.

chemotherapy. Overall, 105 patients were exposed to both platinum and taxane sequentially during the disease treatment.

The patients in the platinum group had a longer PFS trend than patients in the taxane group (7.2 months *versus* 4.9 months, $P = 0.058$; Fig. 2A). However, there was no significant difference in OS between the platinum and taxane groups (13.3 months *versus* 11.7 months, $P = 0.431$; Fig. 2B). Notably, if a patient was exposed to all three drugs (platinum, taxane and fluoropyrimidine) throughout the course of their disease, there was no significant difference in OS regardless of whether they started with platinum or taxane (13.3 months *versus* 13.3 months, $P = 0.997$; Fig. 2C).

The efficacy of the regimens in the patient subgroups is shown in Fig. 3. In the post hoc subgroup analysis, PFS favoured first-line platinum treatment in patients who had intestinal-type GCs (HR 0.28; 95% CI 0.12–0.67; $P = 0.005$) or did not have peritoneal metastasis at the time of diagnosis (HR 0.52; 95% CI 0.30–0.92; $P = 0.03$). However, in terms of OS, there were no significant differences among the subgroups regardless of whether the patients started with a first-line platinum- or taxane-based regimen.

4. Discussion

In this study, we prospectively compared doublet regimens between taxane-based chemotherapy (DF and PF) and platinum-based chemotherapy (SP and FOLFOX), which are widely used front-line regimens. For the first time, this study made direct comparisons of these four regimens simultaneously in Asian/Korean patients with recurrent/metastatic GC.

Table 2
Objective responses.

Variables	SP (N = 45)	FOLFOX (N = 44)	DF (N = 45)	PF (N = 43)
Patients with measurable disease	36 (80%)	38 (86%)	38 (84%)	40 (93%)
Best overall response				
Complete response	0 (0%)	1 (2%)	0 (0%)	0 (0%)
Partial response	8 (18%)	10 (23%)	7 (16%)	14 (33%)
Stable disease	25 (56%)	20 (46%)	27 (60%)	19 (44%)
Non-CR/non-PD	8 (18%)	6 (14%)	6 (13%)	1 (2%)
Progressive disease	4 (9%)	7 (16%)	5 (11%)	9 (21%)
Objective response	8 (18%)	11 (25%)	7 (16%)	14 (33%)
Disease control	41 (91%)	37 (84%)	40 (89%)	34 (79%)

SP, S-1 and cisplatin; FOLFOX, oxaliplatin and 5-FU; DF, docetaxel and 5-FU; PF, paclitaxel and 5-FU; PD, progression of disease; CR, complete response.

Table 3
Treatment-related adverse events.

Variables	SP (n = 45)		FOLFOX (n = 44)		DF (n = 45)		PF (n = 43)	
	Any (%)	G3/4 (%)	Any (%)	G3/4 (%)	Any (%)	G3/4 (%)	Any (%)	G3/4 (%)
Total patients with an event	44 (98)	31 (71)	43 (98)	31 (72)	43 (96)	30 (70)	41 (95)	14 (34)
Discontinuation due to AEs	12 (27)		5 (11)		6 (13)		5 (12)	
Neutropenia	35 (78)	17 (38)	35 (80)	22 (50)	35 (78)	27 (60)	8 (19)	3 (7)
Anaemia	42 (93)	8 (18)	34 (77)	2 (5)	39 (87)	2 (4)	34 (79)	2 (5)
Thrombocytopaenia	24 (53)	6 (13)	25 (57)	1 (2)	6 (13)	1 (2)	7 (16)	1 (2)
Febrile neutropenia	2 (4)	2 (4)	0 (0)	0 (0)	5 (11)	5 (11)	0 (0)	0 (0)
Nausea	22 (49)	3 (7)	22 (50)	7 (16)	20 (44)	3 (7)	16 (37)	2 (5)
Vomiting	6 (13)	1 (2)	14 (32)	2 (5)	4 (9)	0 (0)	7 (16)	0 (0)
Diarrhoea	17 (38)	1 (2)	10 (23)	0 (0)	14 (31)	2 (4)	6 (14)	0 (0)
Constipation	9 (20)	0 (0)	9 (20)	0 (0)	8 (18)	0 (0)	9 (21)	0 (0)
Stomatitis	8 (18)	1 (2)	2 (5)	0 (0)	7 (16)	1 (2)	3 (7)	0 (0)
Anorexia	30 (67)	5 (11)	24 (55)	4 (9)	26 (58)	2 (4)	18 (42)	1 (2)
Fatigue	26 (58)	5 (11)	17 (39)	2 (5)	23 (51)	0 (0)	17 (40)	2 (5)
Neuropathy	11 (24)	0 (0)	22 (50)	1 (2)	9 (20)	0 (0)	18 (42)	1 (2)
Cr elevation	4 (9)	2 (4)	0 (0)	0 (0)	1 (2)	0 (0)	3 (7)	0 (0)
AST elevation	18 (40)	1 (2)	28 (64)	0 (0)	17 (38)	1 (2)	12 (28)	2 (5)
ALT elevation	6 (13)	0 (0)	17 (39)	0 (0)	10 (22)	0 (0)	11 (26)	1 (2)
Dyspnoea	3 (7)	2 (4)	1 (2)	1 (2)	0 (0)	0 (0)	1 (2)	0 (0)

AST, aspartate aminotransferase; SP, S-1 and cisplatin; FOLFOX, oxaliplatin and 5-FU; DF, docetaxel and 5-FU; PF, paclitaxel and 5-FU; ECOG, Eastern Cooperative Oncology Group; ALT, alanine aminotransferase; AE, adverse events.

The SP regimen is a platinum-based regimen and widely used in East Asian countries, especially Korea and Japan [19,20]. In the present study, this regimen demonstrated the favourable survival outcomes in terms of both PFS and OS. In patients treated with SP, the treatment discontinuation due to AEs was the most common (26%) compared with other regimens, and the smallest proportion of patients received subsequent treatments. Because of ethnic differences [21,22], the findings of this study cannot be extrapolated directly and applied to patients in Western countries. Another platinum-based regimen, FOLFOX, is commonly and widely used in both East Asian and Western countries [23,24]. In this study, although FOLFOX induced a relatively higher frequency of peripheral neuropathy than other regimens, toxicity was generally manageable, and the discontinuation rate due to AEs was only 11%. In other words, the efficacy and safety were well-balanced in the FOLFOX regimen. The DF regimen, a taxane-based regimen, also had acceptable efficacy, and the outcomes of the DF regimen in this study were almost comparable to the outcome of S-1 plus docetaxel in the phase III START trial performed previously on Asian patients [25]. In the present study, the DF resulted in frequent febrile neutropenia (11%) and grade 3/4 neutropenia (60%). Although this level is lower than that in the toxic DCF regimen, this degree of febrile neutropenia is still higher than that observed in recently

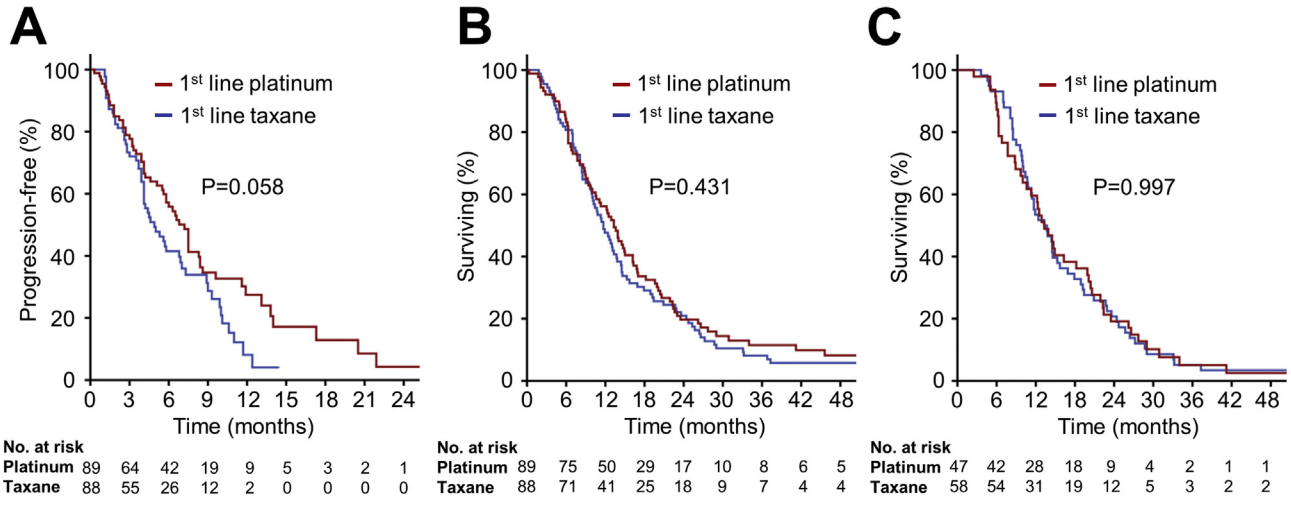

Fig. 2. Progression-free survival (A) and overall survival (B) according to first-line platinum and taxane. Overall survival of patients who exposed to all effective regimens (C).

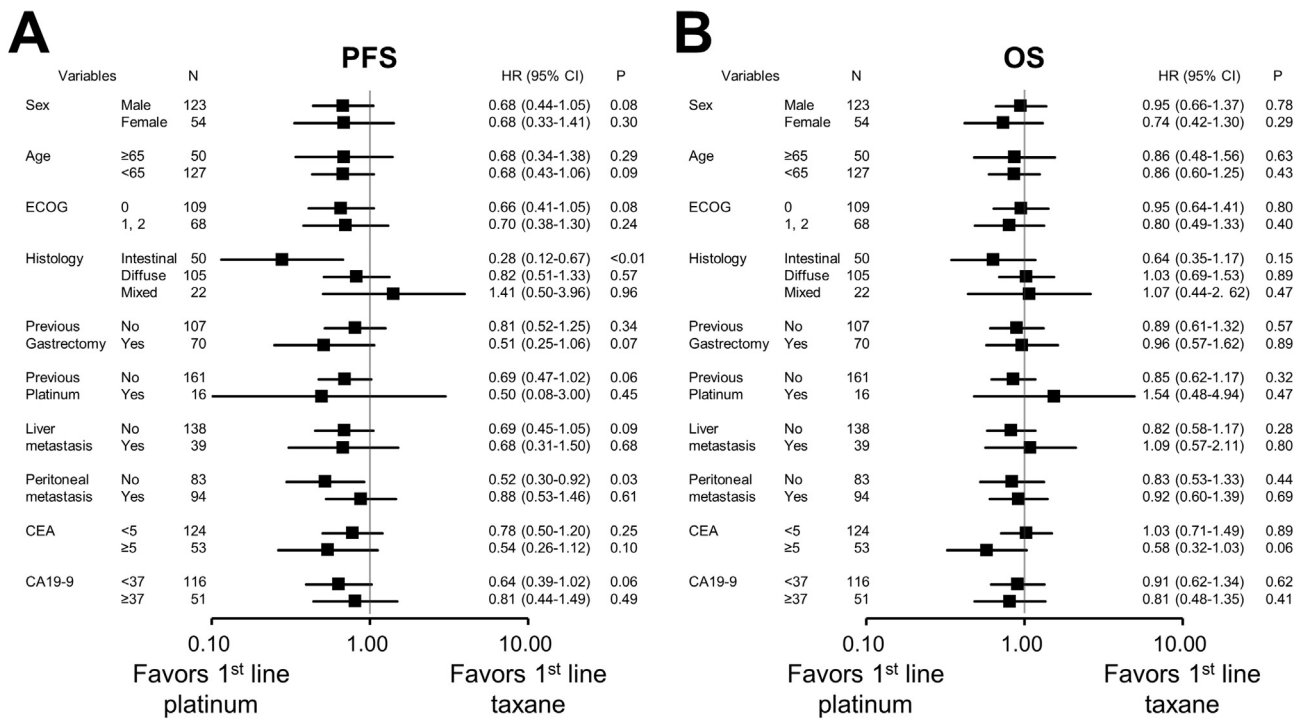

Fig. 3. Progression-free survival (A) and overall survival (B) according to subgroup analysis. ECOG, Eastern Cooperative Oncology Group; HR, hazards ratio; CI, confidence interval; CEA, carcinoembryonic antigen.

developed triplet regimens (2%), such as FLOT or TEF, which are more tolerable. We assume that this is because of ethnic susceptibility to docetaxel in East Asians as it has been reported in various studies that haematologic toxicities are more frequently experienced by East Asians than by Europeans and Americans when given 75 mg/m^2 [26]. However, the rate of treatment discontinuation due to AEs was only 13%, indicating that the DF regimen has good tolerability and the toxicity did not impede patients' quality of life. The PF regimen exhibited the lowest frequency of AEs and highest proportion of patients receiving subsequent treatments. However, its efficacy appears relatively low compared with the other three regimens compared in this study.

In the present study, comparison of platinum- and taxane-based regimens suggested better trends for PFS in patients treated with a first-line platinum-based regimen. In the subgroup analysis, platinum was more effective in patients who have intestinal-type GCs or without peritoneal carcinomatosis. These findings are consistent with previous studies showing that tumour biology and chemosensitivity may differ according to histological subtypes of GC and suggest the need for individualised chemotherapy guided by pathological classification [27–33]. Nevertheless, the superiority of platinum-based regimens in PFS was not translated to OS. Of note, the OS of patients who were eventually exposed to all three regimens through subsequent treatments was almost identical between the platinum and taxane groups. These findings are consistent with the outcome of the pooled analysis of 43 randomised trials in GC patients, in which the postprogression survival after first-line chemotherapy was more closely related with OS than PFS because of an increasing number of patients receiving subsequent treatments worldwide [34]. In other words, if a patient with recurrent/metastatic GC receives adequate subsequent chemotherapy after front-line chemotherapy, the OS may not be different regardless of whether the starting regimen is platinum-based or taxane-based. However, this is the result of a post hoc analysis and may be due to a selection bias of patients with good prognosis and better medical conditions as they received more active treatments during their disease course and had a better outcome. Therefore, it needs to be validated in an independent prospective trial.

The present study has some limitations. First, the number of proposed enrolments could not be achieved due to poor accrual. As numerous competing sponsor-initiated trials began to be actively introduced in Korea in the early 2010s, it was difficult for us to enrol patients in this trial as we initially planned. Second, as there were no approved molecularly targeted agents for GC when this study was initiated, the outcomes regarding the effectiveness of subsequent treatment with targeted agents could not be assessed in this study. Third, although intestinal-type GCs respond better to platinum-based regimens, there were relatively less intestinal-type GCs in the SP and FOLFOX arms compared with the DF and PF arms. Therefore, there is

a possibility that the efficacy of the SP and FOLFOX arms are underestimated in this study. Finally, because the patients enrolled in this study were all East Asians, the findings cannot be applied directly to patients in Western countries.

When this study was first initiated, a wide variety of regimens were used for the first- and second-line treatments of metastatic GC. However, over the past several years, the combination of ramucirumab and paclitaxel has been established as the most effective second-line treatment [35]. With this well-defined second-line taxane-based regimen, the use of the first-line platinum and fluoropyrimidine doublet is the most reasonable choice. Therefore, this is an optimal sequence of treatment to follow for the treatment of metastatic GC now [36].

In conclusion, the present study is the first randomised trial comparatively assessing four different regimens simultaneously and SP showed the most favourable result among the four regimens in terms of PFS. However, this benefit was partially attenuated by subsequent chemotherapies and a significant difference in OS was not observed among the four regimens.

Conflict of interest statement

All authors declare that they have no competing interests.

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Appendix A. Supplementary data

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