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ORIGINAL ARTICLE

Phase II study of S-1, docetaxel and cisplatin combination chemotherapy in patients with unresectable metastatic gastric cancer

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Abstract
Purpose We evaluated the activity and toxicity of docetaxel, cisplatin, and S-1 (DCS) combination chemotherapy in patients with unresectable metastatic gastric cancer.
Methods Patients with histologically proven, unresectable metastatic gastric adenocarcinoma, performance status (PS) 0–2, and no prior chemotherapy were eligible. Patients received oral S-1 (40 mg/m^2 b.i.d.) on days 1–14 and intravenous cisplatin (60 mg/m^2) and docetaxel (60 mg/m^2) on day 8 every 3 weeks.
Results Thirty-four patients were enrolled between March 2005 and April 2007. Three patients were considered ineligible and did not receive the DSC therapy. Clinical characteristics were as follows: median age, 63 years (range, 44–77); PS, 0/1/2: 23/8/0; women/men, 8/23; and well-differentiated/undifferentiated adenocarcinoma, 10/21. The objective response rate was 87.1% with 1 complete response (3.2%) and 26 partial responses (83.9%) in 31 assessable patients. Four had stable disease (12.9%) but none had progressive disease. Of these 27 responders, 8 (25.8%) achieved downstaging and 7 (22.6%) underwent curative surgery. The median survival time and progression-free survival were 687 days [confidence interval (95% CI), 600.0–1,138.1] and 226 days (95% CI, 182.5–379.3), respectively. Most common grade 3/4 hematologic toxicity was neutropenia (77.4%). Most common grade 3 nonhematologic toxicities included anorexia (35.5%) and nausea (32.3%). All treatment-related toxicities resolved, and no toxic deaths were observed.
Conclusions DCS combination chemotherapy is highly active against unresectable metastatic gastric cancer and can be given safely with proper management of adverse events. Further studies of this combination are warranted.

Keywords Gastric cancer · Docetaxel · Cisplatin · S-1 · Chemotherapy

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Introduction

Although global estimates of the incidence of gastric cancer have been declining in recent decades, gastric cancer remains one of the leading causes of cancer deaths

worldwide [1] and still has the highest incidence of any cancer in Japan [2]. Surgical resection during the early stage has improved treatment outcomes of localized gastric cancer with long-term disease-free survival [3].

However, many patients with gastric cancer have recurrences or are diagnosed with stages unsuitable for curative surgery with extremely poor prognoses ranging from 2 to 15% for 5-year survival [4, 5]. For such patients, systemic chemotherapy is the only potential treatment and is mainly administered to provide palliation and prolong survival. Thus, considerable attention has been paid to the development of effective treatment for patients with advanced gastric cancer.

Fluorouracil (5-FU)-based regimens are the most effective and widely used chemotherapy against advanced gastric cancer. However, overall response rates (ORRs) and median survival times (MSTs) of these regimens, even in combination therapy, have been only 7–51% and 6–12 months, respectively [6–8].

Recently, new chemotherapy regimens, including S-1, irinotecan, and taxanes, have been investigated intensively [4]. S-1 is a novel, orally administered 5-FU analog containing three pharmacologic agents: tegafur, 5-chloro-2,4-dihydroxypyridine (a dihydropyrimidine dehydrogenase inhibitor), and potassium oxonate (which reduces 5-FU gastrointestinal toxicity) [9]. The Japan Clinical Oncology Group (JCOG) 9912 trial, which aimed to determine the noninferiority of continuous 5-FU infusion compared with S-1 and the superiority of cisplatin (CDDP) and irinotecan over 5-FU, demonstrated that S-1 was not inferior to 5-FU (hazard ratio, 0.83 [95% confidence interval (CI), 0.68–1.01]); however, it failed to demonstrate the significant superiority of irinotecan + CDDP over 5-FU (hazard ratio, 0.85; 95% CI, 0.70–1.04) [10]. A recent multicenter phase III study (SPIRITS trial) comparing S-1 alone with S-1 + CDDP yielded a significantly higher response rate (RR) and a longer progression-free survival (PFS) and improvement of overall survival (OS) for the S-1 + CDDP arm from 11 to 13 months (hazard ratio, 0.774; 95% CI, 0.608–0.905) than the control arm (S-1 alone) [11]. In Western countries, the multinational phase III study (FLAGS trial) failed to demonstrate superiority of S-1 + CDDP over 5-FU + CDDP (hazard ratio, 0.92; 95% CI, 0.80–1.05). In a subsequent analysis, CDDP + S-1 was at least statistically noninferior to 5-FU + CDDP (hazard ratio, 0.92; 95% CI, 0.80–1.05) and resulted in a significantly better safety profile than 5-FU + CDDP [12]. Therefore, S-1 + CDDP is considered to be one of the standard regimens for advanced gastric cancer based on these results. However, there is room for improvement of efficacy.

Docetaxel also has shown promising activity in gastric cancer, both as a single agent with ORRs ranging from 17 to 24% [13, 14] and in combination with other agents, including CDDP, 5-FU, CDDP + 5-FU (DCF), or S-1, with higher ORRs of 37–56% and MSTs of 9.0–14.3 months [15–17].

To develop a more active and efficacious chemotherapy regimen with two newer agents, S-1 and docetaxel, we previously conducted a phase I study of a triplet combination of docetaxel, CDDP, and S-1 (DCS) for unresectable metastatic gastric cancer [18]. DCS chemotherapy was well tolerated with a quite high ORR (88.2%) and an appreciable downstaging rate in metastatic gastric cancer. Accordingly, we conducted the present phase II study to further assess the efficacy and toxicity profile of this regimen.

Patients and methods

Patient eligibility

Patients were enrolled in the study if they fulfilled the following eligibility criteria: (1) histologic confirmation of stomach adenocarcinoma; (2) unresectable distant metastatic disease (M1 stage, Japanese Classification of Gastric Carcinoma [19]); (3) measurable lesion(s); (4) aged between 20 and 80; (5) PS of 0–2 on the Eastern Cooperative Oncology Group (ECOG) scale; (6) no prior chemotherapy; (7) adequate bone marrow function (WBC count $\geq 4.0 \times 10^9$/l; platelet count $\geq 100 \times 10^9$/l); (8) adequate liver function (serum bilirubin level < 1.5 mg/dl; serum transaminase level ≤ 100 IU/L); (9) adequate renal function (serum creatinine level $<$ upper normal limit; blood urea nitrogen level < 25 mg/dl; creatinine clearance ≥ 60 ml/min); (10) no other severe medical conditions; (11) not pregnant or lactating; and (12) provision of written informed consent. This study was approved by the ethics committee in each institution or hospital.

Study design

In this multicenter, nonrandomized, open-label phase II trial, 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 by intravenous infusion for 2 h at 60 mg/m^2 in 5% glucose followed by docetaxel at 60 mg/m^2 in 5% glucose as a 2-h intravenous infusion on day 8. Cycles were repeated every 3 weeks. To avoid CDDP-induced renal damage, patients were hydrated on days 7–9 with 2,000 ml of 5% dextrose in 0.9% sodium chloride. Prophylactic administration of antiemetic medication (5-HT$_3$ antagonist plus

corticosteroid) at a standard dose was routinely used to prevent nausea and vomiting when CDDP was administered.

Granulocyte colony-stimulating factor (G-CSF) was administered when grade 4 neutropenia or grade 3 or 4 neutropenia with fever had been observed. If G-CSF was administered during the first cycle, prophylactic G-CSF administration was allowed as needed in all subsequent cycles.

In the event of toxicity (National Cancer Institute Common Toxicity Criteria: NCI-CTC Version 3.0), the following treatment delays and dose reductions were planned. CDDP and docetaxel administration on day 8 was skipped in the case of a neutrophil count $< 1.5 \times 10^9$/l, platelet count $< 75 \times 10^9$/L, AST/ALT $>$ 100 IU/l, total bilirubin $>$ 1.5 mg/dl, serum creatinine $>$ upper normal limit, fever $>$ 38.0°C, grade 2 or higher diarrhea, or grade 2 or higher neuropathy. S-1 administration on day 1 in subsequent cycles was delayed in the case of a neutrophil count $< 1{,}5 \times 10^9$/l, platelet count $< 75 \times 10^9$/l, AST/ALT $>$ 100 IU/l, total bilirubin $>$ 1.5 mg/dl, serum creatinine $>$ upper normal limit, ECOG PS 2 or 3, fever $>$ 38.0°C, grade 2 or higher diarrhea, or grade 2 or higher neuropathy. If a patient developed one of the above adverse events during S-1 administration, S-1 was discontinued during that cycle. Doses of docetaxel, CDDP, or S-1 were reduced if any of the following occurred during the previous cycle: febrile neutropenia, platelet count $< 50 \times 10^9$/l, or grade 3 or higher nonhematologic toxicities except nausea, vomiting, anorexia, fatigue, and hypersensitivity. Docetaxel and CDDP doses were reduced by 10% (60 to 54 to 48 mg/m^2). S-1 dose was reduced as follows: 60 to 50 to 40 mg twice daily, but the minimal daily dose was 40 mg twice daily. Treatment was continued until disease progression, unacceptable toxicity, patient's refusal, or physician's decision. When downstaging was achieved and patients were deemed able to tolerate a curative surgical operation, subsequent gastrectomy with lymph node dissection was performed.

Disease evaluation

In the week preceding treatment, disease extent was determined by physical examination, chest and gastrointestinal X-rays, upper gastrointestinal tract endoscopy, abdominal ultrasonography, abdominal computed tomographic scan, barium enema, and bone scintiscan. Peritoneal metastasis was cytologically confirmed by abdominal ascites puncture or culdocentesis. Complete blood cell counts, liver function tests, renal function tests, and urinalysis were assessed at least once per week during treatment. Computed tomographic scanning and imaging of measurable disease were performed once every cycle. Tumor response was assessed according to the response evaluation criteria in solid tumors [20]. Downstaging was defined as the disappearance of all lesions of distant metastases (M0 stage) for 4 weeks. All responses were reviewed by an independent review panel. PFS was defined as the time from registration until objective tumor progression or death. If the patient underwent complete resectional surgery, PFS was measured from initial treatment until documentation of progression after surgery. OS was defined as the time from registration until death from any cause.

Statistical methods

The study design was based on a binominal distribution with no planned interim analysis. The primary end point was to determine the RR. Assuming a null hypothesis of a 40% RR and an alternative hypothesis of a 65% RR, with one-sided type I error = 0.025 and type II error = 0.1, it was necessary to enroll a minimum of 31 patients. All analyses were performed using JMP software version 5.0 (SAS Institute, Inc., Cary, NC, USA). PFS and OS were analyzed according to the Kaplan–Meier method and were updated to January 10, 2009.

Results

Patient characteristics

Thirty-four patients were initially enrolled in this study in our department and 6 affiliated hospitals between March 2005 and April 2007. Three patients were considered ineligible and were excluded. Of these 3 patients, 2 had inadequate laboratory test findings, that is, 1 had liver dysfunction before treatments and the other had marked thrombocytopenia due to disseminated intravascular coagulation (DIC) progression. The other 1 patient had no measurable lesion. These 3 patients had not received DSC therapy. Thus, analysis was performed on the remaining 31 enrolled patients with gastric adenocarcinoma. Patient characteristics are summarized in Table 1. There were 23 men and 8 women, with a median age of 63 years (range, 44–77). Most of these patients were in good general condition (74.2% with a performance status of 0). Histologically, 10 patients had well-differentiated type adenocarcinomas and 21 undifferentiated adenocarcinomas. Three patients had undergone surgical gastrectomy and none had received adjuvant chemotherapy. Twenty-nine patients (93.5%) had distant lymph node metastases, 12 (38.7%) liver metastases, 10 (32.3%) peritoneal metastases and the majority of patients (61.2%) had more than 2 sites of metastases.

Table 1 Patient characteristics

Characteristics	No. of patients	%
No. of patients	31	
Sex, men/women	23/8	74.2/25.8
Age, years		
Median	63	
Range	44–77	
Performance status		
0	23	74.2
1	8	25.8
2	0	0
Histology		
Well differentiated	10	32.3
Undifferentiated	21	67.7
Prior therapy		
Surgery	3	9.7
None	28	90.3
No. of organs involved		
1	2	6.5
2	10	32.3
≥3	19	61.2
Organs involved		
Lymph nodes	29	93.5
Liver	12	38.7
Peritoneum	10	32.3
Bone	2	6.5
Lung	2	6.5
Other	1	3.2

Response

Tumor responses are shown in Table 2. The ORR was 87.1% (95% CI, 75.3–98.9%) with 1 complete response (3.2%) and 26 partial responses (83.9%) in 31 assessable patients. There were 4 stable diseases (12.9%) but no progressive disease.

Notably, 8 of the 31 patients (25.8%) achieved downstaging, that is, distant metastases previously found in the lymph nodes of 6 patients, liver of 2 patients and bone of 1 patient disappeared. Of these 8 patients, 2 had the histologically well-differentiated type and 6 the undifferentiated type. In these downstaged patients, the median treatment cycle to response was 1 (1–6 cycles), which was much less than that of 3 cycles (1–7 cycles) in the other (nondownstaged) partial response patients. Seven of these patients underwent subsequent curative gastrectomy. The metastatic lesions in all 7 patients completely disappeared after surgical gastrectomy with lymph node dissection and 6 of these 7 patients were still alive at the cutoff date of January 10, 2009 (1,394+, 1,293+, 1,039+, 820+, 640+, 594+ and 555 days). These 6 were without evidence of disease. Among the nondownstaged partial response patients, 2 underwent further surgery. One patient underwent total gastrectomy with D2 and radiofrequency ablation for liver metastases after 3 DCS courses. He died of recurrence of the liver metastases 580 days after surgery. The other patient underwent resection of ovarian metastases for tumor reductive intent after 11 DCS courses. The patient died of cancer progression on day 660.

Table 2 Response rate

No. of patients	CR	PR	SD	PD	Response rate (95% CI)
31	1	26	4	0	87.1% (75.3–98.9)

Abbreviations: *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease

Survival analysis

Thirty-one patients were included in the survival analysis on an intent-to-treat basis. The median follow-up time was 640 days (range, 132–1394). PFS and OS were assessed by Kaplan–Meier analyses. The median PFS and OS for all patients were 226 days (95% CI, 182.5–379.3) and 687 days (95% CI, 600.0–1,138.1), respectively (Fig. 1a, b). The 1-year survival rate was 83.9%. Of the patients who did not receive subsequent gastrectomy, the median PFS and MST were 226 days (95% CI, 163.2–291.1) and 575 days (95% CI, 472.5–677.5), respectively.

Treatment administration

Thirty-one patients were administered a total of 142 cycles, with a median of 4 cycles (range, 1–11). The median relative dose intensities were 0.84 for docetaxel (range, 0.53–1.0), 0.83 for CDDP (range, 0.40–1.0), and 0.84 for TS-1 (range, 0.62–1.0). Treatment administration was delayed in 51 of the 142 (35.9%) cycles with 24 (16.9%) of the cycle intervals being delayed for more than 7 days. The major causes of the delayed administrations were treatment-related toxicity such as neutropenia (26/142 cycles, 18.3%), diarrhea (5/142, 3.5%), fever (2/142, 1.4%), and thrombocytopenia (1/142, 0.7%), and 4.2% (6/142) were for personal convenience. Docetaxel and/or CDDP administration on day 8 was skipped in 2 (1.5%) cycles. Dose reductions were performed in 29 (20%) cycles for docetaxel, 30 (21%) for CDDP and 23 (16%) for S-1. The reasons for discontinuation of therapy were adverse events (10/31, 32.3%) followed by further surgery (9/31, 29.0%), progressive disease (6/31, 19.4%), and consent withdrawal (6/31, 16.1%). Ninety-one percent of the patients who did not undergo further surgery (20/22) received the second-line or later chemotherapy: 17, S-1 alone; 13, CPT-11/CDDP; 12, paclitaxel alone; 8, docetaxel/

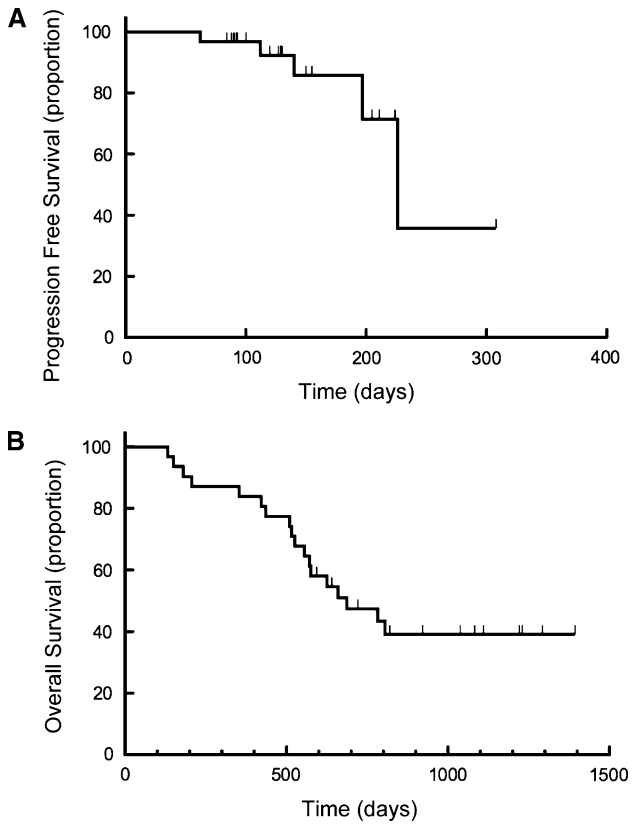

Fig. 1 **a** Kaplan–Meier analysis of progression-free survival for all 31 treated patients. **b** Kaplan–Meier analysis of overall survival for all 31 treated patients

S-1; 4, MTX/5-FU; 3, CPT-11/S-1; 2, FOLFOX4; 2, CPT-11 alone; and 1, UFT.

Toxicity

Toxicities during treatment are listed in Table 3. The most common grade 3–4 toxicities were hematologic, with occurrence of neutropenia (24 patients, 77.4%), leukopenia (20, 64.5%), thrombocytopenia (7, 22.6%), and anemia (6, 19.4%). Five patients (16.1%) each experienced 1 cycle of febrile neutropenia. All cases were manageable with G-CSF administration and had dose reductions that prevented recurrence of this toxicity. The most common grade 3 nonhematologic toxicities were anorexia (11 patients, 35.5%), nausea (10, 32.3%), vomiting (5, 16.1%), and diarrhea (5, 16.1%). No grade 4 cases were observed. All treatment-related toxicities resolved with appropriate care, and no treatment-related deaths were observed.

Discussion

This phase II study was initiated to confirm the anti-tumor effects shown in the previous phase I study of DCS [18]. The DCS regimen in this phase II study produced a very high ORR (87.1%), which was comparable to the ORR at the recommended dose in the phase I study (88.9%) and had an acceptable and manageable toxicity profile.

The ORR achieved in the present study (87.1%; 95% CI, 75.3–98.9%) was among the highest ORRs reported for gastric cancer, such as for 5FU/CDDP [7, 21], 5-FU-doxorubicin-methotrexate [22], epirubicin-CDDP-5-FU [23], and the more recent taxane-, irinotecan-, oxaliplatin-, capecitabine-, or S1-based regimens [4, 14, 24–29], which had ORRs of 33–74%.

Our ORR data was quite reasonable because results from phase II studies in Japan showed an ORR of 22% with docetaxel single therapy [30, 31] and ORRs of 56.3% for the combination of S-1 + docetaxel [32], 56% for CDDP + docetaxel [15], and 74% for S-1 + CDDP [29]. Therefore, our results suggest the synergistic anti-tumor effects of these 3 agents.

Moreover, baseline characteristics of patients enrolled in our study do not appear to be particularly favorable compared to those in previous studies. In studies of DCF [33], ECF [23], S-1/CDDP [11], and our DCS, the proportions of chemo-naive patients were 100, 100, 93, and 100%, respectively; the rates of metastatic disease were 95, 98, 100, and 100%, respectively; and the incidence of liver metastases was 80 (including peritoneal), 36, 36, and 38.7%, respectively. All of these features are associated with ORRs to chemotherapy [5, 34].

In general, high ORRs achieved by various other combination regimens for advanced gastric cancer have failed to translate into major survival benefits and the reported median survival times remain approximately $\leq$13 months [35]. However, in this study, the median OS was estimated to be 23 months, which is quite promising compared with that reported from other combination chemotherapy regimens, such as the combinations of ECF (9.4 months) [36], DF (9.5 months) [16], DCF (9.6 months) [33], DC (10.5 months) [33], FLO (10.7 months) [28], FOLFOX-4 (11.2 months) [37], and S-1/CDDP (13 months) [11]. Although cross-study comparisons should be made with caution, the promising median survival time observed in the present study raises hope that the docetaxel-S-1-CDDP combination may improve survival outcomes for patients with unresectable advanced gastric cancer.

A possible explanation for this good survival is that the observed median survival may be partly influenced by adjuvant surgery performed in 29.0% of the patients, and, as of this analysis, 66.7% of these patients (6/9) were still alive. In fact, the survival benefit of chemotherapy followed by radical surgery in the conversion from unresectable to resectable gastric cancer has been reported [38, 39]. Further observation is necessary to confirm these results.

Table 3 Toxicities

	G1 *n* (%)	G2 *n* (%)	G3 *n* (%)	G4 *n* (%)	G3 ≤*n* (%)
Hematological toxicity					
Leukopenia	1 (3.2)	10 (32.3)	12 (38.7)	8 (25.8)	20 (64.5)
Neutropenia	0 (0)	7 (22.6)	8 (25.8)	16 (51.6)	24 (77.4)
Anemia	2 (6.5)	15 (48.4)	5 (16.1)	1 (3.2)	6 (19.4)
Thrombocytopenia	3 (9.7)	2 (6.5)	5 (16.1)	2 (6.5)	7 (22.6)
Febrile neutropenia	–	–	5 (16.1)	0 (0)	5 (16.1)
Nonhematological toxicity					
Anorexia	4 (12.9)	9 (29.0)	11 (35.5)	0 (0)	11 (35.5)
Nausea	5 (16.1)	8 (25.8)	10 (32.3)	0 (0)	10 (32.3)
Vomiting	6 (19.4)	5 (16.1)	5 (16.1)	0 (0)	5 (16.1)
Diarrhea	3 (9.7)	3 (9.7)	5 (16.1)	0 (0)	5 (16.1)
Fatigue	5 (16.1)	3 (9.7)	3 (9.7)	0 (0)	3 (9.7)
Stomatitis	1 (3.2)	1 (3.2)	2 (6.5)	0 (0)	2 (6.5)
ALT/AST elevation	2 (6.5)	2 (6.5)	1 (3.2)	0 (0)	2 (6.5)
Creatinine elevation	2 (6.5)	0 (0)	0 (0)	0 (0)	0 (0)

Here, good OS was observed despite the unimpressive PFS (226 days). A possible explanation is that most patients were given second-line or more chemotherapy. This high proportion of patients who continued treatment with other regimens probably contributed to the better OS in this study compared to that in previous studies. In fact, the survival data on the patients who did not receive surgery appear promising in this study.

As expected with regimens containing triple agents, hematologic toxicity is clearly the limiting toxicity. In the DCF regimen, marked myelosuppression with an 84% incidence of grades 3/4 neutropenia and 29% incidence of febrile neutropenia were reported [40]. In contrast, the DCS regimen produced a febrile neutropenia rate of only 16.1%, although 77.4% of the patients in this study experienced grades 3/4 neutropenia. Moreover, neutropenia was usually short lasting, and its incidence was reduced by prophylactic G-CSF. These toxicities were also diminished in most cases after dose reductions.

The most common grade 3 nonhematologic toxicities among our study patients were anorexia (35.5%) and nausea (32.3%), rates which were much higher than those induced by the DCF regimen (10 and 14%, respectively) [40], but were similar to those previously reported with the S-1 + CDDP regimen [11]. Grade 3 diarrhea and stomatitis occurred less frequently (16.1 and 6.5%, respectively) than with DCF (i.e., 19 and 21%, respectively) [40]. Notably, most treatment-related toxicities resolved and severe toxicity was prevented by dose reductions, allowing patients to continue treatment without toxicity-induced deaths.

Despite the high incidence of hematologic and nonhematologic toxicities, the median number of cycles administered per patient was 4 with favorable treatment compliance, with the median relative dose intensities for docetaxel, CDDP, and TS-1 being 84, 83, and 84%, respectively. Obviously, DCS treatment necessitates careful observation of these toxicity profile patterns to prevent treatment-associated toxicities.

It is well known that there is an ethnic difference in S-1 pharmacokinetics caused by a polymorphism in the *CYP2A6* gene. Therefore, the appropriate daily dose of S-1 differs between Asians and Caucasians [41]. Indeed, in a phase I trial of S-1 + CDDP in the United States, the recommended dose of S-1 was 25 mg/m^2 twice daily, which was lower than the dose tolerated by Japanese patients [42]. Thus, there may be need to exercise caution before extrapolating our data to patients of different ethnicities.

On the other hand, capecitabine is a very frequently used oral fluoropyrimidine worldwide and has been studied extensively in gastric cancers [43]. As for triplet regimens using capecitabine, the combination of epirubicin, oxaliplatin, and capecitabine (EOX) achieved a 48% RR with a median survival of 11.2 months in advanced oesophagogastric cancer patients [24]. Moreover, the combination of docetaxel, capecitabine, and cisplatin (DXP) achieved a 65% RR and, of interest, 36 of the 49 patients with advanced gastric cancer treated with that regimen were rendered operable [44]. Therefore, direct comparison of these 2 oral fluoropyrimidine (capecitabine and S-1)-containing regimens will be needed.

In conclusion, DCS combination chemotherapy is highly active against unresectable metastatic gastric cancer. But close monitoring and proper management of adverse events is needed for this treatment since a high incidence of G3/4 neutropenia and neutropenic fever was observed in this

study. The present results suggest the applicability of our regimen to integrated treatment approaches, including surgery following preoperative DCS, as evidenced by the absence of progressive disease patients and a certain appreciable rate of downstaging. A phase II trial of neoadjuvant chemotherapy using our regimen is currently underway.

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