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ORIGINAL ARTICLE

Randomized phase II study of CPT-11 versus PTX versus each combination chemotherapy with S-1 for advanced gastric cancer that is refractory to S-1 or S-1 plus CDDP: OGSG0701

Tomono Kawase[1] · Hiroshi Imamura[1] · Masahiro Goto[2] · Yutaka Kimura[3] · Shugo Ueda[4] · Jin Matsuyama[5] · Kazuhiro Nishikawa[6] · Naotoshi Sugimoto[7] · Junya Fujita[8] · Takao Tamura[9] · Norimasa Fukushima[10] · Hisato Kawakami[9] · Daisuke Sakai[11] · Yukinori Kurokawa[12] · Toshio Shimokawa[13] · Taroh Satoh[11]

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Abstract

Background To compare irinotecan-alone, paclitaxel-alone, and each combination chemotherapy with S-1 in patients with advanced gastric cancer (AGC) that is refractory to S-1 or S-1 plus cisplatin (SP).

Methods Patients with AGC after first-line chemotherapy with S-1 or SP, or patients during adjuvant chemotherapy or within 26 weeks after adjuvant chemotherapy completion with S-1 with confirmed disease progression were eligible. Patients were randomly divided into four groups based on treatment: irinotecan-alone (irinotecan; 150 mg/m^2, day 1, q14 days), paclitaxel-alone (paclitaxel; 80 mg/m^2, days 1, 8, 15, q28 days), S-1 plus irinotecan (irinotecan; 80 mg/m^2, days 1, 15, S-1; 80 mg/m^2, days 1–21, q35 days), and S-1 plus paclitaxel (paclitaxel; 50 mg/m^2, day1, 8, S-1; 80 mg/m^2, days 1–14, q21 days). The primary endpoint was overall survival (OS) and secondary endpoints were progression-free survival (PFS), response rate, and safety.

Results From July 2008 to March 2012, 127 patients were enrolled. No difference in median OS was observed in the irinotecan vs. paclitaxel groups or in the monotherapy groups vs. the S-1 combination therapy groups. Median PFS was longer in the paclitaxel group compared with the irinotecan group (4.1 vs. 3.6 months, $p=0.035$), although no difference was observed when comparing monotherapy vs. S-1 combination. The most common grade 3 to 4 hematological adverse events were neutropenia with no difference in incidence rate across the treatment groups.

Conclusions There was no difference in OS between irinotecan and paclitaxel no in OS prolongation of S-1 combination therapy in second-line chemotherapy.

Keywords Gastric cancer · Second-line chemotherapy · Paclitaxel · Irinotecan · S-1

Introduction

Gastric cancer is the sixth most common malignancy, and the third most common cause of cancer mortality worldwide [1]. Currently, platinum and fluoropyrimidine-based combinations are regarded as first-line chemotherapy worldwide. In Japan, S-1 monotherapy for 1 year and S-1 plus cisplatin combination therapy are recommended as a standard adjuvant chemotherapy for patients with stage II or III gastric cancer who underwent D2 gastrectomy and as a first-line chemotherapy regimen, in accordance with the 2010 guideline [2, 3].

When we planned the present study in 2007, taxanes and irinotecan were widely used as second-line chemotherapy. For taxanes, weekly paclitaxel had become the preferable chemotherapy in Japan because it has lower rates of severe neutropenia compared with tri-weekly paclitaxel or docetaxel [4–8]. However, clinical studies had not addressed the efficacy and safety of irinotecan compared with taxanes for advanced gastric cancer (AGC) that is refractory to S-1 or SP.

The combination of S-1 with paclitaxel, docetaxel, or irinotecan showed a synergistic effect in experimental models [9, 10], and this combination had response rates of 48–58% and a favorable median survival time (MST), which

✉ Hiroshi Imamura
imamurahiroshisakai@yahoo.co.jp

Extended author information available on the last page of the article

are higher compared with any cytotoxic drug that was used as a monotherapy. The combination also showed tolerable toxicity in phase II trials [11–14]. Generally, the drugs that failed in first-line treatment should theoretically be omitted from salvage-line treatment. However, for colorectal cancer, fluoropyrimidine has been used beyond progression in the form of FOLFOX followed by FOLFIRI, or vice versa, for decades [15, 16]. Moreover, preclinical studies have demonstrated that combining S-1 with irinotecan enhances the antitumor activity of S-1 against S-1-resistant cell lines in vivo [17]. These data suggest that S-1 combined with taxanes or irinotecan demonstrated efficacy in treating AGC that is refractory to S-1 or SP.

Thus, to clarify these issues, the Osaka Gastrointestinal Cancer Chemotherapy Study Group (OGSG) conducted a multicenter randomized phase II trial (OGSG0701) comparing the efficacy and safety of irinotecan with that of paclitaxel and evaluating the benefit of consecutive S-1 use for AGC that is refractory to S-1 or SP.

Patients and methods

Patient eligibility

Eligible patients were 20–74 years of age with histologically confirmed metastatic or recurrent gastric adenocarcinoma with or without measurable lesions based on RECIST (version 1.0). Other inclusion criteria were an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–2; disease progression confirmed by computed tomography (CT), endoscopy, or other imaging techniques during or within 1 month after the last dose of first-line chemotherapy with S-1 or SP more than 4 weeks or during adjuvant chemotherapy or within 26 weeks after adjuvant chemotherapy completion with S-1; capable of oral intake; adequate organ function; and expected survival of at least 3 months.

Major exclusion criteria were previous chemotherapy except S-1 or SP, severe ascites or pleural effusion, uncontrolled cardiac disease, or other clinically significant, uncontrolled coexisting illness, or concurrent cancer.

Study design

OGSG0701 was a prospective, multicenter, randomized, open-label, phase II clinical trial that was conducted at 22 institutions in Japan. The protocol was approved by the independent ethics committee or institutional review board at each participating institution. This trial was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent before study entry. The trial was registered with the University Hospital Medical Information Network.

Using a 2×2 factorial design, we randomly assigned patients to one of four treatment groups using a 2:2:1:1 ratio, as follows: (1) irinotecan-alone; (2) paclitaxel-alone; (3) S-1 plus irinotecan; and (4) S-1 plus paclitaxel. Random assignment was performed centrally at the data center using a minimization method, with the following adjustment factors: institution, ECOG PS (0 to 1 vs. 2), peritoneal metastasis (presence vs. absence), and timing of progression (during first-line chemotherapy vs. during adjuvant chemotherapy or within 26 weeks after adjuvant chemotherapy completion). Both investigators and patients were aware of study group assignments.

Treatment plan

In the irinotecan-alone group, irinotecan (150 mg/m^2) was administered intravenously on days 1 and 15, every 4 weeks. In the paclitaxel-alone group, paclitaxel (80 mg/m^2) was administered intravenously on days 1, 8, and 15, every 4 weeks. In the S-1 plus irinotecan group, irinotecan (80 mg/m^2) was administered intravenously on days 1 and 15, and S-1 was administered orally on days 1 to 21, every 5 weeks. In the S-1 plus paclitaxel group, paclitaxel (50 mg/m^2) was administered intravenously on days 1 and 8, and S-1 was administered orally on days 1 to 14, every 3 weeks. In the S-1 plus irinotecan and the S-1 plus paclitaxel groups, the dose of S-1 was determined based on the body surface area (BSA), as follows: < 1.25 m^2, 80 mg daily; 1.25 to < 1.5 m^2, 100 mg daily; and 1.5 m^2 or higher, 120 mg daily. The test for UGT1A1 variants in the irinotecan group was not stipulated in the protocol. Dose reduction and/or cycle delays were permitted based on predefined toxicity criteria. The treatment continued until disease progression, occurrence of unacceptable serious toxicity, or patient refusal of further treatment. Subsequent chemotherapy was not specified.

Assessment and data collection

Physical examinations and hematology and biochemistry tests were conducted during drug administration throughout the treatment course. Tumor assessments using CT scans of the chest, abdomen, and pelvis were performed every 4 weeks after treatment initiation and until confirmation of treatment response, and this regimen was repeated every 2 months until discontinuation of protocol treatment. RECIST (version 1.0) was used to evaluate treatment responses. Safety assessments were repeated at each chemotherapeutic agent administration. The adverse event severity was graded in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0). Extramural review of patient eligibility, response, and disease progression were performed.

Statistical considerations

The S-1 plus irinotecan group and S-1 plus paclitaxel group were combined into the S-1 combination therapy groups. The irinotecan-alone group and paclitaxel-alone group were combined into the monotherapy groups. The S-1 combination therapy groups were compared with the monotherapy groups. The MST after completion of S-1 combination chemotherapy with the first-line treatment was reported to be approximately 7 months [13, 18], and, therefore, we expected that overall survival (OS) for the second-line treatment would be similar. However, MST with irinotecan monotherapy and with paclitaxel monotherapy in the second-line treatment was reported to be 150 days [8, 19]. Therefore, we thought that the monotherapy groups would have a MST of 5 months.

When the significance level was $\alpha = 0.10$, the adjusted significance level by Bonferroni's method for comparison between the S-1 combination therapy groups and the monotherapy groups was $\alpha = 0.10/2 = 0.05$. The sample size was 40 subjects in each group of irinotecan-alone, paclitaxel-alone, and S-1 combination therapy when the power $1-\beta$ was 0.80. Thus, the combination therapy groups (S-1 plus irinotecan group and S-1 plus paclitaxel group) were set to 20 subjects for each. Moreover, the power $1-\beta$ was 0.892 when comparing the monotherapy groups ($n = 80$) and the S-1 combination therapy groups ($n = 40$). All statistical analyses were performed using the full analysis set (FAS) under the intention-to-treat principle.

The primary endpoint was the comparison between the irinotecan-containing therapy and the paclitaxel-containing therapy (irinotecan-alone or S-1 plus irinotecan vs. paclitaxel-alone or S-1 plus paclitaxel) and between the monotherapy and the S-1 combination therapy (irinotecan-alone or paclitaxel-alone vs. S-1 plus irinotecan or paclitaxel) using the OS rate in the 2×2 comparisons. The secondary endpoints were the progression-free survival (PFS) rate, overall response rate (ORR), and the incidence of adverse events (AEs).

Survival curves for OS and PFS were estimated using the Kaplan–Meier method, and the 95% confidence intervals (CIs) for the survival rate were estimated using Greenwood's formula. The log-rank test was used to compare the survival curves in each group, and the Cox proportional hazard model was used to estimate the adjusted hazard ratio for paclitaxel/irinotecan and the presence or absence of S-1.

We estimated ORR and 95% CIs using the Clopper–Pearson exact method and the results were compared using Fisher's exact test. All analyses were conducted using R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria). $p < 0.05$ was considered to be significant.

Results

Patients

From July 2008 to March 2012, 127 patients were enrolled from 22 centers in Japan. Among these patients, 42 were allocated to the irinotecan-alone group, 43 to the paclitaxel-alone group, 22 to the S-1 plus irinotecan group, and 20 to the S-1 plus paclitaxel group (Fig. 1). After random assignment, one patient assigned in the S-1 plus irinotecan group received S-1 plus paclitaxel. Therefore, the FAS consisted of 42, 43, 22, and 20 patients, and the safety analysis set (SAS) consisted of 42, 43, 21, and 21 patients in the

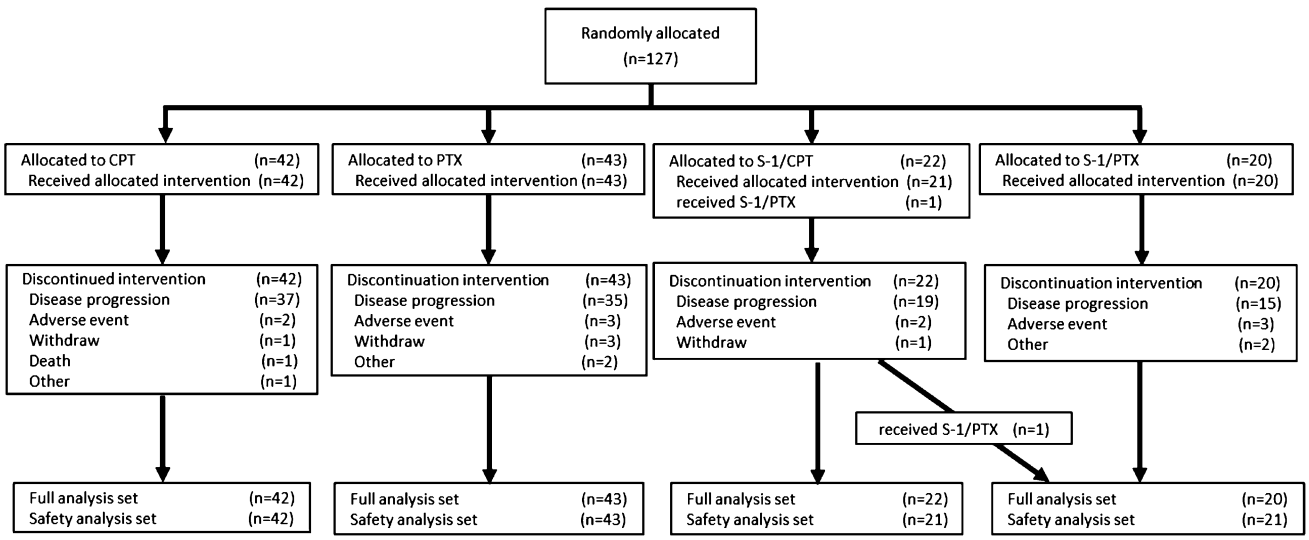


Fig.1 Consort diagram

irinotecan-alone group, paclitaxel-alone group, S-1 plus irinotecan group, and S-1 plus paclitaxel group, respectively. The four groups were well balanced in terms of their baseline characteristics (Table 1).

Exposure to chemotherapy

The median number of treatment cycles was four (range, one to 38) in the irinotecan-alone group, four (range, one to 23) in the paclitaxel-alone group, three (range, one to 7) in the S-1 plus irinotecan group, and 4.5 (range, one to 23) in the S-1 plus paclitaxel group. The proportion of patients in whom treatment was discontinued because of toxicity was 4.7% in the irinotecan-alone group, 6.9% in the paclitaxel-alone group, 9.0% in the S-1 plus irinotecan group, and 15.0% in the S-1 plus paclitaxel group, respectively.

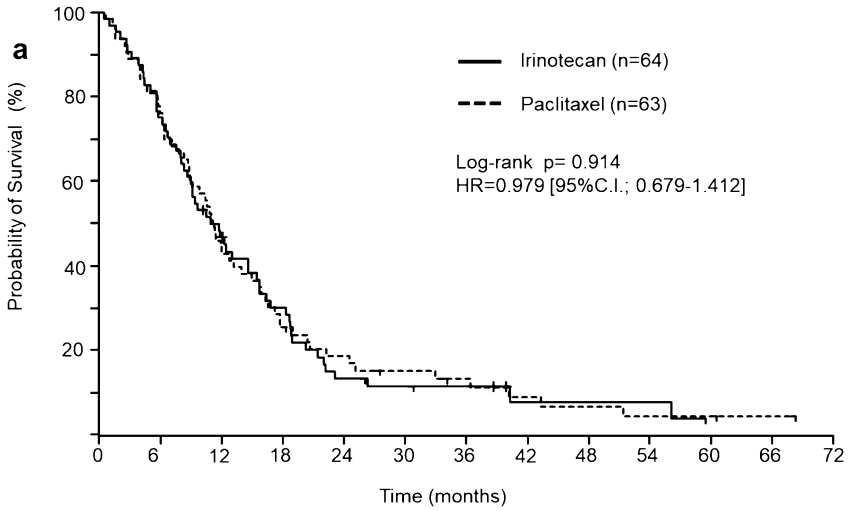
Subsequent chemotherapy was administered to 33 patients (78.6%) in the irinotecan-alone group, 31 patients (72.1%) in the paclitaxel-alone group, 16 patients (72.7%) in the S-1 plus irinotecan group, and 14 patients (70.0%) in the S-1 plus paclitaxel group, respectively. Forty-one patients (64.0%) in the irinotecan group received subsequent chemotherapy containing taxane, whereas 32 patients (50.8%) in the paclitaxel group received subsequent chemotherapy containing irinotecan.

Efficacy

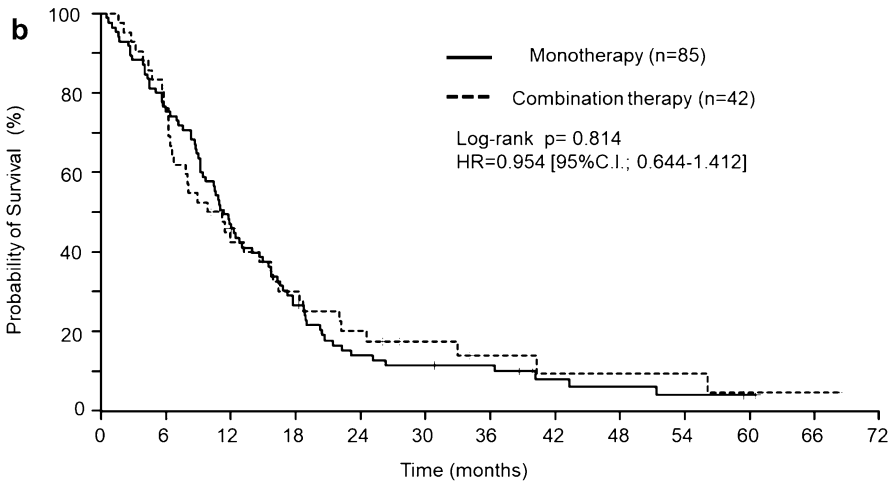
At the time of data cut-off (July 2014) with a median follow-up period of 11.3 months, 116 deaths (91.3%) were reported in the patient cohort. For the primary endpoint of OS, no statistically significant difference was observed between the irinotecan group (irinotecan-alone or S-1 plus irinotecan) vs. the paclitaxel group (paclitaxel-alone or S-1 plus paclitaxel; HR, 0.979; 95% CI 0.679–1.412; log-rank $p = 0.914$; Fig. 2a), as well as between the monotherapy groups (irinotecan-alone or paclitaxel-alone) vs. the S-1 combination therapy groups (S-1 plus irinotecan or paclitaxel; HR, 0.954; 95% CI 0.644–1.412; log-rank $p = 0.814$; Fig. 2b). Median OS was 10.9 months in the irinotecan group, 11.1 months in the paclitaxel group 11.3 months in the monotherapy group, and 10.5 months in the S-1 combination therapy group. For the secondary endpoints, median PFS in the paclitaxel groups was significantly longer compared with the irinotecan groups (4.1 vs. 3.6 months, HR, 0.674; 95% CI 0.468–0.972; log-rank $p = 0.034$; Fig. 3a). There was no statistically significant

Table 1 Baseline patient demographic and characteristics

	lrinotecan-alone ($n = 42$) (%)	Paclitaxel-alone ($n = 43$) (%)	S-l+irinotecan ($n = 22$) (%)	S-l+paclitaxel ($n = 20$) (%)
Sex				
Male	30 (71.4)	35 (81.4)	15 (68.2)	12 (60.0)
Female	12 (28.6)	8 (18.6)	7 (31.8)	8 (40.0)
Age, years				
Median	65	65	67	63
Range	44–74	31–74	47–73	37–74
ECOG PS				
0 or 1	42 (100)	41 (95.3)	21 (95.5)	20 (100)
2	0 (0)	2 (4.7)	1(4.5)	0 (0)
Histology				
Intestinal	24 (57.1)	25 (58.1)	11 (50.0)	12 (60.0)
Diffuse	18 (42.9)	18 (41.9)	11(50.0)	8 (40.0)
Prior gastrectomy				
Yes	22 (52.4)	21 (48.8)	13 (59.1)	13 (65.0)
No	20 (47.6)	22 (51.2)	9 (40.9)	7 (35.0)
Peritoneal metastasis				
Yes	15 (35.7)	15 (34.9)	7 (31.8)	4 (20.0)
No	27 (64.3)	28 (65.1)	15 (68.2)	16 (80.0)
No. of metastatic sites				
0–1	28 (66.7)	31 (72.1)	19 (86.4)	16 (80.0)
≥ 2	14 (33.3)	12 (27.9)	3 (13.6)	4 (20.0)
Prior chemotherapy				
S-1 plus cisplatin	28 (66.7)	24 (55.8)	12 (54.5)	12 (60.0)
S-1	14 (33.3)	19 (44.2)	10 (45.5)	8 (40.0)



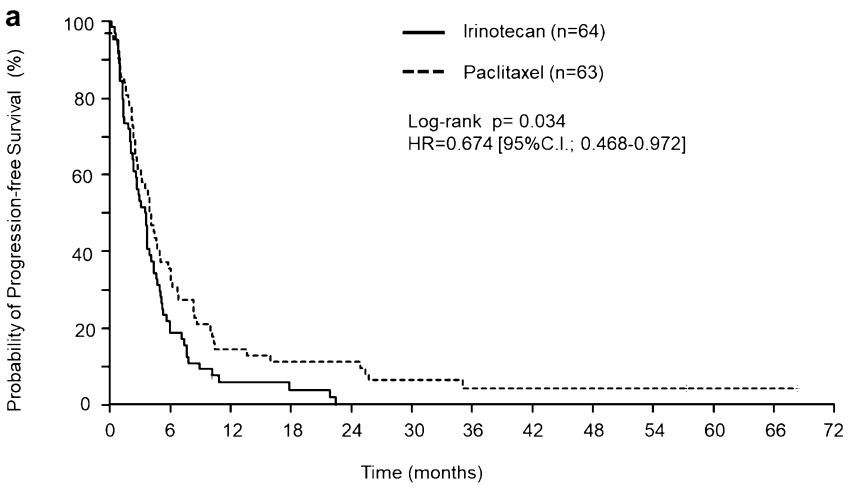
	Irinotecan	Paclitaxel
n	64	63
Events	57	59
Median OS (95% CI) (months)	10.9 (9.0-15.7)	11.1 (8.9-15.7)
OS at 1-year (95% CI) (%)	46.7 (35.9-60.7)	42.9 (32.2-57.0)



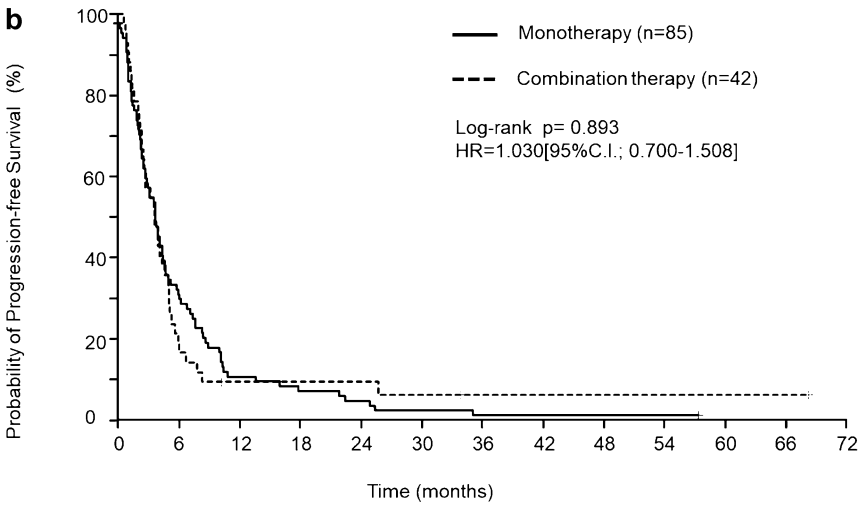
	Monotherapy	Combination therapy
n	85	42
Events	78	37
Median OS (95% CI) (months)	11.3 (9.3-15.0)	10.5 (6.7-16.4)
OS at 1-year (95% CI) (%)	45.9 (36.4-57.8)	42.5 (29.8-60.6)

Fig.2 Overall survival. **a** Overall survival curve for patients by the irinotecan (irinotecan-alone or S-1 plus irinotecan) or the paclitaxel (paclitaxel-alone or S-1 plus paclitaxel). **b** Overall survival curve for patients by the monotherapy (irinotecan-alone or paclitaxel-alone) or the S-1 combination therapy (S-1 plus irinotecan or paclitaxel)

difference between the monotherapy groups and the S-1 combination therapy groups (3.7 vs 3.6 months, HR, 1.030; 95% CI 0.700–1.508; log-rank $p = 0.893$; Fig. 3b). The ORR was 6.3% (95% CI 1.7–15.2) in the irinotecan groups, 12.7% (95% CI 5.6–23.5) in the paclitaxel groups (Table 2a), 11.8% (95% CI 5.8–20.6) in the monotherapy groups, and 4.8% (95% CI 0.6–16.2) in the S-1 combination therapy groups (Table 2b). There was no statistically significant difference between the irinotecan group and the paclitaxel group ($p = 0.241$), or between the monotherapy group and the S-1 combination therapy group ($p = 0.334$).



	Irinotecan	Paclitaxel
n	64	63
Events	63	59
Median PFS (95% CI) (months)	3.6 (2.6-4.3)	4.1 (3.1-5.7)
PFS at 1 year (95% CI) (%)	5.9 (2.1-16.2)	14.5 (7.9-26.6)



	Monotherapy	Combination therapy
n	85	42
Events	83	39
Median PFS (95% CI) (months)	3.7 (2.8-4.7)	3.6 (2.6-5.0)
PFS at 1 year (95% CI) (%)	10.7 (5.8-19.9)	9.5 (3.8-24.2)

Fig.3 Progression-free survival. **a** Progression-free survival curve for patients by the irinotecan (irinotecan-alone or S-1 plus irinotecan) or the paclitaxel (paclitaxel-alone or S-1 plus paclitaxel). **b** Overall survival curve for patients by the monotherapy (irinotecan-alone or paclitaxel-alone) or the S-1 combination therapy (S-1 plus irinotecan or paclitaxel)

Safety

Table 3 lists the main adverse events and the proportion of patients experiencing adverse events during treatment in the SAS. The most common Grade 3 or 4 adverse events were neutropenia (28.6%), leukopenia (11.9%), and anorexia (9.5%) in the irinotecan-alone group; neutropenia (16.3%) and febrile neutropenia (11.6%) in the paclitaxel-alone group; neutropenia (23.8%), anemia (14.3%), and anorexia (14.3%) in the S-1 plus irinotecan group; and neutropenia (23.8%), anemia (14.3%), and anorexia (9.5%) in the S-1 plus paclitaxel group. Grade 3 or 4 neutropenia and anorexia were less frequent in the paclitaxel-alone group compared with the other groups. Diarrhea was frequently observed in the irinotecan group compared

Table 2 Response rates for ITT population

	CR	PR	SD	PD	NE	RR (%) 95% CI	*p*
a							
Irinotecan ($n = 64$)	1	3	32	26	2	6.3 [1.7–15.2]	0.241
Paclitaxel ($n = 63$)	0	8	23	27	5	12.7 [5.6–23.5]	
b							
Monotherapy ($n = 63$)	1	9	33	36	6	11.8 [5.8–20.6]	0.334
Combination therapy ($n = 63$)	0	2	22	17	1	4.8 [0.6–16.2]	

CR complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *NE* not evaluable, without measurable lesions according to RECIST (version 1.0), *RR* response rate

Table 3 Adverse events

Adverse–events	lrinotecan-alone ($n = 42$)		Paclitaxel-alone ($n = 43$)		S-1+irinotecan ($n = 21$)		S-1+paclitaxel ($n = 21$)	
	All grades *n* (%)	Grade3–4 *n* (%)	All grades *n* (%)	Grade3–4 *n* (%)	All grades *n* (%)	Grade3–4 *n* (%)	All grades *n* (%)	Grade3–4 *n* (%)
Leukopenia	25 (59.5)	5 (11.9)	18 (41.9)	3 (7.0)	13 (61.9)	1(4.8)	12 (57.1)	0 (0)
Neutropenia	30 (71.4)	12 (28.6)	19 (44.2)	7 (16.3)	14 (66.7)	5 (23.8)	13 (61.9)	5(23.8)
Anemia	36 (85.7)	3 (7.1)	32 (74.4)	4 (9.3)	16 (76.2)	3 (14.3)	19 (90.5)	3 (14.3)
Thrombocytopenia	14 (33.3)	2 (4.8)	9 (20.9)	1(2.3)	5 (23.8)	0 (0)	4 (19.0)	1(4.8)
Febrile neutropenia	0 (0)	0 (0)	5 (11.6)	5 (11.6)	0 (0)	0 (0)	0 (0)	0 (0)
Anorexia	27 (64.3)	4 (9.5)	19 (44.2)	1(2.3)	13 (61.9)	3 (14.3)	14 (66.7)	2 (9.5)
Nausea	16 (38.0)	3 (7.1)	11(25.6)	1(2.3)	12 (57.1)	2 (9.5)	8 (38.1)	1(4.8)
Vomiting	10 (23.8)	2 (4.8)	3 (7.0)	1(2.3)	4 (19.0)	0 (0)	3 (14.3)	0 (0)
Diarrhea	17 (40.5)	2 (4.8)	5 (11.6)	0 (0)	14 (66.7)	2 (9.5)	7 (33.3)	0 (0)
Neuropathy	1(2.4)	0 (0)	24 (55.8)	0 (0)	1(4.8)	0 (0)	8 (38.1)	0 (0)
Fatigue	27 (64.3)	2 (4.8)	23 (53.5)	1(2.3)	13 (61.9)	2 (9.5)	14 (66.7)	1(4.8)
Bilirubin	6 (14.3)	0 (0)	5 (11.6)	0 (0)	7 (33.3)	0 (0)	5 (23.8)	1(4.8)
AST	9 (21.4)	1(2.4)	13 (30.2)	2 (4.7)	5 (23.8)	0 (0)	7 (33.3)	0 (0)
ALT	8 (19.0)	1(2.4)	10 (23.3)	1(2.3)	5 (23.8)	0 (0)	4 (19.0)	0 (0)

with the paclitaxel group, with an incidence of 40.5% in the irinotecan-alone group and 66.7% in the S-1 plus irinotecan group. The overall neuropathy events were more frequent in the paclitaxel-alone group (55.8%) compared with the S-1 plus paclitaxel group (38.1%). One treatment-related death occurred in the irinotecan-alone group because of renal failure, which was possibly derived from progression of massive ascites.

Discussion

To the best of our knowledge, this was the first randomized phase II trial in a two-by-two design that examined the efficacy and safety in the comparison of irinotecan vs. paclitaxel, with or without consecutive use of S-1 as second-line chemotherapy in AGC patients who were refractory

to S-1 or SP. When we planned this study, no data had indicated the survival benefit of second-line chemotherapy in AGC. In Asian countries, however, patients who were refractory to first-line chemotherapy had routinely received second-line chemotherapy in the clinical practice setting. In the SPRITS phase III trial [2], which established SP as a first-line regimen, 74–75% of the patients received second-line chemotherapy after the failure of initial chemotherapy, extending the survival time after tumor progression beyond that of the PFS. In Japan, various regimens had been used for second-line chemotherapy when this study was planned, including monotherapy of paclitaxel or irinotecan, with or without S-1, raising the following queries: which agent contributes most to the survival benefit; and whether S-1 continuation is necessary for the second-line setting. We, therefore, designed this unique 2 × 2 study to assess these two clinical questions at the same time.

After enrollment into this study had started, the survival benefit of second-line chemotherapy for AGC was first suggested by the AIO [20] and Korean [21] studies, in which a survival benefit of irinotecan and docetaxel were shown compared with best supportive care (BSC). Subsequently, the WJOG 4007 phase III trial, comparing weekly paclitaxel vs. irinotecan in the second-line setting, suggested the use of paclitaxel at least in Japan, with lower toxicity and favorable survival compared with irinotecan, although no significant difference was found [22]. Currently, paclitaxel with ramucirumab is the standard of care in this setting worldwide after the global phase III RAINBOW study [23].

In the current study, no statistically significant differences in OS were observed among treatment groups containing irinotecan vs. paclitaxel, and among treatment groups with or without S-1 continuation. The reason for no difference between paclitaxel group and irinotecan group could be because of the cross-over effect, given that higher proportion of the irinotecan-containing group received third-line chemotherapy compared with the paclitaxel-containing group. However, the paclitaxel groups showed significantly improved PFS compared with the irinotecan groups, supporting the current use of paclitaxel treatment in the second-line setting for AGC. This result was comparable to that of the WJOG 4007 study, where no difference in PFS was observed between paclitaxel and irinotecan [22]. The discordance in PFS difference between our study and WJOG 4007 might be derived from the differences in patient background in the two studies. Our study population included the higher proportion of patients with recurrence after gastrectomy (54.3%) and those with zero to one metastatic site (74.0%) compared with that in WJOG 4007 study (34.7% and 55.3%, respectively) [22]. These data may suggest the tumor burden may affect the efficacy of paclitaxel in this setting, which requires further evaluation.

Although no differences in toxicity were seen between the treatment groups with or without S-1 continuation, our data also revealed that continuous S-1 use is not recommended. Consistent with our finding, the CCOG 0701 phase II trial and the JACCRO GC-05 phase II/III trial reported no benefit of S-1 administration beyond progression in OS, PFS, and the response rate [24, 25]. The treatment group with S-1 continuation also had higher toxicities compared with without S-1 continuation based on the JACCRO GC-05 phase II/III trial. These data suggest that the role of 5-fluorouracil (FU) in the treatment of AGC may be different compared with that of metastatic colorectal cancer in which 5-FU is continued through the first- and second-line treatments in combination with oxaliplatin or irinotecan. This strategy for colorectal cancer cannot be used for AGC. Shitara et al. reported a retrospective analysis that showed that S-1 plus cisplatin was effective in patients with recurrence after 24 weeks from termination of adjuvant chemotherapy with S-1 [26]. However, the results of the current study showed no benefit of S-1 administration for patients with recurrence during adjuvant chemotherapy and within 24 weeks of terminating S-1 adjuvant chemotherapy.

Our study has the following limitation. In this study, the primary endpoint was OS after second-line chemotherapy and one of the secondary endpoints was PFS in second-line chemotherapy for AGC. However, ramucirumab and nivolumab, which are currently used for AGC, were not available at the time of this study. Therefore, OS and PFS in this study are expected to be shorter compared with the current standard treatment for AGC.

The results of this Phase II study support the current use of paclitaxel as a second-line treatment for patients with AGC, although there was no difference in OS between irinotecan and paclitaxel no difference in OS prolongation of S-1 combination therapy. For AGC that is refractory to S-1 or SP, S-1 beyond progression should not be used.

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Author contributions All authors contributed to the study conception and design. HI designed and supervised the research. Material preparation, data collection and analysis were performed by HI and TS. The first draft of the manuscript was written by TK, HK reviewed and modified the manuscript and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Declarations

Conflict of interest Hiroshi Imamura has received honoraria from Taiho Pharmaceutical Co., Ltd., Ono Pharmaceutical Co., Ltd., Eli Lilly Japan K.K., and EA Pharma Co., Ltd. Kazuhiro Nishikawa has received honoraria from Bristol-Myers Squibb Co., Ltd., Chugai Pharmaceutical Co., Ltd., EA Pharma Co., Ltd., Eli Lilly Japan K.K., Ono Pharmaceutical Co., Ltd., Taiho Pharmaceutical Co., Ltd., and Yakult Honsha Co., Ltd. Naotoshi Sugimoto has received honoraria from Taiho Pharmaceutical Co., Ltd., Chugai Pharmaceutical Co., Ltd., Eli Lilly Japan K.K., MSD K.K., Ono Pharmaceutical Co., Ltd., Nippon Kayaku Co., Ltd., fees for promotional materials from Nippon Kayaku Co., Ltd., and research funding from Taiho Pharmaceutical Co., Sumitomo Dainippon Pharma Co., Ltd., Eli Lilly Japan K.K., MSD K.K., Ono Pharmaceutical Co., Ltd., Daiichi Sankyo Co. Ltd., Solasia Pharma K.K. and Astellas Pharma Inc. Takao Tamura has received honoraria from Daiichi Sankyo Co. Ltd., and research funding from Takeda Pharmaceutical Co., Ltd., Chugai Pharmaceutical Co., Ltd., Taiho Pharmaceutical Co., Ltd., BeiGene Ltd., and Ono Pharmaceutical Co., Ltd. Hisato Kawakami has consulting/advisory relationship with Bristol-Myers Squibb Co. Ltd., Ono Pharmaceutical Co. Ltd., Eli Lilly Japan K.K., Taiho Pharmaceutical Co. Ltd, and has received honoraria from Bristol-Myers Squibb Co. Ltd., AstraZeneca K.K., Bayer Yakuhin Ltd., Daiichi Sankyo Co. Ltd., MSD K.K., Ono Pharmaceutical Co. Ltd., Chugai Pharmaceutical Co. Ltd., Daiichi Sankyo Co. Ltd., Takeda Pharmaceutical Co. Ltd., Taiho Pharmaceutical Co. Ltd., and research funding from Chugai Pharmaceutical Co. Ltd., Eisai Co. Ltd. Daisuke Sakai has received honoraria from Chugai Pharmaceutical Co., Ltd., and research funding from Daiichi Sankyo Co. Ltd., Daiichi Sankyo Co. Ltd., Astellas Pharma Inc., Yakult Honsha Co., Ltd., Ono Pharmaceutical Co., Ltd., Chugai Pharmaceutical Co. Ltd., Incyte. Jp and Taiho Pharmaceutical Co., Ltd. Taroh Satoh has received honoraria from Chugai Pharmaceutical Co., Yakult Honsha Co., Ltd., Daiichi Sankyo Co. Ltd., Bristol-Myers Squibb Co. Ltd., and research funding from Daiichi Sankyo Co. Ltd., and scholarship donations from Taiho Pharmaceutical Co., Ltd., and endowed chairs from Chugai Pharmaceutical Co., Yakult Honsha Co., Ltd., and Ono Pharmaceutical Co. Ltd. All the remaining authors have no conflicts of interest to declare.

Ethical approval All procedures in this study were conducted in accordance with the Ethical Standards of the Institutional and/or National Research Committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants before entry into the study.

References

1. IARC (2018) WHOIAfRoC GLOBOCAN 2018: estimated cancer incidence, mortality and prevalence worldwide in 2018.
2. Koizumi W, Narahara H, Hara T et al (2008) S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. Lancet Oncol 9(3):215–221. https://doi.org/10.1016/S1470-2045(08)70035-4
3. Sakuramoto S, Sasako M, Yamaguchi T et al (2007) Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. N Engl J Med 357(18):1810–1820. https://doi.org/10.1056/NEJMoa072252
4. Taguchi T, Sakata Y, Kanamaru R et al (1998) Late phase II clinical study of RP56976 (docetaxel) in patients with advanced/recurrent gastric cancer: a Japanese Cooperative Study Group trial (group A). Gan To Kagaku Ryoho Cancer Chemother 25(12):1915–1924
5. Kodera Y, Ito S, Mochizuki Y et al (2007) A phase II study of weekly paclitaxel as second-line chemotherapy for advanced gastric Cancer (CCOG0302 study). Anticancer Res 27(4c):2667–2671
6. Yamada Y, Shirao K, Ohtsu A et al (2001) Phase II trial of paclitaxel by three-hour infusion for advanced gastric cancer with short premedication for prophylaxis against paclitaxel-associated hypersensitivity reactions. Ann Oncol 12(8):1133–1137
7. Yamaguchi K, Tada M, Horikoshi N et al (2002) Phase II study of paclitaxel with 3-h infusion in patients with advanced gastric cancer. Gastric Cancer 5(2):90–95. https://doi.org/10.1007/s101200200015
8. Hironaka S, Zenda S, Boku N et al (2006) Weekly paclitaxel as second-line chemotherapy for advanced or recurrent gastric cancer. Gastric Cancer 9(1):14–18. https://doi.org/10.1007/s10120-005-0351-6
9. Nukatsuka M, Fujioka A, Nakagawa F et al (2004) Antimetastatic and anticancer activity of S-1, a new oral dihydropyrimidine-dehydrogenase-inhibiting fluoropyrimidine, alone and in combination with paclitaxel in an orthotopically implanted human breast cancer model. Int J Oncol 25(6):1531–1536
10. Sakurai Y, Yoshida I, Kamoshida S et al (2008) Effects of combined administration of DPD-inhibitory oral fluoropyrimidine, S-1, plus paclitaxel on gene expressions of fluoropyrimidine metabolism-related enzymes in human gastric xenografts. Ann Surg Oncol 15(8):2301–2309. https://doi.org/10.1245/s10434-008-9963-5
11. Uedo N, Narahara H, Ishihara R et al (2007) Phase II study of a combination of irinotecan and S-1 in patients with advanced gastric cancer (OGSG0002). Oncology 73(1–2):65–71. https://doi.org/10.1159/000120630
12. Narahara H, Fujitani K, Takiuchi H et al (2008) Phase II study of a combination of S-1 and paclitaxel in patients with unresectable or metastatic gastric cancer. Oncology 74(1–2):37–41. https://doi.org/10.1159/000138978
13. Inokuchi M, Yamashita T, Yamada H et al (2006) Phase I/II study of S-1 combined with irinotecan for metastatic advanced gastric cancer. Br J Cancer 94(8):1130–1135. https://doi.org/10.1038/sj.bjc.6603072
14. Yoshida K, Ninomiya M, Takakura N et al (2006) Phase II study of docetaxel and S-1 combination therapy for advanced or recurrent gastric cancer. Clin Cancer Res 12(11 Pt 1):3402–3407. https://doi.org/10.1158/1078-0432.Ccr-05-2425
15. Rothenberg ML, Oza AM, Bigelow RH et al (2003) Superiority of oxaliplatin and fluorouracil-leucovorin compared with either therapy alone in patients with progressive colorectal cancer after irinotecan and fluorouracil-leucovorin: interim results of a phase III trial. J Clin Oncol 21(11):2059–2069. https://doi.org/10.1200/jco.2003.11.126
16. Tournigand C, Andre T, Achille E et al (2004) FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. J Clin Oncol 22(2):229–237. https://doi.org/10.1200/jco.2004.05.113
17. Ichikawa W, Takahashi T, Suto K et al (2004) Thymidylate synthase predictive power is overcome by irinotecan combination therapy with S-1 for gastric cancer. Br J Cancer 91(7):1245–1250. https://doi.org/10.1038/sj.bjc.6602139
18. Koizumi W, Tanabe S, Saigenji K et al (2003) Phase I/II study of S-1 combined with cisplatin in patients with advanced gastric cancer. Br J Cancer 89(12):2207–2212. https://doi.org/10.1038/sj.bjc.6601413

19. Kanat O, Evrensel T, Manavoglu O et al (2003) Single-agent irinotecan as second-line treatment for advanced gastric cancer. Tumori 89(4):405–407
20. Thuss-Patience PC, Kretzschmar A, Bichev D et al (2011) Survival advantage for irinotecan versus best supportive care as second-line chemotherapy in gastric cancer–a randomised phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). Eur J Cancer 47(15):2306–2314. https://doi.org/10.1016/j.ejca.2011.06.002
21. Kang JH, Lee SI, Lim do H et al (2012) Salvage chemotherapy for pretreated gastric cancer: a randomized phase III trial comparing chemotherapy plus best supportive care with best supportive care alone. J Clin Oncol 30(13):1513–1518. https://doi.org/10.1200/JCO.2011.39.4585
22. Hironaka S, Ueda S, Yasui H et al (2013) Randomized, open-label, phase III study comparing irinotecan with paclitaxel in patients with advanced gastric cancer without severe peritoneal metastasis after failure of prior combination chemotherapy using fluoropyrimidine plus platinum: WJOG 4007 trial. J Clin Oncol 31(35):4438–4444. https://doi.org/10.1200/jco.2012.48.5805
23. Wilke H, Muro K, Van Cutsem E et al (2014) Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. Lancet Oncol 15(11):1224–1235. https://doi.org/10.1016/s1470-2045(14)70420-6
24. Nakanishi K, Kobayashi D, Mochizuki Y et al (2016) Phase II multi-institutional prospective randomized trial comparing S-1 plus paclitaxel with paclitaxel alone as second-line chemotherapy in S-1 pretreated gastric cancer (CCOG0701). Int J Clin Oncol 21(3):557–565. https://doi.org/10.1007/s10147-015-0919-z
25. Tanabe K, Fujii M, Nishikawa K et al (2015) Phase II/III study of second-line chemotherapy comparing irinotecan-alone with S-1 plus irinotecan in advanced gastric cancer refractory to first-line treatment with S-1 (JACCRO GC-05). Ann Oncol 26(9):1916–1922. https://doi.org/10.1093/annonc/mdv265
26. Shitara K, Morita S, Fujitani K et al (2012) Combination chemotherapy with S-1 plus cisplatin for gastric cancer that recurs after adjuvant chemotherapy with S-1: multi-institutional retrospective analysis. Gastric Cancer 15(3):245–251. https://doi.org/10.1007/s10120-011-0101-x

Authors and Affiliations

Tomono Kawase[1] · Hiroshi Imamura[1] · Masahiro Goto[2] · Yutaka Kimura[3] · Shugo Ueda[4] · Jin Matsuyama[5] · Kazuhiro Nishikawa[6] · Naotoshi Sugimoto[7] · Junya Fujita[8] · Takao Tamura[9] · Norimasa Fukushima[10] · Hisato Kawakami[9] · Daisuke Sakai[11] · Yukinori Kurokawa[12] · Toshio Shimokawa[13] · Taroh Satoh[11]

1 Department of Surgery, Toyonaka Municipal Hospital, 4-14-1 Shibahara-cho, Toyonaka, Japan
2 Cancer Chemotherapy Center, Osaka Medical College Hospital, Takatsuki, Japan
3 Department of Surgery, Faculty of Medicine, Kinki University, Sayama, Japan
4 Department of Gastroenterological Surgery, Kitano Hospital, Osaka, Japan
5 Department of Gastroenterological Surgery, Higashiosaka City Medical Center, Higashiosaka, Japan
6 Department of Surgery, Osaka General Medical Center, Osaka, Japan
7 Department of Medical Oncology, Osaka International Cancer Institute, Osaka, Japan
8 Department of Surgery, Sakai City Medical Center, Sakai, Japan
9 Department of Medical Oncology, Faculty of Medicine, Kindai University, Osaka, Japan
10 Department of Surgery, Yamagata Prefectural Central Hospital, Yamagata, Japan
11 Department of Frontier Science for Cancer and Chemotherapy, Osaka University Graduate School of Medicine, Suita, Japan
12 Department of Gastroenterological Surgery, Osaka University Graduate School of Medicine, Suita, Japan
13 Clinical Study Support Center, Wakayama Medical University, Wakayama, Japan