Phase II Study of Weekly Paclitaxel as a Second-line Treatment for S-1-refractory Advanced Gastric Cancer

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Abstract. *Background: We retrospectively evaluated the efficacy of weekly paclitaxel therapy as second-line treatment for patients with advanced gastric cancer that was refractory to S-1. Patients and Methods: In total, 33 patients received intravenous paclitaxel (80 mg m^{-2}) on days 1, 8 and 15 as part of a 4-week cycle. Results: Eight patients showed a partial response, 11 showed stable disease and 14 showed disease progression. In total, 171 courses (mean=5.2; range=3-16) were administered. Thirteen cases subsequently underwent third-line treatment. The median survival time and time to progression from the time of second-line treatment was 8.0 months and 4.2 months, respectively. The most common haematological toxicities were leukopenia and neutropenia. Non-haematological toxicities were generally mild to moderate and controllable. Conclusion: This study showed favourable therapeutic outcomes for advanced gastric cancer patients. However, it will be necessary to confirm the advantages of paclitaxel treatment for S-1-refractory advanced gastric cancer in a larger population.*

Gastric cancer is the second most common cause of cancer-related deaths worldwide (1). In Japan, therapeutic outcomes for gastric cancer are satisfactory due to the high incidence of early gastric cancer (2) and have been improved by a screening survey system developed in Japan to detect gastric cancer (3). However, many patients present with advanced cases (that is, with unresectable status, metastatic disease or recurrence after curative gastrectomy) and the survival times are unsatisfactory in many countries (4-6). Therefore, there is a need to establish an effective chemotherapeutic regimen to improve the survival time for patients with advanced gastric cancer.

S-1 (Taiho Pharmaceutical Company, Tokyo, Japan) is a novel oral anticancer drug composed of tegafur (FT), 5-chloro-2,4-dihydroxypyridine (gimeracil, CDHP) and oteracil potassium (oteracil, Oxo) at a molar ratio of 1:0.4:1 (7). This formulation was designed to enhance the oral efficacy of FT, a prodrug of 5-fluorouracil (5-FU), by the addition of CDHP, which inhibits the activity of the dihydropyrimidine dehydrogenase (DPD) enzyme that degrades 5-FU (8). The efficacy of S-1 alone or in combination with other drugs for advanced gastric cancer has been demonstrated in phase II and III studies (9-13). S-1 is therefore a key drug for the treatment of advanced gastric cancer. However, >50% of the patients who receive first-line chemotherapy with S-1 do not respond to the treatment. Hence, there is a need to establish a second-line regimen for use after the failure of first-line chemotherapy. Taxane derivatives have a unique mechanism of action that differs from those of fluoropyrimidine and platinum. They show little cross resistance and toxicity overlap with other anticancer drugs. Taxane derivatives are thus suitable chemotherapeutic agents for salvage treatment in patients with advanced gastric cancer that is refractory to S-1. The current retrospective study evaluated the response rate, time to progression, overall survival, and tolerability of weekly therapy with paclitaxel (PAC) as second-line treatment for patients with S-1-refractory advanced gastric cancer.

Patients and Methods

Patient selection. Between April 2000 and March 2006, 33 patients with advanced gastric cancer (unresectable tumours in 15 patients, recurrent tumours in 9 patients and non-curatively resected tumours in 9 patients) were treated orally with S-1 alone at 80-120 mg daily according to body surface area (BSA) as first-line chemotherapy (BSA<1.25 m^2, 80 mg/day; 1.25≤BSA<1.50 m^2, 100 mg/day; BSA≥1.50 m^2, 120 mg/day) for 8 weeks with a 2-week interval in

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an outpatient setting at the Department of Surgery, Gastroenterological Centre, Yokohama City University, Japan, and the Department of Gastroenterological Surgery, Yokohama City University Graduate School of Medicine. These 33 received weekly PAC (also known as Taxol; Bristol-Myers Squibb Co., Tokyo, Japan) chemotherapy after the failure of S-1. As a third-line treatment, a regimen of irinotecan (CPT-11) combined with CDDP was administered to patients who had tumours that were refractory to taxane derivatives.

All patients were required to have an Eastern Clinical Oncology Group (ECOG) performance status of ≤2, a life expectancy of >3 months and adequate haematological parameters (that is, a total leukocyte count of >3,500/μl, a neutrophil count of >1,500/μl, a platelet count of >100,000/μl, a serum creatinine level of <1.5 mg/dl, a total serum bilirubin level of <1.5 mg/dl and an aspartate aminotransferase level of <2.5 times the upper limit of the institutional normal range). Patients were excluded from the study if they had any other concurrent or prior malignancy, active uncontrolled infection or disease, or a neurological or mental disease that would prevent adequate comprehension of the information sheet, or if they were receiving concurrent treatment with any other drugs that could potentially interfere with the study evaluation. The pretreatment evaluation consisted of a complete history and physical examination, blood count, serum biochemistry, chest X-ray, and computed tomography (CT) of the thorax and abdomen. Furthermore, bone scintigraphy, aspiration cytology and aspiration or incisional biopsy were optionally employed. All patients gave informed consent before the initiation of second-line treatment.

Study design. In this study, 80 mg/m^2 PAC was diluted in 250 ml of 5% dextrose in water, and administered weekly by 1-h intravenous infusion on days 1, 8 and 15. To prevent hypersensitivity reactions, all of the patients were premedicated with dexamethasone (20 mg *i.v.*) 30 min prior to PAC infusion. This treatment was repeated every 4 weeks as one course at least three courses at the outpatient setting. A new cycle of treatment was begun if the total leukocyte count was >3,000/μl, the neutrophil count was >1,500/μl, the platelet count was >100,000/μl and all of the relevant non-haematological toxicities were grade 2 or below. In the event of toxicity, chemotherapy was postponed until it had been resolved.

The treatments were continued unless patient refusal, unacceptable toxicity or disease progression occurred. If disease progression was judged to be present at the radiographic assessment 2 weeks after the final treatment, another chemotherapeutic regimen comprising 60 mg/m^2 irinotecan hydrochloride and 30 mg/m^2 CDDP was recommended as a third-line treatment.

Study evaluations. All of the responses were principally assessed by physical examination, direct visualization, upper gastrointestinal series, gastrofiberscopy and CT. The tumour evaluation was carried out according to the Response Evaluation Criteria in Solid Tumours (RECIST) (14), and responses were confirmed within 2 weeks after every three courses. A complete response (CR) was defined as total remission of the disease for a minimum of 4 weeks. A partial response (PR) was defined as a >30% reduction in the sum of the maximum diameters of the indicator lesions without the appearance of new lesions for at least 4 weeks. Progressive disease (PD) was defined as a >20% enlargement of an indicator lesion or the development of new lesions. Stable disease (SD) was defined as a lesion that did not meet the criteria for CR, PR or PD. All adverse events were graded using the version 2.0 of the Common Toxicity Criteria of the National Cancer Institute (NCI-CTC) (15) at each cycle. In the event of toxicity according to the NCI-CTC, chemotherapy was postponed until it had been resolved. In patients experiencing a grade 3 or 4 toxicity, agents were reduced by 25% from the next treatment.

Survival analysis. The survival time and the time to progression (TTP) were measured from the time of treatment initiation until progression of the disease, respectively. The duration of each response was measured from the time that the response was documented until progression was identified. Survival data on patients who came off study secondary to a declining performance status were included in the calculation for overall survival and TTP. The Kaplan-Meier method was used to calculate the survival rate. The difference between the curves was assessed using the log-rank test. Results with a p-value ≤0.05 were considered statistically significant.

Results

Patient characteristics. Patient characteristics are shown in Table I. Their median age (range, 52-79) was 64 years, with 27 males and six females. Most of the patients (90.9%) had a good performance status (ECOG 0 or 1). Macroscopically ill-defined, and deeply invasive tumours were frequent. Non-resected tumors (45.5%) were most frequently observed and there was no difference in the site of tumour.

Efficacy of second-line treatment. All patients were assessable for response. No case of CR was observed, while eight patients (24.2%) showed a PR, 11 (33.3%) showed SD and 14 (42.4%) showed PD.

Second-line treatment. In total, 171 courses (mean=5.2 per patient; range=3-16 per patient) were administered. A total of 13 cases subsequently underwent third-line treatment on account of good performance status after disease progression. Third-line treatment was administered to 4 patients who obtained PR, 5 patients who obtained SD, and 4 patients who obtained PD in second line treatment. However, the remaining 20 cases could not undergo third-line chemotherapy due to poor performance status according to disease progression.

Survival. The mean follow-up time after the initial treatment was 18.3±9.0 months. The mean follow-up time after the second-line treatment was 11.7±8.2 months. The median overall survival time (MST) from the time of initial treatment for all patients was 15 months (95% confidence interval [CI]=10-20 months). The 1-year and 2-year survival rate was 71.4% and 21.4%, respectively (Figure 1). The MST from the time of second-line treatment was 8 months (95% confidence interval [CI]=6-9 months) (Figure 2).

Table I. *Patient characteristics*.

Characteristic	(n=33)
Age (years)	
Median	64
Range	52-79
Gender	
Male	27
Female	6
ECOG performance status	
0	8
1	22
2	3
Location of tumour	
Lower third	7
Middle third	6
Upper third	11
Entire of the stomach	9
Macroscopic appearance	
Well-defined	11
Ill-defined	22
Tumor diameter (mm)	
<100	22
≥100	11
Depth of invasion	
T2	9
T3, 4	24
Histological type	
Differentiated	16
Undifferentiated	17
Cause of chemotherapy	
Non-curative	9
Non-resection	15
Recurrence	9
Site of tumour	
Lymph nodes	9
Haematogenous metastasis	10
Peritoneal metastasis	9
Combined	5

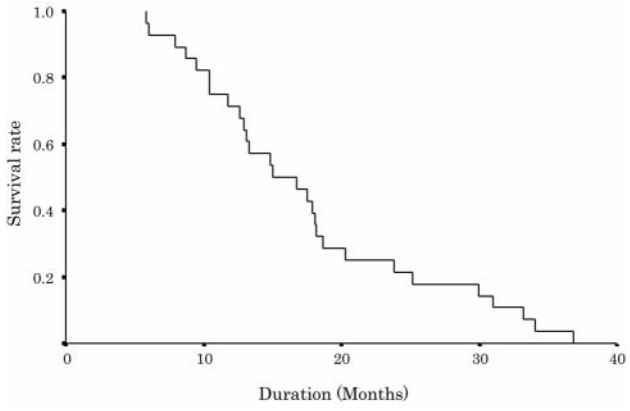

Figure 1. *Overall survival in all registered patients*.

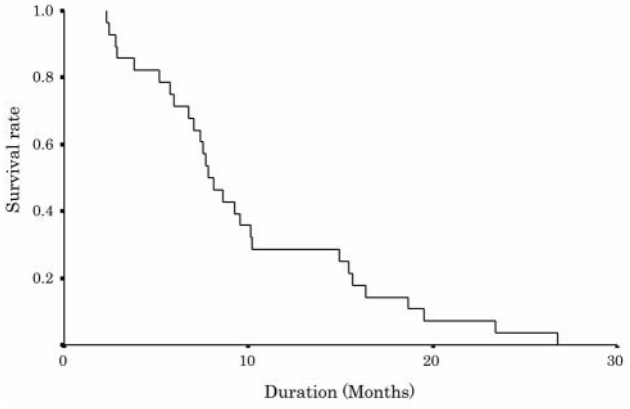

Figure 2. *Survival after second-line administration of paclitaxel*.

Time to progression. The median TTP after the first-line treatment was 5.60 months (95% confidence interval [CI]=4.55-6.55 months). The median TTP after the second-line treatment was 4.20 months (95% confidence interval [CI]=3.23-5.17 months) (Figure 3).

Toxicity. Toxicity was assessed in all of the patients. The chemotherapy toxicities during the total treatment courses are summarized in Table II. The most common haematological toxicities were leukopenia and neutropenia. Grade 3-4 leukopenia and neutropenia were 9.1% and 3.0%, respectively. All of the patients were successfully treated with prophylactic antibiotics and granulocyte colony-stimulating factor (G-CSF). Anaemia and thorombocytopenia were not common in this series. Non-haematological toxicities were generally mild to moderate and controllable. Grade 1-2

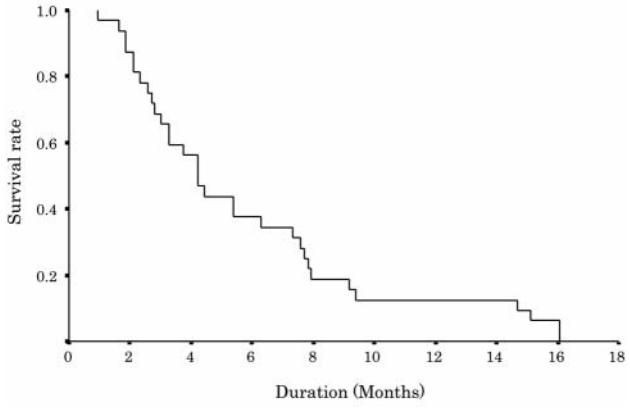

Figure 3. *Time to progression after second-line administration of paclitaxel*.

Table II. *Toxicity.*

Toxicity	Number of patients	
	Grade 1-2	Grade 3-4
Haematological		
Leucopenia	15	3
Neutropenia	13	1
Anaemia	2	1
Thrombocytopenia	0	0
Non-haematological		
Stomatitis	1	0
Anorexia	5	1
Nausea	1	0
Vomiting	0	0
Diarrhoea	1	0
Alopecia	19	
Neuropathy	4	0
Oedema	1	0
Liver dysfunctioin	0	0

alopecia was the most frequent toxicity in this category, followed by anorexia. The incidence of neuropathy was common. All of the toxicities were manageable and none of the patients died as a consequence of the toxicities.

Discussion

In the current retrospective study, weekly PAC as second-line treatment for S-1-refractory advanced gastric cancer provided satisfactory treatment effects and acceptable toxicities. This regimen would be effective for advanced gastric cancer as second-line treatment on an outpatient setting.

Recently, S-1 was shown to be a useful adjuvant regimen for patients with stage II or III gastric cancer in a Japanese randomized controlled trial (16). However, this treatment is not always effective in such patients. A second-line chemotherapeutic regimen is therefore required for patients with S-1-refractory advanced gastric cancer. At our institute, taxane derivatives are preferred, owing to their effectiveness for peritoneal metastasis, which is the most frequent type of relapse seen in advanced gastric cancer.

PAC, which was originally isolated from *Taxus brevifolia*, has been widely used in patients with advanced or recurrent gastric cancer in both first-line and second-line regimens. PAC is commonly administered *via* either a tri-weekly regimen at a dose of 210 mg/m^2 (17) or a weekly regimen at a dose of 80 mg/m^2 (18). Recently, the weekly regimen has been used more frequently in Japan (19), owing to the equivalent therapeutic survival and reduced haematological toxicity compared with the tri-weekly regimen whereas there was no well-designed randomized controlled study comparing the therapeutic outcomes of the weekly and the tri-weekly regimens. Combination therapies involving PAC and other drugs have been reported to have tolerable toxicity and efficacy for advanced gastric cancer (20-23). These studies reported favourable MSTs (9.4 to 13.9 months) although these regimens were the initial treatments for advanced gastric cancer. However, few second-line treatments using PAC have been reported for patients with advanced gastric cancer. Particularly, there have been a few reports discussing PAC monotherapy as second-line treatment (18, 19). Moreover, the first-line treatments were at random in these monotherapy studies.

In the current study, the first-line treatment was S-1 alone in order to allow us to evaluate the efficacy of the second-line treatment more clearly. Therefore, this study is worthwhile. The MST and median TTP from the initiation of second-line treatment in the previous monotherapy studies were 7.8 months and 5.0, and 2.6 months and 2.0 months, respectively. These MST and TTP were worse than these in our study. The differences in patient characteristics and the first-line regimens may account for these results. Therapeutic outcomes of PAC chemotherapy as second-line treatment for advanced gastric cancer should be compared between PAC monotherapy and PAC combined therapy in a well-designed randomized controlled study in order to clarify the superiority of these treatments.

In a previous study, we reported on the efficacy of combined DOC/CDDP chemotherapy as a second-line treatment in patients with advanced gastric cancer (24). The MST from the time of second-line treatment was 6 months in these patients. These results may also be acceptable because the performance status of these patients was poor as compared with those of patients in the current study. Taxane derivatives may be good candidates as second-line treatment for advanced gastric cancer.

The toxicity profiles showed acceptable toxicities. As a result, the number of courses administered was higher and subsequently survival time might be satisfactory on an outpatient basis.

In conclusion, this retrospective study showed favourable therapeutic outcomes for advanced gastric cancer patients treated by the taxane derivatives. However, the statistical power of this study may be weak due to the small number of patients. Therefore, it will be necessary to confirm the advantages of PAC treatment for S-1-refractory advanced gastric cancer in a larger population.

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