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ORIGINAL ARTICLE

A multicenter phase II study of combined chemotherapy with docetaxel, cisplatin, and S-1 in patients with unresectable or recurrent gastric cancer (KDOG 0601)

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Abstract
Purpose We conducted a phase II study to evaluate the efficacy and safety of a triplet regimen of docetaxel, cisplatin, and S-1 in patients with unresectable or recurrent gastric cancer.
Methods Docetaxel (40 mg/m^2) and cisplatin (70 or 60 mg/m^2) were given on day 1 of a 28-day cycle. S-1 (40 mg/m^2) was given twice daily on days 1–14. Treatment with this regimen was continued for a maximum of 6 cycles. Subsequently, patients with no disease progression received a combination of docetaxel and S-1.
Results Fifty-nine patients were enrolled. The median number of administered cycles was 8 (range, 1–25). Because some patients had serious myelosuppression and renal dysfunction with 70 mg/m^2 of cisplatin, dose of cisplatin was reduced to 60 mg/m^2 after 19 patients had been treated. Common severe toxic effects of grade 3 or 4 were leukocytopenia (44%), neutropenia (72%), anemia (15%), and febrile neutropenia (14%). The overall response rate of this group was 81% (95% confidence interval (CI), 71–91%). The median overall survival and progression-free survival were 18.5 (95% CI, 15.6–21.5) and 8.7 (95% CI, 6.7–10.7) months, respectively.
Conclusions Triplet of docetaxel, cisplatin, and S-1 is a well-tolerated and highly active regimen for advanced or recurrent gastric cancer. A 60 mg/m^2 of cisplatin is as effective as 70 mg/m^2 of cisplatin.

Keywords Docetaxel · Cisplatin · S-1 (combination) · Gastric cancer · Phase II

Introduction

Gastric cancer, the most common malignant tumor arising in the gastrointestinal tract, is the second leading cause of cancer-related death in the world, after lung cancer. There are about 700,000 deaths from gastric cancer per year [1, 2]. The 2009 edition of "Vital statistics of Japan" published by the Ministry of Health, Labour and Welfare estimated that in 2007, there were 50,597 deaths from gastric cancer in Japan, accounting for 15% of all cancer-related deaths [3]. Similar to international trends, mortality from gastric cancer is second highest, following that from lung cancer in Japan. A further decrease in mortality would require improved treatment outcomes in patients with unresectable advanced or recurrent gastric cancer.

S-1 is an oral fluoropyrimidine derivative developed in Japan, based on the concept of biochemical modulation. S-1 consists of the following three components in a molar ratio of 1:0.4:1: tegafur, a prodrug which slowly

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metabolized to 5-fluorouracil; gimeracil, which reversibly inhibits dihydropyrimidine dehydrogenase, the rate-limiting degrading enzyme of 5-fluorouracil, thereby increasing the plasma concentration of 5-fluorouracil; and oteracil potassium, which is distributed in high concentrations in gastrointestinal tissue and inhibits phosphorylation of 5-fluorouracil, thereby reducing gastrointestinal toxicity. It was developed to achieve enhanced efficacy with less toxicity when compared to conventional 5-fluorouracil derivatives [4].

In 2007, the Japan Clinical Oncology Group (JCOG) 9912 study reported that the therapeutic efficacy of S-1 monotherapy was noninferior to 5-fluorouracil alone regimen, with a better toxicity profile. The study concluded that S-1 should be a new standard treatment option for advanced gastric cancer [5].

In addition, we also performed a phase III study comparing S-1 plus cisplatin with S-1 alone in patients with advanced gastric cancer (SPIRITS trial). The study demonstrated significantly improved survival with S-1 plus cisplatin compared to S-1 alone [6]. At present, S-1 plus cisplatin is recognized as a standard treatment for unresectable, advanced, or recurrent gastric cancer in Japan. In 2009, the results of the First-Line Advanced Gastric Cancer Study (FLAGS) comparing 5-fluorouracil plus cisplatin with S-1 plus cisplatin were reported. S-1 plus cisplatin was shown to be at least equivalent to 5-fluorouracil plus cisplatin [7]. Because of its good toxicity profile, S-1 plus cisplatin is expected to be used as a first-line treatment in countries other than Japan, especially in East Asia in the near future. However, the efficacy of S-1 plus cisplatin is still unsatisfactory. Development of new treatment regimens is essential for a further decrease in mortality from gastric cancer.

A triplet regimen of 5-fluorouracil, cisplatin, and docetaxel (DCF) is one of the standard treatments for unresectable advanced gastric cancer in Western countries. DCF was associated with significantly better outcomes when compared to 5-fluorouracil plus cisplatin, indicating that the addition of docetaxel in the triplet regimen enhanced effectiveness [8]. We have therefore started to study the effect of adding docetaxel to base treatment with S-1 plus cisplatin to further improve outcomes. Since DCF was reported high hematotoxicity, we adopted 4-weekly regimen, which has 14 days of rest, to manage toxicity and reduce treatment delay, not 3-weekly regimen. And docetaxel and cisplatin was administered on day 1 in terms of convenience. We previously performed a phase I study to evaluate the safety and to determine the maximum tolerated dose and recommended dose of triplet regimen with docetaxel, cisplatin, and S-1 (DCS). DCS was highly active with acceptable toxicity in that phase I study [9]. On the basis of these results, we performed this multicenter single-arm phase II study.

Patients and methods

Patients

Patients had to meet the following eligibility criteria: (1) unresectable or recurrent gastric cancer with a histopathologically confirmed diagnosis of adenocarcinoma; (2) the presence of measurable lesions within 28 days before enrollment; (3) no previous therapy (radiotherapy, chemotherapy, or hormone therapy) for the gastric carcinoma; (4) age between 20 and 80; (5) no severe vital organ dysfunction (bone marrow, heart, lungs, liver, kidneys, etc.), i.e., a leukocyte count $\geq 3 \times 10^3/\mu L$, a platelet count $\geq 100 \times 10^3/\mu L$, a serum total bilirubin concentration ≤ 1.5 mg/dL, serum aspartate aminotransferase (AST) and serum alanine aminotransferase (ALT) concentration ≤ 100 IU/L (in patients with liver metastasis, however, AST and ALT concentration of not more than five times of the upper limit of normal at the institution performing the test), a serum creatinine concentration ≤ 1.5 mg/dL, a serum creatinine clearance (24 h urine specimen) ≥ 50 mL/min, and a normal electrocardiogram; (6) a performance status (Eastern Cooperative Oncology Group scale) of 0–2; (7) being able to tolerate oral intake; (8) life expectancy of at least 8 weeks from the date of enrollment; and (9) written informed consent from each patient.

Ethical, medical, and scientific aspects of the study were reviewed and approved by the ethics committees of each participating institution. The study was conducted in accordance with the declaration of Helsinki of 1975, revised in 2000.

Treatment schedule

DCS was administered as per the doses determined in our previous phase I study. S-1 (body surface area [BSA] <1.25 m^2, 40 mg; BSA ≥ 1.25 to <1.5 m^2, 50 mg; and BSA ≥ 1.5 m^2, 60 mg) was given orally twice daily after breakfast and dinner for 14 consecutive days, followed by 14 days of rest. Docetaxel (40 mg/m^2) was given as a continuous intravenous infusion over the course of at least 60 min on day 1. Cisplatin (70 or 60 mg/m^2) was given as a continuous intravenous infusion over the course of at least 90 min on day 1 with adequate hydration. Treatment with triplet therapy was continued for a maximum of 6 cycles. Subsequently, patients received a combination of docetaxel and S-1 until disease progression.

The doses of both S-1 and cisplatin were reduced in patients who had any of the following: a leukocyte count of less than $1.0 \times 10^3/\mu L$, a neutrophil count of less than $500/\mu L$, a platelet count of less than $2.5 \times 10^4/\mu L$, grade 3 or 4 febrile neutropenia, or grade 3 or 4 nonhematological toxicity except for nausea, vomiting, and anorexia, or if the

start or resumption of treatment had to be delayed for at least 8 days because of toxicity. The dose of S-1 was decreased in a stepwise fashion by up to 2 levels as follows: BSA <1.25 m^2, from 40 to 25 and 20 mg/dose; BSA ≥1.25 to <1.5 m^2, from 50 to 40 and 25 mg/dose; and BSA ≥1.5 m^2, from 60 to 50 and 40 mg/dose. In addition, the dose of cisplatin was decreased in a stepwise fashion by 10 mg/m^2 each, and treatment was continued. In patients who had a serum creatinine level of ≥2 mg/dL or grade 4 anorexia caused by cisplatin, only the dose of cisplatin was reduced. Treatment was discontinued in case of any of the following conditions: distinct evidence of disease progression; development of complications, treatment-related death, or septic shock; the patient refused to continue the study treatment or withdrew consent; postponement of the resumption of treatment for 2 or more weeks.

As supportive treatment for grade 4 neutropenia and grade 3 or 4 febrile neutropenia, granulocyte colony-stimulating factor (G-CSF) and antibiotics administration was used at the investigator's discretion. Prophylactic G-CSF was not allowed.

Toxicity assessment

Toxicity was evaluated according to the Common Terminology Criteria for Adverse Events (version 3.0). During protocol treatment, signs and symptoms, blood counts, liver function, renal function, and electrolytes were assessed once a week.

Response evaluation

Tumor responses to chemotherapy were evaluated according to the guideline of the Response Evaluation Criteria in Solid Tumors (RECIST). Responses were evaluated by computed tomography every 2 months. First, we evaluated in the 1st and 2nd courses, afterward every 2 courses. Radiographs of all evaluable patients were reviewed externally to confirm investigator-designated responses by the independent review committee. Downstaging was defined as the case deemed to be disappeared unresectable factor and to be resectable by computed tomography and magnetic resonance imaging. Progression-free survival was defined as the time from start of treatment to tumor progression or death for any causes that occurs by the end of the study. Patients with no confirmation of progression or death were censored at the date of the last objective tumor assessment. Overall survival was defined as the time from start of treatment to the date of death. If the death has not occurred, the survival time was censored on the last date the patient has known to be alive.

Statistical analysis

The primary endpoint of this study was the objective response rate. Secondary endpoints were safety, progression-free survival, and overall survival. Because the response rates with S-1 plus docetaxel were 46 and 56.3% in previously reported phase II studies [10, 11], we hypothesized that it would be worthwhile to pursue a phase III study if the response rate reached 55% in the present study. We therefore assumed an expected response rate of 55% and a threshold response rate of 30%, with 1-sided alpha error of 0.05 and a beta error of 0.1. The required number of patients was estimated to be 35. Forty patients were required with the inclusion of about 10% follow-up loss. An interim analysis was scheduled to be performed after the enrollment of 20 patients. If the number of patients with a complete or partial response was five or less, the protocol specified that the study was to be discontinued.

Results

Patient characteristics

From October 2006 through August 2008, 59 patients (47 men and 12 women) were enrolled in the study. Table 1 shows the demographic characteristics of the patients. The performance status was 0 in 40 patients, 1 in 18, and 2 in 1. The histological types were intestinal in 25 patients and diffuse in 34. The median number of successive treatment cycles per patient was 8 (6 for DCS therapy and 2 for docetaxel plus S-1; range, 1–25). An interim analysis was performed after 19 patients had been enrolled and confirmed that 15 patients had a partial response. When 19 patients were enrolled, 5 had grade 4 febrile neutropenia. Because it had been judged that examination by the data and safety monitoring board was necessary, an interim analysis was conducted in 19 patients. The criteria for early discontinuation of the study as specified by the protocol were thus not met, and enrollment was continued.

Treatment result

The total treatment cycle of DCS was 514, and the median treatment cycle was 8 (1–25). Dose reductions were required in 25 patients (42%), and relative dose intensities of S-1, docetaxel, and cisplatin were 94.8, 99.0, and 89.9%, respectively. Treatment had to be delayed by 8 or more days in 3 patients. There was one case of treatment discontinuation and drug-related death caused by the perforation

Table 1 Patient characteristics

Patients	*n* = 59
Age (range)	62 (35–75)
Gender M/F	47/12
PS 0/1/2	40/18/1
Metastatic/recurrence	49/10
Histological type	
Intestinal type	25
Diffuse type	34
Metastatic site	
Liver	33
Lymph node	46
Ovary	3
Lung	2
Peritoneum	17
Other	2
CDDP dose (mg)	
60/70	40/19

of the primary tumor. However, this patient refused surgery.

Adverse events

In this phase II study, the initially used dose of cisplatin was 70 mg/m^2, the recommended dose determined in our previous phase I study [9]. After 19 patients had been enrolled, 15 (79%) had grade 3 or higher neutropenia, and 5 (26%) had grade 1 renal dysfunction (elevated creatinine clearance). The dose of cisplatin was therefore reduced to 60 mg/m^2, and the study was continued. And again, the study was continued until the target number.

In the study group as a whole, the incidences of grade 3 or higher adverse events were as follows: leukocytopenia, 44%; neutropenia, 73%; anemia, 15%; febrile neutropenia, 14%; anorexia, 7%; nausea, 5%; vomiting, 3%; fatigue, 2%; and diarrhea, 5%. In patients given 60 mg/m^2 of cisplatin, the incidences of all toxic events were lower than those in patients given 70 mg/m^2 of cisplatin (Table 2). G-CSF and antibiotics were administered to patients who had grade 4 neutropenia and grade 3 or 4 febrile neutropenia ($n = 21$; 12 for CDDP 60 mg/m^2, and 9 for CDDP 70 mg/m^2).

Efficacy

In the study group as a whole, the response rate according to the dose of cisplatin was 79% (95% confidence interval, 61–97%) for 70 mg/m^2 and 83% (95% confidence interval, 71–94%) for 60 mg/m^2. Use of the lower dose of cisplatin thus did not negatively affect the response (Table 3). We could not evaluate one patient because of treatment-related death.

The median overall survival and median progression-free survival were 18.5 months (95% confidence interval (CI), 15.6–21.5) and 8.7 months (95% CI, 6.7–10.7), respectively, during a median follow-up period of 18.5 (95% CI, 0.4–42.3) months (Fig. 1a, b).

Table 2 Adverse events

	CDDP: 70 mg (*n* = 19)					CDDP: 60 mg (*n* = 40)					Overall (*n* = 59)				
	G1	G2	G3	G4	≥G3 (%)	G1	G2	G3	G4	≥G3 (%)	G1	G2	G3	G4	≥G3 (%)
Hematological toxicity															
Leukopenia	1	4	10	2	12 (63)	6	15	13	1	14 (35)	7	19	23	3	26 (44)
Neutropenia		2	7	8	15 (79)	4	7	15	13	28 (70)	4	9	22	21	43 (73)
Anemia	5	7	6		6 (32)	4	18	3		3 (8)	25	15	9		9 (15)
Thrombocytopenia	10	5				17	3				27	8			
Febrile neutropenia				5	5 (26)			3		3 (8)			8		8 (14)
Nonhematological toxicity															
AST/ALT	5	3	2		2 (11)	12	1		1	1 (3)	17	4	2	1	3 (5)
Cr	4	1				6					10	1			
Stomatitis	2					7	3				9	3			
Anorexia	10	5	2		2 (11)	26	10	2		2 (5)	36	15	4		4 (7)
Nausea	8	5	1		1 (5)	26	5	2		2 (5)	34	10	3		3 (5)
Vomiting	6	2	1		1 (5)	12	2	1		1 (3)	18	4	2		2 (3)
Fatigue	7	1				14	3	1		1 (3)	21	4	1		1 (2)
Diarrhea	4	1	1		1 (5)	4	5	2		2 (5)	8	6	3		3 (5)

n number of patients, *G1–G4* grades 1–4, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase

Table 3 Response rate

	n	CR	PR	SD	PD	NE	RR (%)
Overall	59	0	48	10	0	1	81
CDDP 60 mg	40	0	33	6	0	1	83
CDDP 70 mg	19	0	15	4	0	0	79
Liver	31	1	26	3	0	1	87
Lymph node	45	1	35	8	0	1	80
Others	6	1	2	3	0	0	50

CR complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *NE* not evaluable, *RR* response rate

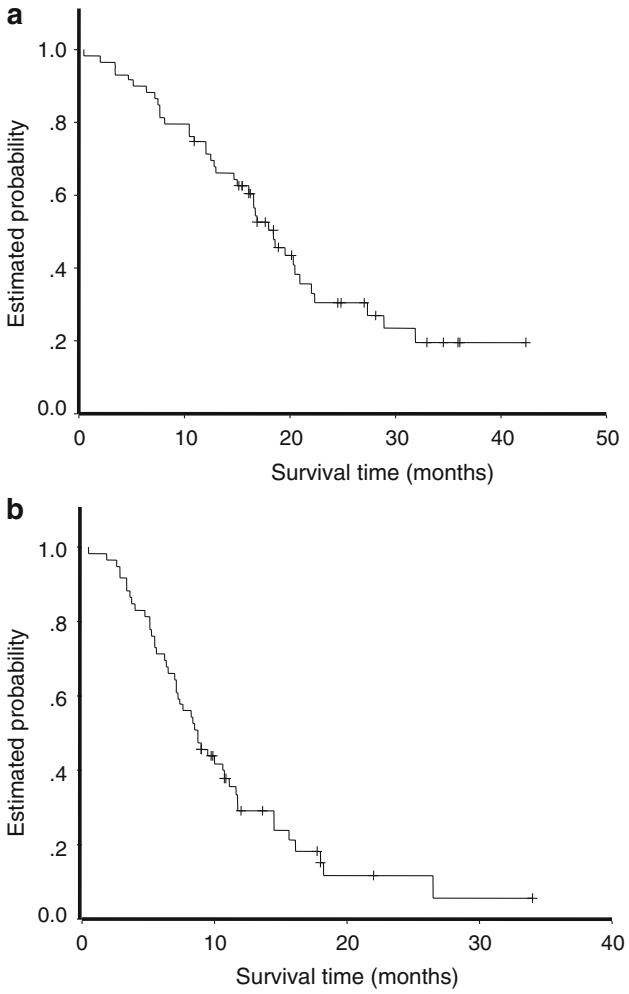

Fig. 1 Kaplan–Meier curves for **a** overall survival and **b** progression-free survival

Second-line treatment

Of the 46 patients who had disease progression during the study, 39 (85%) could receive second-line treatment. Thirty-four of these patients received irinotecan-based regimens (irinotecan alone in 19; irinotecan and cisplatin in 12; irinotecan, 5-fluorouracil, and *l*-leucovorin in 2; and irinotecan and mitomycin C in 1), 4 received S-1 (adjuvant chemotherapy after surgery in 2; modification because of toxicity in 2), and 1 received methotrexate plus 5-fluorouracil.

Discussion

We conducted this phase II study to investigate the efficacy and safety of triplet regimen with DCS in patients with unresectable advanced or recurrent gastric cancer. The response rate was 81%, and the disease control rate was 98%. The median overall survival and progression-free survival were 18.5 and 8.7 months, respectively. Our regimen was effective and feasible as a first-line treatment of advanced or recurrent gastric cancer.

In 2007, the SPIRITS trial demonstrated the superiority of S-1 plus cisplatin regimen as compared with S-1 alone, with a response rate of 53% and a median survival time of 13 months [6]. In Japan, S-1 plus cisplatin is recognized as a standard treatment. On the other hand, doublet regimens combining S-1 with drugs other than cisplatin have been studied extensively. With a combination of S-1 and docetaxel, Yoshida et al. [10] obtained a response rate of 56.3% with overall survival of 14.3 months, and Yamaguchi et al. [11] reported a response rate of 46% with overall survival of 14 months in phase II studies. These results were similar to those obtained with S-1 plus cisplatin. Because of its high antitumor activity and good tolerance, S-1 plus docetaxel is expected to be used as first-line treatment. At present, the START trial, a multicenter, collaborative, phase III study designed to validate the superiority of a combination of S-1 plus docetaxel over S-1 alone (used as a control) in terms of therapeutic usefulness, is ongoing in a Japan–Korea collaborated trial [12].

Van Cutsem et al. [8] conducted a phase III controlled study (V 325) to compare 5-fluorouracil plus cisplatin with DCF therapy as first-line treatment in patients with unresectable advanced gastric cancer. DCF therapy was associated with significantly better outcomes than 5-fluorouracil plus cisplatin, demonstrating that triplet therapy was more effective. As mentioned above, S-1 is a widely used as a key drug for the treatment of gastric cancer in Japan. Since TS-1 was blended gimeracil which was DPD inhibitor, in diffuse type which DPD had high expression, TS-1 was shown higher effectiveness when compared to 5-FU. Moreover, in JCOG9912, the tendency with S-1 better than 5-FU is looked in OS by the track result. Also, in the FLAGS carried out by global study, S-1 was shown better result in diffuse type when compared to 5-FU. So, we believed that antitumor effectiveness would be enhanced by substituting S-1 for 5-fluorouracil in DCF and therefore planned phase I and II clinical trials of triplet therapy with DCS.

Table 4 Adverse events (first 2 courses)

	CDDP: 70 mg (n = 19)					CDDP: 60 mg (n = 40)					Overall (n = 59)				
	G1	G2	G3	G4	>G3 (%)	G1	G2	G3	G4	>G3 (%)	G1	G2	G3	G4	>G3 (%)
Hematological toxicity															
Leukopenia	2	4	7	1	8 (42)	9	11	4	1	5 (13)	11	15	11	2	13 (22)
Neutropenia		5	7	3	10 (53)	8	8	11	3	14 (35)	8	13	18	6	24 (41)
Anemia	3	9	2		2 (11)	10	3	1		1 (3)	13	12	3		3 (5)
Thrombocytopenia	9	1				7	2				16	3			
Febrile neutropenia			4		4 (21)								4		4 (7)
Nonhematological toxicity															
AST/ALT	3	2	2		2 (11)	8			1	1 (3)	11	2	2	1	3 (5)
Cr	3					4					7				
Stomatitis	1					6	2				7	2			
Anorexia	7	5	2		2 (11)	26	7	1		1 (3)	33	12	3		3 (5)
Nausea	6	5	1		1 (5)	19	5	2		2 (5)	25	10	3		3 (5)
Vomiting	4	1	1		1 (5)	8	2	1		1 (3)	12	3	2		2 (3)
Fatigue	6	1				13	3				19	4			
Diarrhea	2	1	1		1 (5)	2	2	2		2 (5)	4	3	3		3 (5)

n number of patients, *G1–G4* grades 1–4, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase

In a phase I study designed to evaluate the optimal dose and dose-limiting toxicity of DCS therapy, the recommended dose of cisplatin was determined to be 70 mg/m^2 [9]. This dose was used in the present phase II study. During the study, an interim analysis was performed according to the protocol to assess the safety and efficacy of DCS therapy. Grade 1 or higher renal dysfunction occurred in 26% of the patients, and grade 3 or higher neutropenia occurred in 79%. The dose of cisplatin was therefore reduced to 60 mg/m^2. This lower dose of cisplatin was associated with a trend toward less toxicity, with no change in the response rate. We therefore consider 60 mg/m^2 of cisplatin to be a reasonable dose for future studies. Although caution is required when comparing the results of different studies, DCS regimen in the present study expected to be more effective than S-1 plus cisplatin in the SPIRITS study.

There are also limitations when comparing our results with those of a previous phase III study, but the V325 study reported that DCF had a response rate of 38.7%, a median progression-free survival of 5.2 months, and a median survival time of 10.2 months. As compared with these results, DCS was promising regimen. DCF was also associated with many serious adverse events, such as neutropenia (82%) and leukopenia (65%), indicating some problems in tolerability. With our DCS regimen, main serious adverse events were also neutropenia (73%) and febrile neutropenia (14%). These toxicities did not lead to discontinuation of treatment due to G-CSF administration and dose reduction of CDDP and S-1. Now phase II study of 2 courses of DCS as neoadjuvant setting for operable gastric cancer with extensive lymph node metastasis is planned by JCOG. Focusing on the first 2 courses with toxicity, DCS was more feasible (Table 4).

A phase II study of triplet regimen of docetaxel, CDDP, and S-1 has also been performed by Sato et al. S-1 was administered orally twice daily on days 1–14 at a dose calculated according to the patient's body surface area as follows: <1.25 m^2, 40 mg; 1.25–1.5 m^2, 50 mg; and >1.5 m^2, 60 mg. CDDP was administered, followed by docetaxel at 60 mg/m^2 on day 8. Cycles were repeated every 3 weeks. They reported a response rate of 87.1% and a disease control rate of 100%. The median overall survival and progression-free survival were 687 days and 226 days, respectively [13]. Although the treatment regimen differed from ours, their DCS regimen was also shown to be effective, consistent with the results of our study. We believe that the high effectiveness of these triplet regimens is reproducible. Both DCS regimens indicated not only high response rate and long PFS but also long OS over 18 months. However, this longer OS is interpreted with caution. According to the NCDB data, prognosis in early stage in Asian race is longer than in other races, but that of Stage IV is similar in Asian and other races [14]. Otherwise, in several trials, overall survival in Japanese trials is longer than those in multinational trials. We speculate that high percentage of patients received second line in Japan might contribute to prolonged survival. And in this study, it may be related to the cases had taken surgery because of the high response rate.

In conclusion, DCS is a regimen that is expected to be highly effective with manageable toxicities. To confirm the therapeutic usefulness of DCS for the first-line treatment of advanced or recurrent gastric cancer, we are also now planning a multicenter, phase III clinical trial comparing with cisplatin plus S-1 as reference arm, currently a standard treatment in Japan.

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Conflict of interest None.

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