Original article

Pharmacokinetic study of weekly administration dose of paclitaxel in patients with advanced or recurrent gastric cancer in Japan

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Abstract

Background. We aimed to clarify the relationship between the maximum tolerated dose and plasma concentration of paclitaxel in Japanese patients with gastric cancer on a weekly paclitaxel administration regimen.

Methods. Thirty-three patients with advanced or recurrent gastric cancer were treated with escalating doses of paclitaxel, administered weekly, along with a fixed dose of 5-fluorouracil or cisplatin.

Results. The plasma concentration of paclitaxel remained above 8.5 ng/ml for 24 h after administration. The mean area under the curve increased significantly with escalating dosage levels ($R = 0.63$; $P < 0.001$). At level 4, patients showing dose-limiting toxicity had a significantly higher plasma paclitaxel concentration than patients without it.

Conclusion. The weekly administration of paclitaxel, for which a single dose is about one-third of the dose for a tri-weekly treatment regimen, is clinically feasible and appropriate in terms of toxicity and the maintenance of an effective plasma concentration.

Key words Paclitaxel · Chemotherapy · Gastric cancer · Pharmacokinetic study · Advanced gastric cancer

Introduction

Paclitaxel (PTX), originally isolated from the bark of the tree *Taxus brevifolia*, is a potent inhibitor of cell replication. The antimitotic activity of PTX results from its ability to block the late G2 and M phases of the cell cycle. PTX has significant antitumor activity in several human tumors, including advanced ovarian, lung, and breast cancers [1]. Chang et al. [2] demonstrated that

PTX inhibited the growth of gastric carcinoma cell lines at clinically attainable concentrations. Several reports describe the effectiveness of PTX in combination chemotherapy with 5-fluorouracil (5-FU) or cisplatin in the treatment of advanced gastric cancer [3–8].

In preclinical studies, the growth inhibitory effect of PTX on primary cultures of gastric cancer was greater than that of other anticancer agents [9]. Therefore, PTX administration is expected to provide a clinical advantage in the treatment of gastric cancer. In a phase II trial of PTX administration by 3-h infusion every 3 weeks for patients with gastric cancer, a 23% response rate was observed [8]. Weekly administration of PTX has been demonstrated to be well-tolerated and feasible in patients with ovarian cancer [10], breast cancer [11], and lung cancer [12]. Furthermore, PTX exerts its cytotoxic effects through a mechanism different from that of cisplatin and 5-FU, and shows no cross-resistance with cisplatin [13–15]. The recommended optimal dose of cisplatin was determined to be more than 20 mg/m² per week [13,14].

Based on these reports, we conducted two phase I clinical studies of combination chemotherapy investigating escalating weekly doses of PTX in patients with advanced or metastatic gastric cancer in Japan. One study included fixed systemic administration of 5-FU for 18 patients and the other included fixed systemic administration of cisplatin for 15 patients. A pharmacokinetic study of PTX was performed to clarify the relationship between dose-limiting toxicity (DLT) and serum PTX concentration.

Patients, materials, and methods

Eligibility

Patients in this study had histologically proven metastatic gastric cancer with/without measurable lesions. Other inclusion criteria were: age 20 to 75 years, Eastern Cooperative Oncology Group (ECOG) performance status less than 2, life expectancy more than 2 months, adequate bone marrow function (white cell count $>4000/\text{mm}^3$, platelet count $>100000/\text{mm}^3$, and hemoglobin level $>9.0\text{ g/dl}$), adequate renal function (creatinine clearance $>50\text{ ml/min}$), adequate hepatic function (bilirubin level $<1.5\text{ mg/dl}$ and GOT, GPT $<$ twice the upper limit of normal), more than a 1-month interval since prior chemotherapy, and no active cancer in other organs. All patients gave written informed consent conforming to institutional guidelines indicating that they were aware of the investigational nature of the study. This protocol was approved by the ethics committees of all participating institutions.

Treatment

In study 1, a fixed dose of 600 mg/m^2 per day of 5-FU was administered by continuous infusion for 5 days on days 1–5 and PTX was infused for 1.5 h on days 8, 15, and 22. In study 2, PTX was infused for 1.5 h on days 1, 8, and 15 following the infusion of a fixed dose of 25 mg/m^2 cisplatin for 2 h. In both studies, PTX was administered after standard prophylactic pretreatment for PTX-associated hypersensitivity reactions, using dexamethasone (20 mg i.v.), diphenhydramine (25 mg p.o.), and ranitidine (50 mg i.v.). The PTX dose was escalated in successive patient cohorts to determine the maximum tolerated dose (MTD). The doses of PTX were as follows: dose level 1 (starting dose), 60 mg/m^2 ; dose level 2, 70 mg/m^2 ; dose level 3, 80 mg/m^2 ; and dose level 4, 90 mg/m^2 . Dose escalation was not performed until safety and tolerance had been assessed at the previous dose level.

Determination of the MTD for paclitaxel was performed by evaluating individual cohorts of three to six patients at each dose level. If the first three patients did not develop DLT at a given dose, the dose was escalated to the next level in a subsequent cohort. If one of the first three patients developed DLT, an additional three patients were recruited and given the same dose level. The PTX dose was escalated only if fewer than two of these additional three patients developed DLT. If two or more out of a cohort of three, or three or more out of a cohort of six patients developed DLT, then accrual of patients at that level of PTX was stopped, and that level was designated the MTD. No inpatient dose escalation was performed.

Toxicity

During treatment, patients had weekly full hematological blood cell counts, determination of liver and renal function, and assessment of nonhematological toxicities. Toxicity, according to National Cancer Institute common toxicity criteria (NCI-CTC) [16], was recorded every week. Dose-limiting hematological and nonhematological toxicities were defined separately. Dose-limiting hematological toxicities were defined as NCI grade 4 leukopenia or grade 4 neutropenia lasting for more than 4 days, grade 3 leukopenia or grade 3 neutropenia accompanied by high fever ($>38^\circ\text{C}$), and grade 4 thrombocytopenia ($<25000/\text{mm}^3$). Dose-limiting nonhematological toxicities were defined as NCI grade 3 and 4 toxicity, with specific exclusion of grade 3 nausea, vomiting, or alopecia.

Pharmacokinetic study

Table 1 shows the characteristics of the patients included in both studies. In study 1, PTX dose levels 1, 2,

Table 1. Patient characteristics

	Study 1 ($n = 18$)	Study 2 ($n = 15$)
Sex		
M	11	11
F	7	4
Mean age (years)	58.7 (22–75)	63.1 (38–74)
Histology		
Well	1	0
Mod	6	5
Por	6	6
Sig	1	4
Pap	1	0
Site		
Lymph node	5	8
Peritoneum	6	5
Liver	2	2
Lung	1	1
Stomach	4	0
Pancreas	0	1
Diaphragm	1	0
PS		
0	5	8
1	9	7
2	1	0
Dose level (DLT) ^a		
1	6 (1)	3
2	3	3
3	6 (2)	3
4	3 (2)	6 (2)

Well, well-differentiated tubular adenocarcinoma; mod, moderately differentiated tubular adenocarcinoma; por, poorly differentiated adenocarcinoma; sig, signet-ring cell carcinoma; pap, papillary adenocarcinoma; PS, Eastern Cooperative Oncology Group (ECOG) performance status [25]

^aNumbers in parentheses, numbers of patients with DLT. In study 1, a case of DLT due to 5-fluorouracil was observed in level 1

3, and 4 were given to 6, 3, 6, and 3 patients, respectively. In study 2, each PTX dose level was given to 3, 3, 3, and 6 patients, respectively.

Blood samples were collected in heparinized tubes before PTX administration and at 0, 0.5, 1.5, 6, 12, and 24 h after completion of PTX administration during the initial treatment course. The samples were then centrifuged, and the supernatant was stored at -20°C until required for assay. Paclitaxel (PTX) concentrations were measured by a reverse-phase high-performance liquid chromatographic assay [17]. The area under the concentration-time curve (AUC) was calculated by the trapezoid rule.

Statistical analysis

Pharmacokinetic parameters, the AUC and the plasma concentration, were reported as mean values $\pm$ SD, unless stated otherwise. Differences in the means of peak plasma concentrations (C_{max}) and AUC between dosage levels were analyzed for significance using a two-tailed *t*-test. The relationships between the AUC and the dosage level and those between C_{max} and the dosage level were analyzed by means of a Spearman's rank correlation coefficient. A *P* value of less than 0.05 was considered to be statistically significant.

Results

In study 1, there was one case of DLT at PTX dosage level 1, shown to be caused by 5-FU, and not PTX, by the Data-Monitoring Committee, because the patient showed grade 3 diarrhea prior to PTX administration. There were two cases of DLT at PTX dosage level 3 (grade 3 stomatitis and grade 3 diarrhea) and two at level 4 (grade 3 diarrhea, grade 3 hyperbilirubinemia, and grade 3 hyponatremia in one patient, and grade 4 leucopenia, grade 4 neutropenia, grade 4 hyperbilirubinemia, and grade 4 liver dysfunction in another patient) in study 1. There were also two cases of DLT at PTX dosage level 4 in study 2 (grade 4 leukopenia and grade 4 neutropenia in both patients; Table 1).

The mean plasma concentrations of PTX are shown in Table 2. After completion of administration, the plasma PTX concentration reached a peak, and then decreased rapidly for 1.5 h before continuing to decrease more gradually. Plasma PTX concentrations were maintained above 8.5 ng/ml for 24 h after PTX administration. Our pharmacokinetic study showed that the plasma PTX concentration was maintained in all patients for at least 24 h between the level required to effectively target cancer cells and the dose cytotoxic to normal cells (Fig. 1).

Table 2. Mean plasma concentration (ng/ml) $\pm$ SD of PTX after administration of PTX at each dose level

Hours	0	0.5	1.5	6	12	24
Level 1 (60 mg/m ²)	1205 $\pm$ 466.6	315.4 $\pm$ 109.9	146.0 $\pm$ 38.6	64.7 $\pm$ 15.2	40.4 $\pm$ 11.2	21.4 $\pm$ 5.5
Level 2 (70 mg/m ²)	1747.7 $\pm$ 822.7	594.3 $\pm$ 326.6	206.0 $\pm$ 47.6	81.7 $\pm$ 16.2	55.0 $\pm$ 21.1	27.8 $\pm$ 7.0
Level 3 (80 mg/m ²)	1482.4 $\pm$ 574.1	440.4 $\pm$ 168.6	219.4 $\pm$ 97.9	93.0 $\pm$ 52.7	54.4 $\pm$ 24.8	34.3 $\pm$ 16.9
Level 4 (90 mg/m ²)	2328.3 $\pm$ 754.3	832.1 $\pm$ 619.0	374.2 $\pm$ 169.8	146.4 $\pm$ 82.0	85.8 $\pm$ 55.4	46.4 $\pm$ 23.8

Levels 1, 2, 3, and 4 had 9, 6, 9, and 9 patients, respectively

Fig. 1. Plasma concentration of paclitaxel (PTX) at each dose level

The mean AUCs for each PTX dose level were 2753.7 ± 617.6 ng·h/ml for level 1 (60 mg/m^2), 3912.6 ± 1188.6 ng·h/ml for level 2 (70 mg/m^2), 4236.1 ± 1972.5 ng·h/ml for level 3 (80 mg/m^2), and 5981.3 ± 2272.2 ng·h/ml for level 4 (90 mg/m^2). The mean AUC increased with escalating paclitaxel dosage levels ($R = 0.63$, $P < 0.001$; Table 3). The mean Cmax values of PTX for dosage levels 1, 2, 3, and 4 were 1205.0 ± 466.6 ng/ml, 1747.7 ± 822.7 ng/ml, 1482.4 ± 574.1 ng/ml, and 2328.3 ± 754.3 ng/ml, respectively (Table 3). The Cmax was also dose-dependent and increased with escalating paclitaxel dosage levels ($R = 0.51$, $P = 0.002$). There were no significant

differences in AUC or Cmax values between the two studies and the correlations between dose level and AUC and dose level and Cmax were similar (AUC, $R = 0.63$ in study 1; $P = 0.005$; $R = 0.59$ in study 2; $P = 0.020$; Cmax, $R = 0.52$ in study 1; $P = 0.026$; $R = 0.48$ in study 2; $P = 0.073$), though the combined drug and the timing of PTX administration were different (Tables 4, 5).

Table 6 shows the plasma PTX concentrations for patients with and without DLT at PTX dosage levels 3 and 4. For level 3, the mean AUC value estimated for patients with DLT was 4286.4 ± 2998.5 ng·h/ml, while for patients without DLT the mean AUC value was 4221.8 ± 1920.5 ng·h/ml. These values were not significantly different ($P = 0.4853$). By comparison, the mean AUC values for patients with and without DLT at PTX dosage level 4 were significantly different ($P = 0.03$), at 7703.2 ± 2391.8 ng·h/ml and 4603.8 ± 836.0 ng·h/ml, respectively. Hematological toxicity was observed in three patients given PTX dosage level 4. The mean AUC of these patients was 8461.1 ± 2266.0 ng·h/ml, which was significantly higher than the mean AUC value of 4603.8 ± 836.0 ng·h/ml for patients without DLT at PTX dosage level 4 ($P = 0.01$; Table 6).

Table 3. Mean AUC (ng·h/ml) $\pm$ SD of PTX and peak plasma PTX level (Cmax) at each dose level

	AUC (ng·h/ml)	Cmax (ng/ml)
Level 1 (60 mg/m^2)	2753.7 ± 617.6	1205.0 ± 466.6
Level 2 (70 mg/m^2)	3912.6 ± 1188.6	1747.7 ± 822.7
Level 3 (80 mg/m^2)	4236.1 ± 1972.5	1482.4 ± 574.1
Level 4 (90 mg/m^2)	5981.3 ± 2272.2	2328.3 ± 754.3

Both the mean AUC and Cmax increased with escalating paclitaxel dosage levels (AUC, $R = 0.63$; $P < 0.001$; Cmax, $R = 0.51$; $P = 0.002$)

Table 4. Mean AUC (ng·h/ml) $\pm$ SD of PTX in each study

AUC (ng·h/ml)	Study 1*	Study 2**	Difference (P value)
Level 1 (60 mg/m^2)	2534.9 ± 567.9	3191.4 ± 537.2	-656.5 (0.14)
Level 2 (70 mg/m^2)	3631.6 ± 1208.6	4193.7 ± 1354.3	-562.1 (0.62)
Level 3 (80 mg/m^2)	4444.8 ± 2370.1	3818.9 ± 1062.4	625.9 (0.68)
Level 4 (90 mg/m^2)	6511.7 ± 2946.3	5716.2 ± 2129.7	795.5 (0.65)

* Study 1: $R = 0.63$; $P = 0.005$

** Study 2: $R = 0.59$; $P = 0.020$

Table 5. Peak plasma PTX level (Cmax) in each study

Cmax (ng/ml)	Study 1*	Study 2**	Difference (P value)
Level 1 (60 mg/m^2)	1119.3 ± 471.0	1376.3 ± 500.3	-257 (0.47)
Level 2 (70 mg/m^2)	1751.7 ± 857.5	1743.7 ± 978.1	8 (0.99)
Level 3 (80 mg/m^2)	1453.7 ± 479.8	1540.0 ± 857.5	-86.3 (0.85)
Level 4 (90 mg/m^2)	2156.7 ± 172.1	2414.2 ± 933.8	-257.5 (0.66)

* Study 1: $R = 0.52$; $P = 0.026$

** Study 2: $R = 0.48$; $P = 0.073$

Table 6. Mean AUC (ng·h/ml) of patients with and without DLT at PTX levels 3 and 4

	DLT (–)	DLT (+)	Hematological toxicity
Level 3 ^a (80 mg/m^2)	4221.8 ± 1920.5 ($n = 7$)	4286.4 ± 2998.5 ($n = 2$)	—
Level 4 ^b (90 mg/m^2)	4603.8 ± 836.0 ($n = 5$)	7703.2 ± 2391.8 ($n = 4$)	8461.1 ± 2266.0 ($n = 3$)

^a The mean AUC of patients with DLT was not significantly higher than that of patients without DLT at level 3 ($P = 0.4853$)

^b The mean AUC of patients with DLT or hematological toxicity was significantly higher than that of patients without DLT at level 4 ($P = 0.03$; $P = 0.01$)

Discussion

Gastric cancer is one of the most common cancers in Japan. Although advances in early diagnosis and surgical techniques have improved the outcome of treatment for gastric cancer, optimal chemotherapy regimens have not been determined for advanced or recurrent gastric cancer.

Several phase I and phase II studies have demonstrated response rates of 40% to 80% for patients with advanced-stage gastric cancers [18,19]. In Western countries, to date, commonly used regimens include EAP (etoposide/doxorubicin/cisplatin) [3], FAP(5-FU/doxorubicin/cisplatin) [4], and FP (5-FU/cisplatin) [5]. In Japan, continuous 5-FU infusion is generally accepted as the standard treatment for patients with advanced-stage gastric cancers, based on survival rates and toxicity [20]. The newly developed oral fluorinated pyrimidine drug, TS-1, is now widely accepted as a first-line treatment for advanced gastric cancers in Japan. Despite the many clinical trials to determine the effectiveness of various chemotherapy regimens, a universally accepted, standard treatment regimen for recurrent or advanced gastric cancer has not yet been established.

Combination chemotherapy studies of the newly developed anticancer agent, PTX, have been conducted, and a phase II clinical study has shown PTX to be effective in treating progressive cancer in 23.3% of patients and useful in 26.9% of patients who had received prior chemotherapy [8,21]. In these phase II studies, the intravenous administration of PTX every 3 weeks for 3h at a dose of 210mg/m² resulted in adverse effects such as peripheral neuropathy and myalgia. By comparison, weekly administration of PTX was shown to reduce the toxicity but not the efficacy of PTX [22].

Recently, patients with advanced gastric cancer have been treated by weekly administration of PTX. According to Norton's dose-density concept, weekly administration of PTX is expected to have a stronger anticancer effect, with reduced toxicity, compared to a tri-weekly single-administration schedule [23]. The effectiveness of weekly administration of PTX is most likely due to the maintenance of plasma concentrations that are cytotoxic to cancer cells [2,24].

The two phase I studies of PTX combination chemotherapy described in the present report revealed a recommended weekly dose for PTX of 80mg/m². Both the AUC and the C_{max} were dose-dependent and increased with escalating paclitaxel dosage levels. The drugs combined with PTX differed in the two studies, and therefore the plasma concentration of PTX may have been influenced differently. However, there have been no reports regarding a relationship between PTX and 5-FU or cisplatin. Blood samples for the pharmacokinetic study were taken during the initial treatment course.

This may have reduced the influence of the combined drugs. The statistical investigation showed that there were no significant differences in AUC or C_{max} between our two studies, and the correlations between dose level and AUC and dose level and C_{max} were similar. The mean AUC was significantly higher for patients with DLT than those without DLT in level 4, but this was not so in level 3. These results demonstrate that the recommended weekly dose of 80mg/m² PTX is appropriate and confirm our estimations of the MTD and DLT values for PTX.

One of our patients, not included in the studies described in this report, received 60mg/m² PTX and had serum PTX levels measured 60h after PTX administration. Another patient, from study 2, given a level 3 PTX dose, had serum PTX levels measured 168h after PTX administration. Data from these two patients revealed that plasma levels of PTX remained within the effective range for 60 and 72h, respectively (data not shown, submitted for publication).

In conclusion, the weekly administration of PTX, for which the single dose is about one-third of the standard dose required for a tri-weekly treatment regimen, is clinically feasible and appropriate in terms of toxicity and the maintenance of an effective plasma concentration.

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