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A Combination Phase I Study of Weekly Paclitaxel and Doxifluridine in Advanced Gastric Cancer Patients

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Abstract. *Background: Preclinical studies have shown that paclitaxel and doxifluridine can act synergistically without overlapping toxicity for the treatment of advanced gastric cancer. The objectives of this study were to determine the maximum tolerated dose (MTD), the dose-limiting toxicity and the recommended Phase II dose for this drug combination. Patients and Methods: Patients with histologically confirmed gastric cancer were eligible for the study. The paclitaxel dose (days 1, 8, 15) was augmented with a fixed dose of doxifluridine (533 mg/m^2, 5 days/week) on a 28-day cycle. Results: Eighteen patients were enrolled. The MTD was not reached until the highest dose level. One patient had Grade 3 myelosuppression. The responses of the 13 suitable patients included 1 complete response and 5 partial responses. Conclusion: Although the MTD level could not be definitively established, upon consideration of the lengthy administration time and the effectiveness, the recommended Phase II dose of paclitaxel was concluded to be 80 mg/m^2 in combination with doxifluridine at 533 mg/m^2.*

Metastatic gastric carcinoma remains an incurable disease with a median survival of only 4 to 8 months. In randomized studies, patients with non-resectable or metastatic gastric cancer who have received systemic chemotherapy plus supportive care, as opposed to supportive care alone, have demonstrated both a survival benefit and a positive impact on their quality of life (1). Various chemotherapeutic combinations, such as low-dose cisplatin (CDDP) with either 5-fluorouracil (5-FU) or irinotecan hydrochloride (CPT-11)/CDDP, have been used with limited success to treat gastric cancer patients who are not candidates for curative surgery. In most of these cases, the patients must be admitted to a hospital or must frequently visit a hospital for treatments (1-3).

Paclitaxel and doxifluridine (5'-DFUR) were shown to act synergistically as a single agent without overlapping toxicity for the treatment of advanced gastric cancer in a preclinical study. As an intermediate of capecitabine, 5'-DFUR is converted to 5-FU by thymidine phosphorylase (TP). TP, which is a member of the pyrimidine nucleoside phosphorylase (PyNPase) family, is found predominantly in humans and is a potent tumor-associated angiogenesis factor that is preferentially expressed in malignant cells (4-7). Paclitaxel enhances the efficacy of 5'-DFUR, presumably by up-regulating the TP level, as was demonstrated in human cancer xenograft models and breast cancer patients (8). Recent studies showed that weekly paclitaxel administration was more active and safer than tri-weekly paclitaxel, suggesting that weekly paclitaxel is one of the most suitable treatment regimens for outpatients with gastric cancer.

The principal objectives of this Phase I study were: i) to determine the maximum tolerated dose (MTD), the dose-limiting toxicity (DLT) and the recommended Phase II dose (RD) for this drug combination; ii) to describe the principal toxicities of the paclitaxel and 5'-DFUR regimens; and iii) to investigate TP and dihydropyrimidine dehydrogenase (DPD) levels in gastric tumor and non-tumor tissues after weekly treatments with paclitaxel plus 5'-DFUR for advanced gastric cancer.

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Patients and Methods

Eligibility. Patients with histologically confirmed non-resectable or recurrent gastric cancer were candidates for this study. The eligibility criteria also included: i) a performance status of 0-2; ii) an age of 20-75 years; iii) a life expectancy of longer than 3 months; iv) no major surgery, radiotherapy, or chemotherapy within 28 days of study entry; v) adequate bone marrow, renal and liver functions as defined by WBC ≥3,500, Hb ≥8.0, PLT ≥80,000, AST/ALT ≤2 times institutional upper normal limits, and total bilirubin <2 times institutional upper normal limits; vi) no significant cardiac disease evident by ECG; and vii) no limitations from prior regimens. Patients gave written informed consent before treatment, according to institutional guidelines.

Treatment schedule and dose escalation. The starting dosage regimen was paclitaxel at 60 mg/m^2 administered as a 60-min infusion weekly on days 1, 8 and 15 with 5'-DFUR at 533 mg/m^2/day for 5 days per week on a 28-day cycle. The dose of 5'-DFUR remained fixed throughout the study, whereas the dose of paclitaxel was increased in each successive cohort of new patients. The paclitaxel dose level was escalated in increments of 10 mg/m^2 until a dose of 100 mg/m^2 was reached, as appropriate. A minimum of three new patients were treated at each dose level.

Toxicities were graded according to the National Cancer Institute's Common Toxicity Criteria, Ver. 2 (NCI-CTC). The following toxicities were defined as dose-limiting if they occurred during the first cycle of treatment: i) Grade 4 leukopenia (neutropenia) lasting longer than 4 days; ii) Grade 4 thrombocytopenia; iii) fever >38˚C with leukopenia ≥Grade 3; iv) schedule delay of longer than 14 days; or v) Grade 3 or greater non-hematological toxicity without nausea or alopecia. The MTD level was defined as the highest paclitaxel dose which, when combined with 5'-DFUR at 533 mg/m^2, resulted in DLT in two or more of the three patients at that dose level. If one of the three patients from a dose group experienced DLT, then three new patients were treated at the same dose level; when two or more of the three new patients experienced DLT, the MTD level was defined.

Drug administration. The paclitaxel and 5'-DFUR doses were calculated according to body surface area. The practical doses of 5'-DFUR were decided based on 200-mg capsules. Paclitaxel 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 h. The following premedication was administered as a 60-min pretreatment prior to paclitaxel: dexamethasone, 20 mg *i.v.*; chlorphenamine, 10 mg *i.v.*; and either ranitidine, 50 mg *i.v.*, or famotidine, 20 mg *i.v.*

Pretreatment assessment and follow-up studies. Medical histories, 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 chemistries. If patients developed toxicity manifested by Grade 3 or 4 abnormalities in hematological or biochemical laboratory parameters, the tests were repeated immediately and then daily until the toxicity resolved. Tumor responses were evaluated based on the criteria of the Japanese Research Society for Gastric Cancer. A complete response (CR) was defined as the disappearance of all disease by two measurements taken at least 4 weeks apart. A partial response (PR) required more than a 50% reduction in the value of the products of the bidimensional measurements of all measurable lesions as documented by two measurements taken at least 4 weeks apart. Progressive disease (PD) was defined as a 25% increase in the value of the products of the bidimensional measurements of all measurable lesions.

Sample preparation. Tumor tissues were obtained from tumor and normal mucosa by punch biopsy. Tissue samples were homogenized in a 10-fold volume of 10 mM Tris-HCl buffer (pH 7.4) containing 15 mM NaCl, 1.5 mM $MgCl_2$ and 50 μM potassium phosphate, and then centrifuged at 10,000 x g for 15 min. The supernatant was stored at –80˚C until used. The protein concentration of the supernatant extracted from the tumor tissues was determined using a DC protein assay kit (Bio Rad Laboratories, Hercules, CA, USA).

TP and DPD ELISA levels. The TP and DPD enzyme levels in the specimens were assayed by an enzyme-linked immunosorbent assay (ELISA) system, as previously described (9, 10). The enzyme levels were expressed as U/mg protein, where 1 U of TP is the amount that produces 1 μg of 5-FU in 1 h, and 1 U in DPD is the amount that catabolizes 1 pmol of 5-FU per min.

Results

Eighteen patients received paclitaxel/5'-DFUR therapy. The patient characteristics are shown in Table I.

Initially, three patients were treated with the first dose level of paclitaxel at 60 mg/m^2 and 5'-DFUR at 533 mg/m^2/day. As no dose-limiting events were observed in any of these patients during the first course, the paclitaxel dose was increased to 70 mg/m^2. However, one of the first three patients treated at this dose level developed DLT as a result of a longer than 2-week delay of administration owing to Grade 2 leukopenia during course one. Three additional patients were added at this dose level. None of these three new patients developed DLT during course one; therefore, the paclitaxel dose was increased to 80 mg/m^2. No dose-limiting events were observed in any of these patients during the first course, so the paclitaxel dose was increased to 90 mg/m^2, and then to 100 mg/m^2 (the highest dose level). No dose-limiting events were observed in any of the patients during the first course at dose levels 4 and 5. The scheduled levels were completed, and the MTD level was not reached until level 5. The numbers of patients and the numbers of DLTs at each level are listed in Table II.

Toxicity. The distribution of the NCI-CTC grades of the most common hematological and non-hematological toxicities observed during the first course are shown in Table III, and the toxicities observed during all courses are shown in Table IV. Leukopenia was the most common hematological toxicity observed. However, the toxicity was

Table I. *Patient characteristics and administration.*

Number of patients:	18
Median age (range):	59 (46-75)
Non-resectable/Recurrence:	12/6
Prior chemotherapy:	9
Median administration cycle:	5 (1-17)

Table II. *DLT.*

Level	Entered	DLT	
1	3	0	
2	6	1	schedule delay
3	3	0	
4	3	0	
5	3		

DLT: dose-limiting toxicity

not severe in this study, with only one out of eighteen patients developing Grade 3 leukopenia. Only one patient at level 2 needed longer than 14 days to recover from Grade 2 leukopenia. Severe anemia and thrombocytopenia did not occur.

For non-hematological toxicity, only one out of eighteen patients experienced nausea and vomiting of more than Grade 3 during the first course. Another six patients experienced nausea and vomiting of less than Grade 2 during the first course. Three (16.7%) patients experienced diarrhea of less than Grade 2 during the first course; the diarrhea was generally mild. Three (16.7%) patients experienced paresthesias of less than Grade 2 during the first course. Twelve (66.7%) patients experienced alopecia during the first course. No one experienced liver or kidney dysfunction during the first course.

Only one patient experienced greater than Grade 3 leukopenia during all the dosage courses. Thirteen (72.2%) out of eighteen patients experienced leukopenia, and two (11.1%) out of eighteen patients experienced less than Grade 2 thrombocytopenia during all the courses. Ten (55.6%) patients experienced nausea and vomiting during all the courses; six (33.3%) patients experienced sensory neuropathy, and two (11.1%) patients experienced motor neuropathy during all the courses. Thirteen (72.2) patients developed alopecia and four experienced Grade 1 liver dysfunction during treatment.

Compliance. The median numbers of courses and rates of effective patients at each level are listed in Table V.

Table III. *Toxicity during first course.*

	#Pts	Grade≥3	Nadir Median (range)
WBC	18	1	3,200 (1,300-9,600)
Hb	18	0	10.4 (8.2-12.3)
PLT	18	0	24.4 (6.4-45.6)
	#Pts	Grade≥3	Appearance rate*
N/Vomiting	18	1	38.9%
Anorexia	18	0	16.7%
Alopecia	18	-	66.7%
Diarrhea	18	0	16.7%

*:Appearance rate of Grade1-2

Table IV. *Toxicities during all courses.*

	Weekly Paclitaxel+Doxifluridine (n=18)				
Toxicity Grade*	0	1	2	3	4
Hematological					
Leukocytes	5	5	7	1	0
Hemoglobin	9	4	5	0	0
Platelets	16	1	1	0	0
Non-hematological					
Fever	14	4	0	0	0
Nausea / Vomiting	8	8	1	1	-
Diarrhea	16	1	1	0	0
Fatigue	14	3	1	0	0
Liver	14	4	0	0	0
Stomatitis	17	1	0	0	0
Neuropathy-motor	16	2	0	0	0
Neuropathy-sensor	12	3	3	0	0
Rash	17	0	1	0	0
Alopecia	5	6	7	-	-
Headache	17	1	0	0	-

*Toxicities are reported for all courses.

Antitumor activity. The relevant details pertaining to the antitumor effects in all patients who participated in the study are depicted in Table VI. Fourteen patients had measurable disease, whereas four patients had bony lesions or ascites that were not measurable. One out of fourteen patients refused computed tomography examination after treatment, therefore, thirteen patients were assessed. Six of the thirteen patients (46.2%; 95% confidence interval, 19.2-74.9%) with measurable disease had major responses, including one CR and five PRs. The median survival time for all eighteen patients was 274 days. One patient, who had completely responded to treatment, experienced a tumor recurrence among para-aortic lymph nodes. He was treated with paclitaxel/5'-DFUR at the 100/533 mg/m^2 dose level.

Table V. *The median numbers of courses and rates of effective patients.*

Level	PTX	median courses	effective Pts
1	9 (6-18)	3	1/3
2	14 (3-50)	4.5	2/6
3	23 (14-24)	7	2/3
4	17 (17-19)	5	0/3
5	9 (9-17)	3	1/3

PTX: administration of paclitaxel

Table VI. *Response rate (13 evaluable cases).*

	CR	PR	NC	PD	Total
Number	1	5	5	2	13
Rate (%)	8	38	38	15	

Overall Response Rate: 46.2%

Overall, four of the nine patients who had been previously treated with high-dose chemotherapy experienced major responses, including one CR response as described above. In five of the six patients with ascites, the accumulated fluid disappeared or substantially receded after treatment.

TP and DPD levels. Informed consent for the measurement of TP and DPD levels in tumors and adjacent normal tissues was received from three patients (one each in levels 2, 3 and 4). Tissue samples for TP and DPD studies were taken once before chemotherapy was initiated and then again after one course of chemotherapy.

The TP level in the tumor tissue nearly doubled after chemotherapy, but remained constant in the normal tissue. In one of the three patients, the DPD levels in the tumor and normal tissue significantly increased after chemotherapy (Table VII).

Table VII. *TP and DPD levels.*

Pt sample (Response)	TP		DPD	
	before	after 1course	before	after 1course
1 tumor	60.7	132.1	57.0	69.4
(PR) normal	92.3	101.4	57.3	55.1
2 tumor	60.1	143.8	25.1	93.4
(PR) normal	43.2	11.3	41.6	110.1
3 tumor	96.3	130.4	18.6	16.3
(NC) normal	67.7	86.1	50.2	39.7

(Unit / mg protein)

Discussion

The median survival time 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 for improving patient prognosis, and the significance of performing chemotherapy for patients with AGC is now recognized (1, 11, 12). However, gastric cancer treatment guidelines in Japan have yet to reach the point of recommending a specific regimen. The NCCN guidelines in the United States also do not indicate a specific regimen; the guidelines instead recommend the use of several regimens containing 5-FU, CDDP, taxanes, or CPT-11.

Of the chemotherapy drugs that are active against AGC, taxanes differ from conventional anticancer agents such as CDDP in that taxanes have been shown to be highly effective against undifferentiated tumors and peritoneal dissemination (13, 14). In addition, taxanes have been shown to be equally as effective in patients previously treated with chemotherapy as in chemotherapy-naïve patients; taxanes are, therefore, expected to be prescribed at a variety of stages in the sequence of AGC therapy (13, 14). However, administered singly to treat AGC, taxanes demonstrate an insufficient level of efficacy of 15-20% (13, 15). Explorations of adjuvant chemotherapy agents, therefore, must be made.

Adjani *et al.* reported on the efficacy of adjuvant docetaxel in a Phase III trial of combined chemotherapy using 5-FU plus CDDP and docetaxel (DCF) (15). The United States has responded to this finding by designating DCF as a standard mode of chemotherapy for the treatment of AGC. However, many clinicians in Japan do not consider DCF therapy to be applicable for use in Japanese patients. In Japan, results have been reported from Phase I/II trials combining DCF with CDDP and S-1, a novel fluorouracil agent; however, few examinations have indicated a marked enhancement of the effects brought about by the adjuvant use (16).

The oral 5-FU chemotherapy agent 5'-DFUR is an intermediate metabolite of capecitabine and is prescribed as frequently for gastric cancer as it is for breast and colon cancer in Japan. Like capecitabine, 5'-DFUR is metabolized to 5-FU by thymidine phosphorylase (TP), a converting enzyme which is frequently highly expressed in the tumor tissue (17, 18). TP has been found to be up-regulated in tumor tissue by certain types of chemotherapy agents, including taxanes (8), cyclophosphamides (CPA) (19) and oxaliplatin (20), as well as by irradiation (21). In an *in vivo* mouse xenograft model using a gastric carcinoma strain, Sawada *et al.* demonstrated that TP is up-regulated by paclitaxel in the tumor tissue and that a higher than additive effect is obtained by combined therapy with 5'-DFUR or capecitabine (8).

In the clinical setting, promising Phase II results have been reported in combination with 5'-DFUR and CPA for breast cancer (22) and with capecitabine and oxaliplatin for colon cancer (20). We, therefore, conducted a Phase I trial to examine the effect of combined 5'-DFUR and paclitaxel for the treatment of non-resectable or recurrent gastric cancer.

In the present Phase I trial, the highest dose level (level 5: paclitaxel 100 mg/m^2 plus 5'-DFUR 533 mg/m^2) was reached, and we failed to determine the MTD. However, the administration was postponed in one of the three patients at level 5 owing to side-effects, which prompted the designation of this level as the maximum acceptable dose. Therefore, the RD in our Phase I trial was paclitaxel at 100 mg/m^2 plus 5'-DFUR at 533 mg/m^2. It is usually appropriate to conduct Phase II trials using this dosing schedule of paclitaxel at 100 mg/m^2 plus 5'-DFUR at 533 mg/m^2. However, a Phase I monotherapy study using the same weekly paclitaxel dose as used in our study reported the RD to be 80 mg/m^2. Furthermore, this combined regimen of chemotherapy is being considered for administration over the long-term on an outpatient basis. The following numbers of patients received median courses and were able to complete the therapy: seven at level 3, five at level 4 and three at level 5. For these reasons, we decided on an RD of that at level 3, paclitaxel at 80 mg/m^2 plus 5'-DFUR at 533 mg/m^2, for the purposes of future Phase II trials.

While antitumor activity was not a primary objective of this study, the present study was conducted as a disease-oriented study. We, therefore, focused our study on a population containing 50% first-line patients. The response rate in patients able to be evaluated was promising at 46.2% (95% CI, 19.2–74.9%), with two out of three patients responding to a dosing level of paclitaxel at 80 mg/m^2 plus 5'-DFUR at 533 mg/m^2, suggesting the appropriateness of using level 3 as the recommended Phase II dose. Furthermore, ascites, a common, recurrent, but unquantifiable disease in poorly-differentiated or signet-ring cell gastric carcinoma, completely or substantially receded in five out of six patients.

The activation of 5'-DFUR to 5-FU occurs *via* TP, while DPD catabolizes 5-FU to inactive molecules. We studied three patients to examine whether the *in vivo* observation that paclitaxel induced TP in tumors could be demonstrated in the clinical setting. We found that the TP activity more than doubled after paclitaxel administration in the two responding patients. When considered with the high efficacy demonstrated in the present study, this suggested promising results for the combined therapy. Furthermore, depending on the cellular context, paclitaxel may also lead to apoptosis, which is inhibited by the over-expression of Bcl-2 (23). Paclitaxel-induced apoptosis has been found to correlate with a concomitant phosphorylation of Bcl-2 (24, 25). This might be related to the increased TP activity induced by paclitaxel or to the reduced apoptosis-related factor, the Bcl-2/Bax ratio, induced by 5'-DFUR (26), both of which could enhance the antitumor effects of paclitaxel and 5'-DFUR when used concurrently.

The good safety profile and promising antitumor activity observed in our present study have also been examined in studies by others. Hidaka *et al.* (27) reported an RD for paclitaxel of 80 mg/m^2 on days 1 and 8 with 5'-DFUR at 600 mg/m^2 for 2 weeks followed by 1 week of rest, while Yoshino *et al.* (28) reported an RD for paclitaxel of 70 mg/m^2 on days 1, 8 and 15 with 5'-DFUR at 600 mg/body daily. The combination of paclitaxel plus 5'-DFUR appears to be a safe and easily administered regimen that is acceptable for use in the palliative treatment of patients with non-resectable or recurrent gastric cancer.

A Phase II trial is ongoing in our group to evaluate the activity in patients with non-resectable or recurrent gastric cancer.

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