Combination Chemotherapy with 5-Fluorouracil, Cisplatin and Paclitaxel for Pretreated Patients with Advanced Gastric Cancer

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Abstract. *Background: Paclitaxel, 5-FU and cisplatin are effective against gastric cancer, but the optimal regimen for combined chemotherapy with these drugs remains unclear. This combination regimen was used here for advanced gastric cancer mainly in a second- or third-line setting. Patients and Methods: Thirty-nine gastric cancer patients were treated with the following regimen. Paclitaxel 40 mg/m^2 infusions were administered on days 1 and 8, combined with cisplatin (6.5 mg/m^2) and 5-FU (350 mg/m^2) on days 1 through 8, followed by 3 weeks' rest. Results: The response rate was 17.9% (7/39); seven patients had a partial response, twelve had stable disease and twenty had progressive disease. The median overall survival was 8.2 months and the median time to progression was 6.4 months. The frequency of grade 3 or 4 neutropenia, fatigue and anorexia was 7.6%, 5.1% and 7.6%, respectively. Conclusion: This combination therapy is recommended as second- or third-line therapy against advanced gastric cancer, with a tolerable and acceptable toxicity profile.*

The prognosis of patients with recurrent or metastatic gastric cancer is very poor. Chemotherapy can prolong survival and improve quality of life when compared with best supportive cares alone. Worldwide, cisplatin-based or 5-fluorouracil (5-FU)-based combination chemotherapy has been recommended (1-3). The therapeutic efficacy of low dose administration of 5-FU and cisplatin has been reported in patients with advanced and recurrent gastric cancer.

Paclitaxel is recognized as one of the active cytotoxic agents for gastric cancer (4-6). In a Japanese Phase II trial of paclitaxel administration by 3-hour infusion every 3 weeks for patients with gastric cancer, the objective response rate was 23% (5). The combination of paclitaxel, 5-FU and cisplatin is also active against adenocarcinoma of the esophagus and gastroesophageal junction (7). Paclitaxel exerts its cytotoxic effects through a mechanism different from that of 5-FU and thus shows no cross-resistance with 5-FU. In tumor cell lines, the combination of paclitaxel and 5-FU has demonstrated additive cytotoxicity, especially with sequential exposure (8). Based on this, we performed combination chemotherapy of paclitaxel, cisplatin and 5-FU for advanced gastric cancer in a mainly second- or third-line setting. Here we report the efficacy and toxicity of this combination therapy for patients with advanced gastric cancer.

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Key Words: Combination chemotherapy, paclitaxel, gastric cancer, 5-FU, cisplatin.

Patients and Methods

Patients. This study consisted of 39 patients with metastatic or recurrent gastric cancer treated with a combination of paclitaxel, cisplatin and 5-FU therapy between September 1997 and March 2006 at the Niigata Cancer Center Hospital, Niigata, Japan.

The eligibility criteria were as follows: (i) histologically proven adenocarcinoma of the stomach; (ii) age of 80 years or less; (iii) performance status of 2 or less on the Eastern Cooperative Oncology Group scale; (iv) no other serious disease; and (v) written informed consent given before the commencement of treatment.

Treatment methods. The treatment (PTX+FP) schedule consisted of 5-FU at 350 mg/m^2/day and cisplatin at 6.5 mg/m^2/day by continuous infusion on days 1 to 8, and paclitaxel at 40 mg/m^2 infusion administered on days 1 and 8. Short-term premedication for paclitaxel-associated hypersensitivity reactions was used: dexamethasone (8 mg), chlorpheniramine maleate (50 mg) and famotidine (20 mg) were administered 30 minutes before the infusion of paclitaxel.

If the cancer had not progressed, then the next cycle was to be repeated 21 days after the first cycle. In the event of serious hematological toxicity, treatment was suspended until recovery. CBC and serum chemistry was monitored before each course.

Response and toxicity assessments. Tumor measurements for response assessment in patients with primary lesions were made every 1 to 2 months by computed tomography (CT), upper gastrointestinal radiography and gastroendoscopy. Objective responses were classified according to response evaluation criteria in solid tumors (RECIST) criteria (9) and criteria for response

Table I. *Patient characteristics.*

Characteristics	
Median age (years) (range)	62 (32-78)
Male/female	24 / 15
Disease status	
Metastatic / recurrent	8 / 31
Histological type	
Differentiated / undifferentiated	15 / 24
Prior chemotherapy	
None / one regimen/ two regimens	4 / 19 / 16
S-1	19
S-1+CDDP	13
MTX+5-FU+CDDP	10
Weekly paclitaxel	2
UFT	3
5'-DFUR	1
MMC+5-FU	1
MMC+carboplatin	1
Epi+MMC+5-FU	1
5-FU+CDDP+leucovorin	1

S-1, tegafur-gimeracil-oteracil-potassium; MTX, methotrexate; 5-FU, 5-fluorouracil; CDDP, cisplatin; UFT, uracil-tegafur, 5'DFUR, doxifluridine; MMC, mitomycin C; Epi, doxorubicin.

assessment of chemotherapy for gastric carcinoma established by the Japanese Research Society of Gastric Cancer (10). The survival period was calculated from the start of treatment to death or the latest follow-up day. Symptomatic toxicity and laboratory data were monitored twice a month at the outpatient clinic. Toxicity was evaluated according to the National Cancer Institute common terminology criteria for adverse events v3.0 (CTCAE v3.0) (11).

Results

The characteristics of 39 patients are summarized in Table I. The median age was 62 (range 32-78) years, and there were 24 males and 15 females. Thirty-one patients had recurrent disease after surgical resection, while 8 patients had metastatic disease. Prior therapies had been given for 35 (89.7%) patients, 19 patients had been treated in a second-line setting and 16 patients in a third-line setting. PTX+FP therapy was used as first-line chemotherapy in only 4 (10.2%) patients.

Efficacy. Seven out of 39 patients with measurable lesions showed a partial response (PR) as the best response (response rate, 17.9%); another 12 patients (30.7%) had stable disease (SD) and the overall tumor control rate (PR+SD) was 48.7% (Table II). Two out of 4 patients with no prior chemotherapy achieved PR (50%). Among the 19 patients who had failed first line chemotherapy, 4 achieved PR (21.1%), but among the 16 patients who had failed second-line chemotherapy, only one patient achieved PR (6.3%). The median overall survival was 8.2 months (range: 1.1-35.0 months) (Figure 1) and the median time to progression (TTP) was 6.4 months (range: 1.9-22.0 months) (Figure 2). The one-year survival rate was estimated to be 36.9% while the 2-year survival rate was 20.4% (Figure 2).

Table II. *Response rate according to setting of PTX+FP.*

	n	CR	PR	SD	PD	RR	PR+SD
Overall	39	0	7	12	20	17.9%	48.7%
Setting of PTX+FP							
First-line	4	0	2	2	0		
Second-line	19	0	4	6	9		
Third-line	16	0	1	4	11		

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; RR, response rate.

Toxicity. The incidence of major adverse events, shown as the maximum grade seen per patient, is listed in Table III. The most common hematological adverse event was neutropenia, which occurred in 7 cases (17.9%) but there were only 3 (7.6%) grade 3/4 cases. Anorexia and fatigue were the most common non-hematological toxicity. Grade 3/4 anorexia and fatigue were observed in 3 cases (7.6%) and 2 cases (5.1%), respectively. There were no treatment-related deaths during this treatment.

Discussion

For many years, 5-FU and cisplatin-based regimens have been recognized mainstream chemotherapy for advanced gastric cancer. Several studies have suggested that low-dose 5-FU plus cisplatin (FP) therapy is effective with low toxicity for advanced and recurrent gastric cancer (12-14). Recently, some new anti-cancer agents such as S-1, CPT-11 and taxanes have been used for advanced gastric cancer. In an early Phase II clinical study of S-1, the partial response rate for gastric cancer was 53.6%, the mean survival time (MST) was 298 days, and the incidence of severe adverse effects was low (15). In a late Phase II clinical study, the partial response rate was 44.2% and the MST was 207 days, whereas the frequency of adverse effects was 2-4% at grade 3 and none at grade 4 (16). Therefore, S-1 or S-1 plus CDDP combination therapies are currently recognized as one of the standard treatments for first-line chemotherapy in Japan (15-18). These therapies have high response rates, but are not indicated for patients unable to take food or liquid by mouth. In addition, patient with a good performance status recurring after first-line treatment may require effective second-line chemotherapy.

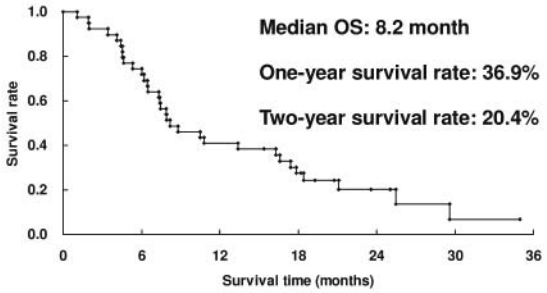

Figure 1. *Overall survival curve. Median overall survival time was 8.2 months. The initial date of reckoning was the first day of the PTX+FP chemotherapy.*

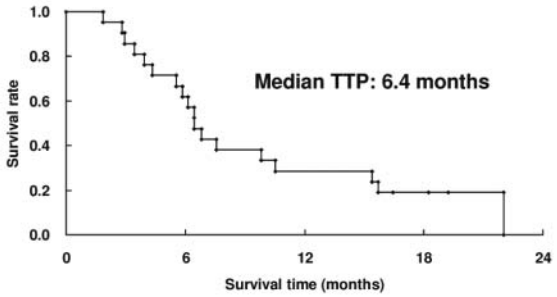

Figure 2. *Progression-free survival curve. Median time to progression was 6.4 months.*

Paclitaxel appears to have a schedule-dependent synergy with platinum compounds, as documented in established human gastric cancer cell lines (19). This synergy has led to the development of paclitaxel-platinum combination regimens in a number of solid tumors, including gastric cancer (20-22).

In the present study, 35 patients (89.7%) had received prior chemotherapy. PTX + FP therapy had mainly been used in a second- or third-line setting, and was indicated even for those patients unable to take oral medications because of gastrointestinal stenosis.

First of all, the dose of paclitaxel had to be determined. We chose 40 mg/m^2 infusion on day 1 and 8 using examples from some combination regimens including paclitaxel (23, 24). This may seem a small amount of paclitaxel, but current phase I studies of combination treatment with paclitaxel use 50-60 mg/m^2 in Japan (25, 26). As a result of treatment, 7 of 39 (17.9%) patients achieved an objective response and 11 (28.2%) showed stable disease, with a median time to progression and median overall survival of 6.8 months and 8.0 months, respectively. The response rate was slightly low compared with other regimens for gastric cancer (27-29), but we cannot easily compare with these previous studies, because these studies are almost in a first-line setting. There are few studies of second-line treatment in advanced gastric cancer (30, 31) and these studies indicated that the response rate was 15-16%. The response rate of our study was 21.1% in the second-line setting (Table II) and is acceptable when compared with previous studies (30, 31). The duration of survival was comparable with previous studies using taxanes with other agents, including 5-FU plus cisplatin (20, 30) or carboplatin alone (22). Because stable disease was observed in12 patients and disease stabilization (PR+SD) in 48.7 % (19/39), this therapy regimen appears to increase survival time. The response rate according to the chemotherapy setting shows that 5 patients (4 as second-line and 1 as third-line) who had failed in previous chemotherapy achieved partial responses. These 5 responders had been treated with UFT, S-1, S-1/CDDP or 5-FU/CDDP/leucovorin. Based on these results, the paclitaxel-containing regimen could be tried as a salvage treatment in refractory gastric carcinoma patients.

Table III. *Adverse reactions (CTCAE v3.0).*

	All grades patients	Grade 3 and 4 patients
Anemia	1 (2.6%)	1 (2.6%)
Neutropenia	7 (17.9%)	3 (7.6%)
Thrombocytopenia	3 (7.6%)	0
Fatigue	16 (41.0%)	2 (5.1%)
Anorexia	23 (58.9%)	3 (7.6%)
Nausea	13 (33.3%)	2 (5.1%)
Diarrhea	5 (12.8%)	1 (2.6%)
Stomatitis	7 (17.9%)	0
Hot flashes	3 (7.6%)	0
Alopecia	14 (35.9%)	-

The toxicity analysis in our study showed that the PTX+FP regimen was well tolerated. Hematological toxicity was not severe. Grade 3/4 neutropenia was documented in only 7.6% of patients and its duration was usually short. Non-hematological toxicity consisted of universal alopecia, anorexia and fatigue. Less toxicity is very important for second- or third-line chemotherapy because patients do not have a good status. The PTX+FP regimen was well tolerated in these groups of patients.

In conclusion, the combination of PTX+FP provides a good tumor control rate for metastatic or recurrent gastric cancer, even as second- or third-line chemotherapy. The adverse effects are few and well tolerated compared with other novel regimens currently available. In addition, PTX+FP has high potential as first-line chemotherapy for patients unable to take medication orally.

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