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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

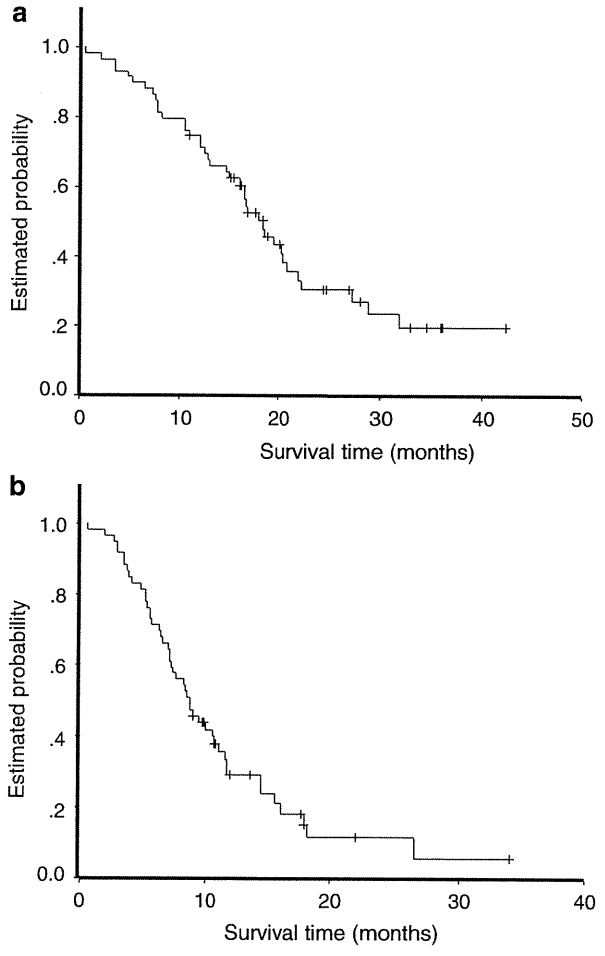

Fig. 1 Kaplan–Meier curves for **a** overall survival and **b** progression-free survival

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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EDITORIAL

Irinotecan is inactive as a first-line treatment, but plays an important part in gastric cancer treatment

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Based on the results of the GC0301/TOP002 (S-1 versus irinotecan plus S-1) randomized control study, which were reported in this journal–*Gastric Cancer* [1]–can we conclude that irinotecan is not important in gastric cancer treatment? Currently, the answer to this question may be "yes", because irinotecan-based regimens did not meet any primary endpoint as a first-line treatment in three randomized control studies, including the GC0301/TOP002 study [1–3]. When these clinical studies were planned, standard treatment in the field of gastric cancer was absent; there was no appropriate, universal control. At that time, the National Comprehensive Cancer Network proposed 5-fluorouracil (FU)-based or cisplatin-based combinations as acceptable standard therapy. 5-FU alone or S-1 (an oral fluoropyrimidine) was standard therapy in Japan, but 5-FU plus cisplatin (CF) was also used frequently. CF was frequently employed in Korea, Japan, many South American countries, and many European countries. Epirubicin plus CF (ECF) was considered the standard in a few European countries and possibly in Canada. Thus, a 5-FU-based or cisplatin-based combination was an appropriate control in the West and, for that matter, in most of the world. Based on this background, the control arms varied among studies. Three randomized control studies (1 in Europe/the United States, 2 in Japan) were conducted to verify the efficacy of irinotecan-based regimens as a first-line treatment.

A study in Europe and the United States was first reported. In these countries, irinotecan was emphasized as a new active agent for gastric cancer. This study was planned as a phase II/III trial [1]. In the phase II part, irinotecan combined with an infusional 5-FU Arbeitsgemeinschaft Internistische Onkologie (AIO) regimen [irinotecan/5-FU (IF)] was selected over irinotecan combined with cisplatin on the basis of the risk/benefit ratio. At the time, the IF regimen was considered to be the most active irinotecan-based regimen available in the West. In the phase III part, the usefulness of IF in comparison with CF was examined with respect to the time to progression (TTP) as a primary endpoint. When reviewing the antitumor effects of IF and CF in this study, the response rates (RRs) were 31.8 and 25.8%, respectively. The TTP was 5.0 and 4.2 months, respectively. The median survival time (MST) was 9.0 and 8.7 months, respectively. The toxicity profile of IF was also markedly more favorable than that of CF. However, with respect to the primary endpoint, TTP, the usefulness of IF in comparison with CF could not be demonstrated. In the protocol, it was also impossible to verify the non-inferiority of IF. Based on the results of this study, IF may not become a standard regimen for first-line treatment; the first study was unsuccessful in the West.

Combination therapy with irinotecan and cisplatin (IC) was initially investigated as a first-line treatment in the JCOG9912 study, which was conducted by the Japan Clinical Oncology Group (JCOG); in this study, the usefulness of combination therapy with IC in comparison with the continuous intravenous infusion of 5-FU (5-FUci) was examined [2]. The RR and time to treatment failure (TTF) were significantly more favorable with IC. However, with respect to the primary endpoint, overall survival (OS), the usefulness of combination therapy with IC in comparison with 5-FUci was not demonstrated to be statistically significant ($p = 0.055$). Clinical studies not only in Europe and the United States but also in Japan failed to propose combination therapy with IC as a standard treatment. When reviewing the survival curve for this combination therapy

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in the JCOG study, the curve within 1 year was markedly more favorable than that for 5-FUci. However, the curve crossed with that for S-1, which was shown to be as effective as 5-FUci, and finally overlapped the survival curve for 5-FUci. On the other hand, the survival curve for S-1 was superior to that for 5-FUci, showing a favorable survival curve. In addition, with respect to prolonged survival, this curve exceeded that for combination therapy with IC. This aspect is important for evaluating the role of irinotecan for gastric cancer treatment.

Based on the results of the JCOG9912 study, single-agent therapy with S-1 has been introduced as a standard regimen in Japan. In a randomized control study reported in this journal, the efficacy of combination therapy with irinotecan and S-1 (IRIS) was investigated [1]. The response rates for S-1 alone and IRIS were 26.9 and 41.5%, respectively, showing a significant difference ($p = 0.035$). Concerning the toxicity, the incidence of Grade 3 or higher adverse reactions after IRIS administration was slightly higher than that after the administration of S-1 alone. However, the adverse reactions were tolerable. The TTF for S-1 alone and IRIS was 3.6 and 4.5 months, respectively; there was no significant difference ($p = 0.157$). With respect to the primary endpoint in this study, OS, the MST on the predetermined cut-off date in the IRIS and S-1 monotherapy groups was 12.8 and 10.5 months, respectively (hazard ratio [HR]: 0.856; $p = 0.223$), showing no significant difference. The 1-year survival rates were 52.0 and 44.9%, respectively, showing an approximately 7% difference. However, the 2-year survival rates were 18.0 and 19.5%, respectively; there was no significant difference between the two arms. After 18 months of treatment, the survival curves for the two therapies overlapped. The results of this study were consistent with those of the JCOG9912 study. On the other hand, the SPIRITS study indicated that the OS in patients treated with cisplatin plus S-1 was significantly longer than that in those treated with S-1 alone [4]. Differences between cisplatin and irinotecan as first-line treatment must be reviewed.

Second-line and subsequent treatment has been important for examining the prolongation of survival in patients with gastric cancer in recently reported clinical studies. In Japan, second-line and subsequent treatment is fully covered by health insurance, differing from the health insurance coverage in Europe and the United States. Recently, second-line treatment has been performed in approximately 80% of the subjects of clinical studies in Japan [1, 3, 4]. In the JCOG9205 study, which was conducted prior to the JCOG9912 study, 5-FUci was also employed as a control arm [5]. This regimen, which was common between the two studies, prolonged the MST by 3.7 months (range 7.1–10.8 months) in the JCOG9912 study. This was possibly because the proportion of patients in whom second-line treatment was introduced had increased [6]. In addition, another factor was an increase in the number of agents that may be active for gastric cancer treatment. Currently, four agents and agent classes, fluoropyrimidine, cisplatin, taxane, and irinotecan, are considered to be effective for the treatment of gastric cancer. Of these, cisplatin is appropriate for combination therapy in first-line treatment, for the following reasons: monotherapy with cisplatin is not effective, and its toxicity is greater than moderate. On the other hand, taxane and irinotecan are commonly used as single agents for second-line and subsequent treatment in Japan [3, 4]. The results of the AIO study comparing the best supportive care with irinotecan alone in second-line treatment, which was reported at the American Society of Clinical Oncology (ASCO) 2009 annual meeting, suggested the usefulness of irinotecan in second-line treatment for gastric cancer [7]. We must review why negative results were obtained in 3 studies in which irinotecan was verified for first-line treatment. We should remember the fact that an irinotecan-based regimen did not show any favorable survival curve with respect to long-term survival. This suggests that, when employing irinotecan as a first-line agent, a second-line or subsequent treatment option is lost. This is the most important difference between cisplatin and irinotecan. The potential benefit of irinotecan-based regimens has been further explored in the past few years, especially with the availability of new targeted agents. To apply irinotecan as a first-line agent in the future, combination therapy with new targeted agents should be performed.

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REVIEW ARTICLE

Second-line chemotherapy for gastric cancer: a new issue lies ahead in global trials

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Abstract Chemotherapy for gastric cancer has been advancing fairly well. It has been indicated that not only advances in first-line chemotherapy but also those in second-line chemotherapy have contributed to the prolongation of overall survival. The Arbeitsgemeinschaft Internistische Onkologie (AIO) study supports the idea that second-line chemotherapy is appropriate in patients with a good general condition. Also, the Japan Clinical Oncology Group (JCOG) integral analysis suggests that advances have been made in second-line chemotherapy. However, most recently reported studies of second-line chemotherapy have been conducted as small-scale phase II or retrospective trials. No randomized control trial to establish standard treatment has been reported. Which regimen is the most appropriate as second-line therapy must be investigated in the future. Currently, molecularly targeted agents for gastric cancer are being developed and tested in global trials. As a new issue in global trials, second-line chemotherapy has been emphasized. In recent global trials, subset analysis showed regional differences in overall survival. This was possibly associated with the regional differences in second-line chemotherapy. When developing new molecularly targeted agents for first-line chemotherapy, we cannot ignore the result that the proportion of patients in whom treatment was switched to second-line chemotherapy was high in Asia. In planning a global trial, this new issue should be sufficiently discussed.

Keywords Gastric cancer · Second-line chemotherapy · Global trial · Molecularly targeted agent

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Introduction

Gastric cancer is frequent in Asia, South America, and Eastern Europe, accounting for more than 800,000 new cases per year worldwide, and it is the second most common cause of cancer death [1]. Because early detection strategies are rarely practiced, except in Japan and Korea, most patients will present with advanced-stage disease, and will therefore need palliative chemotherapy. Some chemotherapy regimens have been established as first-line therapy, and some progress has been made in the treatment of advanced-stage disease [2–12]. However, almost all patients with metastatic gastric cancer will develop progressive disease (PD) after first-line therapy. With the availability of several active chemotherapy drugs, many patients who retain a good performance status after the initial treatment remain good candidates for additional therapy.

However, most clinical studies of second-line chemotherapy have been conducted as phase II, small-scale trials. The data obtained are limited, and there is no standard second-line chemotherapy. In this review, differing from previous reviews of second-line chemotherapy [13, 14], I have clarified the significance of second-line chemotherapy based on the recently reported results of randomized control trials of first-line chemotherapy. On the other hand, I refer to the concept of second-line chemotherapy as a potentially confounding factor in recent global trials.

Evidence for second-line chemotherapy

Chemotherapy for advanced/recurrent gastric cancer has been advancing fairly well. As evidence, the median survival in recent randomized comparative studies involving

patients with advanced/recurrent gastric cancer was markedly longer than that in previous studies [2–12]. It was indicated that not only advances in first-line chemotherapy but also advances in second-line chemotherapy contributed to the prolongation of survival. However, no phase III study has verified the significance of second-line chemotherapy. The results of the Arbeitsgemeinschaft Internistische Onkologie (AIO) comparative study suggest its significance; this study was reported at the 2009 annual meeting of the American Society of Clinical Oncology (ASCO) [15]. In this study, patients in whom first-line therapy led to progressive disease were divided into 2 groups: best supportive care (BSC) and irinotecan groups, to evaluate the usefulness of irinotecan in second-line therapy. In regard to the statistical background, 60 patients per group (2 groups: 120 patients) were required, assuming that irinotecan administration may prolong the median survival time (MST) from 2.5 to 4 months, with an α error (paired) of 5% and a detection power of 80%. However, case registration was insufficient, and the clinical study was completed when 40 patients were enrolled in each of the two groups. The results of analysis were reported. In the irinotecan group, the response rate was 0%. However, the stable disease rate was 58%, and improvement of tumor-related symptoms was achieved in 44% of the patients. In addition, the MSTs in the irinotecan and BSC groups were 123 and 76 days, respectively. Statistically, the overall survival (OS) was longer in the irinotecan group ($p = 0.0027$). These results support the idea that second-line chemotherapy is appropriate in patients with a good general condition. However, which regimen is the most appropriate as second-line therapy must be investigated in the future.

Significance of second-line chemotherapy with respect to randomized comparative studies in Japan

The JCOG 9205 study was started by the Japan Clinical Oncology Group (JCOG) in 1992. Initially, 3 groups, 5-fluorouracil (5-FU), 5-FU + cisplatin, and uracil and tegafur (UFT) + mitomycin C (MMC) groups, were compared [4]. However, the mid-analysis results suggested that UFT + MMC therapy may be less potent than 5-FU therapy. After mid-analysis, the UFT + MMC group was excluded from the subject cohort. Finally, in this study, the results were compared between the 5-FU and 5-FU + cisplatin groups. The OS in the 5-FU + cisplatin group did not exceed that in the 5-FU group. The MST for monotherapy with 5-FU was 7.1 months, and the median progression-free survival (PFS) was 1.9 months. In the JCOG 9912 study, which was conducted subsequently, monotherapy with 5-FU was additionally employed as a control regimen [10]. The MST for monotherapy with 5-FU was 10.8 months, and the median PFS was 2.9 months. Survival data regarding monotherapy with 5-FU, involving different time-related background factors, were obtained in the two randomized comparative studies conducted by the same clinical study group (Table 1). The JCOG performed integral analysis regarding the two studies, focusing on second-line chemotherapy, and reported the results at the ASCO 2010 meeting [16]. To harmonize the inclusion criteria in the two studies, patients with intestinal stenosis in the JCOG 9205 study and those with adjuvant chemotherapy in the JCOG 9912 study were excluded. Overall survival, time to treatment failure (TTF), and OS minus TTF (OS−TTF) were compared after adjusting for baseline factors using the Cox proportional hazard model. Interestingly, the MST after second-line therapy in the 5-FU group was longer in the JCOG 9912 study.

There are two reasons for the above finding: firstly, the number of effective agents available for second-line therapy in the JCOG 9912 study was larger than the number available at the time of the JCOG 9205 study. In the JCOG 9205 study, early-generation drugs such as cisplatin and MMC were used for second-line therapy. On the other hand, in the JCOG 9912 study, newer drugs such as a taxane and irinotecan were primarily employed for second-line therapy; irinotecan- or taxane-containing regimens were selected in 9% (8/94) of the subjects in the JCOG 9205 study and in 67% (157/233) in the JCOG 9912 study. The difference in treatment options for second-line chemotherapy may have contributed to an MST difference of 3.7 months. On the other hand, the proportion of patients in the 5-FU group in whom treatment was switched to second-line chemotherapy should be compared between the two studies. In approximately 52% of patients receiving 5-FU alone in the JCOG 9205 study, treatment was switched to second-line chemotherapy. In the JCOG 9912 study, the percentage was approximately 83%, showing a 31% increase. This difference may also have led to the MST difference of 3.7 months. Even after adjusting for baseline factors, TTF was similar in the two studies; however, both OS and OS-TTF were longer in the JCOG 9912 study than in the JCOG 9205 study. It was concluded

Table 1 Differences of efficacy profiles and second-line treatment in the 5-fluorouracil arms between the JCOG 9205 and JCOG 9912 trials

	ORR (%)	PFS (months)	MST (months)	Second-line treatment (%)
JCOG 9205 trial [4]	9	1.9	7.1	52
JCOG 9912 trial [10]	11	2.9	10.8	83

JCOG Japan Clinical Oncology Group, *ORR* overall response rate, *PFS* progression-free survival, *MST* median survival time

that survival after treatment failure of 5-FU alone was longer in the JCOG 9912 study even when some potential confounding factors were adjusted for. The results of this combined analysis suggest that advances have been made in second-line chemotherapy and support the use of second-line chemotherapy for gastric cancer. Physicians likely play a key role in whether or not patients receive second-line chemotherapy. Unfortunately, we currently have little evidence to guide treatment. I recommend that patients and physicians earnestly discuss the risks and benefits of second-line chemotherapy using the current best evidence on tolerability and effectiveness.

Regional differences in second-line chemotherapy and new issues in global trials

Trials of the same regimen, S-1 plus cisplatin, were conducted in Japan and other countries. When comparing the SPIRITS trial (S-1 vs. S-1 plus cisplatin), which was carried out in Japan, with the FLAGS trial (5-FU plus cisplatin vs. S-1 plus cisplatin), which was conducted as a global study, there was a regional difference in second-line chemotherapy; there was a marked difference in the proportion of patients in whom treatment was switched to second-line chemotherapy between the two trials [9, 11]. The proportion of patients in whom treatment was switched to second-line chemotherapy was 73% in the SPIRITS study in Japan, whereas it was only 31% in the FLAGS trial. Such a low percentage was also common in other recently reported global studies. The second-line chemotherapy rates ranged from 70 to 83% in studies conducted in Japan, including the JCOG 9912 study [10–12], whereas the rate was only 15% in the REAL-2 trial involving the United Kingdom [7]. As a background factor, we must consider that the insurance coverage systems in Japan and other countries differ markedly. In particular, health insurance in the United Kingdom does not cover second-line chemotherapy; therefore, first-line chemotherapy is very important. The median survival in a phase III study recently reported in Japan was 2–3 months longer than that reported in Europe and the United States [7–12]. This finding may be associated with the difference in the proportion of patients in whom treatment was switched to second-line chemotherapy.

Currently, molecularly targeted agents for gastric cancer are being developed primarily in Japan and Korea and are being tested in global trials. As a new issue in these global trials, second-line chemotherapy has been emphasized. The ToGA study, in which Japanese and Korean patients accounted for more than 50% of the subjects, investigated the efficacy of first-line chemotherapy with trastuzumab in human epidermal growth factor receptor 2 (HER2)-positive advanced gastric cancer patients; 584 patients meeting eligibility criteria were randomly assigned to receive 5-FU or capecitabine + cisplatin (FC group: $n = 290$), or 5-FU or capecitabine + cisplatin + trastuzumab (FC + T group: $n = 294$) therapies. The median survival in the FC + T group (13.8 months) was significantly longer than that in the FC group (11.1 months) ($p = 0.0046$), suggesting the usefulness of trastuzumab in HER2-positive gastric cancer patients [17]. In this study, subset analysis showed regional differences in survival; trastuzumab did not influence survival in Asia, but markedly influenced survival in South America. This finding was possibly related to regional differences in second-line chemotherapy, as described above. Approximately 50% of the subjects consisted of Korean and Japanese patients. In these two countries, second-line chemotherapy is positively performed in clinical practice. On the other hand, in South America, second-line chemotherapy is rarely performed. Therefore, the influence of first-line chemotherapy; that is, that of trastuzumab, may have been more marked in South America.

Similarly, in the AVAGAST trial reported at the ASCO 2010 meeting, there were also differences in the proportions of patients in whom treatment was switched to second-line chemotherapy [18]. In that study, there was no influence of bevacizumab on survival in Asia, similar to the lack of influence of trastuzumab in the ToGA trial. In Pan-America, bevacizumab markedly influenced survival. This finding was possibly associated with regional differences in second-line chemotherapy (Table 2). In Asia, the proportion of patients in whom treatment was switched to second-line chemotherapy was high, 66%, whereas the values were 31 and 21% in Europe and Pan-America involving South America, respectively. Briefly, the influence of first-line chemotherapy on survival may be very marked in areas other than Asia. However, when many Japanese/Korean patients are registered, survival after second-line chemotherapy may be prolonged; therefore, there may be no significant difference in the OS. In the future, when developing molecularly targeted agents for first-line chemotherapy, we cannot ignore that there are regional differences in second-line chemotherapy. In planning global trials in the future, this issue should be sufficiently discussed.

Table 2 Proportions of patients receiving second-line chemotherapy by region in the AVAGAST trial [18]

Region	Patients entered (n)	Patients receiving second-line treatment (n)	%
Asia	376	248	66
Europe	249	78	31
Pan-America	149	32	21

Present status and future directions of second-line chemotherapy

Most recently reported studies of second-line chemotherapy consist of small-scale phase II or retrospective trials [19–33]. No randomized control trial to establish standard treatment has been conducted. In clinical practice, irinotecan, docetaxel, or paclitaxel is selected in most patients. However, the effects of monotherapy are limited [20–25]. Various combination therapies have been investigated in small-scale, phase II studies [26–33]. However, according to the results of some recent studies, the response rates ranged from approximately 10 to 20%, and PFS ranged from 2.5 to 4.0 months. There may be no marked differences among these combination therapies (Table 3). One study reported a median survival of 12 months. However, this may have depended on patient selection. As of now, that is all the information we can share. At the time of this writing, I think monotherapy is a reasonable option as a second-line treatment, and combination strategies should be used as a fall-back position. In Japan, weekly paclitaxel is widely used as the second-line chemotherapy in daily clinical practice. On the other hand, the AIO comparative study supported the use of irinotecan for second-line chemotherapy [15]. Much debate has focused on whether irinotecan or weekly paclitaxel is the better second-line agent. Among randomized control trials of second-line chemotherapy that are being conducted, "a randomized phase III study of irinotecan versus weekly paclitaxel in unresectable or recurrent gastric cancer refractory to combination therapy of fluorouracil plus platinum (WJOG 4007G)", has been carried out by the West Japan Oncology Group (WJOG). In this study, the primary endpoint was overall survival. Secondary endpoints were PFS, adverse events, and the response rate in patients with target lesions. The sample size was 220 in total, which allowed for the detection of irinotecan superiority over weekly paclitaxel in terms of OS. Final analysis will be performed in 2011. These study results are very important. It should be clarified which of the two agents, irinotecan or paclitaxel, is appropriate as a biologic, platform agent for second-line chemotherapy, and whether the effects of the two agents are similar.

Currently, several second-line or subsequent molecularly targeted agents are being developed and tested in global studies (Table 4). A randomized control trial of lapatinib involving HER2-positive gastric cancer patients (TYTAN trial) is being conducted (weekly paclitaxel vs. weekly paclitaxel + lapatinib). Furthermore, a randomized control trial of a mammalian target of rapamycin (mTOR) inhibitor, everolimus, for BSC is being performed in patients receiving second- and third-line therapies (GRANITE-1 trial) [34]. For new drug development, global trials are also necessary in the future. However, in randomized control trials in which OS is established as the primary endpoint of first-line chemotherapy, it is difficult to detect a difference unless molecularly targeted agents with a clear target, such as trastuzumab, are employed; this difficulty arises because there are regional differences in second-line chemotherapy. In particular, Japan and Korea,

Table 3 Efficacy profiles of combination chemotherapy in the second-line setting

Regimen	ORR (%)	PFS (months)	MST (months)	Reference number
Paclitaxel/doxifluridine	18.2	4.0	10.7	[26]
Paclitaxel/capecitabine	34.6	4.5	7.5	[27]
Docetaxel/doxifluridine	18.8	2.6	12.7	[28]
Docetaxel/irinotecan	20.4	2.7	8.9	[29]
Docetaxel/oxaliplatin	10.5	4.0	8.1	[30]
Irinotecan/5-fluorouracil	18.2	2.3	5.1	[31]
Irinotecan/capecitabine	17.0	3.1	6.5	[32]
Methotrexate/5-fluorouracil	9.0	NE	7.9	[33]

ORR overall response rate, *PFS* progression-free survival, *MST* median survival time, *NE* not evaluated

Table 4 Phase III studies of targeted agents for second-line treatment in advanced gastric cancer

Agent	Target	Chemotherapy partner	*N*	Endpoint	Status
Lapatinib	HER2 EGFR	Paclitaxel	260	OS	Ongoing
Ramucirumab	VEGFR-2	Paclitaxel	663	OS	Ongoing
Everolimus	mTOR	None	442	OS	Ongoing

OS overall survival, *mTOR* mammalian target of rapamycin, *HER2* human epidermal growth factor receptor 2, *EGFR* epidermal growth factor receptor, *VEGFR-2* vascular endothelial growth factor receptor 2

where second-line chemotherapy is actively performed, play a principal role in registration. For the future development of molecularly targeted agents, it might be necessary to discuss the adoption of PFS as the primary endpoint.

Conclusions

At this time, no standard second-line chemotherapy has clearly emerged in gastric cancer treatment, and none of the new molecularly targeted agents under investigation has been identified as being appreciably useful for second-line-chemotherapy. Given the lack of solid evidence, it is too early to know whether a number of novel regimens will ultimately achieve traction as useful standard second-line chemotherapies. New evidence and new drugs are needed to make the necessary further improvements in the management of gastric cancer. In global trials, however, we have learned of the difficulties in selecting survival benefit as the primary endpoint, with these difficulties arising because of the regional differences in the management of this disease. In planning global trials, this new issue should be sufficiently discussed.

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ORIGINAL ARTICLE

A phase II study of biweekly mitomycin C and irinotecan combination therapy in patients with fluoropyrimidine-resistant advanced gastric cancer: a report from the Gastrointestinal Oncology Group of the Japan Clinical Oncology Group (JCOG0109-DI Trial)

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Abstract
Background Preclinical studies have shown that mitomycin C (MMC) acts synergistically with irinotecan (CPT-11). In this phase II study, we evaluated the efficacy and toxicity of MMC/CPT-11 therapy as second-line chemotherapy for patients with fluoropyrimidine-resistant advanced gastric cancer.
Methods Eligible patients had evidence of tumor progression despite prior treatment with fluoropyrimidine-based regimens or had relapsed within 6 months after completion of therapy with adjuvant fluoropyrimidines. Treatment consisted of MMC (5 mg/m^2) and CPT-11 (150 mg/m^2) administered i.v. every 2 weeks. The primary endpoint was the response rate (RR). Our hypothesis was that this combination therapy was efficacious when the lower boundary of the 95% confidence interval (CI) of the RR exceeded 20% of the threshold RR.

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Results Between April 2002 and July 2003, 45 eligible patients were registered and analyzed. Among the 45 patients, 40 (89%) had previously received chemotherapy for metastasis and 24 (53%) had a performance status (PS) of 0. Thirteen partial responses were obtained among the 45 patients, resulting in an overall RR of 29% (95% CI, 16–42%). The median time to progression was 4.1 months, and the median survival time was 10 months, with a 1-year survival rate of 36%. Grade 4 neutropenia was observed in 29% of the patients, whereas febrile neutropenia occurred in 9%. The incidence rates of grade 3 nausea and diarrhea were 13 and 2%, respectively.

Conclusions Although this study did not achieve the per-protocol definition of activity, the progression-free survival and overall survival appeared to be promising, with acceptable tolerability. Thus, MMC/CPT-11 therapy as second-line chemotherapy for fluoropyrimidine-resistant advanced gastric cancer presents a potential treatment option in patients with a good PS.

Keywords Gastric cancer · Mitomycin-C · Irinotecan · Fluoropyrimidine-resistant · Second-line chemotherapy

Introduction

Gastric cancer is the most common malignancy in Asian countries, with approximately 50,000 deaths in Japan annually [1]. The treatment of choice for this malignancy is primary tumor resection. In patients with curatively resected stage I–III gastric cancer, the 5-year survival proportion is >50%; however, this proportion remains at <10% in stage IV or recurrent disease. Randomized trials have demonstrated that fluorouracil-based regimens improve survival proportions in patients with advanced gastric cancer (AGC) compared with best supportive care (BSC) alone as first-line chemotherapy [2–4]. Moreover, combination chemotherapy results in superior outcomes compared with monotherapy. In Japan, the efficacy and toxicity of the combination of an oral fluoropyrimidine (S-1) and platinum was previously evaluated in the phase III SPIRITS (S-1 plus cisplatin vs. S-1 alone for first-line treatment of AGC) trial. S-1 plus cisplatin resulted in superior overall survival (OS) compared with S-1 alone [hazard ratio (HR), 0.77; 95% confidence interval (CI), 0.61–0.98%; $P = 0.04$], with an impressive median OS of 13.0 months [5]. The Japan Clinical Oncology Group (JCOG) 9912 trial (5-fluorouracil [FU] alone vs. S-1 alone vs. irinotecan [CPT-11] plus cisplatin [CDDP] combination for the first-line treatment of AGC) was also conducted in Japan. S-1 showed significant noninferiority for progression-free survival (PFS) and OS compared with 5-FU alone; however, CPT-11 plus CDDP showed no significant superior effects on PFS and OS compared with 5-FU alone [6]. In Japan, S-1 plus CDDP combination therapy is considered the standard first-line treatment for AGC.

Thuss-Patience et al. [7] reported at the 2009 Annual Meeting of the American Society of Clinical Oncology (ASCO) that CPT-11 monotherapy significantly prolonged OS compared with BSC as second-line chemotherapy. Although that report was the first randomized phase III study investigating second-line chemotherapy for AGC, no objective responses were observed. Thus, a consensus regarding the standard regimen for second-line chemotherapy has not yet been obtained.

Many AGC patients who failed to respond to first-line chemotherapy showed symptoms of pain, weight loss, or nausea due to their progressive disease. Thus, the induction of a tumor response is as important as delaying tumor progression for as long as possible. Patients who received combination chemotherapy showed higher response rates than those who received single-agent chemotherapy alone. Therefore, combination chemotherapy is preferable to single-agent chemotherapy for palliation. Moreover, combination chemotherapy may prolong OS compared with single-agent chemotherapy alone.

CPT-11 is a potent topoisomerase I inhibitor and is effective against AGC. In a phase II trial, the response rate (RR) to CPT-11 alone was 16% in previously treated AGC patients [8]. The administration of a CDDP and CPT-11 combination in AGC patients resulted in a higher RR and longer time to progression (TTP) [9–11]. As mentioned above, CDDP/CPT-11 did not significantly prolong OS over 5-FU, but induced a significantly higher RR than 5-FU in the JCOG9912 trial [6]. A 5-FU, leucovorin (LV), and CPT-11 combination produced a higher RR and longer TTP than CDDP/CPT-11 in AGC patients [12]. In another randomized phase III trial, 5-FU/LV/CPT-11 showed a trend to have superiority in TTP over CDDP/5-FU (5.0 vs. 4.2 months, respectively; HR, 1.23; 95% CI, 0.97–1.57%; $P = 0.088$), and a better safety profile [13]. These results support the finding that CPT-11 is active against AGC.

Mitomycin C (MMC) is also effective against AGC. Preclinical studies have shown that a MMC and CPT-11 combination synergistically inhibits tumor growth in vitro [14]. This is due to the possible induction of topoisomerase I gene expression by MMC, thereby increasing tumor cell sensitivity to CPT-11. A phase I/II study of this combination recommended an MMC dose of 5 mg/m^2 and a CPT-11 dose of 150 mg/m^2 administered biweekly [15]. The dose-limiting toxicities of this combination regimen when administered at 10 mg/m^2 for MMC and 150 mg/m^2 for CPT-11 were grade 4 neutropenia with or without febrile neutropenia and grade 3 diarrhea. The overall RR was 50% (15/30 patients), and 5 of 14 patients (36%) with prior chemotherapy showed a partial response (PR). We

previously showed that MMC and CPT-11 combination chemotherapy was effective and well tolerated in patients with fluoropyrimidine-resistant metastatic colorectal cancer; the RR, median TTP, and median survival time (MST) were 34% (95% CI, 20–49%), 4.2 months, and 11.9 months [16], respectively.

These results led us to conduct the present phase II clinical trial to investigate the efficacy and toxicity of MMC/CPT-11 therapy in patients with AGC resistant to a fluoropyrimidine-containing regimen in the JCOG0109-DI study.

Patients and methods

Eligibility

A patient was considered eligible if there was evidence of a refractory response to one prior chemotherapy containing fluoropyrimidine, which was any of the following types of history of chemotherapy:

1. In the case of unresectable gastric cancer, disease progression detected while receiving front-line chemotherapy containing fluoropyrimidine, or confirmed immediately after the discontinuation for any reason other than disease progression.
2. In the case of recurrent gastric cancer, recurrence detected within 24 weeks from the last dose of postoperative adjuvant chemotherapy containing fluoropyrimidine, and further chemotherapy was not administered after recurrence.
3. In the case of recurrent gastric cancer detected 25 weeks after the last dose of postoperative adjuvant chemotherapy, disease progression detected while receiving front-line chemotherapy containing fluoropyrimidine after recurrence, or confirmed immediately after the discontinuation for any reason other than progression.
4. In the case of recurrent gastric cancer treated with neoadjuvant chemotherapy, the effect of neoadjuvant chemotherapy containing fluoropyrimidine was stable disease, progressive disease, or not evaluated, and recurrence was identified after curative resection. Chemotherapy was not performed following recurrence.
5. In the case of recurrent gastric cancer treated with neoadjuvant chemotherapy, the chemotherapy effect was a complete response or PR, and progression was detected during one chemotherapy containing fluoropyrimidine after recurrence, or confirmed immediately after discontinuation for any reason other than progression.

Disease progression and the nonefficacy of neoadjuvant chemotherapy were believed to represent clinical failure by treating physicians. Elevation of the level of a tumor marker, such as carcinoembryonic antigen (CEA), was not accepted as adequate evidence for treatment failure. Documentation of evidence of a refractory response by computed tomography (CT) and magnetic resonance imaging was required.

For the other eligibility criteria, patients must be between 20 and 75 years of age, and have an Eastern Cooperative Oncology Group performance status (PS) of 0 to 2, adequate baseline bone marrow function [white blood cell (WBC) and platelet counts $\geq$4,000 and 100,000/mm^3, respectively], adequate hepatic function (serum bilirubin level $\leq$1.5 mg/dl and both serum aspartate aminotransferase and alanine aminotransferase levels $\leq$100 U/l), adequate renal function (serum creatinine level $\leq$1.5 mg/dl), adequate respiratory function (arterial partial pressure of oxygen $\geq$70 mmHg), and have received no blood transfusion within 14 days before enrollment. All patients were required to have $\geq$1 measurable lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST).

Patients were excluded if they had symptomatic brain metastasis, symptomatic ascites and/or pleural effusion, previous history of MMC or CPT-11 chemotherapy, pre-existing diarrhea of >4 times/day, suspicion of existing active bleeding which needed blood transfusion at 14 days prior to registration in this study, or a high risk of a poor outcome due to concomitant nonmalignant disease (i.e., cardiac, pulmonary, renal, or hepatic disease; poorly controlled diabetes; or uncontrolled infection), or severe psychiatric disease. Pregnant or lactating women were excluded.

The study protocol was approved by the JCOG Clinical Trial Review Committee and the institutional review board of each participating hospital. All patients gave their written informed consent.

Treatment plan

The treatment schedule consisted of one MMC dose (5 mg/m^2, bolus injection), then CPT-11 (150 mg/m^2, 90-min i.v. infusion) repeated every 2 weeks, as described previously [16]. All patients were treated on an outpatient basis and were recommended to receive both a 5-hydroxytryptamine-3-receptor antagonist and dexamethasone to prevent emesis. Subsequent treatment cycles were withheld until the WBC and platelet counts were $\geq$3,000 and 100,000/mm^3, respectively; diarrhea was $\leq$grade 1; and there were no infection symptoms such as pyrexia ($\geq$38°C). When the treatment course was delayed within 8 days from the planned schedule, the same dosage levels as those used previously were administered. When the treatment course was delayed beyond 8 days and within 21 days from the planned schedule, one lower dose level (CPT-11 level -1,

125 mg/m^2; level -2, 100 mg/m^2) than the previous level was administered, while the MMC dose was maintained at 5 mg/m^2. The treatment course was discontinued if it could not be started within 21 days from the planned schedule. When grade 4 leukopenia or thrombocytopenia occurred in a previous treatment course causing a delay within 8 days, the same dosage levels as those used previously were administered. When grade 2 diarrhea or higher was observed in a preceding course, dosages 1 level lower than the previous dosages were administered.

Treatment was repeated until disease progression or when severe toxicity was observed. The total MMC dose was limited to 50 mg/m^2, to prevent cumulative toxicity (e.g., interstitial pneumonia and hemolytic uremic syndrome), and thereafter CPT-11 alone was administered. This indicates that the maximum number of total treatment cycles of MMC/CPT-11 therapy is 10 cycles.

Evaluation of response and toxicity

During protocol treatment, the patient's signs and symptoms, as well as laboratory data (i.e., WBC with differential counts, liver function tests, urea nitrogen, creatinine, electrolytes, and urinalysis) were examined biweekly. Adverse events were evaluated using the National Cancer Institute-Common Toxicity Criteria version 2.0. Tumor response was assessed by CT every 4 weeks. The response of measurable and evaluable disease sites was assessed by each investigator in accordance with RECIST, and then reviewed by central review at the group meeting.

Statistical analysis

For this study, the primary endpoint was the RR and the secondary endpoints were OS and toxicity. Here, we used the standard design (attained design) of the Southwest Oncology Group [17]. Based on reports of RRs of 22% with paclitaxel alone [18] and 16% with CPT-11 alone [8] in the second-line setting and an RR of 36% in phase I/II studies of MMC/CPT-11 therapy [15], the RR in this study was expected to be within 30–40% for a future phase III trial. Here, the required sample size was calculated to be 45 patients, with the following parameters: $\alpha = 0.05$, $\beta = 0.10$, threshold response rate $(p_0) = 20\%$, and expected response rate $(p_a) = 40\%$. Interim analysis was performed when the number of enrolled subjects reached 25. The significance level for the interim analysis was set as $P < 0.02$. Furthermore, when the number of patients who reached RR was <5 at the interim analysis, the study was prematurely discontinued because it would have been difficult to exceed the expected RR despite further patient accumulation, or because it would not be worth advancing this regimen to an ensuing clinical study. When the study was not completed after the interim analysis, the number of patients was increased to 45 in order to allow the null hypothesis (threshold RR) to be tested. When α was <0.05, or when the lower boundary of the 95% CI of the RR exceeded 20% of the threshold RR, this therapy was considered to be efficacious as chemotherapy for gastric cancer patients who had received pretreatment. That is, when ≥16 of 45 patients had a PR, this study was judged to be positive. Here, patient enrollment was not temporarily discontinued.

OS was defined as the time from the registration date to death as a result of any cause. PFS was defined as the time from the registration date to the first documentation of objective tumor progression. Time-to-event and OS data were summarized using the Kaplan–Meier method.

Results

Patient population and study treatment

Between April 2002 and July 2003, 45 patients (33 men, 12 women) from 12 hospitals were enrolled and analyzed. Table 1 shows the demographic data, baseline disease, and regimens of prior chemotherapy. The median age was 64 years (range 36–75), and all patients had a good PS of 0 or 1. Eighteen patients (40%) had diffuse-type gastric cancer. As for prior chemotherapy, 40 (89%) had previously received chemotherapy for metastasis, whereas 5 had received adjuvant chemotherapy. In the first-line chemotherapy, 33 patients (73%) had received 5-FU or S-1 alone.

In all 45 patients, MMC/CPT-11 therapy was administered 281 times, and the median number of doses was 6 (range 1–10). Of the 45 patients, 10 (22%) completed the planned 10 chemotherapy cycles. In the remaining 35 patients, the reasons for treatment discontinuation were disease progression in 25, toxicity in 6, patient's refusal in 3, and death in 1. Regarding CPT-11 administration, 11 patients (24%) required -1 level dose reduction and 8 (18%) required -2 level reduction because of leukopenia and thrombocytopenia.

Efficacy

Of the 45 patients, 13 showed a PR (RR: 28.9%; 95% CI, 15.6–42.1%) (Table 2). The median PFS was 4.1 months (Fig. 1). The median OS time was 10.1 months (95% CI, 7.3–12.6 months), and the 1-year survival rate was 38% (Fig. 2).

Because the lower boundary of the 95% CI of the RR (15.6%) did not exceed the threshold RR (20%), the