

Preoperative Systemic and Intraperitoneal Chemotherapy Consisting of S-1, Cisplatin and Docetaxel in Patients with Marginally Resectable Gastric Cancer

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Abstract. *Background/Aim:* S-1, cisplatin, and docetaxel (DCS) constitute an effective regimen for gastric cancer. We conducted a retrospective cohort study of systemic DCS and a prospective phase I trial of intraperitoneal DCS in the preoperative setting for marginally resectable gastric cancer. *Patients and Methods:* Under the systemic regimen, patients received cisplatin (60 mg/m²) plus docetaxel (40 mg/m²) intravenously on day 1 and S-1 (80 mg/m²) on days 1-14, of a 28-day cycle. With the intraperitoneal regimen, the schedule for S-1 and cisplatin was the same. Dose escalation for docetaxel started at 30 mg/m² (level 1). *Results:* Between August 2010 and July 2013, 26 consecutive patients were treated with the systemic regimen. Grade 3-4 neutropenia occurred in 81% but the toxicity profile was very tolerable. The response rate based on the Response Evaluation Criteria in Solid Tumors (RECIST) was 89%. Between April 2012 and April 2014, 5 patients with linitis plastica, large ulcero-invasive type tumors, positive washing cytology or peritoneal metastasis were enrolled in the phase I trial of the intraperitoneal regimen. Grade 3-4 elevations in aspartate/alanine aminotransferase (AST/ALT) occurred in the first 2 patients. The next 3 patients, who received docetaxel (20 mg/m²) on days 1 and 15 (level 0), had no dose-limiting toxicity. Four patients, including 3 with peritoneal metastasis and/or positive cytology before treatment, underwent R0 resection after

intraperitoneal chemotherapy. *Conclusion:* Our studies revealed the efficacy of the systemic regimen and the safety of the intraperitoneal regimen. Further investigation of these two types of preoperative DCS chemotherapy is warranted.

Gastric cancer is the second leading cause of cancer-related death worldwide (1). Although surgical resection is the only curative treatment for gastric cancer, the prognosis of patients with advanced gastric cancer remains poor even after curative resection. The recurrence rate is high, especially in patients with linitis plastica (Borrmann type 4), large ulceroinvasive tumors (Borrmann type 3), invasion of the esophagus or adjacent organs or bulky nodal metastasis (2-5). Although R0 resection can be achieved in patients with limited metastasis in the paraaortic lymph nodes, liver or peritoneum, the long-term outcome is extremely poor (6-8). For such marginally resectable cases, preoperative treatment has been employed to reduce recurrence rate.

There is no standard first-line regimen for unresectable or recurrent gastric cancer worldwide, but the Japanese phase III SPIRITS trial established S-1 plus cisplatin (CS) as the standard first-line regimen in the East (9). Recently, a Japanese phase II trial (JCOG0405) of preoperative chemotherapy with CS showed promising results in patients with bulky or paraaortic nodal metastases (10). On the other hand, a triplet regimen with 5-fluorouracil, cisplatin and docetaxel has been widely used as first-line treatment in Western countries (11). A Japanese phase II trial of first-line chemotherapy with a triplet regimen consisting of CS-plus-docetaxel (DCS) for unresectable or recurrent gastric cancer reported higher response rates than CS-alone (12, 13). We, therefore, initiated a preoperative systemic DCS regimen for patients with marginally resectable gastric cancer in August 2010. Furthermore, we conducted a phase I trial of intraperitoneal administration of docetaxel instead of intravenous administration in patients with Borrmann type 4 tumors, large Borrmann type 3 tumors, positive washing cytology (CY1) or

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Table I. Characteristics of the patients who received the systemic regimen.

Characteristic	n=26
Age, years	
Median (range)	63.5 (36-75)
Sex	
Male	21
Female	5
Borrmann macroscopic type	
Type 2	9
Type 3 (<8cm)	9
Type 3 (≥8cm)	5
Type 4	3
Histological type	
Differentiated	13
Undifferentiated	13
Esophageal invasion	
No	16
Yes	10
cT stage	
T3	6
T4a	14
T4b	6
Bulky nodal metastasis	
No	23
Yes	3
Para-aortic nodal metastasis	
No	22
Yes	4
Liver metastasis	
No	24
Yes	2

peritoneal metastasis only in the adjacent peritoneum because these patients usually experience peritoneal recurrence after surgery (2, 3). Thus, we have created a new strategy involving 2 types of preoperative DCS chemotherapy for marginally resectable gastric cancer. Herein, we show the results of the retrospective cohort study of the systemic DCS regimen and the prospective phase I trial of the intraperitoneal DCS regimen in the preoperative setting.

Patients and Methods

Patient population. Between August 2010 and July 2013, we administered systemic DCS to patients with histologically-proven adenocarcinoma of the stomach or gastroesophageal junction. Eligibility criteria for the systemic DCS regimen included resectable Borrmann type 4 tumors, large (≥8 cm) Borrmann type 3 tumors, invasion of the esophagus or adjacent organs (cT4b), bulky nodal metastases or resectable para-aortic nodal or liver metastasis. Tumor staging was based on the seventh edition of the International Union against Cancer (UICC) tumor-node-metastasis (TNM) classification guidelines (14).

In April 2012, we initiated a phase I trial of the intraperitoneal DCS regimen. The eligibility criteria for this phase I trial were as follows: histologically-proven adenocarcinoma of the stomach;

Table II. Adverse events with the systemic regimen (n=26).

Event	Grade				Any (%)	Grade 3-4 (%)
	1	2	3	4		
Neutropenia	0	3	14	7	92	81
Anemia	2	10	1	0	50	4
Thrombocytopenia	6	3	0	0	35	0
Anorexia	7	12	1	0	77	4
Diarrhea	3	6	1	0	38	4
Nausea	4	3	1	0	31	4
Hyponatremia	0	0	4	0	15	15
Oral mucositis	3	0	0	0	12	0
Creatinine increased	1	1	0	0	8	0
Alopecia	2	0	0	0	8	0
Hypertension	0	1	0	0	4	0
Hypoalbuminemia	0	1	0	0	4	0
Hypokalemia	0	1	0	0	4	0
Urinary tract infection	0	1	0	0	4	0
Hiccups	0	1	0	0	4	0
Abdominal pain	0	1	0	0	4	0

Table III. Characteristics of the patients who received the intraperitoneal regimen.

Characteristic	n=5
Age, years	
Median (range)	55 (40-70)
Sex	
Male	2
Female	3
Borrmann macroscopic type	
Type 1	1
Type 3 (≥8cm)	2
Type 4	2
Histological type	
Differentiated	0
Undifferentiated	5
Washing cytology (CY)	
Negative	2
Positive	3
Peritoneal metastasis	
No	2
Yes	3

Borrmann type 4 tumors, large (≥8 cm) Borrmann type 3 tumors, CY1 or peritoneal metastasis only in the adjacent peritoneum; no peritoneal seeding of the diaphragm or distant peritoneum; no massive ascites; no invasion of adjacent organs (not cT4b); no metastasis to distant lymph nodes, liver, lung, pleura, brain and bone; no prior treatments including surgery, chemotherapy or radiation; no active bleeding; sufficient oral intake; Eastern Cooperative Oncology Group

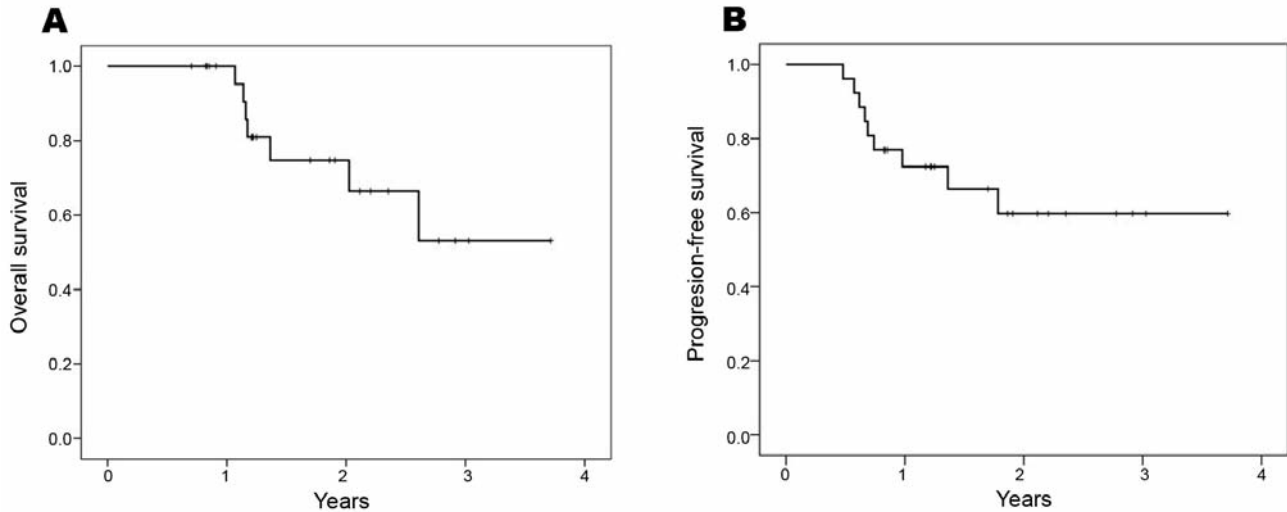


Figure 1. Kaplan-Meier overall survival (A) and progression-free survival (B) curves for 26 patients treated with the systemic regimen.

Table IV. Adverse events with the intraperitoneal regimen.

Patient	Docetaxel dose	No. of cycles	DLT	Adverse events (grade)
Level 1				
1	30 mg/m ² , day 1	2	Yes	ALT increased (3), AST increased (3), Anorexia (2), Nausea (2), Hyponatremia (1), Hypokalemia (1),
2	30 mg/m ² , day 1	1	Yes	ALT increased (4), AST increased (3), Neutropenia (1), Anorexia (1), Hypoalbuminemia (1), Hypokalemia (1)
Level 0				
1	20 mg/m ² , day 1 and 15	2	No	Anemia (1), Anorexia (1), Nausea (1), Hyperkalemia (1), Hiccups (1)
2	20 mg/m ² , day 1 and 15	2	No	Nausea (1)
3	20 mg/m ² , day 1 and 15	4	No	Neutropenia (3), Anemia (2), Anorexia (2), Nausea (2)

DLT, dose limiting toxicity; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

(ECOG) performance status (PS) score of 0 or 1; age between 20 and 75 years; leukocyte count $\geq 3,000/\text{mm}^3$, neutrophil count $\geq 1,500/\text{mm}^3$, hemoglobin ≥ 8.0 g/dl, platelet count $\geq 100,000/\text{mm}^3$, serum bilirubin ≤ 1.5 mg/dl, creatinine clearance (CCR) ≥ 60 ml/min, serum aspartate aminotransferase (AST) ≤ 100 IU/l and alanine aminotransferase (ALT) ≤ 100 IU/l; expected survival longer than 3 months; and written informed consent. The trial protocol was approved by the institutional review board of Osaka University Hospital.

Treatment protocol. With the systemic DCS regimen, patients received cisplatin (60 mg/m²) and docetaxel (40 mg/m²) intravenously on day 1 and oral S-1 (80 mg/m²) on days 1 to 14 of a 28-day cycle. With the intraperitoneal DCS regimen, patients received cisplatin (60 mg/m²) intravenously on day 1 and oral S-1 (80 mg/m²) on days 1 to 14 of a 28-day cycle. On day 1, docetaxel was diluted in 1 l of saline and administered through the implanted peritoneal access port over 1 hour. Dose escalation of docetaxel was planned from 30 mg/m² (level 1) to 35 mg/m² (level 2) and 40 mg/m² (level 3). At least 3 patients were treated at each dose level. If dose-limiting toxicity (DLT) was not observed in the first 3 patients, the dose was escalated to the next level. If 1 of the 3 patients developed any DLT, an additional 3 patients were added at the same dose level. The maximum tolerated dose (MTD) was defined as the dose level at which 2 or more patients developed DLT. Toxicity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. DLTs were defined as follows: grade 4 leukopenia or neutropenia for at least 3 days; grade 3 or 4 febrile neutropenia; grade 4 thrombocytopenia; grade 3 or 4 non-hematological toxicity except for anorexia, nausea, vomiting, oral mucositis, fatigue, hyponatremia or hypernatremia and hypokalemia or hyperkalemia; and unable to start a treatment cycle within 7 days of the planned date. In principle, the recommended dose (RD) was determined as one level down from the MTD. After 2 to 4 cycles of chemotherapy, patients underwent gastrectomy with D2 or more extensive lymph node dissection according to the Japanese Gastric Cancer Association (JGCA) treatment guidelines (15).

Evaluation and statistical analysis. Tumor responses to preoperative chemotherapy were evaluated according to the Japanese Classification of Gastric Carcinoma (JCGC) criteria based on endoscopic examination findings (16). Only patients with measurable lesions were evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.0, based on computed tomography (CT) findings (17). All postoperative events were evaluated according to the Clavien-Dindo classification system (18). Surgical specimens were assessed histologically and tumor response was evaluated according to the histological criteria of the JCGC (19). Briefly, histological evaluations were classified into five categories according to the proportion of the tumor affected by degeneration or necrosis: grade 3, no viable tumor cells remain; grade 2, viable tumor cells remain in less than 1/3 of the tumor area; grade 1b, viable tumor cells remain in more than 1/3 but less than 2/3 of the tumor area; grade 1a, viable tumor cells occupy more than 2/3 of the tumor area; grade 0, no evidence of treatment effect.

Overall survival (OS) was defined as the interval from the initial date of preoperative chemotherapy to the date of death from any cause. Progression-free survival (PFS) was defined as the interval from the initial date of preoperative chemotherapy to first progression or recurrence. PFS was censored at the time of the last follow-up or death without progression or recurrence. *p*-Values <0.05 were considered statistically significant. All statistical analyses were performed using the SPSS Statistics software, version 20 (IBM Corp., Armonk, NY, USA).

Results

Systemic DCS regimen. Between August 2010 and July 2013, 26 consecutive patients were treated with the systemic DCS regimen. The characteristics of these patients are shown in Table I. Among 26 patients, 3 patients (12%) had Borrmann type 4 tumors and 5 (19%) had large Borrmann type 3 tumors. Ten patients (38%) had tumors that invaded the esophagus, 6 (23%) had cT4b tumors, 3 (12%) had bulky nodal metastases, 4 (15%) had para-aortic nodal metastasis and 2 (8%) had liver metastasis.

The median number of chemotherapy cycles was 2 (range=1-4). All adverse events are shown in Table II. There were no treatment-related deaths. Among the hematological adverse events, 81% of patients experienced grade 3-4 neutropenia but none developed febrile neutropenia. The most frequent non-hematological toxicities were anorexia (any grade, 77%), diarrhea (any grade, 38%), and nausea (any grade, 31%). Except for hyponatremia, there were no grade 3 or 4 toxicities that occurred in more than 10% of patients.

The response rate based on JCGC criteria was 85%. Among 18 patients with measurable lesions, the response rate and disease control rate based on RECIST were 89% and 100%, respectively. All 26 patients underwent either R0 (88%) or R1 resection (12%). Total gastrectomy was performed in 15 (58%) patients. Combined resection of other organs was performed in 20 patients (77%) in total. Resected organs included the spleen in 11 (42%), lower esophagus in 10 (38%), part of the pancreas in 6 (23%), liver in 2 (8%), left

kidney in 1 (4%), diaphragm in 1 (4%) and gallbladder in 1 (4%). Fourteen patients (54%) underwent paraaortic lymph node dissection at least in the area lateral to the aorta and above the left renal vein. The median operative time was 304 min and median blood loss was 530 ml. There were 3 patients (12%) who experienced Grade III postoperative complications according to the Clavien-Dindo classification system. Major complications included 1 pancreatic fistula, 1 anastomotic leakage and 1 pneumothorax. All patients recovered and were discharged. The histological responses of the primary lesion according to the JCGC criteria were grade 2 in 4 (15%), grade 1b in 4 (15%) and grade 1a in 18 (69%).

After surgery, 21 out of 26 patients (81%) received adjuvant chemotherapy consisting of an oral fluoropyrimidine (mostly S-1). At the time of analysis (June 2014), the median duration of follow-up for censored patients was 20 months. The Kaplan-Meier OS and RFS curves are shown in Figures 1A and 1B, respectively. The 2-year OS and PFS rates were 75% and 60%, respectively. The initial sites of recurrence consisted of the peritoneum in 5 patients (19%), liver in 2 (8%), lymph nodes in 2 (8%) and bone in 1 (4%). The peritoneal recurrence rate in patients with Borrmann type 4 or large Borrmann type 3 tumors was 50%, compared to 6% with other types of tumors.

Intraperitoneal DCS regimen. Between April 2012 and April 2014, 5 patients were enrolled in the phase I trial of the intraperitoneal DCS regimen. Characteristics of these patients are shown in Table III. Two patients had Borrmann type 4 tumors and 2 had large Borrmann type 3 tumors. Three patients had peritoneal metastasis confirmed by staging laparoscopy or laparotomy. Before chemotherapy, 2 out of the 3 patients with peritoneal metastasis and 1 patient with no peritoneal metastasis were diagnosed with CY1.

All adverse events observed in the 5 patients during this phase I trial are shown in Table IV. There were no treatment-related deaths. For the initial 2 patients enrolled at dose level 1, grade 3 or 4 elevations in AST/ALT occurred. Therefore, the next 3 patients received 20 mg/m² of docetaxel (level 0) intraperitoneally on days 1 and 15. At level 0, none of these 3 patients had any DLTs at all. Based on these results, the MTD and RD were determined to be level 1 and level 0, respectively.

There were 4 of 5 patients who had measurable lesions and all of them showed PR based on RECIST. All but 1 patient (level 0-3), including the 3 patients with peritoneal metastasis and/or CY1, underwent R0 resection with total gastrectomy. The median operative time was 232 min and median blood loss was 700 ml. One patient (level 0-2) experienced Grade III anastomotic leakage but he recovered and was discharged. The histological responses of the primary lesion according to the JCGC criteria were grade 1b in 1 patient and grade 1a in 3 patients.

Discussion

There is currently no worldwide consensus on the standard preoperative chemotherapy regimen for gastric cancer. Although a systemic triplet regimen with 5-fluorouracil, cisplatin and epirubicin has been recommended in the West (20), CS became a commonly used preoperative regimen in Japan based on the promising results of a Japanese phase II trial (JCOG0405) (10). As the V325 phase III trial in the West demonstrated that adding docetaxel to 5-fluorouracil plus cisplatin in the first-line setting significantly improved response rates and survival in gastric cancer (11), a triplet regimen with DCS has been recently attempted in the preoperative setting in Japan. Our retrospective cohort study revealed a high response rate (85% based on JCGC criteria, 89% based on RECIST) with the systemic DCS regimen, with this response rate in the preoperative setting being similar to rates observed in other studies in the first-line setting (12, 13). The toxicity profile of this regimen was very tolerable and all patients were able to safely undergo R0 or R1 surgery. Even in patients with marginally resectable gastric cancer, the 2-year OS and PFS rates reached 75% and 60%, respectively.

Our retrospective cohort study of the systemic DCS regimen showed insufficient efficacy for reducing peritoneal recurrence; the peritoneal recurrence rate in patients with Borrmann type 4 or large Borrmann type 3 tumors reached 50%. Indeed, previous phase II studies of preoperative S-1 alone or CS for patients with Borrmann type 4 or large Borrmann type 3 tumors have also reported high rates of peritoneal metastasis during or after surgery (2, 3). These findings may indicate that systemic chemotherapy cannot effectively kill cancer cells disseminated in the peritoneum. The most effective way to kill them is intraperitoneal administration of chemotherapeutic agents with direct contact of the target cancer lesions in the peritoneal cavity. We, therefore, initiated a phase I trial of intraperitoneal chemotherapy for patients with Borrmann type 4 tumors, large Borrmann type 3 tumors, CY1 or peritoneal metastasis only in the adjacent peritoneum. We have previously reported preliminary results of intraperitoneal chemotherapy using mitomycin C and cisplatin in the preoperative setting (21). However, mitomycin C and cisplatin may be unsuitable for intraperitoneal administration because of immediate absorption through the peritoneum. On the other hand, taxanes, such as docetaxel and paclitaxel, are absorbed slowly *via* lymphoducts due to their high molecular weight and lipophilicity. Ishigami *et al.* reported promising results from a phase II study of intraperitoneal paclitaxel in the first-line setting for unresectable or recurrent gastric cancer with peritoneal metastasis (22). After we confirmed the feasibility of oral S-1 and intraperitoneal docetaxel regimen in the first-line setting

(23), we conducted a new phase I trial of CS plus intraperitoneal docetaxel in the preoperative setting.

In this phase I trial, grade 3 or 4 elevations in AST/ALT occurred in the first 2 patients enrolled at dose level 1. In the second patient (level 1-2), grade 3 elevations in AST/ALT occurred again in the subsequent treatment cycle with CS-alone. Theoretically, taxanes administered in the peritoneum are absorbed slowly *via* the lymphatic system, which results in a gradual increase of blood concentrations (24). Indeed, there have been relatively few studies of intraperitoneal docetaxel or paclitaxel reporting the occurrence of grade 3 or 4 elevations in AST/ALT (22, 23, 25). Although we considered that the relationship between AST/ALT elevation and intraperitoneal administration of docetaxel was unlikely, we decided that docetaxel should be administered intraperitoneally at 20 mg/m² every 2 weeks. Finally, this trial revealed that the RD for the intraperitoneal DCS regimen was 20 mg/m² of docetaxel on days 1 and 15, with 60 mg/m² of intravenous cisplatin on day 1 and 80 mg/m² oral S-1 on days 1 to 14 of a 28-day cycle. The efficacy of this intraperitoneal DCS regimen, including long-term outcomes, should be clarified in further studies.

In conclusion, the results of our studies clearly demonstrate that further investigation of these 2 types of preoperative DCS chemotherapy is required. The systemic DCS regimen may be more effective at controlling lymph node or liver metastasis, while the intraperitoneal DCS regimen would be used in patients with peritoneal metastasis. Proper use of these 2 types of preoperative DCS chemotherapy may represent a promising strategy for treating marginally resectable gastric cancer.

Conflicts of Interest

None of the Authors declares any conflicts of interest.

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