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A randomized phase II trial of S-1-oxaliplatin versus capecitabine–oxaliplatin in advanced gastric cancer

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KEYWORDS
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Abstract *Purpose:* S-1 or capecitabine plus oxaliplatin are considered active and tolerable in gastric cancer patients. We conducted a randomized phase II trial in gastric cancer patients to compare the activity and safety of these combinations.
Methods: The patients received S-1 at 80 mg/m^2 for 14 days, followed by a 7-day rest period within a 3-week schedule in the S-1/oxaliplatin (SOX) arm, and capecitabine at 2000 mg/m^2 for 14 days, followed by a 7-day rest period within a 3-week schedule in the capecitabine/oxaliplatin (CAPOX) arm. Oxaliplatin 130 mg/m^2 was administered every 3 weeks in both arms.
Results: One hundred twenty-nine patients were randomly assigned to SOX ($N = 65$) or CAPOX ($N = 64$). The median time to progression and the overall survival were 6.2 and 12.4 months with SOX, respectively; and 7.2 and 13.3 months with CAPOX, respectively. The overall response rates were 40% and 44% for SOX and CAPOX, respectively. The most frequent grade 3 or 4 toxicities were thrombocytopenia (15.4%) for SOX and neutropenia (18.8%) for CAPOX. The median time to 10% deteriorations in global health scores was similar in both arms (SOX, 4.3 months, CAPOX, 4.9 months).
Conclusion: Both the SOX and CAPOX regimens were equally active and well tolerated in advanced gastric cancer patients.

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1. Introduction

Gastric cancer is the second leading cause of cancer death in the world.[1] Most patients with gastric cancer have an incurable stage at the time of diagnosis. Palliative systemic chemotherapy for advanced gastric cancer (AGC) improves survival and quality of life, compared to the best supportive care. In general, combination chemotherapy regimens provide better response rates and modest survival benefit compared to single agent therapy.[2,3] There is no consensus for a single, global standard regimen for first-line chemotherapy of AGC.

Despite no established standard regimen for AGC, a doublet combination containing cisplatin and 5-flouro-uracil (5-FU) is the most commonly used chemotherapy regimen worldwide.[3–7] In Japan, S-1 mono therapy had been accepted as a standard treatment by the JCOG 9912 study.[8] At present, S-1 plus cisplatin (SP) is recognised as a standard regimen after the SPIRIT trial showed survival benefit with SP compared to S-1 mono therapy.[5] In Korea, fluoropyrimidine-based (S-1 or capecitabine) and platinum-based (cisplatin or oxaliplatin) combinations are widely used for AGC by several recent trials.[4–9] The addition of docetaxel to the combination of cisplatin plus 5-FU (DCF) has recently shown to have higher response rate and superior time to progression in the V-325 trial.[4] In Europe and United States, although triplet therapy has demonstrated better outcomes than doublets, it was restricted to younger patients with a good performance status because of its substantial toxicities.

With regard to the relatively short overall survival (OS) of patients with AGC and the palliative nature of the chemotherapy, the choice of chemotherapy should be based on a favourable efficacy, toxicity profiles and convenience of administration. For this reason, oral fluoropyrimidine (S-1, capecitabine) has been studied as a substitute for continuous infusion of 5-FU. The FLAGS trial revealed a similar efficacy and better toxicity profile of S-1 compared to infusional 5-FU.[6] Kang et al. showed that capecitabine can replace 5-FU and Al-Batran et al. showed that oxaliplatin can replace cisplatin for the treatment of AGC.[7,10] The REAL-2 trial also demonstrated the capecitabine and oxaliplatin are as effective as 5-FU and cisplatin, respectively.[11]

Based on these trials, several recent phase II studies using a combination of these new drugs (S-1 plus oxaliplatin, SOX or capecitabine plus oxaliplatin, CAPOX) have reported favourable efficacies and toxicity profiles.[12–19] However, there have been no studies comparing these two oral fluoropyrimidines in combination with oxaliplatin in gastric cancer patients.

This randomized phase II trial aimed to compare the efficacy and safety of two oral fluoropyrimidines (S-1 or capecitabine) in combination with oxaliplatin for first-line treatment of AGC patients.

2. Patients and methods

2.1. Study design

By using 1:1 randomization, the patients were randomly assigned to one of the two treatment arms (SOX and CAPOX) stratified by the institution and by prior use of cisplatin. Three institutions participated in this study. The protocol was approved by the institutional review board of each participating institution. All the participating patients provided written informed consent, and the study was carried out in accordance with the Good Clinical Practice guideline. A CONSORT diagram is provided in Fig. 1.

2.2. Eligibility

Patients were required to have the following criteria: histologically confirmed metastatic or recurrent gastric adenocarcinoma, chemotherapy-naïve status, measurable or evaluable lesion, a performance status of 0–2 as determined by the Eastern Cooperative Oncology Group (ECOG), and adequate organ function [absolute neutrophil count (ANC) $\geqslant 1500/mm^3$, platelet count $\geqslant 100{,}000/mm^3$, serum creatinine $\leqslant 1.5$ mg/dL, total bilirubin $\leqslant 2.0$ mg/dL, and Aspartate transaminase (AST)/Alanine transaminase (ALT)/alkaline phosphatase $\leqslant 2.5 \times$ the upper limit of normal]. Adjuvant and/or preoperative chemotherapy was allowed if more than six months had elapsed between the end of the therapy and the registration, but any prior therapy could not include S-1, capecitabine, or oxaliplatin. Patients were excluded if they had brain metastasis, a neuropathy more than grade 2, or uncontrolled significant comorbid conditions.

2.3. Treatment plan

In the SOX arm, S-1 was administered orally at 80 mg/m^2/day divided in two daily doses for 14 days, followed by a 7-day rest period in a 3-week schedule. In the CAPOX arm, capecitabine was administered orally at 2000 mg/m^2/day divided in two daily doses for 14 days, followed by a 7-day rest period in a 3-week schedule. Oxaliplatin was administered at 130 mg/m^2 intravenously in 2 h every 21 days in both arms. All the patients received prophylactic anti-emetic medications.

Treatment was delayed for up to 3 weeks when symptomatic toxicity persisted, and the ANC and platelet count were $<1500/mm^3$ and $<75{,}000/mm^3$, respectively. In the event of grade 4 neutropenia, thrombocytopenia, or febrile neutropenia or grade 3 nausea/vomiting, diarrhoea, or stomatitis, the doses of oxaliplatin and S-1 or capecitabine were reduced by 25% starting from the next cycle. If grade 2 neuropathy was not resolved by the end

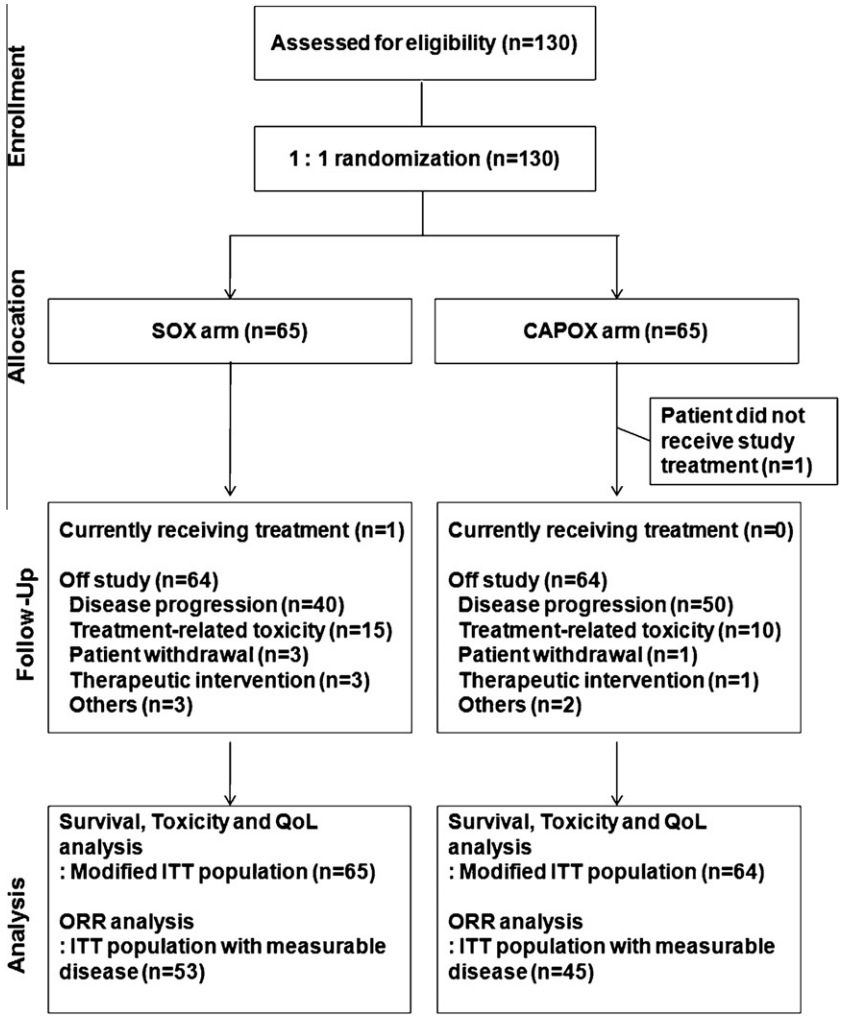

Fig. 1. CONSORT diagram.

of the cycle or grade 3 neuropathy occurred, the dose of oxaliplatin was reduced by 25% starting from the next cycle after recovering to grade 2 or less. Treatment was continued until one of the following events occurred: progression of the disease, withdrawal of consent by the patient, or unacceptable toxicity.

2.4. Assessment and data collection

Toxicity assessments, compliance with S-1 and capecitabine, and blood tests were done weekly during the first cycle and just before each cycle starting from the second cycle. Tumour assessments were done every two cycles by the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.0. Toxicity was assessed by the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTC AE) version 3.0. All patients were asked to complete the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30; version 3.0) on the first day of every other cycle and at the end of the treatment.

2.5. Statistical considerations

The primary objective was the comparison between the SOX and CAPOX regimens using time to progression (TTP) as a measure. This study was designed by a 'pick the winner' format proposed by Liu et al.[20] It was assumed that the median TTP of the inferior arm is 5 months with the hazard ratio of 1.3. Sample sizes for 1-year accrual and 90% correct selection probability were calculated as 117. Taking into consideration a 10% dropout rate, 65 patients per each arm were required to ensure maintenance of the statistical power. The secondary end points included toxicity, OS, overall response rate (ORR) and quality of life (QoL).

An analysis on survival, toxicity and QoL analysis was done in a modified intent to treat (ITT) population. The modified ITT population was defined as all randomly assigned patients who received chemotherapy at least once. The ORR was evaluated in the modified ITT population with measurable lesion.

Survival curves were generated using the Kaplan–Meier method and compared by the log-rank test. An

analysis of the QLQ-C30 questionnaires was done in accordance with the EORTC guidelines.[21] The linear mixed model was used to compare each scale of the QoL by the cycle and treatment arms. Kaplan–Meier methodology was used to measure times to 10% deterioration in QoL scores. Data analysis was done with SPSS software (version 18.0).

3. Results

3.1. Patient characteristics

Between March 2008 and September 2009, 130 patients were randomly assigned to either the SOX arm ($n = 65$) or CAPOX arm ($n = 65$). One patient who was randomly assigned to the CAPOX arm never took a dose of the assigned treatment. Thus, 129 patients were included in the modified ITT population. Both arms were well balanced in terms of baseline clinical characteristics (Table 1).

3.2. Treatment

The overall treatment administration is summarised in Table 2. The median number of cycles was six for SOX (range, 1–34 cycles) and eight for CAPOX (range, 1–28 cycles). Dose reduction and treatment delay occurred in 29 SOX patients (44.6%) and in 33 CAPOX patients (51.6%). Treatment delays of more than 7 days occurred in 40 SOX patients (61.5%) and 41 CAPOX patients (64.1%). A similar proportion of the patients received second-line chemotherapy (SOX = 60%; CAPOX = 62%).

3.3. Efficacy

The median TTP was 6.2 months for SOX (95% confidence interval, 4.92–7.48) and 7.2 months for CAPOX (95% CI, 5.87–8.54) with a hazard ratio (SOX/CAPOX) of 1.06 (95% CI, 0.72–1.57, $p = .767$) (Fig. 2A). With a median follow-up duration of 13 months (range, 0.5–39.2 months), the median OS was 12.4 months for SOX (95% CI, 8.796–16.01) and 13.3 months for CAPOX (95% CI, 10.26–16.34) with a hazard ratio (SOX/CAPOX) of 1.08 (95% CI, 0.74–1.58, $p = .686$) (Fig. 2B). The estimated 1-year survival rate was 52% and 59% for SOX and CAPOX, respectively.

The ORRs by treatment arms are listed in Table 3. The modified ITT population with measurable lesion includes 53 patients in SOX arm and 45 patients in CAPOX arm. The confirmed ORR was 40% for SOX (95% CI, 26–54%) and 44% for CAPOX (95% CI, 29–60%).

Table 1
Patient baseline characteristics.

Baseline characteristics	SOX ($n = 65$)		CAPOX ($n = 64$)		*P*-value
	No. of Patients	%	No. of Patients	%	
Age, years					.606
Median	60		61		
Range	28–77		20–75		
Gender					.748
Male	44	68	45	70	
Female	21	32	19	30	
Performance (Eastern Cooperative Oncology Group (ECOG))					.291
0	11	17	8	13	
1	54	83	54	84	
2	0	0	2	3	
BSA (m^2) (mean ± SD)	1.62 ± 0.18		1.60 ± 0.21		.549
Histology					.293
Well/moderately differentiated	24	37	17	26	
Poorly differentiated	28	43	35	55	
Signet ring cell	12	18	10	16	
Others	1	2	2	3	
Disease status					.956
Metastatic	47	72	46	72	
Recurrent	18	28	18	28	
Number of involved organ					.882
One	16	25	12	19	
Two	21	32	24	38	
>Three	28	43	28	44	
Measurable disease					.136
Yes	53	82	45	70	
No	12	18	19	30	

Abbreviations: SOX, S-1 plus oxaliplatin; CAPOX, capecitabine plus oxaliplatin; BSA, body surface area; SD, standard deviation.

Table 2
Overall treatment summary.

	SOX ($n = 65$)	CAPOX ($n = 64$)	P-value
Treatment administration			
Median number of cycle (range)	6 (1–34)	8 (1–28)	.194
Median treatment duration, weeks (range)	20.9 (3–113.6)	23.5 (3–110.9)	.223
Dose reductions, patients (%)	29 (44.6)	33 (51.6)	.940
Oxaliplatin	27 (41.5)	28 (43.8)	.872
Fluoropyrimidine	27 (41.5)	32 (50.0)	.214
Cycle delays ($\geqslant$7 days), patients (%)	40 (61.5%)	41 (64.1%)	.767
Cycle delays ($\geqslant$7 days), cycle (%)	119 (26.6%)	156 (30.4%)	.172
Median relative dose intensity			
Oxaliplatin	0.89 (0–1.00)	0.91 (0.50–1.00)	.906
Fluoropyrimidine	0.83 (0.41–1.07)	0.76 (0.45–1.04)	.025
Total	0.81 (0.52–1.04)	0.79 (0.48–1.02)	.391

Abbreviations: SOX, S-1-oxaliplatin; CAPOX, capecitabine–oxaliplatin

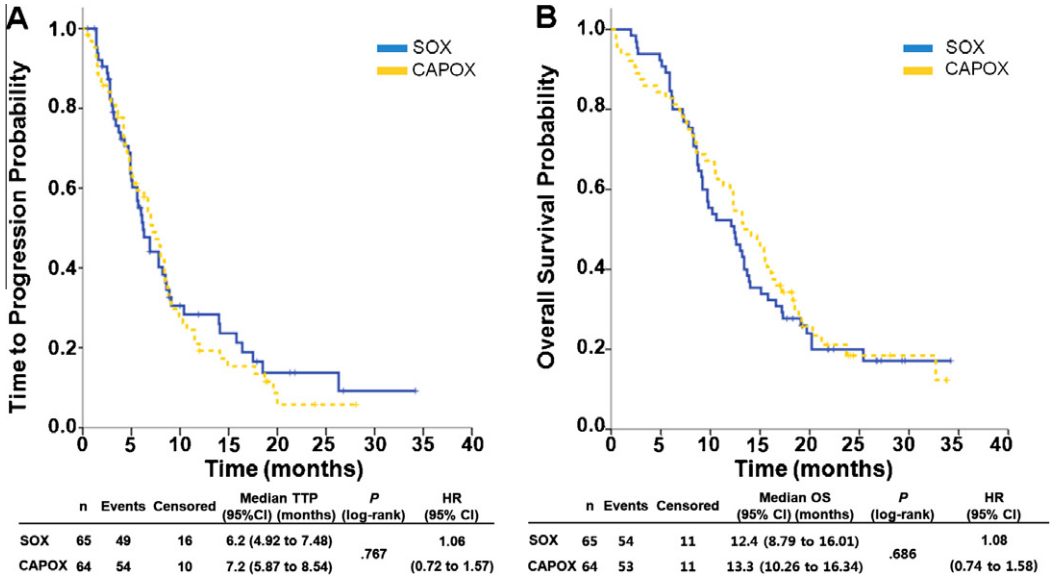

Fig. 2. (A) Time to progression and (B) overall survival by treatment arm (Kaplan–Meier curve). SOX, S-1-oxaliplatin; CAPOX, capecitabine–oxaliplatin; HR, hazard ratio.

Table 3
Response rates for modified ITT population with measurable lesion.

Response	SOX ($n = 53$)		CAPOX ($n = 45$)	
	No.	%	No.	%
Complete response	0	0	1	2
Partial response	21	40	19	42
Stable disease	27	51	18	40
Progressive disease	4	7	7	16
Not assessable[a]	1	2	–	–
Response rate	21	40	20	44
95% CI		26–54		29–60
Disease control rate	48	91	38	84

Abbreviations: ITT, intent to treat; SOX, S-1-oxaliplatin; CAPOX, capecitabine–oxaliplatin; CI, confidence interval.

[a] Not assessable indicate the patients who discontinued treatment before first response evaluation without evidence of progressive disease.

3.4. Toxicity

The toxicity profiles are listed in Table 4. The most common grade 3–4 haematologic toxicity was neutropenia for CAPOX (18.8%) and thrombocytopenia for SOX (15.4%). Febrile neutropenia was observed in one patient according to each arm. The most frequent grade 3 or 4 non-haematologic toxicities were asthenia for CAPOX (7.8%) and infection for SOX (9.2%). Among the non-GI toxicities, neuropathy was the most common grade 3 or 4 toxicity in both arms (SOX = 3.1%; CAPOX = 4.7%). As anticipated, hand foot syndrome (HFS) at any grade was more frequent for CAPOX (SOX = 3%; CAPOX = 25%, $p = .001$), but grade 3–4 HFS only occurred in one patient in the CAPOX arm. There was no treatment-related death in both arms.

Thrombocytopenia was the most frequent reason for dose reduction and cycle delay in the SOX arm, while

Table 4
Common adverse events (National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 3.0).

	SOX ($n = 65$)				CAPOX ($n = 64$)				*P*-value	
	All grades		Grade 3/4		All grades		Grade 3/4		All grades	Grade 3 + 4
	n	%	*n*	%	*n*	%	*n*	%		
Haematologic toxicity										
Neutropenia	37	56.9	6	9.2	40	62.5	12	18.8	.300	.119
Leukopenia	34	52.3	5	7.7	34	53.1	2	3.1	.926	.252
Anaemia	59	90.8	8	12.3	59	92.2	2	3.1	.773	.096
Thrombocytopenia	42	64.6	10	15.4	42	65.6	9	14.1	.861	.832
Non-haematologic toxicity										
Asthenia	27	41.5	1	1.5	32	50.0	5	7.8	.375	.115
Anorexia	34	52.3	2	3.1	32	50.0	2	3.1	.793	1
Nausea	31	47.7	2	3.1	27	42.2	3	4.7	.530	.680
Vomiting	27	41.5	1	1.5	21	32.8	2	3.1	.305	.619
Diarrhoea	20	30.8	3	4.6	22	34.4	3	4.7	.662	1
Neuropathy	27	41.5	2	3.1	31	48.4	3	4.7	.431	.680
Hand foot syndrome	2	3.1	0	0.0	16	25.0	1	1.6	<.001	–
Infection	13	20.0	6	9.2	9	14.1	4	6.3	.370	.744

Abbreviations: SOX, S-1-oxaliplatin; CAPOX, capecitabine–oxaliplatin.

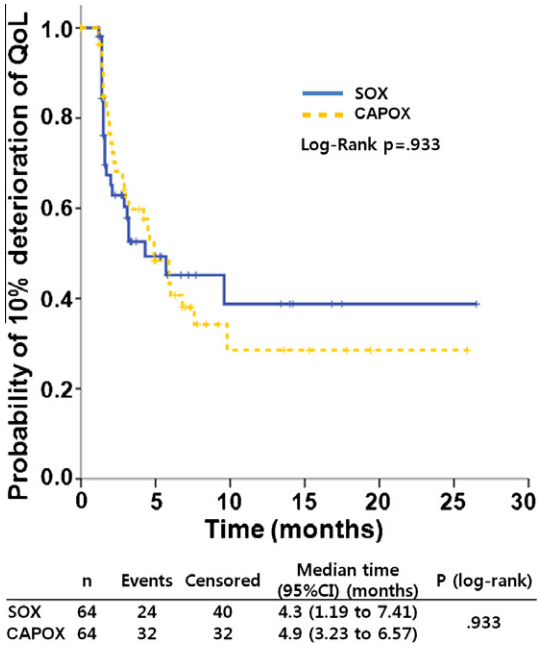

Fig. 3. Median time to 10% deterioration of global health status/quality of life (QoL) score by treatment arms. SOX, S-1-oxaliplatin; CAPOX, capecitabine–oxaliplatin.

neutropenia was the most common reason for dose reduction and treatment delay in the CAPOX arm. Among non-haematologic toxicities, asthenia in the SOX and hand-foot syndrome in the CAPOX arms were the most common reasons for dose reduction and cycle delay.

3.5. QoL Assessment

All the patients except one (who refused to complete the questionnaires) were included in the QoL analysis. The Patients in both arms showed substantially impaired global health status/QoL. Fatigue and appetite loss were the most prominent symptoms at the baseline. There was no difference in the QoL by the treatment arm according to linear mixed model analysis of each scale of the QoL.

The median time to 10% deteriorations in global health scores was similar in both arms (SOX, 4.3 months, 95% CI, 1.19–7.41; CAPOX, 4.9 months, 95% CI, 3.23–6.57, $p = 0.933$) (Fig. 3).

4. Discussion

This is the first randomized trial comparing S-1 (SOX) or capecitabine (CAPOX) in combination with oxaliplatin in patients with recurrent or metastatic gastric cancer. In this study, both the SOX and CAPOX regimens were active as a first-line treatment for AGC. In the SOX arm, the ORR was 40%, the median TTP was 6.2 months, the 1-year survival rate was 52% and the OS was 12.4 months. In the CAPOX arm, the ORR was 44%, the median TTP was 7.2 months, the 1-year survival rate was 59% and the OS was 13.3 months. These results were comparable with several recent SOX or CAPOX phase II studies in AGC patients. Recent phase II trials have shown promising efficacy with SOX (OS, 7.8–16.5 months; TTP, 4.6–6.5 months; ORR, 53–59%) and CAPOX (OS, 9.8–11.9 months; TTP, 5.6–5.8 months; ORR, 42–63%).[12–19]

There was no difference in the overall incidence of grade 3 or 4 toxicities in both arms. However, the toxicity patterns were different. Thrombocytopenia and anaemia for SOX and neutropenia, HFS and asthenia for CAPOX were major toxicities in terms of the incidence, the reasons for dose reduction and cycle delays. These toxicity results were consistent with recent phase II trials.[12–19] Grade 3 or 4 HFS occurred in only one patient

Table 5
Historical data of SOX and CAPOX.

	SOX				CAPOX				
	Park et al.[19]	Koizumi et al.[17]	Oh et al.[18]	Current study	Luo et al.[15]	Park et al.[16]	Liu et al.[14]	Dong et al.[12]	Current study
Number of patients	47	55	41	65	50	54	68	44	64
Fluoropyrimidine dose	100 mg/m^2 D1 ~ 14	80 mg/m^2 D1 ~ 14	80 mg/m^2 D1 ~ 28	80 mg/m^2 D1 ~ 14	2000 mg/m^2 D1 ~ 14	2000 mg/m^2 D1 ~ 14	2000 mg/m^2 D1 ~ 14	2000 mg/m^2 D1 ~ 14	2000 mg/m^2 D1 – 14
Oxaliplatin dose	130 mg/m^2 q 3 weeks	100 mg/m^2 q 3 weeks	85 mg/m^2 D1,15,29 q 6 weeks	130 mg/m^2 q 3 weeks	130 mg/m^2 q 3 weeks	130 mg/m^2 q 3 weeks	130 mg/m^2 q 3 weeks	130 mg/m^2 q 3 weeks	130 mg/m^2 q 3 weeks
Cycle, median	6 (1–9)	6 (1–16)	3 (1–4)	6 (1–31)	4 (1–8)	6 (1–16)	–	5 (1–8)	7(1–22)
Efficacy									
ORR (%)	56	59	54	40	42	63	54	51	44
TTP (months)	6.6 (4.0–9.2)	6.5* (4.8–11.2)	4.6 (3.4–5.8)	6.2 (4.9–7.5)	5.8 (3.4–8.2)	5.8 (4.4–7.2)	5.7 (2.0–8.8)	5.6 (4.6–6.6)	7.2 (5.9–8.5)
OS (months)	12.5 (9.2–15.9)	16.5 (13.2–22.3)	7.8 (6.9–8.7)	12.4 (8.8–16.0)	11.1 (5.6–16.5)	11.9 (8.8–15.1)	10.5 (5.0–15.1)	9.8 (7.4–12.2)	13.3 (10.3–16.3)
Toxicity (grade 3/4) (%)									
Neutropenia	27.6	22	1.8	9	12	8	6.1	13.6	19
Thrombocytopenia	38.7	13	10.5	15	6	11	7.7	11.3	14
Anaemia	17.4	9	4.4	12	4	0	0	2.3	3
Vomiting	2.2	0	0	2	2	2	1.5	4.5	3
Diarrhoea	4.3	2	4.9	5	2	7	6.2	13.6	5
Mucositis	0	0	0	2	0	0	0	0	0
Neuropathy	2.1	4	2.4	3	0	0	0	0	5
Asthenia	8.5	6	2.4	2	–	–	–	–	8
Hand foot syndrome (HFS)	–	0	–	0	2	0	0	9.1	2

Abbreviations: SOX, S-1-oxaliplatin; CAPOX, capecitabine–oxaliplatin; ORR, overall response rate; TTP, time to progression; OS, overall survival.
* Progression free survival (PFS).

Table 6
Comparison of efficacy and toxicity between current study and recent phase III trials.

	Current study		Recent phase III trials		
	SOX	CAPOX	Koizumi et al.[5]	Ajani et al.[6]	Kang et al.[7]
Regimen	SOX	CAPOX	SP	SP	XP
Median number of cycle	6	8	4	4	5
Efficacy					
ORR (%)	40	44	54	29	46
TTP (months)	6.2	7.2	6	4.8	5.6
OS (months)	12.4	13.3	13	8.6	10.5
Toxicity (G3 or 4) (%)					
Neutropenia	9	19	40	32	16
Thrombocytopenia	15	14	5	8	–
Anaemia	12	3	26	21	–
Vomiting	2	3	4	8	7
Diarrhoea	5	5	4	5	5
Mucositis	2	0	1	2	2
Neuropathy	3	5	–	–	–
Asthenia	2	8	4	12	2
Hand foot syndrome (HFS)	0	2	–	0	4

Abbreviations: SOX, S-1-oxaliplatin; CAPOX, capecitabine–oxaliplatin; SP, S-1-cisplatin; XP, capecitabine–cisplatin; ORR, overall response rate; TTP, time to progression; OS, overall survival.

in the CAPOX arm and this lower incidence of HFS was consistent with recent CAPOX trials in AGC patients (0–9.1%).[12–16] Ethnic differences for the rates of grade 3 or 4 HFS (11–17% in Westerners) were observed in a previous study.[22] Although this study was designed for selection, we could not select a winner because there was no difference in both the primary and secondary endpoints. The efficacy and safety data of recent trials comparing our study are presented in Table 5.

In previous phase III clinical trials in AGC patients using doublet regimen, median survival of 8.6 months was reported for SP by the FLAGS trial, 10.5 months was reported for XP by Kang et al., 13.0 months by the SPIRITS trial. Both SOX (12.4 months) and CAPOX (13.3 months) regimen showed that median survival was similar or longer than that of recent phase III studies.[5–7] The incidence of grade 3 or 4 toxicities was similar or slightly lower in SOX or CAPOX regimen compared with those of recent phase III studies. Thrombocytopenia was more frequent in current study because the median number of cycle was higher in current study than that of recent trials (Table 6).

The SOX regimen is now being tested for various cancers in various settings, but the recommended dose of SOX for AGC has not been established yet. Although the phase I/II study of SOX in AGC showed no dose limiting toxicity with 130 mg of oxaliplatin and 80 mg/m^2/day of S-1, we should consider the limitation of the phase I study which cannot predict the cumulative toxicity.[19] In this study, thrombocytopenia increased in a cumulative manner in both arms, but treatment delay and discontinuation due to thrombocytopenia were higher in the SOX arm. In previous phase II trials in colorectal cancer patients with 80 mg/m^2/day of S-1 plus 130 mg/m^2 of oxaliplatin, a high frequency of treatment discontinuation due to prolonged thrombocytopenia was reported.[23,24] In CAPOX regimen, many previous colorectal cancer trials reported the recommended dose which shows tolerable toxicity.[25,26] Several phase II trials with CAPOX in AGC patients using the same treatment schedule (capecitabine 2000 mg/m^2 per day, oxaliplatin 130 mg/m^2) also have shown tolerable toxicity profiles (neutropenia: 6–13.6%, thrombocytopenia: 6–11.3%).[12–16]

However, the Classic trial using CAPOX for AGC in adjuvant setting reported 56% grade 3 or 4 toxicities, 10% of consent withdrawals due to toxicity and 90% dose modifications in patients.[27] A phase III trial in metastatic colorectal cancer patients with SOX versus CAPOX showed a relatively high incidence of grade 2 or more adverse events (SOX, neutropenia 45%, thrombocytopenia 47%; CAPOX neutropenia 41%, thrombocytopenia 28%).[28] Jeung et al. suggested that a S-1 dose of 70 mg/m^2 per day is optimal in a combination regimen for AGC.[29] Based on these trials and our results, we suggest that the initial doses of both regimens need to be reduced or close monitoring of toxicity and continuous dose modification are required for further clinical trial and practice. Also, the further studies of the ethnic difference for oral fluoropyrimidine in Western AGC patients are warranted.

In conclusion, both the SOX and CAPOX regimens were equally active and well tolerated in patients with AGC. Both SOX and CAPOX have the potential of backbone chemotherapy regimen in further clinical trials of AGC.

Clinical trials

This study was registered to ClinicalTrial.gov with the No. NCT00985556.

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Conflict of interest statement

None declared.

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