Feasibility Study of Triplet Combination Chemotherapy of Paclitaxel, Cisplatin and S-1 for Advanced Gastric Cancer

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Abstract. *Background: Docetaxel combined with cisplatin and 5-fluorouracil (5-FU) is active in advanced gastric cancer, but not generally accepted because of its substantial toxicities. We conducted a feasibility study of a triplet combination using paclitaxel, cisplatin and S-1 for advanced gastric cancer. Patients and Methods: Patients were given paclitaxel 160 mg/m^2 infused over 2 hours on day 1, followed by cisplatin 60 mg/m^2 in a 2-hour infusion on day 14, and S-1 80 mg/m^2/day for 14 consecutive days, followed by a 2-week rest, repeated every 4 weeks. Treatment was continued until disease progression or unacceptable toxicity occurred, the patient refused the therapy, or a surgical procedure was performed. Results: Twenty-one patients were prospectively enrolled. A total of 53 courses were administered, with a median of 2 courses (range: 1-7). Leucopenia, neutropenia, and anemia of grade 3 or more occurred in 3, 12, and 3 patients, respectively. Non-hematological toxicities were all grade 2 or less. Planned treatment was delivered with relative dose intensity for paclitaxel, cisplatin, and S-1 as 91.1%, 81.1% and 90.6%, respectively. The overall response rate was 67% with 1 complete response, 13 partial responses, and 6 with stable disease, while 6 out of 13 surgically resected specimens showed a histologic response graded ≥1b. Median survivals of all patients and of 13 patients who underwent curative resection were 543 and 871 days, respectively. Conclusion: Triplet combination chemotherapy with paclitaxel, cisplatin and S-1 demonstrated superior feasibility and promising antitumor activity for advanced gastric cancer.*

Gastric cancer is the second leading cause of cancer mortality worldwide (1, 2), although its global incidence has been declining in recent years. Surgical resection is the mainstay of curative treatment for gastric cancer, however, not infrequently, the disease is too advanced at initial diagnosis to allow for curative surgery. For such patients, chemotherapy is the mainstream choice for symptom palliation and prolongation of survival. Despite the considerable efforts paid to develop effective chemotherapeutic regimens, advanced gastric cancer (AGC) remains a challenging malignancy for physicians as well as for patients, with a median survival of 9-13 months (3-6). Although no established regimen is yet a global standard for AGC, a doublet combination containing 5-fluorouracil (5-FU) and cisplatin is the most commonly used treatment worldwide (3, 7-9). In Japan, S-1 (an oral 5-FU agent) plus cisplatin has recently been established as a standard regimen for AGC based on the results of the SPIRITS trial (5), in which a response rate (RR) of 54% and a durable overall survival (OS) of 13 months were obtained using S-1 plus cisplatin. However, there still remains room for improving the efficacy of chemotherapy. To develop a more active and efficacious chemotherapy regimen, docetaxel, another cytotoxic agent against AGC, has been added to a doublet combination with 5-FU plus cisplatin (3, 10). Although triplet therapy with these three drugs has demonstrated promising outcomes, it has not been generally accepted as a standard of treatment because of its substantial toxicities, in particular high incidences of grade 3/4 neutropenia and febrile neutropenia (3, 10).

Several phase II trials showed that the taxanes, docetaxel and paclitaxel, when used as single agents for AGC, have different toxicity profiles. In particular, grade 3/4 neutropenia was less frequent with paclitaxel than with docetaxel (40% *versus* 80-90%, respectively), while the non-hematological toxicity profile, RR, and OS were quite similar between the two (11-15). From these findings, we speculated that substituting pactitaxel for docetaxel could reduce the toxicity of triplet therapy, while preserving its efficacy.

We therefore conducted the present feasibility study to evaluate the safety and efficacy of triplet combination chemotherapy with paclitaxel, cisplatin and S-1 in patients with AGC.

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Key Words: Triplet combination chemotherapy, paclitaxel, cisplatin, S-1, advanced gastric cancer, feasibility study.

Patients and Methods

Eligibility criteria. Tumor assessment was performed within 4 weeks prior to enrollment, and a complete blood cell count and liver and renal function tests were carried out within 2 weeks prior to enrollment. Patients enlisted in this study were required to fulfill the following criteria: histologically proven gastric adenocarcinoma with measurable lesions; no prior chemotherapy or radiotherapy against any malignancies; age of 80 years or younger; performance status of 1 or less on the Eastern Cooperative Oncology Group (ECOG) scale; adequate bone marrow function (WBC count 3,000-12,000/mm^3, neutrophil count ≥1,500/mm^3, platelet count ≥100,000/mm^3, and hemoglobin ≥8.0 g/dl), hepatic function (total bilirubin ≤2.0 mg/dl and serum aminotransferases ≤5 times the upper institutional limit), and renal function (serum creatinine ≤1.2 mg/dl and creatinine clearance ≥60 ml/min/body); sufficient oral intake or tolerance of enteral tube feeding; no other severe medical conditions; no other concurrent active malignancy; life expectancy of at least 3 months; and provision of written informed consent. This study was approved by the Institutional Ethics Board.

Treatment schedule. Paclitaxel (160 mg/m^2) was given as an intravenous infusion over 2 hours on day 1 and cisplatin (60 mg/m^2) was administered intravenously over 2 hours on day 14, as shown in Figure 1. S-1 was given orally after meals or *via* enteral feeding tube twice daily at a standard dose of 80 mg/m^2/day for 14 consecutive days, followed by a 2-week rest, repeated every 4 weeks. The initial dose of S-1 was assigned according to the body surface area (BSA) of the patient as follows: BSA<1.25 m^2, 80 mg/day; 1.25 m^2≤BSA<1.5 m^2, 100 mg/day; and BSA≥1.5 m^2, 120 mg/day. Dose increases or reductions of paclitaxel, cisplatin, or S-1 were not planned.

The next course was only started if the biological parameters still conformed to the eligibility criteria and any non-hematological toxicity was of grade 1 or less. Otherwise, the treatment was suspended for up to 4 weeks after the last administration of cisplatin.

S-1 was discontinued if the patient developed grade 3 leucopenia and/or neutropenia, grade 3 thrombocytopenia, total bilirubin elevation above 3.0 mg/dl, serum aminotransferase elevation greater than 5 times the upper institutional limit, serum creatinine elevation above 1.5 mg/dl, or other non-hematological toxicity of grade 3 or more.

Cisplatin administration on day 14 was postponed for up to 1 week if the patient developed grade 2 leucopenia and/or neutropenia, grade 2 thrombocytopenia, or serum creatinine elevation above 1.2 mg/dl.

To prevent paclitaxel-induced hypersensitivity, all patients were given dexamethasone (20 mg) and ranitidine (50 mg) intravenously plus diphenhydramine (50 mg) orally or *via* enteral feeding tube at 30 min prior to the delivery of paclitaxel, and every patient was hydrated on day 14 with 2000 ml of 5% dextrose in 0.9% sodium chloride to avoid cisplatin-induced renal damage. Antiemetic drugs were given prophylactically before each administration of cisplatin. Granulocyte colony-stimulating factor (G-CSF) was used only when grade 4 leucopenia/neutropenia and/or grade 3 neutropenia with fever were observed.

The treatment was continued until disease progression or unacceptable toxicity occurred, the patient refused the therapy, or a surgical procedure was performed.

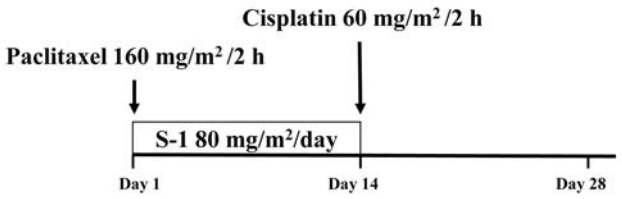

Figure 1. *Treatment schedule used for study patients*.

Evaluation of toxicity and efficacy. A complete blood cell count and measurements of liver and renal function were assessed at least every week during the treatment. Non-hematological toxicities were also verified at least every week by patient interview and physical examination. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 3.0 (16).

During the treatment, patients were evaluated with abdominal computed tomography (CT) scans and assessed for an objective response in measurable lesions every 1-2 months according to the Response Evaluation Criteria In Solid Tumors (RECIST) criteria (17). A complete response (CR) was defined as complete disappearance of the tumor by CT scan. A partial response (PR) was defined as shrinkage of the tumor diameter by ≥30%. An increase of the tumor diameter by ≥20% or the appearance of new lesions was defined as progressive disease (PD). Cases that did not meet criteria for CR, PR, or PD were defined as stable disease (SD). Disease control rate (DCR) represented the combined percentage of CR, PR and SD.

OS was defined as the time since the initiation of chemotherapy to the last follow-up or the date of death from any cause, and the Kaplan-Meier method was used to draw the survival curve. Patients who were alive at the time of our analysis were censored for survival.

Pathological examination. All resected specimens were examined by two pathologists and the graded histologic response of the primary tumor to the treatment was evaluated according to the guidelines of the Japanese Gastric Cancer Association (18). Histologic response of gastric lesions to the treatment was graded from 0 to 3 based on the amount of residual viable carcinoma in relation to areas of fibrosis or fibroinflammation within the gross lesion. Grade 3 (G3) response was defined as the complete absence of histopathologic evidence of malignancy. Grade 2 (G2) response was defined as <33.3% viable tumor cells seen on serial hematoxylin-eosin-stained sections, and grade 1b (G1b) as 33.3% to 66.6% viable cells. Tumors with 66.6% to less than 100% viable cells and those without any effect of chemotherapy on viable cells were scored as grade 1a (G1a) and grade 0 (G0), respectively.

Results

Patient characteristics. Patients' clinical characteristics are shown in Table I. Twenty-one patients, 14 males and 7 females, with a median age of 63 years (range: 30-79 years), were prospectively enrolled in this study between January 2008 and December 2009. Every patient had a performance status of 0-

Table I. *Characteristics of patients with advanced gastric cancer taking part in this study.*

Patient number	Gender	Age (years)	PS	Primary/recurrent GC	Stage/site of relapse	Histology
1	F	60	0	Primary	IIIb: 2T3 bulky N2P0CYXH0M0	Diffuse
2	M	66	0	Recurrent	LN along the splenic artery	Intestinal
3	M	70	1	Primary	IV: 2T3N1P0CYXH1M1	Intestinal
4	M	63	1	Primary	IV: 4T3N2P0CYXH1M0	Intestinal
5	M	64	0	Primary	IV: 2T3N1P0CYXH1M0	Intestinal
6	M	52	0	Primary	IIIb: 3T3 bulky N2P0CYXH0M0	Diffuse
7	F	71	1	Primary	IIIb: 2T4N1P0CYXH0M0	Diffuse
8	M	42	1	Primary	IIIb: 2T4 bulky N1P0CY0H0M0	Diffuse
9	M	64	1	Primary	IV: 2T3 bulky N3P0CYXH1M0	Intestinal
10	M	64	0	Primary	IV: T1 bulky N2+N3P0CYXH0M0	Diffuse
11	M	77	1	Primary	II: 3T3N0P0CYXH0M0 with esophageal invasion	Intestinal
12	F	58	0	Recurrent	Para-aortic LN	Diffuse
13	F	30	0	Primary	IV: 3T3N3PXCYXH1M0	Intestinal
14	M	67	1	Primary	IV:2T3 bulky N2P0CYXH1M0	Diffuse
15	F	62	1	Primary	IV: 2T3 bulky N2+N3P0CYXH0M0	Intestinal
16	M	56	1	Primary	IIIb: 4T4N1P0CY0H0M0	Diffuse
17	M	79	1	Primary	IV: 3T4N2P0CYXH0M0	Intestinal
18	M	55	0	Recurrent	H1 with pancreas and adrenal invasion	Diffuse
19	F	51	1	Primary	IV: 4T3N3P0CYXH0M0	Diffuse
20	F	37	1	Primary	II: 4T3N0P0CY0H0M0	Diffuse
21	M	69	0	Primary	IV: 3T3N3P0CYXH0M0	Intestinal

F: Female, M: male, PS: performance status, GC: gastric cancer, LN: lymph node, T: tumor invasion, N: lymph node metastasis, P: peritoneal dissemination, CY: peritoneal lavage cytology, H: liver metastasis, M: distant metastasis, 0: negative, 1: positive, X: unknown in case of P, CY, H, and M, Number before T-stage represents macroscopic type of primary tumor, with 4 indicating linitis plastica.

1. Twelve patients had primary resectable AGC, 6 patients had primary unresectable AGC, and 3 patients had recurrent GC. According to the guidelines of the Japanese Gastric Cancer Association (16), the primary tumor was classified as stage II in 2 patients, stage IIIb in 5, and stage IV in 11. Bulky nodal disease and/or para-aortic nodal metastasis (N3) were found in 10 patients, liver metastasis (H1) and/or distant metastasis (M1) in 7 patients, and T4 tumor, esophageal invasion, and linitis plastica in 4, 1, and 4 patients, respectively. Two patients, numbered 17 and 20 in Table I, received enteral tube feeding because of gastric outlet obstruction due to the primary tumor. Histologically, 10 patients had intestinal-type adenocarcinoma and 11 had diffuse-type adenocarcinoma.

Toxicity and treatment compliance. Toxicity profiles are shown in Table II. All patients were assessable for toxicity. A total of 53 courses were administered in 21 patients, and the median number of delivered treatment courses was 2 (range: 1-7). Hematological toxicity of grade 3 or more consisted of leucopenia, neutropenia, and anemia occurring in 3 (14%), 12 (57%), and 3 (14%) patients, respectively. Non-hematological toxicities were generally mild and manageable, with no grade 3/4 toxicities observed. There were no treatment-related deaths.

Details of treatment compliance are shown in Table III. Treatment was completed in 13 patients, all of whom subsequently underwent surgery, whereas treatment was discontinued in the remaining 8 patients for the following reasons: grade 2 neutropenia lasting more than 4 weeks after cisplatin administration in 1 patient, physician's decision to discontinue treatment due to cisplatin administration being skipped twice in 1 patient, patient choice arising from

Table II. *Toxicities throughout all 53 courses on a patient basis.*

	NCI-CTC grade			
Toxicity	1	2	3	4
Leucopenia	5	10	3	
Neutropenia		5	8	4
Anemia	10	8	3	
Thrombocytopenia		1		
AST/ALT	5	3		
Cr	1			
Stomatitis				
Diarrhea	3	2		
Anorexia	12	2		
Nausea	9	1		
Vomiting	1	2		
Fatigue	13	1		
Alopecia	1	20		
Urticaria		4		
Allergic reaction				
Arthralgia	3			
Neuropathy (sensory)	10			

Table III. *Treatment compliance*.

Patient number	Number of delivered chemotherapy treatments	Reason for treatment discontinuation	Unscheduled dosing of cisplatin
1	1	G2 neutropenia lasting more than 4 weeks followed by gastrectomy	
2	4	Cisplatin skipped twice	Skip × 2 due to G3 neutropenia
3	2	Patient refusal (depression)	Patient refusal × 1
4	3	Patient refusal (G2 fatigue)	Delay × 2 due to G2 fatigue and G4 neutropenia
5	3	Gastrectomy	
6	2	Gastrectomy	Delay × 2 due to G4 neutropenia
7	2	Gastrectomy	Delay × 2 due to G3 and G4 neutropenia
8	2	Patient refusal (depression)	
9	7	Progressive disease	
10	2	Pancreatoduodenectomy	Delay × 1 due to G3 neutropenia
11	2	Gastrectomy	
12	4	Lymphadenectomy	Delay × 1 due to G3 neutropenia
13	2	Progressive disease	
14	3	Progressive disease	Delay × 1 due to G3 neutropenia
15	2	Gastrectomy	Skip × 1 due to G3 neutropenia
16	2	Probe laparotomy	
17	2	Gastrectomy	Delay × 2 due to G3 and G4 neutropenia
18	2	Hepatic resection	
19	2	Gastrectomy	Skip × 1 due to G3 neutropenia
20	2	Gastrectomy	
21	2	Gastrectomy	Delay × 1 due to G3 neutropenia Skip × 1 due to G3 neutropenia

G: Grade.

Table IV. *Clinical efficacy of triplet combination chemotherapy for advanced gastric cancer.*

Patient number	Best response	Therapy subsequent to the triplet chemotherapy	Graded histological response of resected specimen	OS (days) (status*)
1	PR	Gastrectomy	0	424 (D)
2	PR	Paclitaxel + S-1		1167 (A)
3	SD	S-1 + Irinotecan		250 (D)
4	PR	Irinotecan		199 (D)
5	CR	Gastrectomy	3	1142 (A)
6	SD	Gastrectomy	1a	1061 (D)
7	PR	Gastrectomy	1a	872 (D)
8	SD	None		67 (D)
9	PR	S-1 + Irinotecan		616 (D)
10	PR	Pancreatoduodenectomy	1a	381 (D)
11	PR	Gastrectomy	2	869 (A)
12	PR	Lymphadenectomy	1b	778 (A)
13	SD	Paclitaxel		123 (D)
14	PR	Irinotecan		262 (D)
15	SD	Gastrectomy	0	245 (D)
16	PD	Probe laparotomy		146 (D)
17	PR	Gastrectomy	1b	544 (D)
18	PR	Hepatic resection	3	532 (A)
19	PR	Gastrectomy	2	501 (D)
20	SD	Gastrectomy	1a	507 (A)
21	PR	Gastrectomy	1a	505 (A)

CR: Complete response, PR: partial response, SD: stable disease, PD: progressive disease. *Status as of May 5, 2011: D: dead, A: alive.

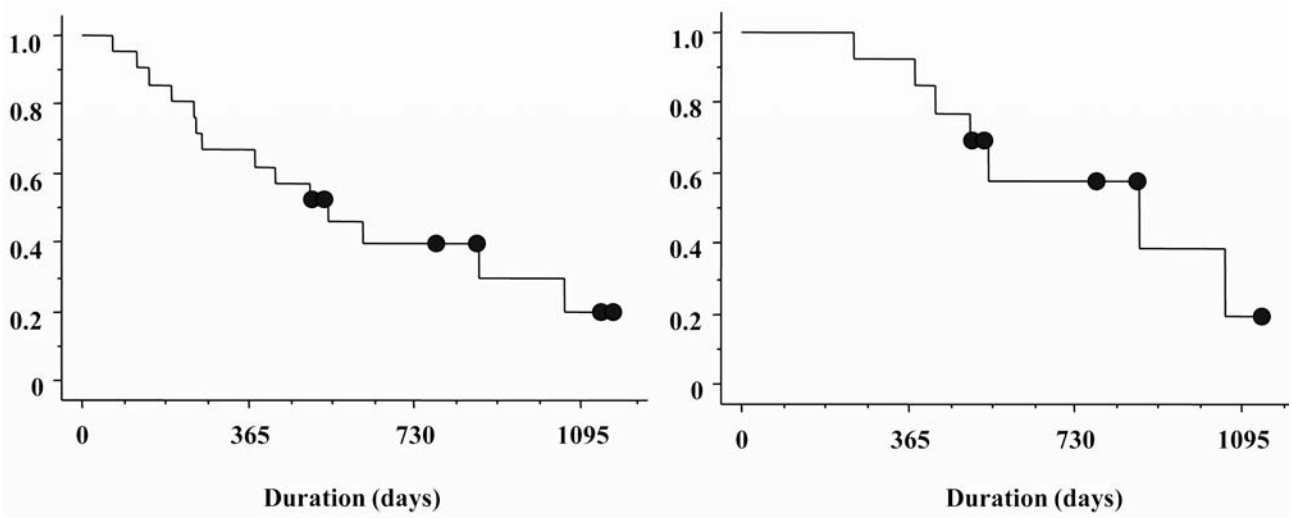

Figure 2. *Overall survival of the all patients (left) and of patients undergoing curative resection with no residual tumor (right). Closed circles indicate censored cases.*

depression in 2 patients and grade 2 fatigue in 1 patient, and disease progression in 3 patients. Cisplatin administration on day 14 was delayed in 12 out of 53 courses (22.6%) due to grade 3 neutropenia in 6 courses, grade 4 neutropenia in 5 courses, and grade 2 fatigue in 1 course, while it was skipped in 6 courses (11.3%) because of grade 3 neutropenia in 5 courses and patient refusal in 1 course on day 21. Although no dose reductions were planned, the dose of paclitaxel was reduced by 20% twice and that of cisplatin by 20% once (patient no. 2) based on the physician's decision. S-1 dosing was also reduced by 20% for 20 days in 1 patient (patient no. 4) and skipped for 6 days in 1 patient (patient no. 15) at the discretion of a physician. The relative dose intensities (RDIs) of paclitaxel, cisplatin, and S-1 were 91.1%, 81.1%, and 90.6%, respectively, throughout all 53 courses.

Clinical efficacy. Best objective responses to treatment are shown in Table IV. The overall RR was 67% with 1 CR and 13 PRs, while 6 patients maintained SD, yielding a DCR of 95%.

Histologic responses to treatment of 13 surgically resected specimens were grades 3, 2, 1b, 1a, and 0 in 2, 2, 2, 5, and 2 patients, respectively, with 6 patients (46%) demonstrating grade 1b or greater.

At a median follow-up of 505 (range: 67-1167) days (322 days in 14 dead patients and 778 days in 7 living patients) after the initiation of triplet chemotherapy, median survival time (MST) of all patients was 543 days, and that of 13 patients who underwent curative resection with no residual tumor subsequent to the triplet chemotherapy was 871 days, as shown in Figure 2.

Discussion

Doublet chemotherapy with cisplatin and 5-FU (CF) is currently considered a reference standard worldwide, with overall response rates of 25-51% and MSTs of 7.3-9.3 months (3, 7-9). However, because of the modest RR and limited OS derived from the CF regimen, there exists a clear need to develop more active chemotherapy regimens. Docetaxel, another active agent used for AGC, has been added to a doublet combination with CF in randomized phase II (10) and phase III trials (3); this novel triplet therapy of docetaxel plus CF (DCF) has demonstrated a survival benefit over the CF doublet. In addition, the substitution of oral 5-FU drug for continuous infusion of 5-FU in the CF regimen has successfully avoided the inconvenience associated with infusional chemotherapy without jeopardizing the efficacy or safety of the CF therapy (4, 6, 9). Therefore, a new combination of docetaxel, cisplatin plus capecitabine or S-1, an oral alternative to infusional 5-FU, has recently been tried in several phase I/II studies (19-22).

Triplet therapy with DCF showed a survival benefit over a standard doublet therapy with CF in patients with AGC, but was associated with severe hematological toxicities including grade 3/4 neutropenia in 80-82% of patients and febrile neutropenia/neutropenic infectionin in 29-41% (3, 10). These high incidences of G3/4 neutropenia and febrile neutropenia limit the use of DCF as a standard of care for AGC. A new combination of docetaxel and cisplatin plus S-1 (DCS) or capecitabine (DCX) also demonstrated substantial hematological toxicities, with grade 3/4

neutropenia in 69-77% of cases and febrile neutropenia in 4-16% (20-22). In contrast, the overall toxicity of our triplet combination with paclitaxel, cisplatin, and S-1 (PCS) was highly acceptable, as shown in Table II. Grade 3/4 neutropenia occurred in 57% of patients, with no febrile neutropenia observed. Our results are consistent with recent phase II studies of PCS showing that the incidence of grade 3/4 neutropenia was 26-47% and that of febrile neutropenia was 0-9% (23, 24). Although variations in the types, doses, and schedules of delivered taxanes limit the degree to which different treatments can be compared, the hematological toxicities associated with PCS regimens seem to be milder and less frequent compared to the DCS and DCX regimens. In terms of non-hematological toxicities with the PCS regimen, Iwase *et al*. reported that no grade 3/4 non-hematological toxicities were observed when patients with AGC received intravenous paclitaxel (160 mg/m^2) on day 1 plus cisplatin (60 mg/m^2) as a 24-h infusion on day 14, and S-1 (70 mg/m^2/day) on days 1-14 of every 28-day cycle (23). Kim *et al*. also showed a low incidence of non-hematological toxicities greater than grade 3, including nausea (2.4%), vomiting (4.8%), stomatitis (2.4%), and diarrhea (4.8%) when patients received intravenous paclitaxel (80 mg/m^2) plus cisplatin (30 mg/m^2) on days 1 and 8, and S-1 (70 mg/m^2/day) on days 1-14 based on a 3-week cycle (24). These findings are consistent with our results, in which no grade 3/4 toxicities were observed. Such a low toxicity profile favors the administration of paclitaxel when combined with cisplatin and 5-FU.

With respect to the compliance with triplet combination chemotherapy with taxane (docetaxel or paclitaxel), cisplatin, and S-1, the RDIs of taxane, cisplatin, and S-1 were reported to be 84-96.5%, 83-97.3%, and 84-97.2%, respectively (21, 24). Our triplet PCS regimen showed equivalent tolerability, with RDIs of paclitaxel, cisplatin, and S-1 of 91.1%, 81.1% and 90.6%, respectively.

Compared to the modest overall RR of 25-51% and limited OS of 7.3-9.3 months delivered by the CF doublet (3, 7-9), PCS regimens demonstrated an RR of 59-63% and OS of 11.2-15.0 months in patients with AGC (23, 24), and DCS regimens achieved an RR of 81-87% and OS of over 18 months (20, 21). DCS triplets seem to be more active than PCS triplets, including our PCS regimen, which showed an RR of 67% and OS of 17.9 months.

Of note, in the present study, 13 patients who underwent curative resection following the PCS triplet demonstrated a prolonged MST of 871 days, as shown in Figure 2, despite advanced disease at initial diagnosis. A durable OS of 700 days or more was also obtained for AGC patients who received curative resection subsequent to the DCS/DCX chemotherapy (21, 22). Triplet combination chemotherapy with taxane, cisplatin, and S-1 is likely to be an appropriate neo-adjuvant treatment as well as palliative treatment for AGC. A Swiss group advocated this possibility for a DCF regimen in a study where the DCF regimen led to a rapid tumor shrinkage with a shorter time to response of 1.6 months (10). In addition, a histologic response of grades ≥1b was obtained in 46% of all resected specimens in the present study. A graded histologic response of 1b or greater was found in approximately 50% of patients who showed promising outcomes after receiving preoperative chemotherapy for AGC in other studies (25, 26), and a high graded histologic response of the primary tumor was identified as a predictor of durable survival in patients receiving preoperative chemotherapy or chemoradiotherapy (27, 28). Our PCS triplet might become a promising regimen in the neo-adjuvant setting.

In conclusion, although the present study was a small-scale analysis performed at a single institution, our triplet combination chemotherapy with paclitaxel, cisplatin and S-1 demonstrated superior feasibility with manageable toxicity and encouraging antitumor activity for patients with AGC. These promising results warrant further study to establish the role of this triplet combination regimen.

References

1 Parkin DM, Bray F, Ferlay J and Pisani P: Global cancer statistics, 2002. CA Cancer J Clin *55*: 74-108, 2005.

2 Kamangar F, Dores GM and Anderson WF: Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. J Clin Oncol *24*: 2137-2150, 2006.

3 Van Cutsem E, Moiseyenko VM, Tjulandin S, Majlis A, Constenla M, Boni C, Rodrigues A, Fodor M, Chao Y, Voznyi E, Risse ML and Ajani JA; V325 Study Group: Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. J Clin Oncol *24*: 4991-4997, 2006.

4 Cunningham D, Starling N, Rao S, Iveson T, Nicolson M, Coxon F, Middleton G, Daniel F, Oates J and Norman AR; Upper Gastrointestinal Clinical Studies Group of the National Cancer Research Institute of the United Kingdom: Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med *358*: 36-46, 2008.

5 Koizumi W, Narahara H, Hara T, Takagane A, Akiya T, Takagi M, Miyashita K, Nishizaki T, Kobayashi O, Takiyama W, Toh Y, Nagaie T, Takagi S, Yamamura Y, Yanaoka K, Orita H and Takeuchi M: S-1 plus cisplatin *versus* S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. Lancet Oncol *9*: 215-221, 2008.

6 Boku N, Yamamoto S, Fukuda H, Shirao K, Doi T, Sawaki A, Koizumi W, Saito H, Yamaguchi K, Takiuchi H, Nasu J and Ohtsu A; Gastrointestinal Oncology Study Group of the Japan Clinical Oncology Group: Fluorouracil *versus* combination of irinotecan plus cisplatin *versus* S-1 in metastatic gastric cancer: a randomised phase 3 study. Lancet Oncol *10*: 1063-1069, 2009.

7 Kim NK, Park YS, Heo DS, Suh C, Kim SY, Park KC, Kang YK, Shin DB, Kim HT, Kim HJ, Kang WK, Suh CI and Bang YJ: A phase III randomized study of 5-fluorouracil and cisplatin *versus* 5-fluorouracil, doxorubicin, and mitomycin C *versus* 5-fluorouracil alone in the treatment of advanced gastric cancer. Cancer *71*: 3813-3818, 1993.

8 Ohtsu A, Shimada Y, Shirao K, Boku N, Hyodo I, Saito H, Yamamichi N, Miyata Y, Ikeda N, Yamamoto S, Fukuda H and Yoshida S: Randomized phase III trial of fluorouracil alone *versus* fluorouracil plus cisplatin *versus* uracil and tegafur plus mitomycin in patients with unresectable, advanced gastric cancer: The Japan Clinical Oncology Group Study (JCOG9205). J Clin Oncol *21*: 54-59, 2003.

9 Kang YK, Kang WK, Shin DB, Chen J, Xiong J, Wang J, Lichinitser M, Guan Z, Khasanov R, Zheng L, Philco-Salas M, Suarez T, Santamaria J, Forster G and McCloud PI: Capecitabine/cisplatin *versus* 5-fluorouracil/cisplatin as first-line therapy in patients with advanced gastric cancer: a randomised phase III noninferiority trial. Ann Oncol *20*: 666-673, 2009.

10 Roth AD, Fazio N, Stupp R, Falk S, Bernhard J, Saletti P, Köberle D, Borner MM, Rufibach K, Maibach R, Wernli M, Leslie M, Glynne-Jones R, Widmer L, Seymour M and de Braud F: Docetaxel, cisplatin, and fluorouracil; docetaxel and cisplatin; and epirubicin, cisplatin, and fluorouracil as systemic treatment for advanced gastric carcinoma: a randomized phase II trial of the Swiss Group for Clinical Cancer Research. J Clin Oncol *25*: 3217-3223, 2007.

11 Sulkes A, Smyth J, Sessa C, Dirix LY, Vermorken JB, Kaye S, Wanders J, Franklin H, LeBail N and Verweij J: Docetaxel (Taxotere) in advanced gastric cancer: results of a phase II clinical trial. EORTC Early Clinical Trials Group. Br J Cancer *70*: 380-383, 1994.

12 Taguchi T, Sakata Y, Kanamaru R, Kurihara M, Suminaga M, Ota J and Hirabayashi N: Late phase II clinical study of RP56976 (docetaxel) in patients with advanced/recurrent gastric cancer: a Japanese Cooperative Study Group trial (group A). Gan To Kagaku Ryoho *25*: 1915-1924, 1998. (Japanese)

13 Bang YJ, Kang WK, Kang YK, Kim HC, Jacques C, Zuber E, Daglish B, Boudraa Y, Kim WS, Heo DS and Kim NK: Docetaxel 75 mg/m^2 is active and well tolerated in patients with metastatic or recurrent gastric cancer: a phase II trial. Jpn J Clin Oncol *32*: 248-254, 2002.

14 Cascinu S, Graziano F, Cardarelli N, Marcellini M, Giordani P, Menichetti ET and Catalano G: Phase 11 study of paclitaxel in pretreated advanced gastric cancer. Anticancer Drugs *9*: 307-310, 1998.

15 Yamada Y, Shirao K, Ohtsu A, Boku N, Hyodo I, Saitoh H, Miyata Y and Taguchi T: Phase II trial of paclitaxel by three-hour infusion for advanced gastric cancer with short premedication for prophylaxis against paclitaxel-associated hypersensitivity reactions. Ann Oncol *12*: 1133-1137, 2001.

16 Trotti A, Colevas AD, Setser A, Rusch V, Jaques D, Budach V, Langer C, Murphy B, Cumberlin R, Coleman CN and Rubin P: CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. Smin Radiat Oncol *13*: 176-181, 2003.

17 Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC and Gwyther SG: New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst *92*: 205-216, 2000.

18 Japanese Classification of Gastric Carcinoma, 2nd English Edition: Gastric Cancer *1*: 10-24, 1998.

19 Nakayama N, Koizumi W, Sasaki T, Higuchi K, Tanabe S, Nishimura K, Katada C, Nakatani K, Takagi S and Saigenji K: A multicenter, phase I dose-escalating study of docetaxel, cisplatin and S-1 for advanced gastric cancer (KDOG0601). Oncology *75*: 1-7, 2008.

20 Nakayama N, Koizumi W, Sasaki T, Tanabe S, Nishimura K, Higuchi K, Takagi S, Katada C, Azuma M and Saigenji K: Phase II study of combination therapy with docetaxel, cisplatin and S-1 (DCS) for advanced gastric cancer: (KDOG0601). J Clin Oncol *27*: abstr 4555, 2009.

21 Sato Y, Takayama T, Sagawa T, Takahashi Y, Ohnuma H, Okubo S, Shintani N, Tanaka S, Kida M, Sato Y, Ohta H, Miyanishi K, Sato T, Takimoto R, Kobune M, Yamaguchi K, Hirata K, Niitsu Y and Kato J: Phase II study of S-1, docetaxel and cisplatin combination chemotherapy in patients with unresectable metastatic gastric cancer. Cancer Chemother Pharmacol *66*: 721-728, 2010.

22 Sym SJ, Chang HM, Ryu MH, Lee JL, Kim TW, Yook JH, Oh ST, Kim BS and Kang YK: Neoadjuvant docetaxel, capecitabine and cisplatin (DXP) in patients with unresectable locally advanced or metastatic gastric cancer. Ann Surg Oncol *17*: 1024-1032, 2010.

23 Iwase H, Tsuzuki T, Shimada M, Ina K, Shinoda M, Kumada J, Okamura S, Haruta J, Sugihara M and Goto H: Multicenter phase II study of triple combination with S-1 and cisplatin (CDDP) plus paclitaxel (TXL) in patients with advanced gastric cancer. J Clin Oncol *26*: abstr 4539, 2008.

24 Kim JY, Do YR, Park KU, Kim JG, Chae YS, Kim MK, Lee KH, Ryoo HM, Bae SH, Baek JH and Song HS: Multicenter phase II trial of S-1, paclitaxel and cisplatin triplet combination chemotherapy in patients with advanced gastric cancer. Cancer Chemother Pharmacol *67*: 527-532, 2011.

25 Fujitani K, Sasako M, Iwasaki Y, Yoshimura K, Sano T, Nashimoto A, Fukushima N, Arai K, Kinoshita K, Kobayashi O and Tanemura H: A phase II study of preoperative chemotherapy (CX) with S-1 and cisplatin followed by gastrectomy for clinically resectable type 4 and large type 3 gastric cancer: JCOG 0210. J Clin Oncol *25*: abstr 4609, 2007.

26 Nashimoto A, Yabusaki H, Nakagawa S, Takii Y, Tsuchiya Y and Tanaka O: Preoperative chemotherapy with S-1 and cisplatin for highly advanced gastric cancer. Anticancer Res *29*: 4689-4696, 2009.

27 Lowy AM, Mansfield PF, Leach SD, Pazdur R, Dumas P and Ajani JA: Response to neoadjuvant chemotherapy best predicts survival after curative resection of gastric cancer. Ann Surg *229*: 303-308, 1999.

28 Ajani JA, Winter K, Okawara GS, Donohue JH, Pisters PW, Crane CH, Greskovich JF, Anne PR, Bradley JD, Willett C and Rich TA: Phase II trial of preoperative chemoradiation in patients with localized gastric adenocarcinoma (RTOG9904): Quality of combined modality therapy and pathologic response. J Clin Oncol *24*: 3953-3958, 2006.

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