Intraperitoneal Administration of Paclitaxel Followed by Paclitaxel, Cisplatin, and S-1 Chemotherapy for Cytology-positive Gastric Cancer: A Feasibility Study

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Abstract. *Background/Aim:* A preliminary study evaluating the feasibility of single intraperitoneal (IP) administration of paclitaxel followed by paclitaxel and cisplatin with S-1 (PCS) systemic chemotherapy for cytology-positive (CY1) gastric cancer. *Patients and Methods:* Staging laparoscopy was performed to confirm CY1 and P0 status. Initially, patients received IP paclitaxel. Beginning 7 days later PCS was given every 3 weeks followed by second-look laparoscopy. *Results:* Nine patients were enrolled. The toxic effects of IP and systemic chemotherapy were acceptable. After chemotherapy, 8 patients converted from CY1P0 to CY0P0 and 1 patient from CY1P0 to CY1P1. Gastrectomy was performed on 8 patients except for the CY1P1 patient. Four patients were alive without recurrence. The 2-year overall and progression-free survival rates were 76% and 65%, respectively. *Conclusion:* Combination chemotherapy with IP paclitaxel and sequential PCS is safe and may be effective for CY1 gastric cancer.

Gastric cancer is the most common type of cancer and the second leading cause of cancer-related mortality in Japan (1). Peritoneal metastasis (P1) is the most common type of metastasis in patients with advanced gastric cancer and is associated with an extremely poor prognosis (2). Additionally, positive peritoneal lavage cytology (CY1) is a predictor of peritoneal dissemination and poor prognosis (3).

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Therefore, CY1 is categorized as distant metastasis in both the TNM and Japan Gastric Cancer Association classifications (4, 5). Though there is no standard treatment for CY1P0 gastric cancer, in clinical practice in Japan and Korea these patients undergo standard gastrectomy with D2 lymph node dissection and adjuvant chemotherapy. Koderá *et al.* reported a phase II study of gastrectomy followed by postoperative chemotherapy with S-1 for CY1P0 gastric cancer (CCOG0301 study) in which a high frequency of peritoneal recurrence was shown with a 2-year survival rate of 47% (6). To improve the prognosis of CY1P0 gastric cancer, eradication of intraperitoneal (IP) free cancer cells is required. An effective method of eradicating these cells is thought to be IP chemotherapy. IP chemotherapy was originally developed to enhance antitumor activity against peritoneal metastasis by maintaining a high concentration of the drug in the peritoneal cavity for a long period of time.

Recently, we reported that IP administration of paclitaxel achieved high and long-lasting concentrations of paclitaxel in the peritoneal cavity in gastric cancer patients with peritoneal metastasis and demonstrated that IP free cancer cells showed vacuolization of the cytoplasm and abnormal morphology six hours after IP administration of paclitaxel. No viable cancer cells were detected 24 hours after IP administration of paclitaxel even after only one administration (7). As for systemic chemotherapy, S-1 and cisplatin (CS) is regarded as the standard first-line regimen for highly advanced gastric cancer in Japan, according to the results of the SPIRITS trial (8). Conversely, paclitaxel has a high transition rate into the peritoneal cavity even when intravenously administered (9). We hypothesized that the addition of paclitaxel to CS intravenously could eradicate IP free cancer cells. Recently, Kim *et al.* reported a phase II study of paclitaxel, cisplatin and S-1 (PCS) triplet combination chemotherapy showing good efficacy with

favourable response rates in patients with advanced gastric cancer (10). Here we evaluate the feasibility of combination chemotherapy with single IP paclitaxel followed by intravenous PCS triplet regimen for CY1P0 advanced gastric cancer.

Patients and Methods

Patient population. This was a prospective clinical study. All patients with gastric cancer and histologically confirmed P0 and CY1 at staging laparotomy in our department between December 2010 and March 2016 were reviewed. All patients enrolled in the study met the following eligibility criteria that are frequently used in conventional clinical trials (11, 12): histologically proven gastric adenocarcinoma; adequate bone marrow function (leucocyte count 3,000-12,000/mm³, neutrophil count $\geq 1,500/\text{mm}^3$, platelet count $\geq 100,000/\text{mm}^3$); adequate liver function (total serum bilirubin ≤ 1.5 mg/dl and serum transaminase ≤ 2 times the upper limit of normal); adequate renal function (serum creatinine ≤ 1.5 mg/dl); Eastern Cooperative Oncology Group (ECOG) performance status 1 or less; aged 20-80 years; no metastasis to distant lymph nodes, liver, lung, pleura, brain, or bone; no other severe medical conditions or active malignancies; and no previous systemic chemotherapy.

In accordance with the ethical standards of the committee responsible for human experimentation and with the Helsinki Declaration of 1964 and later versions, written informed consent was obtained from all patients before the initiation of treatment. Patients anticipated to be eligible were informed before treatment about the therapeutic strategy, emphasizing its potential benefits as well as the possible risks of mortality and morbidity. Informed consent was obtained from all patients at the time of first staging laparoscopy.

Treatment protocol. Paclitaxel 60 mg/m² was administered intraperitoneally during the staging laparoscopy, followed by systemic chemotherapy initiated within 1 week of the laparoscopy (13). Systemic chemotherapy consisted of a 21-day cycle of intravenous (IV) paclitaxel 80 mg/m² and IV cisplatin 30 mg/m² each administered over 1 h on days 1 and 8 and orally administered S-1 80 mg/m²/day for 14 days followed by 7 days of rest. The PCS regimen used in this study was a modification of that developed by Kim *et al.* (10). Treatment was administered every 3 weeks and continued until disease progression, development of unacceptable toxicity, or patient refusal for a maximum 8 cycles. Treatment was followed by second-look laparoscopy except in patients with disease progression.

Evaluation and statistical analysis. Tumour response was evaluated according to the Japanese Classification of Gastric Carcinoma (JCGC) criteria based on endoscopic examination findings (14). Only measurable lesions were evaluated according to the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 (15). Toxicity and adverse events were described using the National Cancer Institute Common Toxicity Criteria grading version 4.0. Intraoperative and postoperative complications were reported according to the Clavien–Dindo classification (16). Surgical specimens were assessed based on JCGC histological criteria (5). In this study pathological response was defined as above Grade 1b. Overall survival (OS) was calculated from the date of the first staging laparoscopy to death from any cause or the last follow-up

Table I. Patient characteristics (n=9).

	Number
Age (years)	
Median (range)	66 (60-79)
Gender	
Male	6
Female	3
Macroscopic findings	
Type1	0
Type2	1
Type3	5
Type4	3
Histological subtype	
Differentiated	3
Undifferentiated	6
Clinical T stage	
T1	0
T2	0
T3	0
T4a	9
T4b	0
Clinical N stage	
N0	2
N1	2
N2	5
N3	0
Washing cytology (CY)	
Negative	0
Positive	9
Peritoneal metastasis	
No	9
Yes	0

Japanese Classification of Gastric Carcinoma (3rd English edition).

date. Progression-free survival (PFS) was calculated from the date of the first staging laparoscopy to the first observation of disease progression or the day the first recurrence was diagnosed after curative surgery. All statistical analyses were performed using SAS software (version 9.4; SAS Institute, NC, USA).

Results

Patient characteristics. Between December 2010 and March 2016, 9 patients received IP administration of paclitaxel and sequential systemic PCS regimen. Characteristics of these patients are shown in Table I. In all patients the T status was estimated to be T4a, and 7 patients had lymph node metastasis. Positive washing cytology (CY1) and absence of peritoneal metastasis (P0) were confirmed for all patients by staging laparoscopy.

Safety and efficacy. The median number of chemotherapy cycles was 5 (range=2-8 cycles). The number of adverse events associated with IP chemotherapy was very low; no

Table II. Adverse events associated with intraperitoneal and systemic chemotherapy (n=9).

Toxicities	Intraperitoneal chemotherapy					Systemic chemotherapy				
	Grade 1	Grade2	Grade 3	Grade 4	%Grade 3/4	Grade 1	Grade 2	Grade 3	Grade 4	%Grade 3/4
Hematologic										
Leukopenia	1	1	0	0	0	3	2	1	1	22
Neutropenia	1	1	0	0	0	1	2	0	1	11
Thrombocytopenia	0	0	0	0	0	1	0	0	0	0
Anaemia	2	1	0	0	0	1	1	1	0	11
AST	1	0	0	0	0	3	0	0	0	0
ALT	1	0	0	0	0	3	0	0	0	0
Bilirubin	1	0	0	0	0	1	0	0	0	0
BUN	0	0	0	0	0	2	0	0	0	0
Creatinine	0	0	0	0	0	2	0	0	0	0
Gastrointestinal										
Stomatitis	0	0	0	0	0	1	0	0	0	0
Anorexia	0	0	0	0	0	3	0	0	0	0
Nausea	0	0	0	0	0	2	1	0	0	0
Vomiting	0	0	0	0	0	0	0	0	0	0
Diarrhoea	0	0	0	0	0	1	1	0	0	0
Fatigue	0	0	0	0	0	3	1	0	0	0
Allergy	0	0	0	0	0	0	0	1	0	11
Neurosensory	0	0	0	0	0	0	0	0	0	0

AST: Aspartate aminotransferase; ALT: alanine aminotransferase; BUN: blood urea nitrogen.

patients developed grade 3-4 adverse reactions after IP chemotherapy (Table II). Two patients receive only four courses: one because of Grade 4 leukopenia and neutropenia and the other was because of Grade 3 anaemia. Conversely, nonhematologic toxicities were generally mild and manageable except for 1 patient who developed a Grade 3 infusion allergy to cisplatin in the middle of the second treatment course. Fatigue was the most common nonhematologic toxicity (Table II). There were no treatment-related deaths. The response rate based on Japan Clinical Oncology Group (JCOG) criteria was 67% (PR, 6; SD, 3). Among the 5 patients who had measurable lesions, the response rate was 60% (PR, 3; SD, 2) by RECIST criteria. No patients had disease progression. All patients underwent second-look laparoscopy between 14 and 38 days (mean=30) after completion of chemotherapy. The peritoneal cytology findings converted from positive (CY1) to negative (CY0) in 8 (89%) patients. Only 1 patient (11%) converted from CY1P0 to CY1P1. Gastrectomy with D2 dissection was performed on the 8 CY1P0 patients but not on the CY1P1 patient. Four patients underwent splenectomy. Other surgical findings are shown in Table III. Surgical complications were observed in 2 patients (22%). A pancreatic fistula scored as grade 1 occurred in 1 patient. There were no surgery-related deaths. The histological response of the primary lesion according to JCGC criteria were Grade 1a in 2 patients, Grade 2 in 5 patients, and Grade 3 in 1 patient. After surgery,

7 out of 8 patients (87.5%) received a postoperative course of weekly paclitaxel and S-1 adjuvant chemotherapy for at least 1 year. One patient refused postoperative adjuvant chemotherapy. At the time of analysis (April 2018), the median duration of patient follow-up for censored patients was 40 months. The median survival time (MST) of all patients was 34 months and the Kaplan–Meier OS and PFS curves are shown in Figure 1A and B, respectively. The 2- and 5-year OS rates were 76% and 34%, respectively, and the 2- and 5-year PFS rates were 65% and 39%, respectively. 4 patients were still alive without recurrence and 5 patients had died owing to peritoneal recurrence and disease progression.

Discussion

The optimal therapeutic approach for patients with positive peritoneal cytology (CY1) as the only marker of metastatic disease has not been established.

Most of these patients have a poor prognosis, with a very high risk for peritoneal recurrence, even in the absence of overt peritoneal carcinomatosis (3).

In Japan, upfront surgery and subsequent S-1 chemotherapy is frequently selected for CY1 gastric cancer patients, and the 2- and 5-year survival rates are 47% and 26%, respectively, based on the CCOG0301 study (17). Similarly, Kano *et al.* reported the efficacy of postoperative

Figure 1. Kaplan–Meier curves for the 9 patients. A) Overall survival, B) Progression-free survival.

Table III. Surgical findings and complications (n=9).

	Number
Washing cytology (CY)	
Negative	8
Positive	1
Peritoneal metastasis	
Negative	8
Positive	1
Type of resection	
Total gastrectomy	7
Distal gastrectomy	1
Not resected	1
Residual tumour	
R0	8
R1	0
R2	1
Operative time (min)	
Median, range	245, 30-440
Intraoperative bleeding (ml)	
Median, range	380, 10-858
Surgical Complications	
Leakage	0
Postoperative bleeding	0
Pancreatic fistula	1
Intra-abdominal abscess	0
Pneumonia	0
Wound infection	1
Stomal Stenosis	0

Japanese classification of gastric carcinoma (3rd English edition).

S-1 chemotherapy for CY1 gastric cancer patients who received prior surgery, and the 2- and 5-year survival rates were 38.9% and 17.8%, respectively (18). Both Kodera and Kano reported that the most frequent pattern of disease recurrence was peritoneal carcinomatosis, occurring in 62% and 52.9% respectively. Presumably improvement in the prognosis for patients with CY1 disease requires the eradication of IP free cancer cells.

Ott *et al.* reported that neoadjuvant chemotherapy (NAC) had the potential benefit of eradicating IP free cancer cells and, consequently, improved prognosis (19). Some studies evaluated the role of primary resection in combination with NAC for CY1 gastric cancer patients. Mezhier *et al.* examined the outcome of 291 patients with positive peritoneal cytology who received cisplatin-based chemotherapy (20) and Lorenzen *et al.* examined the effect of cisplatin and folinic acid plus fluorouracil as part of NAC for patients with positive peritoneal cytology (21). However, in these studies, the rate of negative change of CY status following a course of NAC was reported to be only 56% and 37% respectively (20, 21).

In this preliminary study, our new regimen achieved an 89% conversion rate of peritoneal cytology findings from positive to negative (8/9). The conversion rate in this study was higher than that of these previous NAC studies. In addition, in this study, the 2- and 5-year survival rates reached 76% and 34%, respectively. Our treatment method has the potential to improve the clinical outcome of OS in

patients with CY1 disease to a greater extent than that of the CCOG0301 study. One explanation for the improvement in prognosis in our study may be the high conversion rate of peritoneal cytology findings from positive to negative from treatment with IP paclitaxel and systemic PCS chemotherapy.

Because grade 3-4 toxicities did not occur with single IP paclitaxel, the single administration of IP paclitaxel is considered to be a safe treatment option. For systemic PCS chemotherapy, leukopenia was shown to be the main toxicity. The incidence of hematologic adverse events in our study was similar to that of the previous phase II study of a combination of PCS triplet chemotherapy in patients with unresectable or metastatic gastric cancer (10). Additionally, most nonhematologic toxicities were relatively mild with the exception of 1 patient who developed a Grade 3 allergy to cisplatin. As for surgical complications, a postoperative morbidity rate of 22% was observed, which is comparable to a previous report of surgery after NAC for advanced gastric cancer (22). In this study, there were no surgery-related deaths.

Single IP administration of paclitaxel combined with IV administration of paclitaxel, cisplatin plus S-1 was well-tolerated and is a feasible treatment, but it did not show sufficient efficacy for patients with CY1 disease. However, the clinical response of our new regimen is promising because 8 out of 9 patients enrolled had no cancer cells on peritoneal cytology and no macroscopic peritoneal deposits after chemotherapy. Further clinical trials are warranted to examine the clinical significance of this regimen.

In conclusion, our preliminary study provided evidence that combination chemotherapy including single IP paclitaxel followed by intravenous paclitaxel and cisplatin with S-1 is a safe regimen and warrants further clinical trials to clarify its significance for cytology-positive gastric cancer.

Conflicts of Interest

None of the Authors have any conflicts of interest to declare.

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