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ORIGINAL ARTICLE

A phase I study of paclitaxel, cisplatin, and fluorouracil (TCF) for advanced gastric cancer

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Abstract
Purpose A phase I study of TCF therapy, which consists of paclitaxel (TXL: Taxol®) + cisplatin (CDDP) + 5-fluorouracil (5-FU), in advanced gastric cancer patients was performed to determine the recommended dose (RD) for a phase II study by checking the dose-limiting toxicity (DLT) and maximum-tolerated dose (MTD) of 5-FU above the fixed dose of TXL and CDDP.
Methods The doses of TXL and CDDP were fixed at 80 and 25 mg/m^2, respectively, while that of 5-FU was increased by 100 mg/m^2 in each cohort from 300 mg/m^2 (level 1) to a maximum of 600 mg/m^2 (level 4). One cycle consisted of administration of these agents once per week for 3 weeks, every 4 weeks.
Results A total of twelve eligible patients were included in this study. At level 1, two of three cases showed grade 3 leukopenia. At level 2, one of three cases showed grade 4 neutropenia (recovered within 3 days), and another one case showed grade 3 neutropenia. At level 3, one of three cases showed grade 3 neutropenia, and at level 4, one of three cases showed grade 4 neutropenia (recovered within 3 days), with grade 3 neutropenia in the other two cases. Even at the highest dose administered, none of the patients showed DLT. Moreover, no non-hematological toxicity judged to be DLT was observed through all levels. Six of the twelve patients had measurable disease, and the overall response rate was 83%.
Conclusions Although the MTD level was not determined, based on the observed efficacy and the results of other clinical trials, the recommended doses of TXL, CDDP, and 5-FU for the TCF regimen were set as 80, 25, and 600 mg/m^2, respectively, and a phase II study to investigate the clinical effectiveness and safety of this regimen has now begun.

Keywords Gastric cancer · Phase I study · Paclitaxel · Cisplatin · 5-Fluorouracil · Weekly administration

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Introduction

Approximately 100,000 people develop gastric cancer in Japan each year. Although progress in diagnostics and surgical procedures has resulted in a gradual decline in the mortality rate, approximately 50,000 people still die from gastric cancer each year. As the prognosis of advanced non-resectable or recurrent gastric cancer is poor, this disease represents 1/6 of all deaths due to malignant neoplasms in Japan [7].

5-Fluorouracil (5-FU) is the main agent used in chemotherapy for the treatment of gastric cancer [16]. Following the introduction of cisplatin (CDDP),

regimens involving combinations of other agents with 5-FU, such as FAP (5-FU, doxorubicin, CDDP), FP (5-FU, CDDP), and ECF (epirubicin, CDDP, 5-FU), have been shown to be effective in the treatment of advanced gastric cancer [12, 17, 31, 32].

New anti-cancer drugs, including taxans, S-1, and irinotecan (CPT-11), which are expected to be effective against gastric cancer, have recently become available [11, 28]. Among these, paclitaxel (TXL: Taxol®; Bristol-Myers Squibb, Tokyo, Japan), isolated from *Taxus brevifolia*, shows anti-tumor effects by accelerating the polymerization of microtubule proteins, followed by stabilization and excessive microtubule formation. Consequently, it inhibits cell division, and thereby shows an anti-tumor effect [26]. In previous phase II studies of this agent for treatment of gastric cancer, Ajani reported a response rate of 17% at a dose of 200 mg/m^2, while Cascinu reported a response rate of 22.2% at a dose of 225 mg/m^2 [1, 4]. Another phase II study in Japan showed a response rate of 23% at a dose of 210 mg/m^2. However, all of these studies were performed with a regimen consisting of administration every 3 weeks, and there was also a high incidence of adverse effects, including neutropenia and neuropathy [33]. In a previous study regarding administration of the TXL regimen in ovarian cancer patients, Rosenberg reported superior safety with weekly administration rather than infusion every 3 weeks [25]. Seidman reported a higher tolerance with a weekly administration schedule in a phase II study in breast cancer patients [27].

The combination of TXL and CDDP has been shown to be effective in the treatment of ovarian cancer and lung cancer and is also considered effective in gastric cancer, based on the results of previous clinical studies [3, 15]. Nagata reported that no dose-limiting toxicity (DLT) developed in an interim report of a phase I study of weekly TXL + CDDP treatment (days 1, 8, 15, every 4 weeks) for gastric cancer at doses of 80 and 25 mg/m^2, respectively [20]. 5-FU is a representative anti-cancer drug considered to have a degree of anti-tumor effect against gastric cancer, and excellent response rates have been reported in clinical trials with the combination of TXL, CDDP, and 5-FU. However, these regimens require hospitalization [8, 10].

Therefore, a phase I study of TXL + CDDP + 5-FU (TCF) therapy in patients with advanced gastric cancer was performed. In this regimen, all of the drugs were administered weekly and over a short period (bolus administration of 5-Fu and 1-h administration of TXL) to facilitate treatment at hospital visits on an outpatient basis. The primary objective of the study was to determine the recommended dose (RD) for a phase II study by checking DLT and maximum-tolerated dose (MTD) of 5-FU, the concentration of which was raised gradually above the fixed doses of TXL and CDDP during the study. The secondary objectives of this study were to investigate the safety, anti-tumor effects, and pharmacokinetics of TXL.

Patients and methods

Eligibility

The patients enrolled in this study had histologically confirmed non-resectable or recurrent gastric cancers. Other criteria for inclusion were as follows: (1) Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, (2) up to one regimen of prior chemotherapy (completed 1 month previously), (3) adequate bone marrow, liver, and renal functions as defined by WBC >4,000, <12,000/mm^3, PLT >100,000/mm^3, Hb >8.0 g/dl, AST/ALT <2 times institutional upper limits, total bilirubin <1.5 mg/dl, creatinine <1.5 mg/dl, and creatinine clearance >60 ml/min, (4) no significant cardiac disease evident on electrocardiogram (ECG), (5) expected survival period >3 months, (6) no active cancer in other organs, and (7) age at least 20 years [23]. Patients who showed severe organ dysfunction, history of hypersensitivity, inflammatory disease, massive ascites and/or pleural effusion, or brain metastasis were excluded from the study. This study was approved by the Institutional Review Boards of each institution and all patients gave their written informed consent to participation in the study, in accordance with the institutional guidelines.

Treatment schedule and dose escalation

TXL with 200 ml of 0.9% sodium chloride solution was administered by infusion over a period of 1 h, followed by a bolus infusion of 5-FU and 1.5–3 h infusion of CDDP with 500 ml of 0.9% sodium chloride solution. To prevent hypersensitivity reactions, premedication (dexamethasone, 16 mg i.v.; diphenhydramine, 50 mg p.o.; ranitidine 50 mg or famotidine 20 mg i.v.) was given 30 min before TXL administration. One cycle consisted of administration of these agents once per week for 3 weeks (day 1, 8, 15), every 4 weeks. Patients were given at least 1 course of treatment, and therapy was continued for as long as possible (until confirmation of progressive disease or events, such as toxicity and patient refusal, made continuation impossible).

In this study, the doses of TXL and CDDP were fixed at 80 and 25 mg/m^2, respectively, while that of

5-FU was increased by 100 mg/m^2 in each cohort from 300 mg/m^2 (level 1) to a maximum of 600 mg/m^2 (level 4), unless MTD was achieved (Table 1).

Evaluation

Pretreatment evaluation included determination of baseline medical history and physical examinations, in addition to laboratory studies (complete blood cell counts, electrolytes, liver and renal function tests, and urinalysis), chest X-ray, abdominal computed tomography (CT), and ECG. CT or other imaging tests were also performed to document the disease when measurable, and were repeated at the end of every course of treatment. In addition, the responses were classified according to response criteria in solid tumors (RECIST) [29].

Toxicity was monitored and graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0. During treatment, patients underwent weekly laboratory studies and assessment of non-hematological toxicities. The following toxicities during the first course of treatment were defined as DLT: (1) Grade 4 leukopenia or neutropenia lasting for 4 days or more; (2) Grade 3 leukopenia or neutropenia accompanied by high fever (>38°C); (3) thrombocytopenia (<20,000/mm^3); (4) Grade 3 and 4 non-hematological toxicity (except anorexia, nausea, vomiting, and alopecia); and (5) administration of granulocyte-colony stimulating factor (G-CSF). Cases in which the course of treatment could not be completed within 6 weeks because of toxicity were also categorized as showing DLT. The MTD level was defined as the highest 5-FU dose that resulted in DLT in two or more of the three patients at that dose level. If one of the three patients in a given dose group experienced DLT, then three new patients were treated at the same dose level; when one or more of the three new patients experienced DLT, the MTD level was defined as this dose. Before proceeding to the next dose level, all previously treated patients in the same cohort had received at least one course of treatment.

Table 1 Dose escalation scheme

Dose level	Paclitaxel (mg/m^2)	Cisplatin (mg/m^2)	5-Fluorouracil (mg/m^2)
1	80	25	300
2	80	25	400
3	80	25	500
4	80	25	600

Pharmacokinetic study

Blood samples for pharmacokinetic studies were collected from a subset of patients to allow characterization of the pharmacokinetics. To measure TXL concentrations during the initial treatment course, whole blood samples were collected at 0, 0.5, 1.5, 6, 12, and 24 h after completion of drug administration. Samples were collected into heparinized tubes, centrifuged, and the supernatant was stored at –20°C until assayed. TXL concentrations were measured in plasma by reverse-phase high-performance liquid chromatographic assay, as described previously [14]. The peak plasma concentration (C_{max}) was determined from the actual value, and the area under the plasma concentration-versus-time curve (AUC) was calculated by the trapezoidal method.

Results

Patient characteristics

Fourteen patients were enrolled in this study between August 2003 and March 2005. However, two patients were ineligible and were excluded from evaluation: one rescinded consent, while the other was diagnosed as having active lung cancer. The characteristics of the remaining twelve cases are summarized in Table 2. These twelve patients received at least one course of therapy, representing a total of over 62 courses of treatment (median, 3.5; range, from 1 to more than 11, treatment is still ongoing in two cases). Six patients had no measurable lesions to allow evaluation of treatment efficacy.

Table 2 Patient characteristics

Number of patients	12
Male/Female	8/4
Median age, years (range)	63.5 (54–73)
EOCG PS, 0/1	7/5
Non-resectable/Recurrence	6/6
Prior chemotherapy	0
Histology	
Intestinal	4
Diffuse	8
Metastatic site	
Lymph node	4
Liver	4
Peritoneum	7

ECOG PS Eastern Cooperative Oncology Group performance status

Table 3 Toxicity during first course of treatment

	Level 1 (n = 3)				Level 2 (n = 3)				Level 3 (n = 3)				Level 4 (n = 3)			
Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Leukopenia			2		1		2			1	1			2	1	
Neutropenia		1	1			1	1	1[a]		1	1				2	1[a]
Hemoglobin	2	1			2		1		2	1			1	2		
Thrombocytopenia	1				1								1			
Body weight loss													2			
Nausea		1			3					2	1					
Vomiting					1				1	1						
Diarrhea	1				2	1			1							
Anorexia		1			1	1	1			1	1		2			
Fatigue	3				3				2	1			2			
Neuropathy	1								1							
Abdominal pain	1				1				1	2						
Alopecia	1	2			3				2	1			2			

[a] Recovered within 3 days

Toxicities

Twelve cases were evaluated for adverse reactions, and the adverse reactions observed at each level during the first course of treatment are summarized in Table 3. At level 1, three patients were treated with the first dose level of TXL at 80 mg/m^2, CDDP at 25 mg/m^2, and 5-FU at 300 mg/m^2 (weekly dose intensities were as follows: TXL, 60 mg/m^2/week; CDDP, 18.75 mg/m^2/week; and 5-FU, 225 mg/m^2/week). Two of three cases showed grade 3 leukopenia, but did not reach DLT. The 5-FU dose was then increased to 400 mg/m^2 (300 mg/m^2/week), and three patients were assigned to receive dose level 2. However, one showed grade 4 neutropenia (recovered within 3 days) and grade 3 leukopenia, and another showed grade 3 neutropenia and leukopenia; no DLT was observed in these patients. At level 3 (5-FU 500 mg/m^2, 375 mg/m^2/week), one of three cases showed grade 3 neutropenia and leukopenia, and at level 4 (5-FU 600 mg/m^2, 450 mg/m^2/week), one patient showed grade 4 neutropenia (recovered within 3 days) and grade 3 leukopenia, and another two showed grade 3 neutropenia. However, even at the highest dose level, none showed DLT. Moreover, no non-hematological toxicity judged to be DLT was observed through all levels, and there were no cases in which the treatment could not be completed due to adverse events.

Anti-tumor activity

Only six of the twelve treated patients with this regimen had measurable disease, and these patients were subjected to at least two cycles of therapy. Five cases showed partial response (PR) and one case showed stable disease (SD). Therefore, the overall response rate (RR) with RECIST was 83.3% (Table 4). The response rates for liver metastases and lymph node metastases were 100% (4/4) and 75% (3/4), respectively.

Pharmacokinetic study

As shown in Table 5, plasma specimens were collected from a total of eleven patients on day 1 of course 1, and TXL concentration levels were assessed (one patient refused the pharmacokinetic examination). The area under the curve (AUC) was calculated in ng/ml, and mean AUC (0–24 h ng/ml) ± SD for each 5-FU dose level were as follows: level 1, 3,693 ± 1,344; level 2, 3,032 ± 709; level 3, 3,025 ± 438; and level 4, 2,477 ± 161.

Discussion

The prognosis of advanced or recurrent gastric cancer remains poor, with a median survival period of generally 3 to 4 months if left untreated. Systemic chemotherapy has been shown to be effective in improving both the prognosis and quality of life of gastric cancer patients, and previous clinical studies suggested that improvement of the response rate could be achieved by

Table 4 Anti-tumor activity

Level	Metastatic site	Response	No. of courses of administration
1	Lymph node, Liver	PR	3
1	Lymph node	SD	3
3	Liver	PR	2
3	Lymph node	PR	5
4	Liver	PR	4
4	Lymph node, Liver	PR	>11

PR partial response, *SD* stable disease

Table 5 Pharmacokinetics of TXL

Level	Patients	Mean concentration (SD) of TXL (ng/ml)				Mean AUC (SD) (0–24 h ng/ml)
		0 h (C_{max})	6 h	12 h	24 h	
1	3	2,723 (289)	107 (43.8)	82.0 (36.2)	29.3 (12.0)	3,693 (1,344)
2	3	2,403 (410)	89.0 (29.6)	45.3 (9.61)	22.3 (4.51)	3,031 (709)
3	2	2,825 (460)	94.5 (10.6)	55.5 (4.95)	32.5 (0.70)	3,025 (438)
4	3	2,230 (775)	74.3 (17.0)	38.0 (13.5)	25.6 (7.02)	2,477 (161)

SD standard deviation, *TXL* Taxol (paclitaxel), *AUC* area under the curve

multidrug regimens [6, 19, 24]. However, no regimen has been established that can surpass 5-FU alone with regard to survival time, and no particular regimen is recommended for treatment of this disease [5, 9, 22].

As patients with gastric cancer often show poor compliance with oral intake of drugs, intravenous administration rather than the more frequently employed oral administration may also have contributed to the more stable effect seen in this study. The characteristics of TXL include its effectiveness, particularly in poorly differentiated adenocarcinoma and peritoneal metastasis, as well as in patients with a previous history of chemotherapy because of a lack of cross-reactivity with other anti-cancer drugs and the achievement of a favorable survival period [1, 4, 18, 33]. However, TXL alone gives a response rate of at most 20–30%, irrespective of the regimen used. Therefore, the development of a novel regimen capable of improving both the anti-tumor effect and the survival period by combination with other agents is urgently required. In the present study, 5-FU was used in combination with weekly administration of TXL + CDDP. Ajani reported that the response rate of a regimen consisting of docetaxel + CDDP + 5-FU, which uses a similar Taxan derivative, was 43%. However, an excellent response rate was obtained with this weekly regimen, although the number of patients was too small to allow definitive conclusions to be drawn [2].

Not only was a reduction of adverse events observed but also an improved anti-tumor effect was expected due to the prolonged duration of the cytotoxic concentration by fractionated administration of TXL [25, 27, 30]. Our pharmacokinetic investigation showed that the hematologically toxic concentration (>100 ng/ml) persisted for about 6 h and the cytotoxic effect (>10 ng/ml) continued for more than 24 h after the initial administration. There were no differences in 5-FU levels. These observations indicated that 1-h administration of TXL, as used in the weekly regimen, was a rational schedule, and all patients showed excellent compliance with this regimen [13, 27].

The present phase I study could not define MTD due to the absence of adverse events corresponding to the specified DLT, although the dose of 5-FU was increased gradually to the initially specified level 4. Defining MTD by further increasing the dose of 5-FU was considered unnecessary based on previous reports: Nagata recommended doses of weekly TXL + CDDP of 80 mg/m^2 and 25 mg/m^2, respectively, based on the results of a phase I study, and Ninomiya reported a phase II study using the recommended dose of intravenous administration of 5-FU in combination with weekly TXL at 600 mg/m^2 and 80 mg/m^2, respectively, based on their phase I study and the extremely efficient anti-tumor effect of this regimen [20, 21]. Based on these observations, the recommended doses for TCF were as follows: TXL, 80 mg/m^2; CDDP, 25 mg/m^2; and 5-FU, 600 mg/m^2. A phase II study to investigate the clinical effectiveness and safety of this regimen has now begun.

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