Dual anti-cancer effects of weekly intraperitoneal docetaxel in treatment of advanced gastric cancer patients with peritoneal carcinomatosis: A feasibility and pharmacokinetic study

SACHIO FUSHIDA, JUN KINOSHITA, YASUMICHI YAGI,
HIROSHI FUNAKI, SHINICHI KINAMI, ITASU NINOMIYA, TAKASHI FUJIMURA,
GENICHI NISHIMURA, MASATO KAYAHARA and TETSUO OHTA

Department of Gastroenterologic Surgery, Kanazawa University Hospital, Kanazawa, Japan

Abstract. This study evaluated the feasibility and pharmacology of intraperitoneal docetaxel (IP docetaxel) when administered weekly for 3 consecutive weeks, followed by 1 week without treatment. A total of 24 patients with peritoneal carcinomatosis of gastric cancer (10 preoperative, 7 postoperative and 7 recurrent) were enrolled in this study. Docetaxel was dissolved in an isotonic saline to a final 1 liter solution and was administered in a 1 h dosage of 25, 35, 45 and 60 mg/m² to determine the maximum tolerated dose (MTD). To measure the docetaxel concentration, blood and peritoneal fluid samples were collected 0.5, 1, 2, 3, 6 and 24 h after administering the drug to 15 patients. A total of 109 chemotherapy cycles were administered, with a median of four cycles per patient (range 2-9). The MTD of the weekly IP docetaxel was defined at 60 mg/m². At a docetaxel dosage of 60 mg/m² per week, the dose-limiting events of grade 3 abdominal pain and grade 3 diarrhea, which may be associated with local toxicity, occurred. Peak concentrations of peritoneal fluid ranged from 24.5 to 68.7 μg/ml. The mean ratio of the area under concentration (AUC) in the peritoneal fluid to the plasma concentration was 515. Furthermore, the mean of plasma AUC by IP docetaxel was 5.63 μg·h/ml versus that of IV docetaxel at a dose of 60 mg/m². The response rate of the preoperative IP docetaxel was 80% (4 CR, 4 PR, 1 NC and 1 PD), which was judged with laparoscopy and peritoneal lavage cytology. Gastrectomy, with D2 lymph node dissection, was performed on all of the patients evaluated as CR. The weekly IP docetaxel demonstrated a low toxicity and high efficacy for peritoneal carcinomatosis with dual anti-cancer effects via the peritoneal surface and capillary blood supply due to its unique pharmacokinetic property.

Correspondence to: Dr Sachio Fushida, Department of Gastroenterologic Surgery, Kanazawa University Hospital, Takara-machi 13-1, Kanazawa 920-8641, Japan
E-mail: fushida@surg2.m.kanazawa-u.ac.jp

Introduction

One of the most characteristic features and frequent causes of death from gastric cancer is peritoneal dissemination. In a recent multicentric prospective study (1), the median survival time was 3.1 months for gastric cancer patients. For two decades now, the treatment of peritoneal dissemination has consisted of systemic chemotherapy with sequential methotrexate (MTX) and 5-FU, or intraperitoneal chemotherapy (IPC) with mitomycin C (MMC), cisplatin (CDDP), OK-432 and other agents. Sequential MTX and 5-FU have been widely used as systemic chemotherapy because of their high efficacy against poorly-differentiated adeno-carcinoma, persisting high concentrations in ascites and a tendency to have low-grade toxicity (2,3). However, gastric cancer is only moderately sensitive to chemotherapy and peritoneal metastasis is known to be relatively resistant to systemic chemotherapy due to the poor blood supply and oxygenation of cancer cells in the peritoneum. Therefore, to enhance the efficacy of anti-cancer drugs, IPC has generally been accepted as a regional intensive chemotherapy for the prevention and treatment of peritoneal dissemination.

IPC with MMC or carbon-adsorbed MMC has been reported to improve the survival of gastric cancer patients by preventing peritoneal recurrence (4,5), but the efficacy of these therapies in patients with peritoneal dissemination has yet to be established. Intraperitoneal CDDP treatment has been performed safely and effectively in ovarian cancer patients by many investigators (6,7).

The usefulness of intraperitoneal CDDP has to be confirmed by controlled clinical studies. However, a multi-center randomized trial, JCOG 9701 (Japan Clinical Oncology Group), which aimed to compare adjuvant intraperitoneal CDDP with no adjuvant treatment, was stopped because of the difficulty of randomizing patients into the no treatment group.

Although three large randomized phase III trials comparing IP vs. IV cisplatin-based chemotherapy have shown a survival benefit of IPC, this approach has yet to be accepted as a standard treatment for gynecological tumors (8-10).

The efficacy of IPC is mainly affected by the extent of the peritoneal tumor and ascites. Most of the positive results were obtained for patients without peritoneal dissemination in an

adjuvant setting or for patients with microscopic residual tumors, even if hyperthermia was added in anticipation of its synergy effect (11-17).

Taxanes such as docetaxel and paclitaxel bind to tubulin, leading to microtubule stabilization, mitotic arrest and, subsequently, cell death (18,19). The activity of taxanes may depend on the property of killing tumor cells in the absence of the wild-type p53 function (20), unlike other drugs requiring wild-type p53, and taxanes may therefore be effective against gastric cancer cells, which frequently have p53 mutations (21,22). Furthermore, these compounds have a high sensitivity against poorly-differentiated adenocarcinoma, which is a common type of peritoneal tumor, and some of these compounds, when administered intravenously, are transported into the peritoneal cavity (23,24). These findings suggest that taxanes are also candidates for first-line drugs for peritoneal carcinomatosis.

Several studies of intraperitoneal paclitaxel showed a minimal toxicity and pharmacokinetic advantage. However, few reports about the feasibility, pharmacokinetics and efficacy of IP docetaxel exist. In this study, we examined the disposition kinetics of docetaxel and paclitaxel after intraperitoneal administration in patients with peritoneal carcinomatosis of gastric cancer.

Patients and methods

Patients. The patients with cytologically or histologically confirmed peritoneal carcinomatosis were eligible for this study. Other eligibility criteria were: age 18-75 years, Eastern Cooperative Oncology Group (ECOG) performance status 0-2, no history of previous chemo- or radiotherapy, adequate bone marrow function (<3000/mm³ white cell count or <1500/mm³ neutrophil count, platelet count >80,000/mm³ and hemoglobin >8.0 g/dl), adequate liver function (bilirubin level <1.5 mg/dl, and aspartate and alanine aminotransferase within twice the upper limit of the normal). All of the patients gave written informed consent, conforming to institutional guidelines.

Treatment plan. The docetaxel (Taxotere®, Sanofi-Aventis Ltd.) dose was dissolved at room temperature in an isotonic saline to a final 1 liter solution and was instilled into a peritoneal cavity through the catheter for 1 h. Prior to therapy, patients received dexamethasone and the 5-HT₃ antagonist intravenously 30 min before the taxane to prevent hypersensitivity reactions. After instillation, patients were asked to lie on a bed and change positions at 30-min intervals for 24 h to ensure adequate intraperitoneal drug distribution.

The standard dosing regimen for docetaxel is 75-100 mg/m² administered every 3 weeks. In this study, patients received weekly IP docetaxel for 3 consecutive weeks, followed by 1 week without treatment because several clinical studies showed that a weekly administration of docetaxel achieves the equivalent efficacy of a 3-week schedule (25,26). The initial starting dose of docetaxel was 25 mg/m² (dose level 1) and step-wise dose increases up to 60 mg/m² were planned for successive patient cohorts.

At least three assessable patients were treated at each dose level and an assessment of DLTs was conducted only in the first treatment cycle. If one or more patients at a dose level

experienced DLT, then three additional patients were treated at that dose level. The MTD was defined as the dose level that produced DLT in ≥3 patients or the initial 3 patients. The recommended dose was to be the dose immediately below the MTD. Toxicity was measured by the common toxicity criteria of the National Cancer Institute, version 2.0.

Pharmacokinetic analysis. To measure the docetaxel and paclitaxel concentration, blood and peritoneal fluid samples were collected whenever possible before administration, 0.5, 1, 2, 3, 6 and 24 h after drug instillation ended. Samples were collected in tubes containing EDTA, centrifuged and the supernatant was stored at -20°C until assay. The assays for docetaxel and paclitaxel were performed according to Loss *et al* (27). All samples were analyzed on an HPLC system and the absorbance was detected at a wavelength of 230 nm. The limit of quantification was ~0.05 mg/ml.

Pharmacokinetic parameters were calculated using the one-compartment model according to Kuzuya *et al* (28). The area under the drug concentration-time curve from 0-24 h in the peritoneal fluid (AUCper, 0-24 h) or in plasma (AUCpl, 0-24 h) was estimated by using the trapezoidal method.

Response criteria. Peritoneal dissemination is considered to be a non-evaluated lesion because it was difficult to detect peritoneal dissemination by conventional radiological examinations. In this study, defined new response criteria for treatment against peritoneal dissemination were followed (Table I): CR, no visual peritoneal tumor confirmed by laparoscopy and cytology negative; PR, at least a 50% decrease of peritoneal tumor confirmed by laparoscopy or cytology negative; SD, no unequivocal progression of peritoneal dissemination and PD, unequivocal progression of peritoneal dissemination.

Results

Patient characteristics. Between June 2000 and October 2004, 24 patients with peritoneal dissemination of gastric cancer were entered in this study. The patient characteristics are listed in Table II. Peritoneal carcinomatosis, was classified by the Japanese Research Society for Gastric Cancer (29) as: P1, cancerous implants to the region directly adjacent to the stomach peritoneum (above the transverse colon) including the great omentum; P2, several scattered metastases to the distant peritoneum and ovarian metastasis alone and P3, numerous metastases to the distant peritoneum. P1 was observed in 3 patients, P2 in 8 patients and P3 in 13 patients. Seven of the postoperative patients were diagnosed with peritoneal dissemination at laparotomy and underwent cytoreductive surgery, the remainder (10 preoperative and 7 recurrent) had to undergo laparoscopy for diagnosis. The total course of IP docetaxel was 109 and the median course was 4 (range 2-9).

Toxicity. To evaluate the local toxicity of the treatment, an abdominal pain score was used, originally applied in the phase I study of intraperitoneal paclitaxel (30) (Table III). No local toxicity was evident at dose level 1 (25 mg/m²) but a mild one was detected at dose level 2 (35 mg/m²). At a dose level of 4 (60 mg/m²), 2 out of 3 patients had severe abdominal pain

Table I. New response criteria for treatment against peritoneal carcinomatosis.

Complete response (CR)	No visual peritoneal tumor (by laparoscopy or laparotomy)
	Cytology (lavage cytology) negative
Partial response (PR)	<50% of residual peritoneal tumor
	Cytology (lavage cytology) negative
Stable disease (SD)	No unequivocal progression of peritoneal carcinomatosis
Progressive disease (PD)	Unequivocal progression of peritoneal carcinomatosis

Table II. Patient characteristics.

Gender (F/M)	15/9
Performance status (0/1/2)	12/10/2
Timing of chemotherapy	
(preoperative / postoperative / recurrent)	10/7/7
Peritoneal carcinomatosis (P1/P2/P3)	3/8/13
Ascites ($0/1^+/2^+/3^+$)	12/7/4/1

Table III. Abdominal pain score.

Grade	Performance
0	No pain
1	Mild pain
	Narcotic analgesia not required
	Minimal interference with daily activities
	lasts for <72 h
2	Moderate pain
	Narcotic analgesia not required
	Moderate interference with daily activities
	lasts for >72 h
3	Severe pain
	Narcotic analgesia required
	Confines patient to bed
	Severe interference with daily activities

Table IV. Local and systemic toxicity associated with IP docetaxel.

	Dose level (mg/m^2)			
Toxicity grade	25	35	45	60
No. of evaluated patients	3	3	15	3
Abdominal pain				
0	3	2	11	0
1	0	1	2	0
2	0	0	2	1
3	0	0	0	2
Diarrhea				
0	3	2	11	0
1	0	1	1	1
2	0	0	3	1
3	0	0	0	1
Leucocytopenia				
0	3	2	11	0
1	0	1	3	2
2	0	0	1	1
3	0	0	0	0
Alopecia				
0	3	3	12	1
1	0	0	2	1
2	0	0	1	1

and the other one had grade 3 diarrhea (Table IV). Diarrhea was relatively frequent, with grade 2 diarrhea being observed in 4 patients and grade 3 in 1 patient which may have induced intestinal edema as local toxicity. Nausea and/or vomiting were mild and easily controlled. Bone marrow suppression was also mild.

From these results, the MTD and RD were determined to be level 4 and 3, respectively.

Pharmacokinetic results. Abdominal fluid and plasma samples were obtained from 15 patients at a dose level of 3 (45 mg/m^2), which was determined to be the recommended dose. The pharmacokinetic analyses are summarized in Table V. The peak concentrations of the peritoneal fluid ranged from 24.5 to 68.7 μg/ml. The mean ratio of AUC in the peritoneal fluid to plasma concentration was 515 (Table V). The mean value of the peak plasma concentration was extremely low versus that of the abdominal fluid but the mean value of plasma AUC was 5.63 μg·h/ml which was equivalent to that of intravenous docetaxel (31) (Table VI).

Efficacy. The response rate of the preoperative intraperitoneal docetaxel was 80% (4 CR, 4 PR, 1 NC and 1 PD), which was judged with laparoscopy and peritoneal lavage cytology. Gastrectomy, with D2 lymph node dissection, was performed on all the patients evaluated as CR. Of the patients that underwent gastrectomy against the T3 tumor for postoperative intraperitoneal docetaxel, 6 out of 7 had no peritoneal recurrence after the gastrectomy. However, a lower response
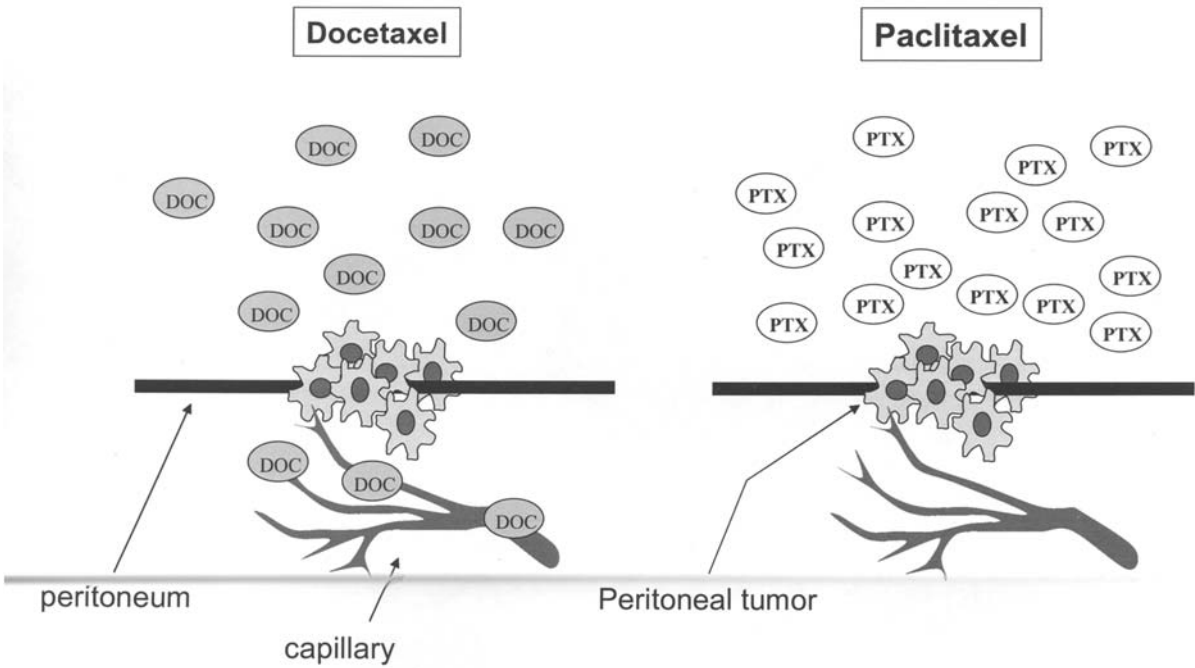
Figure 1. The kinetic disposition between docetaxel and paclitaxel after intraperitoneal administration. Docetaxel may affect the peritoneal tumor via the peritoneal surface and capillary blood supply due to its unique pharmacokinetic property.

Table V. Peritoneal pharmacokinetics.

Mean peak peritoneal concentration	40.1 μg/ml (24.5-68.7)
Mean peritoneal AUC	473.6 μg·h/ml (197.3-1278.2)
Mean $AUC_{peritoneal}/AUC_{plasma}$	515 (22-1773)

Table VI. Plasma pharmacokinetics.

	IV docetaxel (60 mg/m^2)	IP docetaxel (45 mg/m^2)
Mean peak plasma Concentration (μg/ml)	1.61	0.20
Mean plasma AUC (μg·h/ml)	2.44	5.63

rate (57%) was found in the patients with peritoneal recurrence than in the preoperative ones.

Discussion

The pharmacokinetic properties of many anti-cancer agents have been examined, following intraperitoneal administration in phase I studies. The ideal agents for intraperitoneal delivery have a high ratio of either a peak peritoneal drug concentration or area under the peritoneal concentration versus the time curve (AUC) relative to systemic concentration, i.e., they have

a low peritoneal but a high plasma clearance. Such a pharma-cokinetic advantage for peritoneal cavity exposure is favored by high molecular weight, water solubility, high solution volume and easy ionization. The pharmacokinetic advantage has been reported to range from 20-fold for cisplatin (7) and carboplatin (32), to as high as 1000-fold for paclitaxel (30).

Since mitomycin C, commonly used intraperitoneally, is rapidly absorbed through the capillary walls in the subperito-neum due to its low solubility in water, mitomycin C has only a 20-30-fold pharmacokinetic advantage and disappears from the blood within 3 h (33).

Cisplatin, whose molecular weight is relatively low, is also rapidly absorbed by the subperitoneal capillaries and transported into the systemic circulation. Pharmacokinetic studies confirmed that the plasma AUC is similar after the intraperitoneal or intravenous administration of cisplatin. The adverse effects after the intraperitoneal administration of cisplatin are similar to those after intravenous administration, and include effects such as emesis, nephrotoxicity and neurotoxicity, with minimal local adverse events. Considered together, these findings indicate that intraperitoneally administered cisplatin may exert anti-cancer effects regionally and systemically (34). However, it has been shown that cisplatin is useful for patients with microscopic but not

pic residual tumors. Therefore, it is necessary to ...r another highly effective agent for intraperitoneal administration in gastric cancer.

Paclitaxel is retained in the peritoneal cavity at cytotoxic concentrations for at least 7 days, implying that very limited amounts of paclitaxel enter the systemic compartment after intraperitoneal administration (35). This is reasonable, considering that the dose-limiting factor for paclitaxel is abdominal pain from direct peritoneal irritation. These findings suggest that the cytotoxic activity of intraperitoneal paclitaxel is exerted by direct penetration into the regional tumor alone.

In contrast, docetaxel has a pharmacokinetic advantage of two logs associated with its intraperitoneal delivery, and the systemic AUC after intraperitoneal administration is two times greater than after standard intravenous administration (36). These data indicate that docetaxel occupies a position between cisplatin and paclitaxel from the pharmacokinetic viewpoint (Fig. 1). Paclitaxel and docetaxel have similar chemical and physiological characteristics, and the pharmacokinetic difference between them seems to be attributable to the differential absorption in solubility (36). The injection preparation of paclitaxel, Taxol, contains a high concentration of Cremophor EL as the surfactant vehicle, which suppresses the permeation of the anti-cancer drug into tissues and cells, which may explain why intraperitoneally administered Taxol shows a lower systemic transportation than that of Taxotere, which contains a low concentration of Polysorbate-80 as the surfactant (37).

The present study suggested that it is feasible to use docetaxel at a dose level of 45 mg/m^2. The response rate of this study was 70% in 17 valuable cases and 4 cases were evaluated as CR, while Morgan *et al* (37) reported that there were no objective responses to 100 mg/m^2 of IP docetaxel every 3 weeks. This weekly administration appeared to have improved results because of this high dose intensity compared to the usual 3-week administration. Furthermore, weekly IP docetaxel may also have shown the anti-cancer effect as being weekly intravenously (IV) docetaxel, because the systemic AUC of the IP docetaxel was comparable to that of the IV docetaxel whose pharmacokinetic properties are well described (31).

This study showed that weekly IP docetaxel is the best treatment for peritoneal carcinomatosis with dual anti-cancer effects via the peritoneal surface and capillary blood supply.

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