Phase I Study of Combination Chemotherapy Consisting of Paclitaxel, Cisplatin, and S-1 in Patients with Unresectable Gastric Cancer (KOGC-02)

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Abstract. *Background: Triplet combination chemotherapy has the potential to improve the prognosis of patients with unresectable gastric cancer. We conducted a phase I trial of triplet combination chemotherapy consisting of paclitaxel, cisplatin, and S-1 (PCS) for unresectable gastric cancer. Patients and Methods: Patients with metastatic or incurable disease were enrolled. S-1 was administered on days 1-14. Paclitaxel and cisplatin were infused on days 1 and 15. The starting doses of paclitaxel and cisplatin were 100 and 20 mg/m^2, respectively. Dose levels of paclitaxel and cisplatin were escalated as follows: 120 and 20 mg/m^2, respectively (level 2); 120 and 30 mg/m^2, respectively (level 3). End-points: Dose-limiting toxicities included grade 3 nausea, vomiting, and general fatigue, and grade 4 febrile neutropenia. The maximum tolerated dose and recommended dose were established at level 3 and level 2, respectively. Conclusion: Although further clinical trials are recommended to more thoroughly evaluate safety and efficacy, PCS appears to be an excellent candidate for a standard treatment strategy for unresectable gastric cancer.*

Gastric cancer is one of the most frequent causes of death from malignant disease worldwide, especially in East Asia, South America, and in parts of Central and Eastern Europe (1). Although the prognosis of metastatic or recurrent gastric cancer is poor, several clinical trials have demonstrated that systemic chemotherapy provides a significant benefit over best supportive care (2-4). Until recently, 5-fluorouracil (5-FU) played a key role in patients with unresectable gastric cancer (5, 6). 5-FU-based chemotherapy, especially in combination with cisplatin, was adopted for use in the treatment of several types of cancer (7-9). However, outcomes for 5-FU plus cisplatin (CF) combination therapy have not always been satisfactory with respect to improving prognosis. Therefore, an active regimen for patients with advanced gastric cancer is urgently needed.

In the late 1990s, the introduction of novel anticancer drugs, such as camptothecin, taxanes, third-generation platinums, and new oral fluoropyrimidines, improved the clinical outcomes of patients with unresectable and recurrent gastric cancer (10-12). To meet the challenge of highly-advanced gastric cancer cases, triplet combination chemotherapy regimens including these newer chemotherapeutic agents have been evaluated with the goal of achieving improved prognoses compared to conventional doublet chemotherapy, such as the CF regimen. In the V325 trial, combination chemotherapy consisting of fluorouracil, cisplatin, and docetaxel (DCF) resulted in improved time-to-progression (TTP), overall survival (OS), and response rate (RR) compared with CF (13). As a result, this triplet chemotherapy regimen was established as one of the standard chemotherapy regimens for unresectable gastric cancer.

Recent clinical trials have shown that infusional 5-FU can be replaced by oral 5-FU drugs such as S-1 and capecitabine (12, 14). S-1 is a synthetic compound containing tegafur, gimeracil (which inhibits the 5-FU-degrading enzyme), and oteracil (which reduces gastrointestinal toxicity) (15). In Japan, S-1 is a key drug, and the cisplatin/S-1 combination regimen (CS) is recognized as first-line chemotherapy for unresectable gastric cancer (16, 17). In the FLAGS trial, the CS regimen resulted in approximately equivalent efficacy but less toxicity compared to CF in patients with gastric cancer (14). CS could also be considered for use as a more convenient and safer doublet regimen for unresectable gastric cancer in Western countries.

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Key Words: Combination chemotherapy, gastric cancer, paclitaxel, S-1, cisplatin.

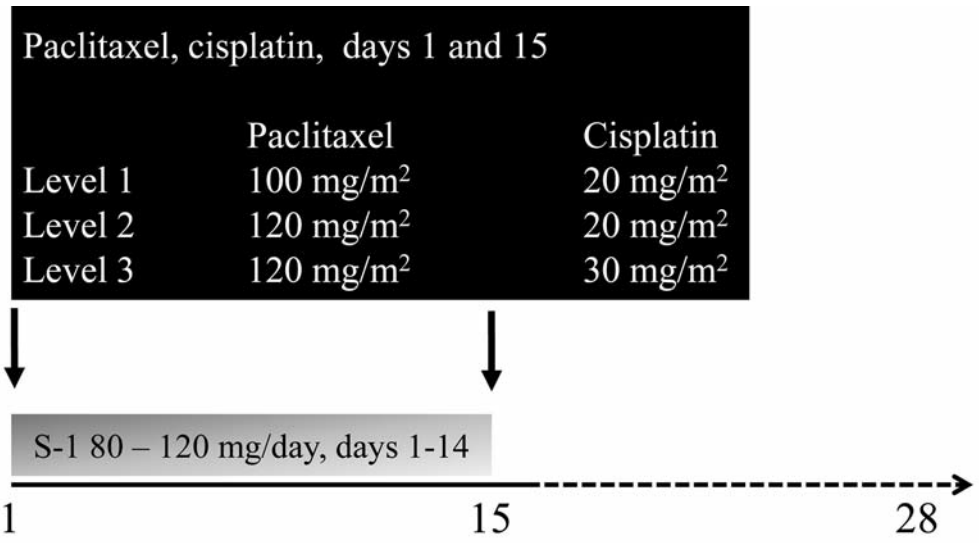

Figure 1. *Treatment schedule*.

We conducted a phase I trial of triplet combination chemotherapy consisting of CS plus paclitaxel (PCS) for unresectable or metastatic gastric cancer. A great need exists for an effective chemotherapy regimen that can be administered in an outpatient setting for patients with gastric cancer with good performance status (PS). In the present study, the PCS regimen was evaluated to determine the maximum tolerated dose (MTD) and recommended dose (RD) of both cisplatin and paclitaxel, and also to examine the preliminary therapeutic effect of this triplet combination therapy in outpatients with gastric cancer.

Patients and Methods

Eligibility criteria. Eligibility criteria included histological confirmation of gastric adenocarcinoma, metastatic or incurable disease, measurable lesion(s) or evaluable disease, age >20 and <80 years, Eastern Cooperative Oncology Group (ECOG) PS 0 or 1, no prior chemotherapy, adequate liver and renal function, and the ability to take medications orally. All eligible patients provided written informed consent to participate, and this study was approved by the Ethics Committee at our hospital.

Chemotherapy schedule. S-1 was administered orally every day on days 1-14, and the total dose was based on the patient's body surface area (BSA) as follows: <1.25 m^2, 80 mg; 1.25-1.5 m^2, 100 mg, and >1.5 m^2, 120 mg. Paclitaxel and cisplatin were infused on days 1 and 15 for 60 min without hydration. The starting doses of paclitaxel and cisplatin, given to the first three patients enrolled, were 100 mg/m^2 and 20 mg/m^2 (defined as level 1), respectively. The following paclitaxel and cisplatin doses could be given to subsequent cohorts of patients depending on safety findings observed in the previous cohort: level 2, 120 mg/m^2 and 20 mg/m^2, respectively; level 3, 120 mg/m^2 and 30 mg/m^2, respectively. This treatment cycle was repeated every four weeks and is summarized in Figure 1.

Determination of MTD and RD. Toxicity was evaluated using the Common Terminology Criteria for Adverse Events (v 3.0) (18). Dose-limiting toxicity (DLT) was defined as follows: grade 4 neutropenia; grade 4 leukocytopenia; higher than grade 3 thrombocytopenia; higher than grade 3 febrile neutropenia; higher than grade 3 non-hematological toxicity excluding anorexia, nausea, and vomiting; delay of second administration of paclitaxel and cisplatin; or total administration of S-1 for <7 days. At each dose level beginning with level 1, three patients were enrolled. If a DLT was recognized in one out of the three patients, three additional patients were to be evaluated at that dose level. If two patients experienced a DLT at the same dose level, that level was defined as the MTD. The RD was defined as the dose level immediately below the MTD.

Clinical evaluation. Abdominal computed-tomography and upper gastrointestinal endoscopy were performed during each treatment cycle. Clinical response to treatment was evaluated using the revised Response Evaluation Criteria in Solid Tumors (RECIST version 1.1) for metastatic and primary lesions (19).

Results

Patients' characteristics. Between September 2010 and October 2011, 11 patients were entered into this study. Patients' characteristics are summarized in Table I. The median age was 61.6 years (range 50-73 years); there were 10 males and one female. Nine patients had a PS of 0 and two had a PS of 1. Histological types included intestinal (n=6) and diffuse (n=5) subtypes. Two patients had one metastatic site and the remaining nine patients had multiple

Table I. *Patients' characteristics*.

Median age, years±SD (range)	61.6±7.74 (50-73)
Gender	
Male/female	10/1
ECOG performace status	
0/1	9/2
Microscopic type	
Intestinal/diffuse	6/5
Number of metastatic sites	
1/2/3 and >3	2/7/2
Site	
Peritoneum	9
Liver	5
Lymph node	7
Lung	1
Bone	1

Table II. *Hematological toxicity*.

	Level	Grade				
		1	2	3	4	3/4 (%)
Leukocytopenia	1	0	2	1	0	33
	2	2	0	1	0	33
	3	2	1	1	0	20
Neutropenia	1	0	0	3	0	100
	2	1	0	2	0	67
	3	1	1	1	0	20
Anemia	1	1	1	0	0	0
	2	2	0	0	0	0
	3	2	0	0	0	0
Thrombocytopenia	1	0	0	0	0	0
	2	0	0	1	0	33
	3	1	0	0	0	0
Febrile neutropenia	1	-	-	0	0	0
	2	-	-	0	0	0
	3	-	-	0	1*	20

*Dose-limiting toxicity.

Table III. *Non-hematological toxicity*.

	Level	Grade				
		1	2	3	4	3/4 (%)
Fatigue	1	1	0	0	0	0
	2	2	0	0	0	0
	3	3	0	1*	0	20
Anorexia	1	1	0	0	0	0
	2	2	0	0	0	0
	3	2	1	0	0	0
Nausea	1	1	0	0	0	0
	2	1	0	0	0	0
	3	2	1	1*	0	20
Vomit	1	0	0	0	0	0
	2	0	0	0	0	0
	3	0	1	1*	0	20
Diarrhea	1	0	0	0	0	0
	2	0	0	0	0	0
	3	0	1	0	0	0
AST/ALT elevation	1	1	0	0	0	0
	2	1	1	0	0	0
	3	1	0	0	0	0
ALP elevation	1	1	0	0	0	0
	2	1	0	0	0	0
	3	1	0	0	0	0
Bilirubin	1	0	0	0	0	0
	2	0	0	0	0	0
	3	2	1	0	0	0
Creatinine	1	0	0	0	0	0
	2	0	0	0	0	0
	3	1	0	0	0	0
Rash	1	0	0	0	0	0
	2	0	0	0	0	0
	3	0	1	0	0	0
Neuralgia	1	2	1	0	0	0
	2	1	1	0	0	0
	3	1	2	0	0	0
Epiphora	1	2	1	0	0	0
	2	1	1	0	0	0
	3	1	3	0	0	0
Mucositis (oral)	1	1	1	0	0	0
	2	0	1	0	0	0
	3	0	1	0	0	0

AST, Glutamic pyruvic transaminase; ALT, glutamic oxaloacetic transaminase; ALP, alkaline phosphatase. *Dose-limiting toxicity.

metastatic sites, including peritoneum (n=9), liver (n=5), and extra-regional lymph nodes (n=7).

MTD and RD. Hematological and non-hematological toxicities are summarized in Tables II and III. The first three patients enrolled at level 1. Although all three patients experienced grade 3 neutropenia and one experienced grade 3 leukocytopenia, no DLTs were observed. The next three patients enrolled at level 2. Out of these patients, two developed grade 3 neutropenia and one developed grade 3 leukocytopenia and thrombocytopenia. However, no DLTs occurred at this level. Therefore, the next three patients were enrolled at the highest level (level 3). One patient developed grade 3 nausea, vomiting, and general fatigue, which comprised of a DLT. Therefore, additional patients were enrolled at this level to confirm the MTD, and the second additional patient experienced grade 4 febrile neutropenia. Based on these results, the MTD and RD were determined to be the level 3 (paclitaxel: 120 mg/m^2, cisplatin: 30 mg/m^2) and level 2 (paclitaxel: 120 mg/m^2, cisplatin: 20 mg/m^2) doses, respectively.

Table IV. *Clinical outcomes*.

	No. of courses	Response		PFS (days)	Survival (days), status
		Measurable	Non-measurable		
Level 1 (n=3)					
Case 1	7	PR	IR/SD	706	706, Alive
Case 2	3	SD	IR/SD	95	322, Dead
Case 3	5	PR	IR/SD	95	274, Dead
Level 2 (n=3)					
Case 4	3	PR	IR/SD	440	454, Dead
Case 5	8	PR	IR/SD	219	302, Dead
Case 6	5	PR	IR/SD	260	260, Alive
Level 3 (n=5)					
Case 7	6	PR	IR/SD	140	259, Dead
Case 8	3	PR	IR/SD	232	448, Alive
Case 9	4	PR	IR/SD	242	379, Alive
Case 10	5	SD	IR/SD	122	427, Alive
Case 11	1	SD	IR/SD	71	183, Dead
Median Total (n=11)	5	-	-	219	454

PR: Partial response; IR: incomplete response; SD: stable disease; PFS: progression-free survival.

Clinical outcomes. Clinical outcomes are summarized in Table IV. Overall, two out of the three patients at level 1, all three patients at level 2, and three out of the five patients at level 3 experienced a partial response (PR), for an overall RR of 73%. Median progression-free survival (PFS) at all levels was 219 (range 71-706) days. Five patients remain alive, and four of them received second-line or third-line chemotherapy. One patient appeared to be eligible for curative resection due to down-sizing of a solitary liver metastasis and bulky lymph node metastases. Therefore, he underwent curative interventional surgery and total gastrectomy with D2 lymph node dissection and partial hepatectomy. Pathological examination revealed the chemotherapeutic effect to be grade 2 for the primary lesion and grade 3 (complete response) for the metastatic liver tumor. He received adjuvant chemotherapy with S-1-alone and remains alive without recurrence. Median overall survival (OS) at all levels was 454 (range 183-706) days.

Discussion

The recent introduction of new chemotherapeutic agents, including molecularly-targeted therapies, has improved the prognosis of patients with advanced gastric cancer (10-17, 20). When considering long-term treatment, preservation of a patient's quality of life, while continuing chemotherapy is critical. Chemotherapy administration at outpatient clinics may be ideal for patients with gastric cancer with a good PS. Therefore, establishment of an outpatient chemotherapy regimen that does not compromise of antitumor efficacy is warranted. Combination chemotherapies including cisplatin, which plays an important role in gastric cancer therapy, have been associated with two major problems when administered in the outpatient setting. One issue is nephrotoxicity, which is caused by molecular damage to renal tubules. Although cisplatin-induced nephrotoxicity can be prevented by hydration, it is difficult to administer an adequate volume of fluid at an outpatient clinic. Therefore, hospitalization would be required at the time of cisplatin administration. Previous reports have indicated that fractional administration of cisplatin does not cause nephrotoxicity, even without a great volume of hydration (21-24). Such cisplatin administration schedules that do not require hydration enable use in the outpatient clinic. In the present study, no nephrotoxicity was experienced at any level, suggesting that this treatment schedule, which also does not include hydration, does not negatively impact renal function.

Another major toxicity associated with cisplatin is chemotherapy-induced nausea and vomiting (CINV). High doses of cisplatin (≥50 mg/m^2) are classified as having high emetic risk (25). However, cisplatin doses <50 mg only carry a moderate emetic risk. Therefore, fractional administration of CDDP reduces emetic risk, potentially enabling treatment at an outpatient clinic. In addition, recent advances in antiemetic therapy, including palonosetron and aprepitant, could make the use of chemotherapeutic agents, including emetic agents, manageable at the outpatient clinic (26, 27). Since one patient developed grade 3 nausea and vomiting at level 3, these toxicities were confirmed as DLTs. However, nausea and vomiting were manageable in all patients at

levels 1 and 2 due to the use of newer antiemetic agents. Therefore, the dose at level 2, which was the RD, is expected to be tolerable as outpatient chemotherapy.

We previously reported that the antitumor activity of cisplatin depends on the total administered dose and the cumulative area under the curve (AUC), whereas its toxicity is related to the peak plasma concentration *in vivo* (28). Based on these experimental data, we reported the efficacy and feasibility of fractional administration of cisplatin for advanced gastric cancer (23, 24). Thus, CS, which is a standard regimen, was administered with fractional cisplatin at an outpatient clinic without hydration at our hospital. Therefore, we conducted this phase I study to establish a triplet chemotherapy regimen that added paclitaxel to this tolerated fractional CS regimen aiming to improve the prognosis of patients with unresectable gastric cancer and enable outpatient treatment. The efficacy and feasibility of triplet regimens have been reported in several previous studies and they are recognized as a standard strategy for advanced gastric cancer in order to achieve a more favorable prognosis (12, 13). Even though the toxicities associated with triplet chemotherapy, particularly myelosuppression, are severe compared to those associated with doublet chemotherapy, their antitumor efficacy is expected to yield favorable clinical outcomes. Indeed, the major toxicities in the present study were myelosuppression and grade 3/4 toxicities at all levels, including neutropenia in 55% (6/11) of patients and leukocytopenia in 27% (3/11) of patients. Although one of five patients at level 3 developed grade 4 febrile neutropenia, which was defined as a DLT, myelosuppression was manageable at level 2, which was confirmed as the RD, indicating that this regimen can be used in the outpatient clinic.

In conclusion, the RDs of paclitaxel and CDDP were established as 120 mg/m^2 and 20 mg/m^2, respectively, and the safety and feasibility of this triplet regimen as first-line chemotherapy at an outpatient clinic are supported by the results of this study. Although further clinical trials on a larger number of patients are recommended to confirm the efficacy and safety of triplet chemotherapy with PCS, this triplet chemotherapy regimen appears to be an excellent candidate for a standard treatment strategy for unresectable advanced gastric cancer.

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Received August 23, 2012
Revised October 11, 2012
Accepted October 12, 2012