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ORIGINAL ARTICLE

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A phase I study of doxifluridine combined with weekly paclitaxel for metastatic gastric cancer

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Abstract *Purpose*: Based on the synergistic effect in preclinical studies, a phase I clinical trial for the combination of paclitaxel and doxifluridine (an intermetabolite of capecitabine) was performed to determine the recommended dose for the treatment of patients with metastatic gastric cancer. *Methods*: The dose of paclitaxel was increased from 60 mg/m^2 at level 1 to 90 mg/m^2 at level 5. It was administered as a 1-h infusion on days 1 and 8. The dose of doxifluridine was fixed at 600 mg/m^2 per day up to level 3, and escalated to 800 mg/m^2 per day at levels 4 and 5. It was administered orally for 2 weeks. The treatment was repeated every 3 weeks. *Results*: A total of 28 patients were enrolled. No dose-limiting toxicity (DLT) was observed at levels 1 and 2 (paclitaxel 70 mg/m^2). A DLT of grade 4 neutropenia lasting for more than 4 days was observed in one patient at level 3 (paclitaxel 80 mg/m^2). In addition, the first five of six patients in this group experienced grade 3 neutropenia during the first treatment cycle. A further six patients were added in order to confirm the safety of this dosage level, and no more DLTs except for grade 3 nausea in one patient were observed in the second cohort. No DLT was seen in three patients at level 4 (paclitaxel 80 mg/m^2). DLTs (grade 3 neuropathy in one patient and a treatment delay of the second cycle for more than 1 week due to grade 3 neutropenia in another) were observed in two out of six patients at level 5 (paclitaxel 90 mg/m^2), and this dose level was determined as the maximum tolerated dose. The tumor response rate was 42% (95% confidence interval 20–67%) in 19 patients with measurable lesions. *Conclusions*: The recommended dose was determined as 80 mg/m^2 of paclitaxel (days 1 and 8) and 800 mg/m^2 of doxifluridine (days 1–14) every 3 weeks. The results of this phase I study are encouraging and a phase II trial is thus warranted.

Keywords Doxifluridine · Thymidine phosphorylase · Taxane · Gastric cancer · Clinical trial

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Introduction

The incidence of gastric carcinoma is still high in Asia and it remains one of the leading causes of death [13, 28]. The prognosis for patients with unresectable or metastatic gastric carcinoma is poor, but chemotherapy confers a benefit when compared with best supportive care alone [9, 23]. In the past over 20 years, several anticancer drugs such as 5-fluorouracil (5-FU), cisplatin, methotrexate, doxorubicin, epirubicin, mitomycin, and etoposide, have been studied either alone or in combination as treatments for this disease. However, no new combination has yet emerged that is superior to 5-FU alone or to 5-FU plus cisplatin in terms of overall survival [13, 22, 31]. There is a pressing need for the evaluation of new agents such as the oral fluoropyrimidines and taxanes.

Paclitaxel promotes microtubule assembly and then exhibits its antitumor effect by arresting the cell cycle in the G_2/M phase. This mechanism of action is different from conventional anticancer drugs, and it has therefore been suggested that combination therapy with other anticancer drugs may be clinically effective [17]. The efficacy of paclitaxel has previously been confirmed clinically in various tumors including gastric cancer [1, 5, 10, 18, 19, 21, 33]. Furthermore, some promising regimens of paclitaxel combined with 5-FU/leucovorin/cisplatin, or with 5-FU/cisplatin have been reported in advanced gastric cancer [11, 14].

Preclinical studies have shown that paclitaxel induces thymidine phosphorylase (dThdPase) specifically in various human tumor tissues [26]. The oral fluoropyrimidine capecitabine and its intermetabolite doxifluridine are prodrugs that are converted to 5-FU by dThdPase in tumor tissues [6, 12]. A synergistic effect on inhibition of tumor growth has been reported when these agents are combined with paclitaxel [26]. Modest activity of capecitabine and doxifluridine has been reported in the treatment of advanced gastric cancer [7, 15, 20, 32]. Doxifluridine was approved for use in the treatment of advanced gastric cancer in 1987 in Japan, but capecitabine is still under investigation for this disease.

Thus, we conducted a phase I clinical trial in order to study the feasibility of paclitaxel/doxifluridine combined therapy. The tumor response was also investigated.

Patients and methods

Patients

All patients had to fulfill the following eligibility criteria: (1) histological confirmation of gastric adenocarcinoma; (2) inoperable metastatic disease or recurrent metastatic disease after surgery; (3) measurable or evaluable lesions; (4) aged from 20 to 75 years; (5) performance status (PS) ≤ 2 on the Eastern Cooperative Oncology Group (ECOG) scale; (6) a maximum of one prior chemotherapy other than paclitaxel or doxifluridine for advanced disease (prior chemotherapy for advanced disease must have been completed at least 4 weeks prior to enrollment); (7) adequate bone marrow function (absolute granulocyte count $\geq 1500/mm^3$ and platelet count $\geq 100{,}000/mm^3$; (8) adequate liver function (serum bilirubin < 1.5 mg/dl and serum transaminase < 100 U/l); (9) adequate renal function (serum creatinine < 1.2 mg/dl); (10) no other severe medical conditions; (11) no other active malignancies; (12) no pregnant or lactating patients; (13) no peripheral neuropathy; and (14) provision of written informed consent.

This study was approved by the Institutional Review Board of the National Shikoku Cancer Center.

Dose-limiting toxicity and maximum tolerated dose

Dose-limiting toxicities (DLTs) were determined during the first treatment cycle. The definitions of DLTs were as follows: (1) grade 4 neutropenia lasting for at least 4 days, or grade 3 or 4 neutropenia with fever, (2) grade 4 thrombocytopenia, (3) grade 3 non-hematological toxicity, and (4) treatment delay of more than 2 weeks following the last administration of doxifluridine. The maximum tolerated dose (MTD) was defined as the dose level at which two of the three to six treated patients experienced DLT, and the recommended dose (RD) was determined at one level below.

Baseline evaluation included a complete medical history, physical examination, complete blood cell count, serum chemistry, urinary analysis, ECG, gastroscopy, gastrography, abdominal CT scan, and chest radiography. Blood, chemistry, urinary analyses, and subjective/objective symptoms for toxicity were monitored on a weekly basis during the treatment. Blood cell counts were determined at least every 2 days if hematological toxicities of grade 3 or more were seen in the first treatment cycle. When patients received the subsequent treatment cycle, they had to fulfill the previous eligibility criteria (7), (8), and (9), and their non-hematological toxicities had to recover to grade 1.

Toxicities were evaluated according to the National Cancer Institute common toxicity criteria (version 2.0).

Dosage and administration

The previous reports of phase I clinical trials studying the weekly administration of paclitaxel as a single agent in breast and ovarian cancer revealed that the RD was 80–100 mg/m^2 [16, 27]. We set the starting dose of paclitaxel (Taxol; Bristol-Myers Squibb Company, Tokyo, Japan) at 60 mg/m^2 and the dose was escalated by 10 mg/m^2 for each dose level up to dose level 3. Paclitaxel dissolved in 500 ml of an isotonic sodium chloride solution was administered on days 1 and 8 as an intravenous (i.v.) drip injection over 60 min following the short premedication (dexamethasone sodium phosphate 20 mg i.v. drip, diphenhydramine hydrochloride 50 mg orally, and ranitidine hydrochloride 50 mg i.v. 30 min before paclitaxel administration). Because 600–800 mg/m^2 per day of doxifluridine (Fulturon; Chugai Pharmaceutical Company, Tokyo, Japan) was considered the dose for patients with gastric cancer and this dose had been approved as the single-agent RD in Japan [20, 33], we fixed doxifluridine at the dose of 600 mg/m^2 per day and administered it orally at regular intervals four times a day (after each meal and before sleep) for 14 days. If the MTD did not reach level 3, the dose of each drug in the subsequent level was escalated in tandem by 10 mg/m^2 of paclitaxel and by 200 mg/m^2 of doxifluridine as shown in Table 1.

This treatment was repeated every 3 weeks (one cycle each) until disease progression or unacceptable toxicity was seen. The first cycle of the treatment was performed in the in-patient setting in our center. If the patient experienced DLT followed by no disease progression, the subsequent cycle was started at the next lower level after complete recovery from the toxic effects of the previous cycle.

Tumor response

Tumor response was evaluated every 6 weeks by means of CT scan. Measurable lesions were assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) [30].

Table 1 Dose level, number of patients enrolled, and DLT

Level	Paclitaxel (mg/m^2)	Doxifluridine (mg/m^2)	No. of patients	DLT
1	60	600	4	None
2	70	600	3	None
3	80	600	12	One grade 4 neutropenia lasting more than 4 days; one grade 3 nausea
4	80	800	3	None
5	90	800	6	One grade 3 neuropathy; one treatment delay due to neutropenia

Results

A total of 28 patients were enrolled, with 4 patients dosed at level 1, 3 at level 2, 12 at level 3, 3 at level 4, and 6 at level 5 from September 2001 to January 2003 (Table 1). Because one patient dosed at level 1 developed a grade 1 hypersensitivity reaction during the first treatment cycle and refused further treatment, a replacement patient was added to this dosage group. The patient characteristics are shown in Table 2. Of the 28 patients, 21 exhibited a good PS (0 or 1), and 22 had had a prior chemotherapy. The most frequent prior chemotherapy was 5-FU (17 patients). Nine patients had differentiated histological gastric adenocarcinoma, and the remainder had the undifferentiated type. The major metastatic sites were peritoneum, lymph nodes and liver.

The adverse events in the first cycle are summarized in Table 3. The most frequently observed toxicity was neutropenia. DLTs were not observed at levels 1 and 2, but a DLT (grade 4 neutropenia which continued for more than 4 days) was observed in the second patient at level 3. Then three patients were added to this dosage group. No DLT was observed in these additional patients. However, grade 3 neutropenia was observed in five patients (83%) in the first treatment cycle at this dose level. In addition, a 1-week postponement of the second cycle was needed due to the neutropenia in one patient and grade 4 neutropenia developed in another patient in the second cycle. Therefore, an additional six patients were enrolled in order to confirm the safety of this dose level. No DLT except for grade 3 nausea in one patient was observed in this second cohort, and we moved to the next dosage level. At level 4, grade 3 neutropenia was observed in two of three patients. However, no DLT was seen in this cohort. DLT (more than a 1-week treatment delay due to grade 3 neutropenia) was observed in the third patient at level 5. Three patients were added to this level. DLT (grade 3 peripheral neuropathy) was observed in the sixth patient. Grade 2 neuropathy appeared following the first administration of paclitaxel on day 1 and increased to grade 3 immediately after the second administration on day 8. The treatment was continued up to three cycles at the next lower dosage level, although grade 1 or 2 peripheral neuropathy developed during every cycle. From these results, level 5 was determined as the MTD and level 4 (paclitaxel 80 mg/m^2, doxifluridine 800 mg/m^2) was set as the RD. The lowest neutrophil counts in the first cycle at each dosage level are shown in Table 4. The medians of the lowest absolute neutrophil counts were graded as grade 3 neutropenia in levels 3, 4 and 5. Their values were apparently lower than those in levels 1 and 2. The period of recovery to grade 1 was around a week in levels 3, 4, and 5. It was also longer than that in levels 1 and 2.

The main toxicity of this combined therapy was myelotoxicity, neutropenia in particular. Grade 3 or 4 neutropenia was observed in 0 of 12 cycles (0%) at level 1, 1 of 20 cycles (5%) at level 2, 14 of 76 cycles (18%) at level 3, 3 of 13 cycles (23%) at level 4, and 3 of 15 cycles (20%) at level 5. Non-hematological toxicities of greater than grade 3 were observed in four patients during all treatment cycles. Two of these were the DLT. One of the remaining two patients showed grade 3 diarrhea in the fourth cycle at level 4, and the other patient showed grade 3 peripheral neuropathy after five cycles at level 5. A total of seven patients needed dose reduction during all treatment cycles. Four patients with DLT (Table 1) and two patients with grade 3 diarrhea and grade 3 peripheral neuropathy, respectively, were included. The other was the patient who showed grade 4 neutropenia in the second cycle at level 3. Peripheral neuropathy of grade 1 or 2 occurred in 2 of 12 patients at level 3, 1 of 3 patients at level 4, and 3 of 6 patients at level 5. It tended to be more severe following repeated administration of paclitaxel and seemed cumulative. Hand-foot syndrome

Table 2 Characteristics of patients

Age (years)	
Median	63
Range	44–75
Sex	
Male/female	16/12
Performance status (ECOG)	
0/1/2	10/11/7
Prior therapy	
Gastrectomy	20
Chemotherapy (5-FU)	22 (17)
Histological type	
Differentiated	9
Undifferentiated	19
Sites of metastasis	
Liver	6
Abdominal lymph nodes	17
Lung	5
Peritoneum	19
Spleen	2

Table 3 Adverse reactions during the first treatment cycle

Toxicity	Level 1 ($n=4$)		Level 2 ($n=3$)		Level 3 ($n=6$)				Level 4 ($n=3$)		Level 5 ($n=6$)	
	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Hematological												
Leukopenia	2	0	2	1	5	1	1	2	2	0	5	0
Neutropenia	3	0	2	1	1	5[a]	3	2	0	3	3	2[a]
Lymphocytopenia	4	0	1	1	1	0	1	1	2	0	6	0
Anemia	3	1	3	0	4	1	5	0	0	2	4	1
Thrombocytopenia	2	0	0	0	0	0	2	0	0	0	1	0
Non-hematological												
Hypersensitivity reaction	1	0	0	0	0	0	0	0	0	0	0	0
Infection	0	0	0	0	0	0	0	0	0	0	0	0
Fatigue	2	0	0	0	1	0	1	0	3	0	0	0
Nausea	2	0	0	0	0	0	1	1[a]	0	0	2	0
Vomiting	0	0	0	0	0	0	1	0	0	0	0	0
Anorexia	1	0	0	0	1	0	0	0	2	0	1	0
Diarrhea	0	0	0	0	2	0	1	0	2	0	0	0
Stomatitis	1	0	0	0	0	0	0	0	0	0	1	0
Alopecia	1	–	0	–	3	–	2	–	2	–	5	–
Edema	0	0	0	0	0	0	0	0	0	0	0	0
Hand-foot syndrome	0	0	0	0	0	0	0	0	0	0	0	0
Rash	1	0	0	0	0	0	1	0	0	0	0	0
Palpitations	0	0	0	0	0	0	1	0	1	0	0	0
Peripheral neuropathy	0	0	0	0	0	0	0	0	1	0	0	1[a]

[a]DLT was observed in one patient

Table 4 Lowest absolute neutrophil count (LNC) during the first treatment cycle

Level	LNC (per mm^3)		Time to LNC (days)		Recovery from LNC (days)	
	Median	Range	Median	Range	Median	Range
1	1860	1287–1884	14	12–22	2	2–6
2	1700	558–1768	14	4–17	3	2–10
3	904	200–1672	14	6–16	8	4–15
4	867	738–996	14	14	8	7–8
5	902	801–1824	14	13–17	6	6–21

was not observed in any patient during any treatment cycle. There was no treatment-related death.

The median numbers of administration cycles were 2 (range 1–8) for level 1, 6 (range 3–11) for level 2, 6 (range 2–13) for level 3, 4 (range 3–6) for level 4, and 3 (range 2–5) cycles for level 5.

An objective tumor response was not observed in the patients at dosage levels 1 and 4. Three patients showed a partial response (PR) at level 2. Two patients showed a complete response (CR) and one patient showed a PR at level 3. Two patients showed a PR at level 5. The overall response rate in all 19 patients with measurable lesions was 42% (95% confidence interval 20–67%). The response rate in pretreated patients was 43% (6/14) and that in chemonaive patients was 40% (2/5). The ascites disappeared in two of three patients without measurable lesions at level 3.

Discussion

Based on the results of phase I and II clinical trials of paclitaxel, the RD was set at 210 mg/m^2 over a 3-week dosing schedule in Japan, and a relatively high tumor response rate of 23% has been reported for advanced gastric cancer [29, 33]. In addition, paclitaxel yielded the same response rate in the second-line setting (23%) as in the first line setting (24%), and non-cross resistance with other anticancer drugs was suggested. In terms of the toxicity, leukopenia and neutropenia of higher than grade 3 were observed in 28% and 58% of patients, respectively. These results are supported by other studies [1, 5]. In recent years, the concept of dose-dense therapy whereby the interval between administrations is shortened to reduce the time for regrowth of neoplastic cells has been proposed [8]. Several clinical studies involving weekly dose-dense therapy of paclitaxel have been performed in lung, breast, and ovarian cancer [16, 24, 27]. Following a phase I clinical trial in 60 patients with advanced cancer who had been treated previously with systemic chemotherapy other than taxanes, the RD was 80 mg/m^2 of paclitaxel weekly, and grade 3 or higher toxicities were rarely observed [16]. In addition, a recent randomized trial comparing two administration methods of paclitaxel with the same dose intensity (conventional 3-week regimen of 200 mg/m^2 and weekly regimen of 67 mg/m^2) in patients with recurrent ovarian cancer revealed equal response rates and overall survival, and reduced toxicities with the weekly schedule [24]. Thus, weekly dosing of paclitaxel has been confirmed to have equal efficacy and lower toxicity than the conventional dosing regimen.

Capecitabine is still under investigation for advanced gastric cancer in Japan. Instead, the immediate precursor to capecitabine, doxifluridine, has been approved for the treatment of advanced gastric cancer. In preclinical evaluations, the therapeutic index of doxifluridine has been shown to be much more than that of 5-FU [4]. In clinical studies, high oral bioavailability of doxifluridine has been noted, and it has shown prominent antitumor activity in patients with breast, colorectal, and gastric cancers [2, 7, 20]. The DLT of doxifluridine is diarrhea. Recently, it has been reported that several anticancer drugs, including paclitaxel, upregulate the expression of dThdPase specifically in tumor tissues and that paclitaxel in combination with doxifluridine shows the synergistic activity in several human cancer xenograft models [26]. Furthermore, the major toxicities of paclitaxel and doxifluridine do not overlap. Therefore, we adopted a weekly dosing regimen of paclitaxel in combination with doxifluridine.

Neutropenia was the most frequently observed toxicity with this combination therapy, and was dose-limiting. However, no neutropenic fever was seen in this study. At dose level 3, one patient experienced a DLT (grade 4 neutropenia for more than 4 days), and five of six patients, including the patient with DLT, exhibited grade 3 or more neutropenia in the first treatment cycle. Based on these results, the investigators and the independent efficacy and safety committee considered it appropriate to stop dose loading at level 3. However, the MTD was not achieved at this level. Then six patients were added to confirm the safety of this dose level. No DLT except for a patient with grade 3 nausea was observed in this additional cohort. Thus, dose escalation was reopened and no grade 4 neutropenia was observed at level 4. Non-hematological toxicity was generally mild. Peripheral sensory neuropathy, one of DLTs of paclitaxel, was well tolerated up to level 4, and diarrhea, a DLT of doxifluridine, was not severe in the initial few cycles at all levels. At level 4, there was only one patient who needed dose reduction due to diarrhea after four treatment cycles. The median numbers of cycles administered were 6 (range 2–13) at level 3 and 4 (range 3–6) at level 4. The main reason for stopping the treatment was disease progression at levels 3 and 4. From

these results, the dosage schedule at level 3 or 4 seems to be highly feasible.

Conventional 3-h infusion of paclitaxel with a 3-week interval combined with infusional 5-FU and cisplatin was studied in Korean group in a phase II trial in advanced gastric cancer [14]. A high response rate of 51% and good tolerability was reported in this study. Recently, it has been reported from Germany that weekly administration of paclitaxel with a combination of 5-FU/folinic acid and cisplatin showed a reduced incidence of hematological toxicity, particularly leukopenia, and other toxicities, apart from a slightly higher incidence of peripheral neuropathy, were also comparable between the weekly regimen and the conventional regimen [11]. The response rate (50%) in this German phase II study in advanced gastric cancer was well maintained with the weekly regimen.

Active oral fluoropyrimidines, such as capecitabine, S-1, and uracil/ftorafur (UFT) plus leucovorin have recently been developed [3, 15, 25]. Based on promising reports, trials are being urgently undertaken in many countries to determine whether 5-FU combined with various agents could be replaced by these new oral fluoropyrimidines. Although most patients in our study had received prior chemotherapy, this doxifluridine and paclitaxel combined therapy yielded a high response rate of 42% (95% confidence interval 20–67%). In addition, elimination of ascites was observed in two of three patients. The efficacy of this combination therapy would also be expected in patients with peritoneal dissemination that is frequently seen in advanced gastric cancer. These results encouraged us to move to further trials.

In conclusion, we performed a phase I clinical trial using a combination of paclitaxel and doxifluridine, and determined the RD as 80 mg/m^2 of paclitaxel on days 1 and 8, and 800 mg/m^2 per day of doxifluridine for 2 weeks in a 3-week treatment schedule. The results of our present study are promising and a phase II clinical trial of this combination therapy is planned in which the safety of the RD will be investigated carefully in the first six or more patients.

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