

ORIGINAL**Intraperitoneal infusion of paclitaxel with S-1 for peritoneal metastasis of advanced gastric cancer : phase I study**

Nobuhiro Kurita, Mitsuo Shimada, Takashi Iwata, Masanori Nishioka, Shinya Morimoto, Kozo Yoshikawa, Jun Higashijima, Tomohiko Miyatani, and Toshihiro Nakao

Department of Digestive Surgery and Transplantation, Institute of Health Biosciences, the University of Tokushima Graduate School, Tokushima, Japan

Abstract : Background : Intraperitoneal administration of taxanes revealed excellent anti-tumor effect for peritoneal metastasis of gastric cancer in some experimental models. The aim of this study is to determine maximum tolerated dose (MTD), dose limiting toxicity (DLT) and recommended dose (RD) of intraperitoneally infused paclitaxel (PTX) with S-1 as a phase I study. **Patients and Methods :** Eighteen patients with advanced gastric cancer in addition to confirmed peritoneal metastasis using laparoscopy were enrolled in this study. The regimen consists of oral administration of S-1 (Dose 80 mg : BSA < 1.25 m², 100 mg : 1.25 < BSA < 1.5 m², 120 mg : BSA > 1.5 m²) for 14 days and intraperitoneal infusion of PTX (Dose escalation : level I : 40, II : 60, III : 80, level IV : 90, V : 100 mg/m²) at day 1 and 14. PTX concentrations in serum and ascites were determined at 4, 8, 12, 24, 48 hours after the infusion, which was repeated twice every 4 weeks. **Results :** The number of patients were as follows : Level I : 3, Level II : 6, Level III : 3, Level IV : 3, Level V : 3. Grade 3 leukocytopenia was confirmed in 1 (Level II) and 2 (Level V). MTD is 90 mg/m², RD is 80 mg/m² and DLT is Grade 3 leukocytopenia. The average serum PTX concentrations remained in optimal range except for all 3 of level V patients. In all cohorts, the PTX concentrations in the ascites were approximately 1000 folds higher than those in serum for 48 hours after the infusion. **Conclusions :** MTD and RD were PTX 90 mg/m², 80 mg/m², respectively. These findings were supported by pharmacokinetics of PTX. *J. Med. Invest.* 58 : 134-139, February, 2011

Mini-Abstract : In intraperitoneal infusion of PTX with S-1, DLT was leukocytopenia, MTD and RD were PTX 90 mg/m², 80 mg/m², respectively. These findings were supported by pharmacokinetics of PTX

Keywords : paclitaxel, S-1, intraperitoneal infusion, peritoneal metastasis, gastric cancer

Received for publication December 21, 2010 ; accepted January 12, 2011.

Address correspondence and reprint requests to Mitsuo Shimada, Department of Digestive Surgery and Transplantation, Institute of Health Biosciences, the University of Tokushima Graduate School, Kuramoto-cho, Tokushima 770-8503, Japan and Fax : +81-88-631-9698.

INTRODUCTION

Median survival time, even with the best supportive care, for patients with unresectable or metastatic gastric cancer is only 3.1 months (1). Although peritoneum is the most common metastatic site of

advanced gastric cancer, a standard regimen has not been established despite the number of trials and the survival rate is very low.

Recently new chemotherapy agents have been developed. In particular S-1 revealed a high response rate of 49% for advanced gastric cancer in late phase II study (2), which has been widely accepted as a key drug even for adjuvant setting in Japan (3).

Taxanes stabilize and excessively form microtubules, which is a different mechanism from other agents. In phase II study, response rate of paclitaxel (PTX) for advanced gastric cancer was 21% and not affected by differentiation of adenocarcinoma (4, 5). High concentrations approximately 1000 times of PTX in the peritoneal cavity maintained compared with those in serum after intraperitoneal administration because of fat solubility and heavy molecular weight; 853.92 (6). Excellent pharmacokinetics and anti-tumor effect to the peritoneal dissemination of gastric cancer was reported in the experimental model (7).

It is considered that S-1 and PTX is one of the best combinations for the treatment peritoneal metastasis of gastric cancer. The aim of this study is to determine the appropriate doses and feasibility of intraperitoneal infusion of paclitaxel (PTX) with orally administered S-1.

PATIENTS AND METHODS

Patient eligibility

Patients with peritoneal metastasis of advanced gastric cancer were eligible for this clinical trial. Before initiation of the study, relevant study documentation was submitted to and approved by the responsible ethics committee: the University of Tokushima hospital clinical research Ethical Review Board, Tokushima, Japan.

The guidelines of the World Medical Association Declaration of Helsinki in its revised edition (Edinburgh, Scotland, October 2000) and other applicable regulatory requirements were strictly followed. Written informed consent was obtained from each patient before any study-specific screening procedures were undertaken.

Inclusion criteria

Patients aged 20-75 years, had to have histologically or cytologically confirmed peritoneal metastasis of gastric cancer using laparoscopy under general anesthesia, who had not received abdominal surgery

and any prior chemotherapy regimens.

Exclusion criteria

Patients with ischemic heart disease that needed medication, liver cirrhosis, lung fibrosis, pneumonia, intestinal bleeding or other severe complications were excluded.

Treatment plan

An initial laparoscopy was performed under general anesthesia for the patients with advanced gastric cancer histologically diagnosed. Peritoneal metastasis was histologically confirmed by removal of disseminated nodules or peritoneal cytology.

The catheter for intraperitoneal infusion of PTX was passed through the wound of trocar port in the right side of the umbilicus, which was connected to the port implanted in the abdominal wall for the patient diagnosed peritoneal metastasis.

S-1 was orally administered with a fixed quantity (Dose 80 mg : Body Surface Area (BSA) < 1.25 m², 100 mg : 1.25 < BSA < 1.5 m², 120 mg : BSA > 1.5 m²) for 14 days. PTX was infused intraperitoneally through the implanted catheter at day1 and 14. Dose of PTX was escalated; level I : 40 mg/m², level II : 60 mg/m², level III : 80 mg/m², level IV : 90 mg/m², level V : 100 mg/m². Intraperitoneal PTX with S-1 was repeated two cycles every four weeks.

Adverse events were coded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. Dose Limiting Toxicity (DLT) was defined two patients had nonhematologic or hematologic grade 3 or greater adverse events. If one patient had Grade 3 or more adverse events, the cohort was expanded to three patients owing to occurrence of a DLT. As a result, the dose of PTX was increased to the level that two patients had a DLT in turn. The Maximum Tolerated Dose (MTD) was defined as one escalation level lower than that DLT was confirmed. Recommended dose (RD) was defined as one level lower than MTD.

Analytic methods and pharmacokinetics

Blood samples for pharmacokinetic analysis were drawn before infusion, at 4, 8, 12, 24 and 48 h after the infusion of PTX. Ascites samples were aspirated through the catheter for PTX infusion at the same time points. High performance liquid chromatography (Ultra-Violet absorbance detector : Ultra-violet of 227 nm in wave length) was used to analyze PTX concentrations of serum and ascites in SRL, Inc

(Tokyo, Japan).

RESULTS

Patient demographics

Patient demographics are shown in Table 1. The 18 patients were enrolled in this study after histologically confirming peritoneal metastasis. Two of the 18 patients had adenocarcinoma cells in peritoneal cytology without macroscopically detected metastatic nodules. Curative operation was not impossible for all 18 patients.

Table 1 : Patient demographics

Sex (male/female)	14/4
Age (years) (median/min/max)	56/49/75
WHO Performance status (0/1)	14/4
Macroscopic types III / IV	10/8
Histological typing well/poorly differentiated	3/15
Positive adenocarcinoma cells in peritoneal cytology	18
Macroscopically detected metastatic nodules	16
Gastrectomy	12

Clinical safety and tolerability

All 18 enrolled patients were evaluated for safety. A summary of the patient- and investigator-reported drug related clinical adverse events is shown in Table 2. Current regimen was generally well tolerated, with 6 patients clinically significant drug-related adverse events. The most frequently reported adverse event was Grade 3 leukocytopenia. Grade 1 or 2 anemia, vomiting and abdominal pain were confirmed.

The 40, 80, 90 and 100 mg/m² cohort enrolled three patients. After the one patient had Grade 3 leukocytopenia in 60 mg/m² cohort, this cohort was expanded to 6 patients without Grade 3 or more adverse events. Grade 3 leukocytopenia was confirmed

Table 2 : Drug-related adverse events

	Grade 1	Grade 2	Grade 3	Grade 4
BLOOD/BONE MARROW				
Hemoglobin	1 (5.6%)			
Leukocytes			3 (16.7%)	
GASTROINTESTINAL				
Vomiting	1(5.6%)			
PAIN				
Abdominal pain		1 (5.6%)		

consecutively 2 patients in 100 mg/m² cohort.

DLT was leukocytopenia, MTD was 90 mg/m² and RD was 80 mg/m², respectively.

Pharmacokinetics of PTX

The average serum PTX concentrations in 40, 60, 80 and 90 mg/m² cohort were maintained between the lower limit of cytotoxic effects and upper limit of blood system disorder, which were over upper limit of blood system disorder in all 3 patients of 100 mg/m² cohort. In all cohorts, PTX concentrations in the ascites were approximately 1000 folds higher than those in serum for 48 hours after the infusion (Figure 1).

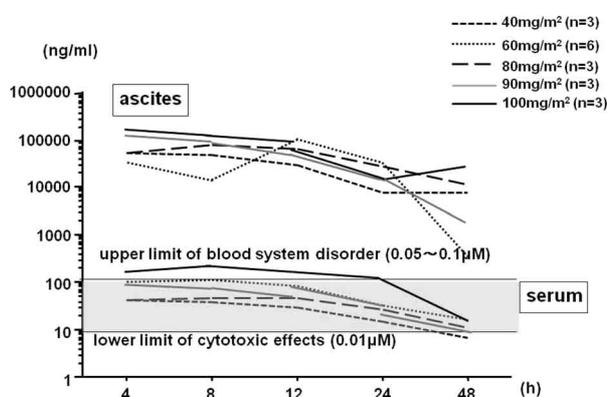


Figure 1 : Pharmacokinetics of PTX

The PTX concentrations in 40, 60, 80 and 90 mg/m² cohort remained in the optimal range. In 100 mg/m² cohort, the PTX concentrations were over upper limit of blood system. PTX concentrations in the ascites were approximately 1000 times higher than those in serum.

Clinical activity

All 18 patients were evaluated for efficacy. Objective clinical response was assessed according to Response Evaluation Criteria in Solid Tumors (RECIST). The 2 patients had partial response. The 15 patients was recorded as stable disease, however, positive adenocarcinoma cells in peritoneal cytology became negative in 2 patients, remarkable decrease of ascites was found in 2 patients. Down staging according to the 13th Japanese Classification of Gastric Carcinoma was possible in 2 patients (2 : positive cytology became negative). There was one patient classified as having progressive disease.

Gastrectomy was performed for 12 of 18 patients, which had curative potential in the patients with down staging. The median survival time was 11 months. Survival time of the 2 patients whose positive cytology became negative was 32 and 48 months, respectively (Table 3).

Table 3 : Clinical activity

Case	Level	RECIST	Down staging	Gastrectomy	Prognosis	Survival time (months)
1	1	PR	-	+	death	8
2	1	SD	-	+	death	10
3	1	SD	+*	+	alive	48
4	2	SD	-	+	death	17
5	2	PR	-	+	death	21
6	2	SD	-	-	death	15
7	2	SD	-	-	death	14
8	2	SD	-	+	death	10
9	2	SD	-	-	death	11
10	3	SD	+*	+	alive	32
11	3	SD	-	+	alive	30
12	3	SD	-	+	death	8
13	4	SD	-	+	death	9
14	4	SD	-	-	death	6
15	4	SD	-	+	death	5
16	5	PD	-	-	death	14
17	5	SD	-	-	death	7
18	5	SD	-	+	alive	11

* Positive adenocarcinoma cells in peritoneal cytology became negative.

DISCUSSION

Intraperitoneal infusion of PTX was generally well tolerated. The most frequently reported adverse event was Grade 3 leukocytopenia. DLT was leukocytopenia, MTD was 90 mg/m² and RD was 80 mg/m², respectively. These findings were supported by pharmacokinetics of PTX.

Because S-1 is the most widely accepted drug for gastric cancer in Japan, a lot of combination trials based on S-1 have been performed (8-10). Median overall survival was significantly longer in patients assigned to S-1 plus cisplatin (13.0 months) than in those assigned to S-1 alone (11.0 months) in the Phase III trial for advanced gastric cancer, however, peritoneal dissemination held 34%, 24% of each group, respectively (8). Significant differences in overall survival compared with S-1 alone revealed in any other regimens. It has not been established standard regimens for peritoneal metastasis of gastric cancer.

Intraperitoneal PTX in the phase II trial for the patients with small-volume residual carcinomas of the ovary, fallopian tube, or peritoneum was well tolerated, which included only moderate abdominal pain (grade 2 : 15.7%, grade 3 ; 1.3%) and minimal neutropenia (grade 2 ; 3.9% ; grade 3 ; 1.3%) (11).

The incidence of Grade 3 neutropenia were observed in 32% of the patients with advanced gastric cancer in the treatment schedule comprised an intravenous infusion of 80 mg/m² PTX, repeated weekly three times for 4 weeks (12). These data suggested that intraperitoneal administration of PTX did not increase the incidence of drug-induced toxicities (13).

A pharmacokinetics study demonstrated that the PTX concentration in ascites remained in the range of the lower limit of cytotoxic effects and upper limit of blood system disorder from 4 to 72 hours after intravenous infusion of 60 and 80 mg/m² PTX. On the other hand, plasma concentrations of PTX were over upper limit of blood system disorder at 4 hours (14). In contrast, the PTX concentrations in 40, 60, 80 and 90 mg/m² cohort in this study remained in the optimal range. In 100 mg/m² cohort, the PTX concentrations were over upper limit of blood system. PTX concentrations in the ascites were approximately 1,000 folds higher than those in serum.

A major advantage after intraperitoneal delivery of PTX is high concentration in the peritoneal cavity (550-2,000 folds) compared with the systemic compartment (13). Drug exposure of high concentration is considered to have an advantage because anti-tumor effects increased dose dependent manner

as far as could be seen there were no severe toxicities in the experimental model (7).

Although this study is a phase I study, the response rate and survival could not be described exactly, two patients with positive adenocarcinoma cells and no macroscopically detected disseminate nodules had a long survival of over 30 months. The overall 5-year survival (43.8%) of advanced gastric cancer patients with intraperitoneal free cancer cells without overt peritoneal metastasis (CY+/P-) after extensive intraoperative peritoneal lavage followed by the intraperitoneal chemotherapy (EIPL-IPC: peritoneal lavage of 10 times using 1 L of physiological saline following cisplatin at a dose of 100 mg/body into the peritoneal cavity) was significantly better than that of the intraperitoneal chemotherapy (4.6%) and the surgery alone (0%) (15). It is important to detect positive adenocarcinoma cells in the peritoneal cavity to improve survival of the patients with peritoneal metastasis (16).

Concerning patients with macroscopically detected peritoneal metastasis, the utility of peritonectomy with chemohyperthermic peritoneal perfusion (CHPP) was reported, however, there are some problems regarding peritonectomy: complicated procedures and CHPP: severe stress to the patients and needs of specific and expensive instruments (17).

Fat solubility of PTX is suitable for intraperitoneal infusion, in contrast, Cremophor EL and ethanol is necessary as a solvent for clinical use, which causes acute hypersensitivity (18). For better and safe drug delivery system, various modifications of PTX have been developed and phase I trials were reported (19-21). Intraperitoneal PTX using the water-soluble solvent revealed excellent pharmacokinetics compared with Cremophor EL (22).

Intraperitoneal PTX including new modified drugs has high potentials to improve survival for the peritoneal metastasis of gastric cancer.

CONFLICT OF INTEREST STATEMENT

Mitsuo Shimada received a research grant from Research Support Foundation of the University of Tokushima and TAIHO Pharmaceutical. Co. Ltd.; Other authors have no conflict of interest.

ACKNOWLEDGEMENTS

Grant support was provided by the Research

Support Foundation of the University of Tokushima and TAIHO Pharmaceutical CO., LTD.

REFERENCES

1. Pyrhonen S, Kuitunen T, Nyando P, Kouri M: Randomised comparison of fluorouracil, epidoxorubicin and methotrexate (FEMTX) plus supportive care with supportive care alone in patients with non-resectable gastric cancer. *Br J Cancer* 71 : 587-91, 1995
2. Sakata Y, Ohtsu A, Horikoshi N, Sugimachi K, Mitachi Y, Taguchi T: Late Phase II Study of Novel Oral Fluoropyrimidine Anticancer Drug S-1 (1M Tegafur-0.4M Gimestat-1M Otastat Potassium) in Advanced Gastric Cancer Patients. *Eur J Cancer* 34 : 1715-20, 1998
3. Sakuramoto S, Sasako M, Yamaguchi T, Kinoshita T, Fujii M, Nashimoto A, Furukawa H, Nakajima T, Ohashi Y, Imamura H, Higashino M, Yamamura Y, Kurita A, Arai K; ACTS-GC Group: Adjuvant Chemotherapy for Gastric Cancer with S-1, an Oral Fluoropyrimidine. *N Engl J Med* 2007 357 : 1810-20, 2007
4. Ohtsu A, Boku N, Tamura F, Muro K, Shimada Y, Saigenji K, Akazawa S, Kitajima M, Kanamaru R, Taguchi T: An early phase II study of a 3-hour infusion of paclitaxel for advanced gastric cancer. *Am J Clin Oncol* 21 : 416-9, 1998
5. Yamada Y, Shirao K, Ohtsu A, Boku N, Hyodo I, Saitoh H, Miyata Y, Taguchi T: Phase II trial of paclitaxel by three-hour infusion for advanced gastric cancer with short premedication for prophylaxis against paclitaxel-associated hypersensitivity reactions. *Ann Oncol* 12 : 1133-37, 2001
6. Markman M, Rowinsky E, Hakes T, Reichman B, Jones W, Lewis JL Jr, Rubin S, Curtin J, Barakat R, Almadrones L: Intraperitoneal administration of Taxol in the management of ovarian cancer. *J Natl Cancer Inst Monogr* 15 : 103-6, 1993
7. Yonemura Y, Endou Y, Bando E, Kuno K, Kawamura T, Kimura M, Shimada T, Miyamoto K, Sasaki T, Sugarbaker PH: Effect of intraperitoneal administration of docetaxel on peritoneal dissemination of gastric cancer: *Cancer Lett* 210 : 189-96, 2004
8. Koizumi W, Nakahara H, Hara T, Takagane A, Akiya T, Takagi M, Miyashita K, Nishizaki T, Kobayashi O, Takiyama W, Toh Y, Nagaie T,

- Takagi S, Yamamura Y, Yanaoka K, Orita H, Takeuchi M : S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial) : a phase III trial. *Lancet Oncol* 9(3) : 215-21, 2008
9. Boku N, Yamamoto S, Fukuda H, Shirao K, Doi T, Sawaki A, Koizumi W, Saito H, Yamaguchi K, Takiuchi H, Nasu J, Ohtsu A : Fluorouracil versus combination of irinotecan plus cisplatin versus S-1 in metastatic gastric cancer : a randomised phase 3 study. *Lancet Oncol* 10 : 1063-9, 2009
 10. Kakeji Y, Oki E, Egashira A, Sadanaga N, Takahashi I, Morita M, Emi Y, Maehara Y : Phase II study of biweekly docetaxel and S-1 combination therapy for advanced or recurrent gastric cancer. *Oncology* 77 : 49-52, 2009
 11. Markman M, Brady MF, Spirtos NM, Hanjani P, Rubin SC : Phase II trial of intraperitoneal paclitaxel in carcinoma of the ovary, tube, and peritoneum : a Gynecologic Oncology Group Study. *J Clin Oncol* 16 : 2620-4, 1998
 12. Hironaka S, Zenda S, Boku N, Fukutomi A, Yoshino T, Onozawa Y : Weekly paclitaxel as second-line chemotherapy for advanced or recurrent gastric cancer. *Gastric Cancer* 9 : 14-18, 2006
 13. Fushida S, Furuji N, Kinami S, Ninomiya I, Fujimura T, Nishimura G, Ohta T, Yokogawa K, Miyamoto K, Miwa K : Pharmacologic study of intraperitoneal paclitaxel in gastric cancer patients with peritoneal dissemination. *Jpn J Cancer Chemother* 29 : 2164-7, 2002
 14. Kobayashi M, Sakamoto J, Namikawa T, Okamoto K, Okabayashi T, Ichikawa K, Araki K : Pharmacokinetic study of paclitaxel in malignant ascites from advanced gastric cancer patients. *World J Gastroenterol* 12 : 1412-5, 2006
 15. Kuramoto M, Shimada S, Ikeshima S, Matsuo A, Yagi Y, Matsuda M, Yonemura Y, Baba H : Extensive intraoperative peritoneal lavage as a standard prophylactic strategy for peritoneal recurrence in patients with gastric carcinoma. *Ann Surg* 250 : 243-6, 2009
 16. Sugita Y, Fujiwara Y, Taniguchi H, Mori T, Ishii T, Niwa H, Okada Y, Takiguchi S, Yasuda T, Yano M, Monden M : Quantitative molecular diagnosis of peritoneal lavage fluid for prediction of peritoneal recurrence in gastric cancer. *Int J Oncol* 23 : 1419-23, 2003
 17. Yonemura Y, Kawamura T, Bandou E, Takahashi S, Sawa T, Matsuki N : Treatment of peritoneal dissemination from gastric cancer by peritonectomy and chemohyperthermic peritoneal perfusion. *Br J Surg* 92 : 370-375, 2005
 18. Kloover JS, den Bakker MA, Gelderblom H, van Meerbeek JP : Fatal outcome of a hypersensitivity reaction to paclitaxel : a critical review of premedication regimens. *Br J Cancer* 90 : 304-5, 2004
 19. Boddy AV, Plummer ER, Todd R, Sludden J, Griffin M, Robson L, Cassidy J, Bissett D, Bernareggi A, Verrill MW, Calvert AH : A Phase I and pharmacokinetic study of paclitaxel poliglumex (XYOTAX), investigating both 3-Weekly and 2-Weekly schedules. *Clin Cancer Res* 11 : 7834-40, 2005
 20. Nyman DW, Campbell KJ, Hersh E, Long K, Richardson K, Trieu V, Desai N, Hawkins MJ, Von Hoff DD : Phase I and pharmacokinetics Trial of ABI-007, a novel nanoparticle formulation of Paclitaxel in patients with advanced nonhematologic malignancies. *J Clin Oncol* 23 : 7785-93, 2005
 21. Hamaguchi T, Kato K, Yasui H, Morizane C, Ikeda M, Ueno H, Muro K, Yamada Y, Okusaka T, Shirao K, Shimada Y, Nakahama H, Matsumura Y : A phase I and pharmacokinetic study of NK105, a paclitaxel-incorporating micellar nanoparticle formulation. *Br J Cancer* 97 : 170-6, 2007
 22. Soma D, Kitayama J, Konno T, Ishihara K, Yamada J, Kamei T, Ishigami H, Kaisaki S, Nagawa H : Intraperitoneal administration of paclitaxel solubilized with poly(2-methacryloxyethyl phosphorylcholine-co *n*-butyl methacrylate) for peritoneal dissemination of gastric cancer. *Cancer Sci* 100 : 1979-85, 2009