A Phase II Study of Weekly Paclitaxel and Doxifluridine Combination Chemotherapy for Advanced/Recurrent Gastric Cancer

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Abstract. *Background: Paclitaxel and doxifluridine (5'-DFUR) have distinct mechanisms of action and toxicity profiles. This study evaluated the antitumor activity and toxicities of combination chemotherapy with these drugs in patients with advanced/recurrent gastric cancer (AGC). Patients and Methods: Patients with histologically confirmed AGC, which was either unresectable or metastatic, were included in this study. The treatment consisted of 80 mg/m^2 paclitaxel given i.v. on days 1, 8, and 15 every 4 weeks, and 533 mg/m^2 doxifluridine given orally on days 1-5 every week. Results: One hundred and four patients were evaluated for toxicity and 93 patients were evaluated for a therapeutic response. The overall response rate was 33.3% (1st line: 41.7%, 2nd line: 25.0%), including a complete remission in two patients, a partial remission in 29, stable disease in 39, progressive disease in 17; the response was not evaluable in six patients. The median overall survival was 287 days. Commonly observed grade 3/4 adverse events were leukopenia (13.5%), anorexia (3.8%), fatigue (3.8%) and diarrhea (2.9%). Conclusion: Paclitaxel and doxifluridine combination chemotherapy is a well-tolerated and convenient treatment regimen that can be given on an outpatient basis with promising efficacy for AGC.*

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The incidence of gastric cancer remains high, and the disease is one of the leading causes of death worldwide. The median survival of patients receiving best supportive care (BSC) for advanced, non-resectable gastric cancer (AGC) is 3 to 4 months. Phase III trials have demonstrated the superiority of chemotherapy over BSC in improving patient prognosis, and the significance of administering chemotherapy to patients with AGC is now recognized (1-3). However, the guidelines for gastric cancer treatment in Japan have not yet recommended any specific regimen as of 2007. Various combination chemotherapeutic regimens, such as low-dose cisplatin (CDDP) with either 5-fluorouracil (5-FU) or irinotecan hydrochloride (CPT-11)/CDDP, have been used to

treat gastric cancer for which curative surgery is not indicated, with a low success rate. Most of these patients had to be hospitalized or if treated on an outpatient basis, had to receive frequent treatments at clinic (4, 5).

In fact in the JCOG9912 study (6), CPT-11 plus CDDP was less effective than 5-FU alone, on the other hand S-1 was not inferior to 5-FU. The SPIRITS trial (7) showed that median survival was significantly longer in patients with AGC who were treated with S-1 plus CDDP than in those who received S-1 alone and this became the standard first-line therapy.

Of the chemotherapeutic agents that are active against AGC, taxanes differ from conventional anticancer agents such as CDDP in that they have been shown to be highly effective against undifferentiated tumors and peritoneal dissemination (8-10). In addition, taxanes have been shown to be equally as effective in patients previously treated with chemotherapy as in chemotherapy-naïve patients; they are therefore expected to be used at various stages in the sequence of AGC therapy (8-10). However, when administered alone to treat AGC, taxanes demonstrate insufficient efficacy, with a response rate of 15-20% (8-10).

Paclitaxel (PTX) and doxifluridine (5'-DFUR; an intermediate metabolite of capecitabine) have distinct mechanisms of action and toxicity profiles, and have been shown to have considerable single-agent activity in the treatment of gastric cancer. A synergistic interaction between these two drugs has been suggested from the taxane-induced up-regulation of thymidine phosphorylase (TP), which converts 5'-DFUR to 5-FU (11). TP is frequently expressed in tumor tissue (11, 12). In an *in vivo* mouse xenograft model using a gastric carcinoma strain, Sawada *et al*. demonstrated that TP is up-regulated by PTX in the tumor tissue and that a higher additive effect is obtained after combined treatment with 5'-DFUR or capecitabine (11). Our previous phase I study also demonstrated that TP was activated in the tumors of patients (13). Recent studies have also shown that when administered weekly, PTX had a modest activity and was safer than the tri-weekly regimen, thus suggesting that the weekly regimen is the most suitable treatment option for outpatients with gastric cancer (14, 15).

A phase II trial was thus performed to evaluate the antitumor activity and toxicities of combination therapy with PTX and 5'-DFUR in patients with advanced/recurrent gastric cancer.

Patients and Methods

Patients. Patients with histologically confirmed non-resectable or recurrent gastric cancer were eligible for this study. The inclusion criteria were as follows: a performance status of 0-2; age 20 years or older; a measurable target according to Response Evaluation Criteria in Solid Tumors (RECIST); a life expectancy of longer than 3 months; no major history of surgery, radiotherapy or chemotherapy within 28 days before study entry; adequate bone marrow, renal and liver functions as defined by white blood cell count (WBC) of 3000×10^6/l or more, Hb of 8.0 g/dl or more, platelet count (PLT) of 80×10^9/l or more, asparatate aminotransferase/alanine aminotransferase (AST/ALT) of 100 IU/l or less, and total bilirubin of 1.5 mg/dl or less; no significant cardiac disease as established by ECG and no restriction on prior regimens. All the patients gave written informed consent before entering the study, according to the institutional guidelines.

Treatment schedule. In our previous phase I trial, patients were able to tolerate even the highest dose used (level 5: PTX 100 mg/m^2 plus 5'-DFUR 533 mg/m^2) (13). However, treatment was postponed in one of the three patients at this dose level owing to adverse effects, which prompted the recognition of this level as the maximal acceptable dose. Therefore, the recommended dose (RD) in the phase I trial was PTX at 100 mg/m^2 plus 5'-DFUR at 533 mg/m^2. It is usually appropriate to conduct a phase II trial using this regimen of PTX (100 mg/m^2) plus 5'-DFUR (533 mg/m^2). However, a phase I study using the same weekly regimen of PTX alone demonstrated the RD to be 80 mg/m^2. Because we intended to propose the use of the combined regimen of chemotherapy with PTX and 5'-DFUR for long-term administration on an outpatient basis, we wanted to ensure that the patients would be able to complete their course of treatment. The dose levels used in the patients who received median courses and were able to complete the therapy were as follows: level 3 in 7 patients, level 4 in 5, and level 5 in 3. For these reasons, the RD was considered to be level 3, *i.e*., paclitaxel at 80 mg/m^2 plus 5'-DFUR at 533 mg/m^2, for the purposes of this phase II trial (13). The regimen consisted of PTX infusion at 80 mg/m^2 weekly on days 1, 8 and 15, with 5'-DFUR at 533 mg/m^2/day orally 5 days per week on a 28-day cycle (Figure 1).

While the doses of PTX and 5'-DFUR were determined according to the patient's body surface area, the practical doses of 5'-DFUR were decided based on 200-mg capsules. The PTX was diluted with 250 ml of either 0.9% sodium chloride solution or 5% dextrose solution, and the final solution was administered by *i.v.* infusion for 1 hour. The following pretreatment was administered for 60 minutes prior to PTX: dexamethasone at 20 mg *i.v.*, chlorphenamine at 10 mg *i.v.* and either ranitidine at 50 mg *i.v.* or famotidine at 20 mg *i.v.*.

Toxicities were graded according to the National Cancer Institute's Common Toxicity Criteria, Ver. 3 (NCI-CTC). The following toxicities were defined as dose-limiting if they occurred during the treatment: grade 4 leukopenia (neutropenia) persisting longer than 4 days; grade 4 thrombocytopenia; a fever greater than 38˚C with grade 3 or greater leukopenia; a study schedule delay of more than 14 days or grade 3 or greater non-hematological toxicity without nausea or alopecia.

Pretreatment assessment and follow-up studies. Medical histories were recorded and physical examinations and routine laboratory studies were performed once before treatment and weekly during treatment. Routine laboratory studies included complete blood cell counts with differential WBC counts, serum electrolytes, and blood chemistries. If patients developed toxicity associated with grade 3 or 4 clinical manifestations in hematological or biochemical laboratory parameters, the tests were repeated immediately and then daily until the toxicity resolved.

End-points and evaluation of treatment. The primary end-point was response rate (RR). The tumor response was evaluated every cycle

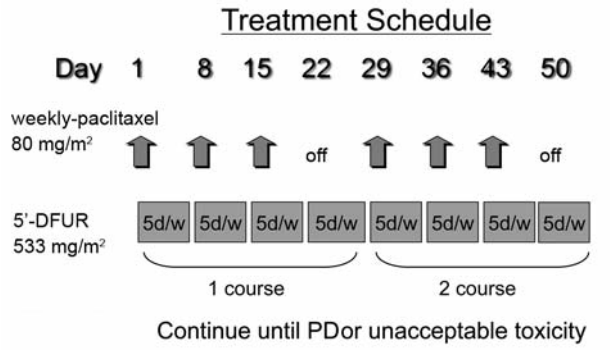

Figure 1. *Treatment schedule. d/w: Days per week; PD: progressive disease.*

Table I. *Patient characteristics.*

	n=104
Gender: male/female	87/17
Median age, years (range)	67 (36-82)
PS (ECOG): 0/1/2	55/37/12
No. of prior chemotherapy: 0/1/2	51/46/7
(including S-1)	(–/33/5)
Ascites : +/-	30/74
Histology: undifferentiated/differentiated	62/42
Stage: advanced/recurrent	43/61

by means of a CT scan. Measurable lesions were assessed according to the RECIST criteria. The secondary end-points were overall survival (OS) and the incidence of adverse events. Intention-to-treat (ITT) analysis was used to evaluate patients for their response, survival and toxicity.

Results

Between April 2003 and May 2006, a total of 104 patients were enrolled in this study. The patient demographic characteristics are shown in Table I. Their median age was 67.0 years (range: 36-82) and 87 patients were males. Forty-three patients had advanced gastric cancer and 61 had recurrent gastric cancer. After a median of 3 (range: 1-21) cycles of chemotherapy, 104 patients were evaluated for toxicity. Eleven patients were excluded from response evaluation because of protocol violation, thus, a total of 93 patients were evaluated for response by RECIST. Eighty-five (81.7%) out of the 104 patients received more than two courses of chemotherapy (Table II).

Antitumor activity. In the ITT analysis, the overall response rate was 33.3% (95% CI, 23.8-42.9%), including a complete remission in two patients, a partial remission in 29, stable disease in 39, progressive disease in 17, and the response was not evaluable in six patients. The regimen was given as first-line therapy to 48 patients (primary advanced or surgery alone) in whom the response rate was 41.7% (95% CI, 27.7-55.6%). The regimen was second-line therapy for 40 patients (72.5% S-1 failure) in whom the response rate was 25.0% (95% CI, 11.6-38.4%; Table III). The median overall survival was 287 days (Figure 2). The actual dose intensity was 81.7% (85/104) of the planned dose during the first two cycles of these drugs.

Table II. *Treatment delivery.*

Eligible pts	104
Median no. of courses (range)	3 (1-21)
Paclitaxel	120 (80-152) mg
5'-DFUR	600 (600-1000) mg
Received 2 courses	81.7% (85/104)

Table III. *Response rate according to background by RECIST criteria.*

Line	CR	PR	SD	PD	NE	RR (95% CI)
1st (n=48)	1	19	18	8	2	41.7% (27.7-55.6)
2nd (n=40)	1	9	17	9	4	25.0% (11.6-38.4)
3rd (n=5)	0	1	4	0	0	20.0% (–15.1-55.1)
Total (n=93)	2	29	39	17	6	33.3% (23.8-42.9)

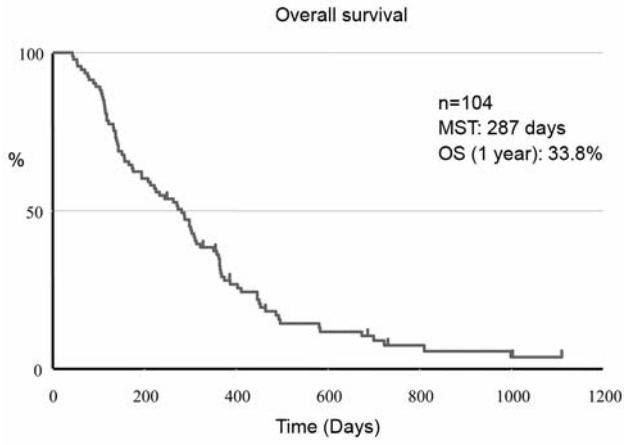

Figure 2. *Overall survival curve. MST: Median survival time, OS: overall survival.*

Toxicity. The distribution of the NCI-CTC grades of the most common hematological and non-hematological toxicities observed during all the treatment courses are shown in Table IV. The most common hematological toxicity observed was leukopenia. However, the toxicity was not severe in this

Table IV. *Toxicity profile of weekly paclitaxel and 5'-DFUR therapy (104 assessable patients).*

	Toxicity grade				
	0	1	2	3	4
Toxicity*	n (%)	n (%)	n (%)	n (%)	n (%)
Hematological					
WBC	42 (40)	30 (29)	18 (17)	13 (13)	1 (1)
Hgb	26 (25)	22 (21)	46 (44)	8 (8)	2 (2)
PLT	102 (98)	1 (1)	1 (1)	- -	- -
Non-hematological					
Fever	94 (90)	3 (3)	5 (5)	1 (1)	1 (1)
Vomiting	91 (88)	5 (5)	6 (6)	2 (2)	- -
Stomatitis	97 (93)	6 (6)	- -	- -	1 (1)
Diarrhea	91 (88)	8 (8)	2 (2)	3 (3)	- -
Anorexia	65 (63)	16 (15)	19 (18)	3 (3)	1 (1)
Fatigue	70 (67)	17 (16)	13 (13)	3 (3)	1 (1)
Neuropathy, motor	98 (94)	3 (3)	1 (1)	2 (2)	- -
Neuropathy, sensory	75 (72)	19 (18)	8 (8)	2 (2)	- -
Arthralgia	98 (94)	5 (5)	1 (1)	- -	- -
Myalgia	99 (95)	4 (4)	1 (1)	- -	- -
Alopecia	40 (38)	29 (28)	35 (34)		
T-Bil	82 (79)	14 (13)	6 (6)	2 (2)	- -
AST	81 (78)	11 (11)	10 (10)	2 (2)	- -
ALT	73 (70)	17 (16)	8 (8)	6 (6)	- -

*Common Terminology Criteria for Adverse Events v.3.0 (CTCAE).

study, with only 14 out of 104 (13.5%) patients experiencing grade 3/4 leukopenia. For non-hematological toxicity, the most frequently observed grade 3/4 adverse events were anorexia (3.8%), fatigue (3.8%) and diarrhea (2.9%).

Discussion

In the present study, the overall response rate was 33.3%. The response rate in the first line therapy group was 41.7%, which was satisfactory. Even in the second-line therapy group, the response rate was 25% (72.5% for those with S-1 failure), which is also an acceptable result. In fact, compared with the success rate for S-1 alone therapy in the JCOG9912 study (6): median survival time (MST) was 11.4 months, progression-free survival (PFS) was 4.2 months, and 28%; and in the SPIRITS trial (7): MST 11.0 months and RR 31%, the success rate of the PTX plus 5'-DFUR combination therapy was more favorable, especially with regard to RR. On the other hand, the median overall survival was only minimally prolonged (287 days). However, this may have been due to the fact that many of the patients received the combination as second-line therapy and most of the patients were already in a relatively poor overall condition.

Regarding the incidence of adverse events, leukopenia was the most common hematological toxicity observed. However, the toxicity was not severe in this study, with only 14% of the patients reporting grade 3/4 leukopenia. Severe thrombocytopenia did not occur in the study. Only 2% of the patients experienced non-hematological toxicity of grade 3 or greater nausea and vomiting. A few other patients experienced grade 3 or greater diarrhea, anorexia, or fatigue.

The good safety profile and promising antitumor activity observed in the present study have also been demonstrated in other studies. For example, Moriwaki *et al*. (16) reported an RD for PTX of 80 mg/m^2 on days 1 and 8 with 5'-DFUR at 600 mg/m^2 for 2 weeks followed by a 1-week interval, while Yoshino *et al*. (17) reported an RD for PTX of 70 mg/m^2 on days 1, 8, and 15 with 5'-DFUR at 600 mg daily. The combination of PTX plus 5'-DFUR appears to be a safe treatment option that is easily administered and is acceptable for use in the palliative treatment of patients with non-resectable or recurrent gastric cancer.

In a phase II study of 35 patients, Takiuchi *et al*. (18) reported that patients who received PTX plus 5'-DFUR treatment for AGC showed resistance to S-1. Their regimen was the same as that used by Moriwaki *et al*. (16). The response rate was 18.2 %, median PFS was 119 days, and MST was 321 days. Severe (grade 3) hematological toxity was reported in only 22.9% of their patients.

In Japan, the current standard first-line therapy for advanced and recurrent gastric cancer is the S-1 plus CDDP regimen. However, some east Asian patients experience severe adverse

events. Many Caucasian people also have severe adverse events associated with S-1. In a US phase I trial of the S-1 plus CDDP regimen performed by Ajani and co-workers (19), the recommended dose of S-1 was 25 mg/m^2 twice daily, which was lower than the actual starting dose in Japan because of the main dose-limiting toxicity of diarrhea. The difference in RD might be attributed to the higher activity of the cytochrome P-450 2A6 enzyme systems (which catalyzes the conversion of tegafur to 5-FU) in Caucasians than in Japanese, and the larger body surface area in North American people, leading to higher serum concentrations of 5-chloro-2,4-dihydroxypyridine and 5-FU (19). In such cases, it is thought that PTX plus 5'-DFUR treatment may be used as the first-line therapy. Furthermore, we believe that this regimen will be applicable for second-line or subsequent therapy because the present study demonstrated that it appears to be effective for these purposes.

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