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Cisplatin Plus Capecitabine After Adjuvant S-1 in Metastatic Gastric Cancer: A Phase II T-CORE1102 Trial

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Abstract. *Background/Aim: This phase II study assessed the efficacy of capecitabine plus cisplatin in patients with advanced gastric cancer refractory to adjuvant S-1. Patients and Methods: This single-arm, open-label, multicenter, phase II study was conducted by Tohoku Clinical Oncology Research and Education Society (T-CORE) in Japan. Patients aged ≥20 years with advanced HER2-negative gastric cancer that was refractory to S-1 were enrolled. Patients received 80 mg/m^2 cisplatin on day 1 intravenously and 1,000 mg/m^2 capecitabine twice daily from day 1 to day 14, in 3-week cycles. The primary endpoint was progression-free survival (PFS). The threshold overall response rate (ORR) was estimated to be 15%. The secondary endpoints were overall survival (OS), time to treatment failure, ORR, and toxicities. Results: In total, 21 patients were enrolled from seven hospitals. The median patient age was 63 years. Nineteen patients received the protocol treatment. Median PFS was 3.7 months [90% confidence interval (CI)=2.7-5.6 months], which did not reach the predefined threshold of 4.0 months. ORR was 5.9% (95%CI=0.0-17.1%). Median OS was 11.9 months (95% CI 6.3-19.4 months). Febrile neutropenia was observed in 5.3% of patients. The most frequently observed grade 3 non-hematologic toxicities were nausea (15.8%) and hyponatremia (15.8%). Conclusion: The addition of a fluoropyrimidine to a platinum agent after adjuvant therapy is not suitable for gastric cancer.*

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Gastric cancer is the third leading cause of cancer death globally, being responsible for approximately 800,000 deaths annually (1). For patients with unresectable, metastatic gastric cancer, chemotherapy is the first-line treatment option. The combination of a fluoropyrimidine with cisplatin or oxaliplatin is the standard first-line treatment for this population. For example, the SPIRITS trial found that S-1 plus cisplatin was more effective than S-1 alone as a first-line treatment for advanced gastric cancer (2). The G-SOX trial reported that S-1 plus oxaliplatin is non-inferior to S-1

plus cisplatin in terms of progression-free survival (PFS) and overall survival (OS), whereas the former regimen had a better toxicity profile excluding sensory neuropathy (3). On the other hand, efficacy of S-1 plus non-platinum agents has been controversial in the 1st line treatment of patients with gastric cancer (4-7).

For patients with stage II or III gastric cancer who underwent D2 gastrectomy, adjuvant chemotherapy with a fluoropyrimidine-based regimen is a recommended treatment option. The ACTS-GC trial revealed the efficacy of S-1 in the adjuvant setting for patients with stage II or III gastric cancer, including a higher 3-year OS rate than surgery alone [80.1% *vs.* 70.1%, hazard ratio (HR)=0.68, 95% confidence interval (CI)=0.52-0.87, p=0.003] (8). The updated analysis reported superior 5-year OS (72% *vs.* 61%, HR=0.67, 95%CI=0.54-0.83) and disease-free survival rates (65% *vs.* 53%, HR=0.65, 95%CI=0.54-0.79) in the adjuvant treatment arm (9). More recently, the CLASSIC trial reported an estimated 5-year disease-free survival rate of 68% (95%CI=74-82%) in patients with stage II-IIIB gastric cancer who received adjuvant capecitabine and oxaliplatin, versus 53% (95%CI=47-58) in those who underwent observation alone (HR=0.58, 95%CI=0.47-0.72) (10). In addition, the JACCRO GC-07 trial found that adjuvant S-1 plus docetaxel is superior to S-1 alone in patients with stage III gastric cancer (3-year disease-free survival rate 66% *vs.* 50%, HR=0.63, 99.99% CI=0.400-0.998) (11).

In 2011, when we planned the present phase II trial, no randomized phase III study had validated whether S-1-based combination therapy is effective in patients with stage II-III gastric cancer resistant to adjuvant S-1 monotherapy. Shitara *et al.* performed a single-institutional retrospective analysis of 51 patients with gastric cancer who experienced recurrence after adjuvant S-1 therapy and found that ORR was significantly lower in 21 patients who received an S-1-based regimen as salvage therapy than in 30 patients who received a regimen without S-1 (0% *vs.* 16%, p=0.02) (12). PFS was significantly shorter in the S-1 group (median, 2.3 *vs.* 4.6 months, p=0.02) (12). These results suggested that S-1-based therapy is not effective in patients with recurrent gastric cancer after adjuvant S-1 therapy. Kang *et al.* performed a phase II study and reported that among 32 patients with recurrent gastric cancer after fluoropyrimidine-based adjuvant chemotherapy who subsequently received capecitabine plus cisplatin, ORR was 24%, PFS was 5.8 months, and median OS was 11.2 months (13). In that study, S-1, nor capecitabine was used for prior adjuvant chemotherapy (13). These results indicated that switching from a fluoropyrimidine to another drug provides some benefits, although this strategy is more effective in fluoropyrimidine-naïve patients. Whether capecitabine-based therapy is effective in patients with recurrent gastric cancer after S-1-based adjuvant chemotherapy was not clarified.

The present phase II study evaluated the efficacy and toxicity of capecitabine plus cisplatin in patients who underwent resection of gastric cancer and developed recurrence during or after adjuvant S-1 therapy.

Patients and Methods

Patients and study design. This single-arm, phase II trial enrolled patients at seven institutions that participate in the Tohoku Clinical Oncology Research and Education Society (T-CORE) (14) in Japan. The study was conducted in accordance with the Declaration of Helsinki. The protocol was approved by institutional ethics committee of Tohoku University Graduate School of Medicine (2018-1-680), and institutional ethics committees or institutional review boards of all other participating institutions. Written informed consent was obtained from all patients.

The eligibility criteria were as follows: age ≥20 years; Eastern Oncology Group Performance Status (ECOG-PS) of 0-2; receipt of R0 surgery for the primary region of histologically confirmed HER2-negative gastric adenocarcinoma; receipt of one S-1-based chemotherapeutic regimen as adjuvant therapy for at least 6 months after surgery; recurrence during or after adjuvant S-1 therapy; survival for at least 3 months after study enrollment; and appropriate bone marrow and liver function (white blood cell count ≥3,000/mm^3, neutrophil count ≥1,500/mm^3, hemoglobin ≥10.0 g/dl, platelet count ≥10.0×10^4/mm^3, aspartate aminotransferase ≤100 U/l, alanine aminotransferase ≤100 U/l, total bilirubin ≤2.0 mg/dl, and creatine clearance ≥60 ml/min).

Treatment. Capecitabine (1,000 mg/m^2) was administered orally twice daily from day 1 to day 14, followed by an intravenous dose of 80 mg/m^2 of cisplatin delivered over 120 min with sufficient hydration every 3 weeks. The dose reduction protocol was as follows: capecitabine level −1, 800 mg/m^2; capecitabine level −2, 600 mg/m^2; cisplatin level −1, 60 mg/m^2; cisplatin level −2, 40 mg/m^2. If grade 4 neutropenia or grade 3 febrile neutropenia occurred, dose reduction to level −1 was performed for both capecitabine and cisplatin. If grade 4 thrombocytopenia or grade 4 febrile neutropenia occurred, dose reduction to level −2 was performed for both capecitabine and cisplatin, or protocol treatment was stopped, depending on the physician's choice. If grade 2 non-hematological toxicity occurred, dose reduction to level −1 was performed for capecitabine. If grade 3 non-hematological toxicity occurred, dose reduction to level −1 was performed for both capecitabine and cisplatin. If grade 4 non-hematological toxicity occurred, dose reduction to level −2 was performed for both capecitabine and cisplatin, or protocol treatment was stopped, depending on the physician's choice.

Endpoints. The primary endpoint was PFS, and the secondary endpoints were ORR, OS, time to treatment failure, and toxicities. PFS was defined as the time from the initiation of protocol treatment to the first radiologic confirmation of disease progression or death from any cause. OS was defined as the time from the initiation of protocol treatment to death from any cause. Tumor response was evaluated by computed tomography every 8 weeks according to Response Evaluation Criteria in Solid Tumors version 1.1. ORR was defined as the number of patients with a

Table I. *Characteristics of patients enrolled in this study (N=21).*

Factor		N	%
Gender	Male	17	81
	Female	4	19
Age	Median	63	
	Range	57-69	
T factor on surgery	T1	1	5
	T2	3	14
	T3	12	57
	T4a	5	24
N factor on surgery	N0	1	5
	N1	6	29
	N2	4	19
	N3	10	48
Histology	Intestinal	11	52
	Diffuse	10	48
Recurrent timing	During adjuvant therapy	1	5
	After adjuvant therapy	20	95
	Less than 6 months	13	62
	6 months or more	7	33
Recurrent site	LN	10	48
	Liver	7	33
	Peritoneum	4	19
	Local	1	5
	Others	2	10
ECOG-PS	0	20	95
	1	1	5
	2	0	0

complete response (CR) or partial response (PR) divided by the number of all patients with measurable lesions. The disease control rate (DCR) was defined as the number of patients with CR, PR, or stable disease (SD) divided by the number of response-evaluable patients.

Statistical analysis. In light of prior study findings (12), the threshold PFS was set to 4 months, and the expected PFS was set to 6 months. At a one-sided significance of 0.05 and power of 80%, the minimum number of patients required was estimated to be 37. Estimating a withdrawal rate of about 10%, we set the target enrollment for this phase II study at 40 patients. The planned patient registration period was 2 years starting in December 2011, and the planned follow-up period was 2 years.

Results

Patient characteristics. In total, 21 patients were enrolled from seven institutions in Japan between February 2012 and September 2016. Because patient accrual was slower than initially planned, patient registration was extended to September 2016 and then stopped because of the slow pace of recruitment. The median follow-up period was 9 months (range=3-18 months). The clinicopathological characteristics of the patients are presented in Table I. The median patient age was 63 years (range=49-78 years). The cohort included 17 men and 4 women. ECOG-PS was 0 in 20 patients and 1 in 1 patient. Nine patients completed adjuvant S-1 therapy, and 12 patients stopped adjuvant treatment for various reasons. One patient experienced recurrence during S-1 adjuvant therapy, 13 patients experienced recurrence within 6 months after the cessation of S-1 adjuvant therapy, and seven patients experienced recurrence more than 6 months after the cessation of S-1 adjuvant therapy.

Efficacy. Among the 21 patients enrolled in this study, two patients were excluded from the study because their resection for gastric cancer was found to be non-curative, and thus, 19 patients received the protocol therapy. The reasons for the cessation of protocol treatment were disease progression, toxicity, patient's request, and conversion surgery in 10, 7, 1, and 1 patient, respectively. One patient who was unable to start protocol treatment because of progression of renal dysfunction after enrollment was excluded from further analysis. All 18 treated patients had measurable lesions, but one patient was excluded from the ORR and PFS analyses because renal toxicity prompted treatment termination before the completion of therapy.

Median PFS was 3.7 months (90%CI=2.7-5.6 months, Figure 1A). Median OS was 11.9 months (95%CI=6.3-19.4 months, Figure 1B). The median time to treatment failure was 2.8 months (95%CI=1.2-3.6 months, Figure 1C). PR was achieved in one patient, and no CRs were observed (Table II). ORR was 5.6% (95%CI=0.0-17.1%). SD was observed in 10 patients (59%), and DCR was 65% (Table II).

Median PFS and OS among patients with recurrence within 6 months after the cessation of S-1 adjuvant therapy were 3.4 (90%CI=2.7-5.6 months, Figure 2A) and 10.8 months (95%CI=6.3-19.4 months, Figure 2B), respectively, whereas median PFS and OS among patients with recurrence more than 6 months after the cessation of S-1 adjuvant therapy were 10.2 (90%CI=2.1 months-not reached, Figure 2A) and 23.5 months (95%CI not reached, Figure 2B).

Adverse events. Among the 19 patients who received protocol treatment, toxicities of any grade were observed in 90% of patients. Toxicities observed in two or more patients included anemia (90%), thrombocytopenia (68%), neutropenia (63%), fatigue (68%), hypoalbuminemia (68%), creatinine increased (63%), nausea (53%), hyponatremia (53%), diarrhea (42%), hypokalemia (32%), fever up (32%), neuropathy (32%), stomatitis (26%), abdominal pain (16%), and vomiting (11%), as presented in Table III. Grade 3 or higher toxicities observed in two or more patients included anemia (26%), neutropenia (26%), nausea (16%), hyponatremia (16%), fatigue (11%), and hypokalemia (11%). Febrile neutropenia was observed in only one patient (5.3%, Table III). No treatment-related deaths occurred.

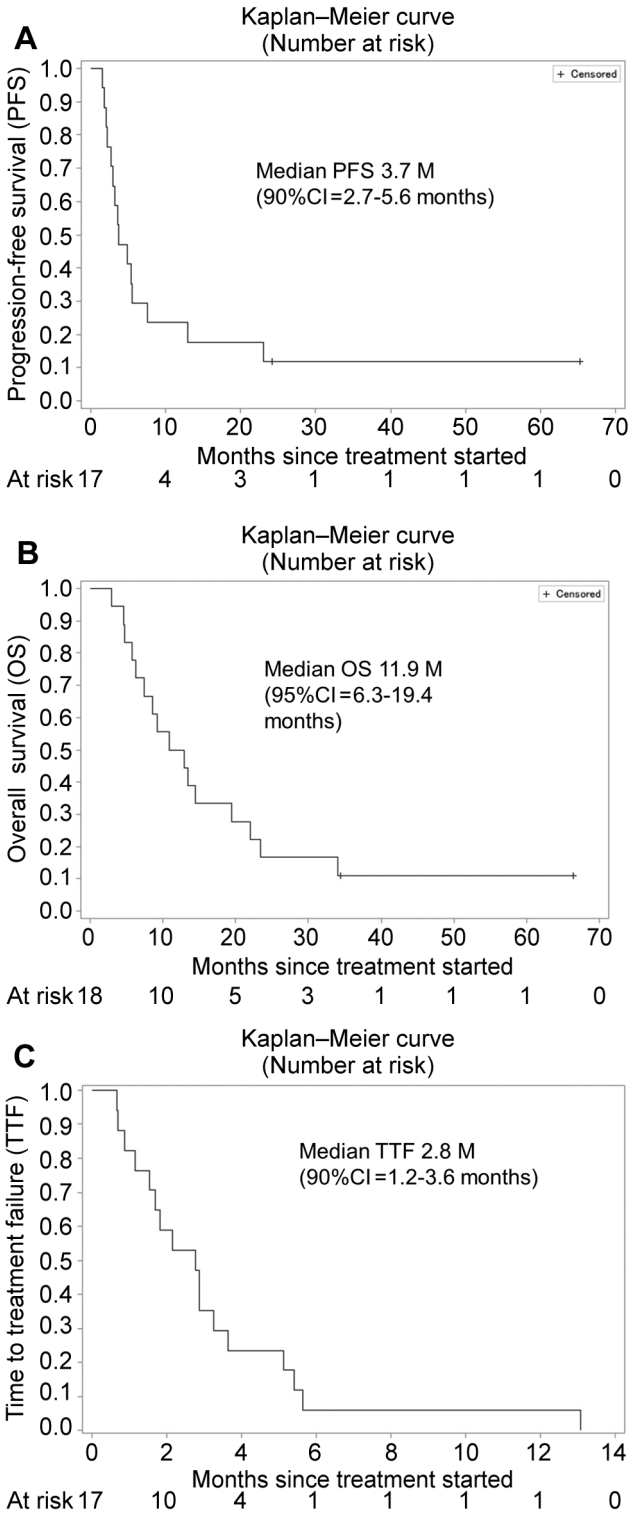

Figure 1. *Progression-free survival, overall survival, and time to treatment failure of patients enrolled in this study. (A) Kaplan–Meier curve for progression-free survival among patients enrolled in this study. (B) Kaplan–Meier curve for overall survival among patients enrolled in this study. (C) Kaplan–Meier curve for time to treatment failure among patients enrolled in this study.*

Table II. *Best tumor response, overall response rate, and disease control rate (N=17).*

Factor		N	%
Best tumor response	CR	0	0.0
	PR	1	5.9
	SD	10	58.9
	PD	4	23.5
	NE	2	11.8
ORR			5.9
DCR			64.7

CR: Complete response; PR: partial response; SD: stable disease; PD: progressive disease; NE: not evaluable; ORR: overall response rate; DCR: disease control rate.

Discussion

This phase II trial did not demonstrate that capecitabine plus cisplatin therapy was an effective regimen in patients with advanced gastric cancer who were refractory to adjuvant S-1 therapy. The efficacy of capecitabine plus cisplatin in this study appears inefficient in light of the accumulated results of several clinical trials analyzing the efficacy of first-line chemotherapy in patients with gastric cancer excluding those with early recurrence during or after adjuvant therapy. For example, the SPIRITS trial reported an ORR of 54% and PFS of 6.0 months in the S-1 plus cisplatin arm (2), and the XParTS-II randomized phase II trial reported an ORR of 69% and PFS of 5.1 months in the capecitabine and cisplatin arm (15). Conversely, OS in our study appears comparable to those of previous studies, including the 13.0 months in SPIRITS and 12.6 months in XParTS-II, which might be attributable to treatment received after the protocol treatment, although information on post-treatment was not available.

Since our study was started, a handful of clinical trials that analyzed the efficacy of fluoropyrimidine plus platinum regimens for early relapse during or after S-1 adjuvant therapy have been reported. In their retrospective analysis, Shitara *et al*. reported an ORR of 19.4%, median PFS of 4.8 months, and median OS of 12.2 months among patients who had recurrence after S-1 adjuvant therapy and subsequently received S-1 plus cisplatin (16). In their analysis, patients with recurrence-free survival of fewer than 6 months after S-1 adjuvant therapy responded less strongly to study treatment (ORR=5.0% *vs*. 37.5%; PFS 2.3 months *vs*. 6.2 months; OS 7.3 months *vs*. 16.6 months) than those with recurrence-free interval more than 6 months after S-1 adjuvant therapy (16). Their findings suggest that patients with early relapse after S-1 adjuvant therapy are unlikely to benefit from S-1-based salvage therapy. Nishikawa *et al*. recently conducted a single-arm phase II study (XParTS-1) in which patients with

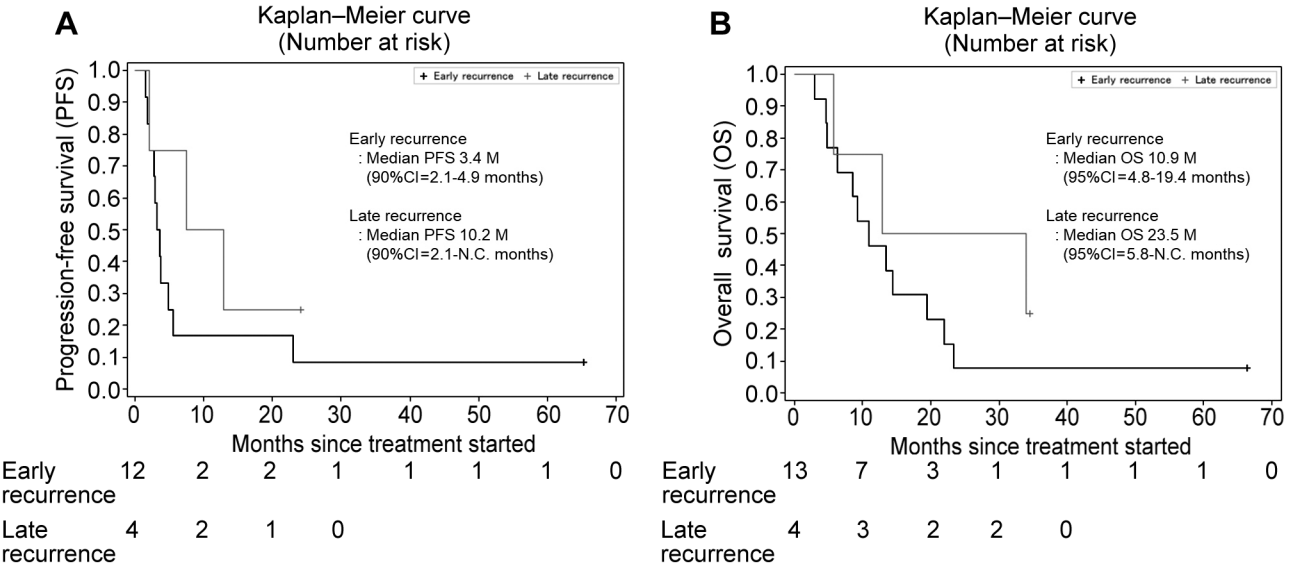

Figure 2. *Progression-free survival and overall survival of patients with early recurrence within 6 months after the completion of S-1 adjuvant therapy and those with late recurrence more than 6 months or later after the completion of S-1 adjuvant therapy. (A) Kaplan–Meier curves for progression-free survival among patients with early recurrence within 6 months after the completion of S-1 adjuvant therapy and those with late recurrence more than 6 months or later after the completion of S-1 adjuvant therapy. (B) Kaplan–Meier curves for overall survival among patients with early recurrence within 6 months after completion of S-1 adjuvant therapy and those with late recurrence more than 6 months after the completion of S-1 adjuvant therapy.*

Table III. *Grade 3 or 4 adverse events observed in >5% among all enrolled patients (N=19).*

	Grade 1		Grade 2		Grade 3		Grade 4		All		Grade 3-4	
Factor	N	%	N	%	N	%	N	%	N	%	N	%
Hematological												
Anemia	8	42.1	4	21.1	5	26.3	0	0.0	17	89.5	5	26.3
Thrombocytopenia	10	52.6	2	10.5	0	0.0	1	5.3	13	68.4	1	5.3
Neutropenia	1	5.3	6	31.6	2	10.5	3	15.8	12	63.2	5	26.3
Febrile neutropenia	n.a.	n.a.	n.a.	n.a.	0	0.0	1	5.3	1	5.3	1	5.3
Non-hematological												
Fatigue	6	31.6	5	26.3	2	10.5	0	0.0	13	68.4	2	10.5
Hypoalbuminemia	13	68.4	3	15.8	0	0.0	0	0.0	13	68.4	0	0.0
Creatinin increased	9	47.4	2	10.5	1	5.3	0	0.0	12	63.2	1	5.3
Nausea	3	15.8	4	21.1	3	15.8	0	0.0	10	52.6	3	15.8
Hyponatremia	7	36.8	0	0.0	3	15.8	0	0.0	10	52.6	3	15.8
Diarrehea	5	26.3	3	15.8	0	0.0	0	0.0	8	42.1	0	0.0
Hypokalemia	4	21.1	0	0.0	1	5.3	1	5.3	6	31.6	2	10.5
Fever	4	21.1	2	10.5	0	0.0	0	0.0	6	31.6	0	0.0
Neuropathy	4	21.1	2	10.5	0	0.0	0	0.0	6	31.6	0	0.0
Stomatitis	4	21.1	0	0.0	1	5.3	0	0.0	5	26.3	1	5.3
Abdominal pain	3	15.8	0	0.0	0	0.0	0	0.0	3	15.8	0	0.0
Vomiting	2	10.5	0	0.0	0	0.0	0	0.0	2	10.5	0	0.0

n.a: Not applicable.

HER2-negative gastric cancer treated with adjuvant chemotherapy including mainly S-1 who experienced relapse within 6 months after adjuvant therapy, subsequently received capecitabine plus cisplatin. ORR was 26.7%, and median PFS was 4.4 months (17). These studies suggest that the switching to different fluoropyrimidines, at least from S-1 to capecitabine, results in efficacy in some patients. However, in our phase II study, efficacy appeared worse than

that of the XParTS-I study, even though our study included four patients (23.5%) who experienced recurrence within 6 months after the completion of S-1 adjuvant chemotherapy and used the same doses of capecitabine and cisplatin as those used in the XParTS-1 study. The reason for the low efficacy in our study is unknown.

In the TRICS randomized phase III trial, the efficacy of irinotecan plus cisplatin and irinotecan alone was compared in the second-line treatment of patients with gastric cancer who experienced tumor progression after at least one course of S-1 therapy or who did not experience recurrence within 6 months after the completion of adjuvant S-1 therapy (18). The study did not reveal differences in OS (median, 13.9 months *vs*. 12.7 months, HR=0.83, 95%CI=0.60-1.17), PFS (median, 4.6 months *vs*. 4.1 months), or ORR (16.9% *vs*. 15.4%) between the groups (18). Moreover, an additional subgroup analysis of the TRICS study focused on the efficacy of irinotecan plus cisplatin versus irinotecan alone in patients with early recurrence during or within 6 months after the completion of adjuvant S-1 therapy, revealing no significant differences in OS (median, 14.0 months *vs*. 14.0 months), PFS (median, 5.0 months *vs*. 4.0 months), or ORR (19.6% *vs*. 23.3%) (19). These studies suggest that addition of cisplatin, at least to CPT-11, is not beneficial in patients with gastric cancer who had early recurrence after S-1 adjuvant therapy.

In light of the established efficacy of the current standard second-line regimen of paclitaxel plus ramucirumab, exemplified by median PFS of 4.4 months and ORR of 28% as reported in the RAINBOW trial (20), the combination of a fluoropyrimidine and platinum may not be a recommended option for patients with S-1-refractory gastric cancer with early recurrence.

Our study had several limitations. First, this study had a single-arm setting. Second, this study had a small sample size. The planned sample size was 40, but enrollment was terminated after 21 patients were accrued because of the slow pace of enrollment. Nevertheless, based on the low efficacy of capecitabine plus cisplatin observed in this study (median PFS, 3.7 months; ORR=5.6%), it appears unlikely that the combination regimen will be sufficiently effective in the second-line setting after progression during or early after S-1 adjuvant therapy, even if the number of enrolled patients was doubled.

In conclusion, our phase II study did not demonstrate any efficacy of capecitabine plus cisplatin therapy for patients with recurrent gastric cancer treated with S-1-based adjuvant therapy.

Conflicts of Interest

Masanobu Takahashi reports receiving lecture fees from Daiichi-Sankyo and research funding from Ono Pharmaceutical Company. Chikashi Ishioka reports receiving lecture fees from Taiho, Chugai, Takeda, Bayer, Pfizer, Mochida, Asahi Kasei, Bristol-Myers Squibb, Daiichi-Sankyo, Merck Serono, and Novartis, and research funding from Chugai, Taiho, Bristol-Myers Squibb, Daiichi-Sankyo, Merck Serono, Yakult, Ono, and Novartis. The other Authors have no conflicts of interest.

Authors' Contributions

TY, HS, and CI conceived the design of this study. TY, MT, US, AO, TF, YM, YS, HI, HO, HS, NC, YS, TN, NF, and HS obtained informed consent and clinical data from the patients. MT and TY performed the data analysis. TY, MT, TY, and CI interpreted data and wrote the manuscript.

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