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Phase II study of weekly intravenous and intraperitoneal paclitaxel combined with S-1 for advanced gastric cancer with peritoneal metastasis

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Background: A phase II study to evaluate the efficacy and tolerability of weekly i.v. and i.p. paclitaxel (PTX) combined with S-1 was carried out in gastric cancer patients with peritoneal metastasis.
Patients and methods: Gastric cancer patients with peritoneal dissemination and/or cancer cells on peritoneal cytology were enrolled. PTX was administered i.v. at 50 mg/m^2 and i.p. at 20 mg/m^2 on days 1 and 8. S-1 was administered at 80 mg/m^2/day for 14 consecutive days, followed by 7 days rest. The primary end point was the 1-year overall survival (OS) rate. Secondary end points were the response rate, efficacy against malignant ascites and safety.
Results: Forty patients were enrolled, including 21 with primary tumors with peritoneal dissemination, 13 with peritoneal recurrence and six with positive peritoneal cytology only. The median number of courses was 7 (range 1–23). The 1-year OS rate was 78% (95% confidence interval 65% to 90%). The overall response rate was 56% in 18 patients with target lesions. Malignant ascites disappeared or decreased in 13 of 21 (62%) patients. The frequent grade 3/4 toxic effects included neutropenia (38%), leukopenia (18%) and anemia (10%).
Conclusion: Combination chemotherapy of i.v. and i.p. PTX with S-1 is well tolerated and active in gastric cancer patients with peritoneal metastasis.
Key words: gastric cancer, i.p. chemotherapy, paclitaxel, phase II study, S-1

introduction

Peritoneal metastasis is the most frequent and most life-threatening mode of metastasis in patients with gastric cancer. Various methods have been tried to treat peritoneal metastasis, including systemic chemotherapy, i.p. chemotherapy, hyperthermia and aggressive surgery; however, none of these have resulted in a satisfactory clinical outcome [1–3]. Recently, systemic chemotherapy for gastric cancer has progressed steadily, and 5-fluorouracil (5-FU)-based or cisplatin-based regimens are generally accepted as possible standard chemotherapy [3, 4]. However, regarding the specific efficacy of these regimens on peritoneal metastasis, only a few trials have been reported. So far, sequential methotrexate and 5-FU therapy has been reported to decrease malignant ascites in gastric cancer patients, although the 1-year survival rate was 16.2% in 37 patients [5]. Another study has shown the efficacy of modified FOLFOX-4, where the 1-year survival rate was 27.2% in 48 gastric cancer patients with malignant ascites [6]. Due to the low survival rates in these phase II studies, neither regimen has been accepted as the standard chemotherapy.

S-1 is an oral fluoropyrimidine derivative, combining tegafur with two modulators. In recent phase III studies, S-1 showed response rates of 27%–31% and median survival times (MSTs) of 10.5–11.4 months [7–9], and it is considered to be a pivotal agent for gastric cancer in Japan. Paclitaxel (PTX) showed response rates of 20%–28% and MSTs of 7.8–11 months in single-agent phase II studies for gastric cancer [10–12]. S-1 and PTX share two favorable characteristics for the treatment of peritoneal metastasis: a high efficacy against diffuse-type adenocarcinoma, which can easily be disseminated, and a high rate of transition into the peritoneal cavity [12–15]. Therefore, the combination chemotherapy of S-1 and i.v. PTX is expected to be effective for peritoneal metastasis. In gastric cancer patients with measurable lesions, several clinical trials have already reported on the safety and efficacy of this combination therapy [16–18].

Intraperitoneal administration of PTX was developed to enhance antitumor activity against peritoneal metastasis by maintaining a high concentration of the drug in the peritoneal cavity over a long period, and its clinical effects have been verified by a number of convincing clinical trials in ovarian

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cancer with peritoneal metastasis [19–22]. Meanwhile, no clinical trial has been carried out in peritoneal metastasis of gastric cancer, although several effective cases have been reported [23–25].

Therefore, we developed a new regimen that added weekly i.p. PTX to an established systemic chemotherapy of S-1 and i.v. PTX for the treatment of peritoneal metastasis of gastric cancer. First, we examined the safety of the regimen in a phase I dose-escalation study and determined the recommended dose of i.p. PTX to be 20 mg/m^2 [26]. In this study, we carried out a phase II clinical trial in order to evaluate the efficacy and tolerability in gastric cancer patients with peritoneal metastasis.

patients and methods

eligibility

The eligibility criteria were as follows: histologically proven unresectable or recurrent gastric adenocarcinoma; peritoneal metastasis and/or cancer cells on peritoneal cytology; age >20 years; Eastern Cooperative Oncology Group performance status of zero to two; adequate bone marrow function (leukocyte count 3000–12 000/mm^3, hemoglobin ≥ 8.0 g/dl and platelet count ≥ 100 000/mm^3); adequate liver function (total serum bilirubin ≤ 2.0 mg/dl and serum transaminases ≤ 100/UI); adequate renal function (serum creatinine within the upper limit of normal) and an expected survival period of >3 months. Patients who had previously received chemotherapy were also eligible. Patients were excluded if they had metastasis to distant organ sites (such as the liver, lungs or bone), other active concomitant malignancies or other severe medical conditions. Written informed consent was obtained from all patients. This study was carried out in accordance with the Declaration of Helsinki. This study protocol was approved by the institutional review board of the University of Tokyo.

treatment

Patients newly diagnosed with advanced gastric cancer underwent staging laparoscopy and were enrolled in this study when peritoneal dissemination and/or cancer cells on peritoneal cytology were confirmed. Noncurative gastrectomy for tumor reduction was not carried out. A peritoneal access port was implanted in the s.c. space of the lower abdomen, with a catheter placed in the pelvic cavity. Patients with peritoneal recurrence diagnosed by imaging were implanted with ports by mini-laparotomy under local anesthesia.

S-1 was administered orally twice daily at a dose of 80 mg/m^2/day for 14 consecutive days, followed by 7 days rest. PTX was administered i.v. at a dose of 50 mg/m^2 and i.p. at 20 mg/m^2 on days 1 and 8. PTX was diluted in 1 l of normal saline and administered through the implanted peritoneal access port over 1 h concurrently with i.v. infusion after standard premedication. The treatment course was repeated every 3 weeks until observation of unacceptable toxicity, disease progression or response which enabled macroscopically curative operation.

evaluation of tumor response and toxicity

The baseline evaluations included a medical history, physical examination, laboratory studies (complete blood cell count, liver and renal function test, electrolytes and urinalysis), electrocardiogram, chest X-ray, gastroendoscopy, upper gastrointestinal radiography and computed tomography (CT).

The primary end point was the 1-year overall survival (OS) rate. Secondary end points were the overall response rate (ORR), efficacy against malignant ascites and safety. The 1-year survival rate was estimated according to the Kaplan–Meier method. Objective tumor responses were evaluated every two courses during the study and classified based on the RECIST guidelines. To evaluate the antitumor effects of the treatment on peritoneal metastasis, the amount of malignant ascites and peritoneal cytology were also taken into account. According to the Japanese Classification of Gastric Carcinoma [27], the amount of ascites was assessed by radiologists using CT. Cytology of ascites or peritoneal lavage fluid collected through a peritoneal access port was carried out using Papanicolaou staining at the end of each course. Toxicity was monitored weekly and graded according to the National Cancer Institute—Common Terminology Criteria for Adverse Events version 3.0.

statistical methods

The required number of patients was calculated according to the Southwest Oncology Group One Arm Survival program [28]. Recent studies in advanced or metastatic gastric cancer including patients with peritoneal metastasis showed 1-year OS rates of ∼50% [7–9, 17, 18]. A 1-year OS rate of 70% could be expected, as seven of nine patients survived >1 year in our pilot study of this regimen. Assuming a null hypothesis of 50% and an alternative hypothesis of 70% with one-sided type I error of 0.05 and power of 0.8, with an accrual time of 1.5 years and follow-up of 0.5 years after closure of recruitment, it was necessary to enroll 32 fully assessable patients.

results

From August 2006 to December 2007, 40 patients were enrolled in this study and were fully evaluated for OS and toxicity. Eighteen patients with measurable target lesions were assessed for ORR. Patient characteristics are listed in Table 1.

OS and response

A median of seven courses were administered with a range from 1 to 23. Combination chemotherapy was discontinued due to

Table 1. Patient characteristics (n = 40)

Characteristic	No. of patients	%
Sex		
Male	24	60
Female	16	40
Age, years		
Median	62	
Range	29–86	
ECOG performance status		
0	23	57.5
1	15	37.5
2	2	5
Prior treatment		
Gastrectomy	13	33
Chemotherapy	17	43
Histological type		
Intestinal	12	30
Diffuse	28	70
Metastasis		
Peritoneum	34	85
Peritoneal cytology	28	70
Malignant ascites	21	53
Ovary	6	15
Lymph node	16	40

ECOG, Eastern Cooperative Oncology Group.

severe adverse events in five patients and due to disease progression in 15 patients. In 16 other patients, chemotherapy was suspended for operation after response to chemotherapy. OS was calculated in all 40 patients, and the 1-year OS rate was 78% [95% confidence interval (CI) 65% to 90%] at a median follow-up time of 20.3 months. The 2-year OS rate was 46% (95% CI 24% to 65%), and the MST was 22.5 months (95% CI 16.6 months to not reached). The Kaplan–Meier survival curve is shown in Figure 1.

The ORR was 56% (95% CI 32% to 79%), with 10 patients showing a partial response. Malignant ascites disappeared or decreased in 13 of 21 (62%) patients. Cancer cells ceased to be detected by peritoneal cytology in 24 of 28 (86%) patients. Details are summarized in Table 2.

safety

Hematological and non-hematological toxic effects are listed in Table 3. The incidences of grade 3/4 hematological and non-hematological toxic effects were 40% and 15%, respectively. The frequent grade 3/4 toxic effects included neutropenia (38%), leukopenia (18%) and anemia (10%). None of the patients experienced abdominal pain or any other toxicity related to i.p. infusion. Obstruction of i.p. catheter in one patient was the only complication related to the peritoneal access device. There were no treatment-related deaths.

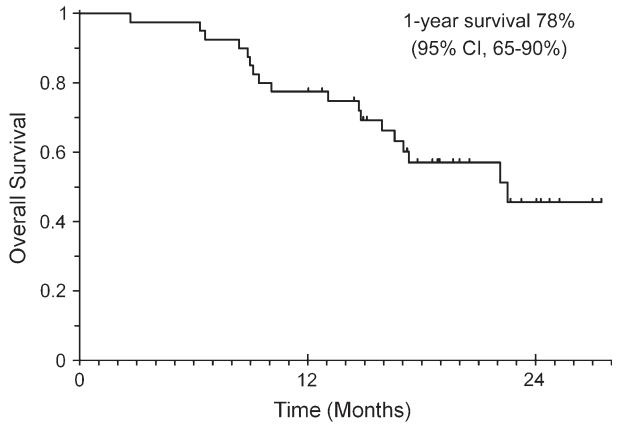

Figure 1. Kaplan–Meier plot for overall survival ($n = 40$)

Table 2. Tumor responses ($n = 40$)

Response	No. of patients	%
RECIST guideline ($n = 18$)		
Complete response	0	0
Partial response	10	56
Stable disease	6	33
Progressive disease	2	11
Malignant ascites ($n = 21$)		
Disappeared	5	24
Decreased	8	38
Peritoneal cytology ($n = 28$)		
Turned negative	24	86

discussion

Intraperitoneal administration of anticancer drugs enables an extremely high concentration of drugs to directly contact the target cancer lesions in the peritoneal cavity. However, i.p. administration of mitomycin C or cisplatin yielded no apparent therapeutic effects against peritoneal metastasis of gastric cancer due to immediate absorption through the peritoneum [29]. In contrast to these drugs, PTX is absorbed slowly through the lymphatic system after i.p. administration, due to its large molecular weight and fat solubility. Because the antitumor effect of PTX has been shown to depend on its concentration and exposure time in *in vitro* experiments [30], i.p. PTX was expected to demonstrate high efficacy for peritoneal metastasis. On the other hand, two shortcomings are that the drug infiltrates only the surface of the peritoneal metastasis and that the drug is not delivered where adhesion exists in the peritoneal cavity. To address these difficulties and to maintain systemic antitumor effects against the primary tumor or metastasis of organ sites other than the peritoneum, we developed a novel regimen combining i.p. PTX with established systemic chemotherapy of S-1 plus i.v. PTX [16–18].

In this study, our new combination regimen showed a 1-year OS rate of 78% with an MST of 22.5 months. Recent studies targeting unresectable or recurrent gastric cancer patients have shown 1-year OS rates around 50% overall [7–9]. Considering that the patients with peritoneal metastasis generally show particularly poor prognosis, our survival results are encouraging. Furthermore, effects were observed in regard to malignant ascites.

Neutropenia was the main toxicity of this combination chemotherapy. It was more frequent and severe as compared with S-1 plus i.v. PTX [17, 18]. A consistent increase in blood concentration by gradual absorption of i.p. administered PTX may account for the progression of neutropenia. Non-hematological toxic effects were relatively mild and were similar to those reported in previous studies of S-1 monotherapy or S-1 plus i.v. PTX [13, 17, 18]. As for complications related to the peritoneal access device, an i.p. catheter was obstructed in one patient. No other complications such as infection, leak or

Table 3. Number of patients with toxic effects ($n = 40$)

Toxicity	Grade (CTCAE v3.0)				
	1	2	3	4	3/4 (%)
Leukopenia	3	13	5	2	18
Neutropenia	3	5	11	4	38
Anemia	14	21	3	1	10
Thrombocytopenia	3				0
Fatigue	19	4			0
Anorexia	13	7	2		5
Nausea/vomiting	8	6	3		8
Diarrhea	5	5	1		3
Abdominal pain	8	1			0
Rash	1	2			0
Mucositis	11	1			0
Neuropathy	8	5			0

CTCAE, Common Terminology Criteria for Adverse Events.

access inability developed during the period of observation. Abdominal pain in relation to i.p. administration, a dose-limiting toxicity of i.p. PTX reported at doses >60 mg/m^2 in ovarian cancer [20], was not observed in our study. Overall, the toxic effects were tolerable, and there were no treatment-related deaths.

In conclusion, combination chemotherapy of i.v. and i.p. PTX with S-1 is well tolerated and active in gastric cancer patients with peritoneal metastasis. This regimen should be evaluated further in a randomized phase III trial.

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disclosures

The authors report no conflicts of interest.

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