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Multicenter Phase II Study of Intravenous and Intraperitoneal Paclitaxel With S-1 for Pancreatic Ductal Adenocarcinoma Patients With Peritoneal Metastasis

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Objective: To evaluate the clinical efficacy and tolerability of intravenous (i.v.) and intraperitoneal (i.p.) paclitaxel combined with S-1, ''an oral fluoropyrimidine derivative containing tegafur, gimestat, and otastat potassium'' in chemotherapy-naive pancreatic ductal adenocarcinoma (PDAC) patients with peritoneal metastasis.

Background: PDAC patients with peritoneal metastasis (peritoneal deposits and/or positive peritoneal cytology) have an extremely poor prognosis. An effective treatment strategy remains elusive.

Methods: Paclitaxel 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/d for 14 consecutive days, followed by 7 days of rest. The primary endpoint was 1-year overall survival (OS) rate. The secondary endpoints were antitumor effect and safety (UMIN000009446).

Results: Thirty-three patients who were pathologically diagnosed with the presence of peritoneal dissemination (n = 22) and/or positive peritoneal cytology (n = 11) without other organ metastasis were enrolled. The tumor was located at the pancreatic head in 7 patients and the body/tail in 26 patients. The median survival time was 16.3 (11.47–22.57) months, and the 1-year survival rate was 62%. The response rate and disease control rate in assessable patients were 36% and 82%, respectively. OS in 8 patients who underwent conversion surgery was significantly higher than that of nonsurgical patients (n = 25, $P = 0.0062$). Grade 3/4 hematologic toxicities occurred in 42% of the patients and nonhematologic adverse events in 18%. One patient died of thrombosis in the superior mesenteric artery.

Conclusions: This regimen has shown promising clinical efficacy with acceptable tolerability in chemotherapy-naive PDAC patients with peritoneal metastasis.

Keywords: intraperitoneal chemotherapy, paclitaxel, pancreatic ductal adenocarcinoma, peritoneal metastasis, S-1

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Pancreatic ductal adenocarcinoma (PDAC) continues to have a dismal prognosis with a 5-year survival rate of <5% even in the modern era.[1,2] The median survival time (MST) of patients with distant organ metastasis, including peritoneal metastasis,[3] is extremely poor at less than 12 months. Moreover, the presence of peritoneal metastasis is associated with development of intestinal obstruction, massive ascites, and malnutrition, leading to poor performance status,[4] which, in turn, deprives the patients of the opportunity to receive chemotherapy.[5] MST of these patients has been reported to be 6 weeks from a population-based study in the Netherlands,[3] and 7 weeks in another series of 73 patients with malignant ascites.[4] Pharmacokinetic studies revealed that anticancer drugs administered systemically do not necessarily enter the peritoneal cavity. Compared with systemic chemotherapy, intraperitoneal (i.p.) chemotherapy seems to be advantageous for treatment of peritoneal dissemination due to a high drug concentration in the peritoneal cavity to directly contact tumor nodules.[6–10]

The clinical effects of i.p. paclitaxel (PTX) in patients with peritoneal metastasis have been favorably reported in clinical trials for ovarian cancer,[6,7] gastric cancer,[8,9] and even PDAC.[10] Most notably, Ishigami et al[8] conducted a phase II study of weekly intravenous (i.v.) and i.p. PTX with S-1 in gastric cancer with peritoneal metastases, with remarkable results such as overall response rate (ORR) of 56%, disappearance or marked decrease in malignant ascites in 62%, and 1-year overall survival (OS) rate of 78%. Kamei et al[11] demonstrated that i.p. administration of PTX nanoparticles resulted in high accumulation in disseminated nodules, presumably due to its superior penetrating activity directly into malignant tissue in a mouse. Thus, i.p. chemotherapy using PTX is considered to be an ideal therapeutic approach for peritoneal carcinomatosis from the viewpoint of drug delivery. In addition, S-1 is an oral fluoropyrimidine derivative which significantly prevented peritoneal carcinomatosis in gastric cancer in the postoperative adjuvant setting, and has shown efficacy also in the treatment of pancreatic cancer.

Therefore, we have conducted a phase II study in a multicenter setting to evaluate the clinical efficacy and tolerability of i.v. and i.p.

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SS and TF contributed equally to this study.

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PTX combined with S-1[8] in PDAC patients with peritoneal metastasis, but without other distant organ metastases.

METHODS

Patient Recruitment

From December 2012 to March 2015, 33 patients were enrolled in this phase II study at 7 Japanese centers. The eligibility criteria were as follows: histologically proven PDAC; presence of cancer cells on peritoneal cytology performed using staging laparoscopy in patients with radiographically defined unresectable locally advanced PDAC, or peritoneal dissemination in all types of PDAC on staging laparoscopy or open laparotomy; chemotherapy-naive; Eastern Cooperative Oncology Group performance status 0 to 1; adequate bone marrow function (leukocyte count 3500–12,000/mm^3, hemoglobin >8.0 g/dL, and platelet count >100,000/mm^3); adequate liver function (serum total bilirubin <2.0 mg/dL and serum transaminases <150 IU/L); adequate renal function (serum creatinine <1.2 mg/dL); age >20 years and <80 years. The exclusion criteria were as follows: presence of metastasis in other distant organs such as the liver, lungs, bone or others, positive peritoneal washing cytology in patients with resectable or borderline resectable PDAC; other active concomitant malignancies; other severe medical conditions. Written informed consent was obtained from all patients. This study was conducted in accordance with the Declaration of Helsinki, and the study protocol was approved by the institutional review board of the affiliated hospital. The registration number of this clinical trial is UMIN000009446.

Treatment

On diagnosing peritoneal dissemination or positive peritoneal cytology during staging laparoscopy or open laparotomy, a peritoneal access port was implanted in the lower abdomen, with a catheter placed in the pelvic cavity. S-1 was administered orally twice daily at a dose of 80 mg/m^2/d for 14 consecutive days, followed by 7 days of 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. These dosages had been determined by a phase I study in gastric cancer,[22] and the safety at the same dosages was confirmed in a feasibility study involving 6 patients with peritoneal metastasis from pancreatic cancer. PTX was diluted in 1 L of normal saline and administered through the implanted peritoneal access port over 1 hour concurrently with i.v. infusion after standard premedication. The treatment course was repeated every 3 weeks until observation of unacceptable toxicity, disease progression, or surgery. Surgical resection (conversion surgery) was performed at a discretion of the surgeons when exceptional response to the chemotherapy was observed. Although the criteria for conversion to surgery had not been prespecified in the protocol, there had been a consensus among the participating investigators that a patient who fulfilled all of the following without deterioration in the performance status could be indicated for surgical resection: tumor remission was observed by the contrast-enhanced computed tomography (CT) in case it had been unresectable locally advanced tumor, tumor markers decreased, peritoneal washing cytology turned negative in case it had been positive, and peritoneal deposits became invisible by the staging laparoscopy in case it had been observed at the time of inclusion into the trial. Although there were no strict rules regarding the number of courses or the duration of chemotherapy to be given before surgery, our previous finding that the interval longer than 8 months between the initial treatment and surgical resection was associated with favorable prognosis in PDAC patients with initially unresectable disease[23] had been shared by the investigators.

Primary and Secondary Endpoints

The primary endpoint was 1-year OS rate, and the secondary endpoints were ORR, frequency of negative peritoneal washing cytology, ascites-onset rate within 1 year after initial treatment, resection rate, and safety. Objective tumor responses were evaluated every 2 months during the study, and classified based on the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines.[12] To evaluate the antitumor effects on peritoneal metastases, peritoneal washing cytology through a peritoneal access port was examined using Papanicolaou and May-Giemsa staining every 2 months. Toxicity was monitored weekly and graded according to the National Cancer Institute–Common Terminology Criteria for Adverse Events version 4.0.

Statistical Analysis

The sample size was calculated as follows. An estimated 1-year survival rate of patients with metastatic PDAC was 25%. Assuming a null hypothesis of 25% and an alternative hypothesis of 45% with 1-sided type I error of 0.05 and power of 0.8, with an accrual time of 2 years and follow-up of 1 year after closure of recruitment, enrollment of 24 patients was required. Continuous variables were expressed as median and range. The MST was estimated using the Kaplan-Meier method. Patients alive at the time of follow-up were censored. The last follow-up date was December 2015. Statistical analyses were performed using JMP statistical discovery software (JMP version 11.0, SAS Institute, Cary, NC). A P value <0.05 was considered statistically significant.

RESULTS

Clinical Background

As shown in Table 1, 33 patients were enrolled, including 22 patients with peritoneal dissemination (of which peritoneal washing cytology was positive in 21 patients), and 11 patients with positive peritoneal washing cytology. Malignant ascites was observed in 15 patients on laparoscopy or laparotomy. Primary tumors were categorized as unresectable locally advanced disease in 19 patients, borderline resectable in 3 patients, and resectable in 11 patients, respectively. Median age was 69 years (range 42–79), and the male-to-female ratio was 14:19. The tumor was located at the pancreatic head in 7 patients and the body/tail in 26 patients, and the median diameter of the tumor was 40 (22–105) mm. The median carbohydrate antigen 19–9 (CA19–9) level was 344 (1–25,850) U/mL at the baseline. Performance status was 0 in 20 patients and 1 in 13 patients. Five patients underwent biliary drainage due to obstructive jaundice before the enrollment.

TABLE 1. Patient Characteristics

Parameters	All Eligible Patients (n = 33)
Age (range), y	69 (42–79)
Male:female	14:19
Body mass index (range)	21.42 (13.34–24.17)
Performance status (%), 0:1	20 (61%): 13 (39%)
Tumor location, head:body/tail	7:26
Tumor diameter (range), mm	40 (22–105)
Resectable: borderline resectable: unresectable*	11:3:19
Ascites, −:+	18:15 (45%)
Peritoneal dissemination, −:+	11:22 (67%)
Peritoneal (washing) cytology, −:+	1:32 (97%)
Albumin (range), g/L	3.9 (2.7–4.3)
CA19–9 (range), U/mL	344 (1–25850)
Duration of protocol therapy (range), mo	8.8 (0.8–22.6)

The data are expressed as median and range.
*Resectability status was defined according to the NCCN guideline.

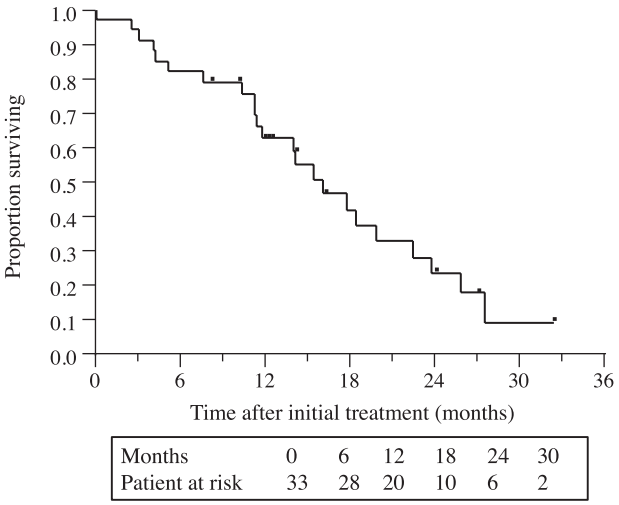

FIGURE 1. Overall survival curve of 33 PDAC patients with peritoneal metastasis. The median survival time was 16.3 months, and 1- and 2-year survival rates were 62% and 23%, respectively.

Survival and Objective Response

This regimen was administered for a median of 8.8 (0.8–22.6) months. As shown in Figure 1, 23 out of 33 patients have already died, with a median observation period of 13.4 (8.2–32.6) months or until death. Thirty-one out of 33 patients were followed up for at least 12 months. The MST was 16.3 (11.47–22.57) months, and 1 and 2-year OS rates were 62% and 23%, respectively (Fig. 1). As shown in Table 2, the ORR by RECIST criteria was 36% and the disease control rate was 82%. Peritoneal washing cytology turned negative in 18 of 33 patients (55%). During treatment, the median rate of CA19–9 decrease was 51%, and normalization of CA19–9 was observed in 35% of patients. Malignant ascites was observed in 15 of 33 patients at diagnosis of peritoneal metastasis. During treatment, ascites disappeared in 9 of 15 patients within 1 year of initial treatment; the remaining 6 patients currently have malignant ascites. Another 4 patients newly developed malignant ascites. Overall, 10 out of 33 patients (30%) had malignant ascites within 1 year of initial treatment.

Conversion Surgery

Of the 33 patients, 8 patients (24%) including 5 patients who had peritoneal dissemination and 3 patients with positive peritoneal washing cytology status plus unresectable locally advanced cancer underwent pancreatectomy (Table 3). All patients underwent surgical resection more than 8 months after the initiation of chemotherapy. Distal pancreatectomy with celiac axis resection was performed in 2 patients, radical antegrade modulated pancreatosplenectomy was performed in 2 patients, distal pancreatectomy was performed in 2 patients, total pancreatectomy with portal vein resection was performed in 1 patient, and pancreatoduodenectomy with portal vein resection in 1 patient. Five out of 8 patients underwent concomitant major artery and/or portal vein resection. The consequences were R0 resection in 6 patients and R1 resection in 2 patients. No in-hospital deaths occurred in patients who underwent surgical resection. Pathological staging revealed T3N1M0 in 6 patients and T3N0M0 in 2 patients. Evans classification[13] was IIA in 6 patients and IIB in 2 patients. As shown in Figure 2, OS of patients who underwent conversion surgery was significantly better than that of patients who did not undergo conversion surgery ($P = 0.0038$), and MST was also longer (27.8 vs 14.2 mo, respectively).

TABLE 2. Clinical Responses

Parameters	All Eligible Patients (n = 33)
Minimum value of CA19–9 (range), U/mL	30.2 (0.7–6.548)
Decreased rate of CA19–9 (range), %	51 (−59.3–99.7)
Normalization of CA19–9, %	9/26 (35)
Tumor response	
Complete response, %	0 (0)
Partial response, %	12 (36)
Stable disease, %	15 (46)
Progressive disease, %	2 (6)
Not evaluated, %	4 (12)
Peritoneal cytology, turned negative, %	18 (55)

Adverse Event Profile

Overall results are listed in Table 4, grade 3/4 hematologic adverse events included neutropenia (42%), leukopenia (18%), febrile neutropenia (6%), and anemia (3%). Grade 3/4 nonhematologic adverse events included appetite loss in 12%, nausea in 9%, vomiting and diarrhea in 6%, and mucositis in 6%. A total of 3 patients discontinued treatment after 1 month. One of these patients died of superior mesenteric arterial thrombosis after the first infusion of this regimen, and this case was regarded as a treatment-related death. Other severe adverse events were anaphylactic reaction during the first infusion of this regimen and severe mucositis and diarrhea. Complications related to the peritoneal access device presented as infection of the i.p. catheter in 1 patient, and dislocation of the device in 2 patients.

DISCUSSION

Recent progress in chemotherapy has provided an improved prognosis in patients with unresectable PDAC.[14,16] In particular, MST of patients with metastatic disease has increased up to 11.5 months with the FOLFIRINOX regimen[15] and 8.5 months with the gemcitabine + nab-PTX regimen.[14] ORR of FOLFIRINOX (oxaliplatin, irinotecan, 5-FU, and leucovorin) and gemcitabine + nab-PTX regimen was 31%[15] and 23%,[14] respectively. Given the pharmacokinetics of intravenously administered agent, it remains doubtful whether these advances in systemic treatment also translate into improvements in the outcome of patients with peritoneal metastasis. In reality, prognosis of PDAC patients with peritoneal metastasis remains extremely poor (MST 6–7 wks).[3,4,17–19]

A standard chemotherapy regimen for unresectable PDAC in Japan is S-1 (MST 9.7 mo), survival of which was revealed to be noninferior to that of gemcitabine (MST 8.8 mo) in the GEST study (randomized phase III study of Gemcitabine plus S-1, S-1 alone, or Gemcitabine alone in patients with locally advanced and metastatic pancreatic cancer).[16] A few authors reported i.v. PTX as a potential treatment option in patients with gemcitabine-refractory pancreatic cancer.[20–22] Ishigami et al[8,23] established i.v./i.p. PTX + S-1 therapy in gastric cancer patients with peritoneal metastasis in a phase I/II study. These investigators suggested that i.p. administration of anticancer drugs enabled an extremely high concentration of drugs to directly contact the target cancer lesions in the peritoneal cavity due to its large molecular weight and fat solubility.[8,23]

The present study focused on the clinical efficacy and feasibility of i.v./i.p. PTX + S-1 therapy in chemotherapy-naive patients with peritoneal metastasis without metastasis in other distant sites. The MST was 16.3 months (11.47–22.57), and the 1-year OS rate was 62%. Ferrone et al[18] reported an MST of 7 months in PDAC

TABLE 3. Clinical Characteristics of Patients Who Underwent Conversion Surgery

No.	Age/ Sex	Location/ Size, mm	Reason for Unresectability	RECIST	CA19–9, IU/L	Time to Surgery, mo	Type of Surgery	Surgical Time, min	EBL, mL	Blood Tx, U	R Grading	Evans*	TNM Staging T	N	M
1	69/M	Pbt/43	LA/P	PR	1464—>69	8	RAMPS	292	1255	0	0	IIa	3	1	0
2	60/F	Pb/35	LA with CY+	PR	150—>16	9	DPCAR (PV)	467	1207	0	0	IIa	3	1	0
3	75/M	Pt/44	LA/P	PR	598—>74	10	RAMPS	347	1397	4	1	IIa	3	1	0
4	50/F	Pb/25	LA/P	PR	1164—>17	12	mDPCAR (PV)†	493	5673	8	0	IIb	3	1	0
5	74/F	Ph/48	LA with CY+	PR	3400—>13	13	TP (PV)	866	6301	12	0	IIb	3	0	0
6	73/M	Pt/22	PR/P	PR	106—>70	10	DP‡	497	593	0	1	IIa	3	1	0
7	73/F	Ph/34	LA with CY+	PR	175—>21	8	PD (PV)	522	1071	0	0	IIa	3	0	0
8	67/M	Pt/26	PR/P	PR	26—>24	8.5	Lap-DP	426	100	0	0	IIa	3	1	0

*Evans grading indicates the histologic grading of the extent of residual tumor: grade I, <10%; grade IIa, 10% to 50%; grade IIb, 51% to 90%; grade III, >90%; grade IV, no residual tumor.
†mDPCAR indicates DPCAR with preservation of left gastric artery.
‡DP indicates concomitant resection of partial gastric tube resection and rt gastroepiploic artery resection and reconstruction.
(m)DPCAR indicates (modified) distal pancreatectomy with celiac axis resection; blood Tx, blood transfusion; CY, peritoneal cytology; DP, distal pancreatectomy; EBL, extent of blood loss; F, female; LA, locally advanced; Lap, laparoscopic; M, male; P, peritoneal dissemination; Pb, pancreatic body; Pbt, pancreatic body and tail; PD, pancreatodeuodenectomy; Ph, pancreatic head; PR, partial response; Pt, pancreatic tail; PV, portal vein resection; R grading, residual tumor grading; R, resectable; RAMPS, radical antegrade modular pancreatosplenectomy; TP, total pancreatectomy.

FIGURE 2. Comparison of survival curves between patients who underwent conversion surgery (n = 8, solid line) and no surgery (n = 25, broken line). Overall survival of patients who underwent conversion surgery was significantly longer than that of patients without conversion surgery ($P = 0.0038$), and MST was 27.8 months in the former group and 14.2 months in the latter group.

patients with peritoneal dissemination, and 6 months in patients with locally advanced disease who had positive peritoneal washing cytology during staging laparoscopy. Our previous report also revealed that ascites occurred within 1-year after initiation of chemotherapy in approximately 70% of patients with peritoneal metastasis diagnosed by staging laparoscopy for radiographically defined locally advanced PDAC.[5] Considering that the patients with peritoneal metastasis generally have a particularly poor prognosis, the present survival results are encouraging.

In the current study, the high response and disease control rates (36% and 82%, respectively) in addition to the efficacy in eliminating peritoneal deposits and intraperitoneal free cancer cells allowed surgeons to perform conversion surgery in selected patients. Surprisingly, the rate of conversion surgery was 24% in this study, and pathological response of some extent was observed in all patients who underwent conversion surgery. Moreover, the MST in patients who underwent conversion surgery was 27.8 months, which was comparable to that in patients with resectable PDAC. The MST after conversion surgery for PDAC has actually been reported to reach 30 to 52 months.[24–28] Unfortunately, only a small fraction of PDAC is eligible for conversion surgery, and in our experience, only 13 of 130 patients (10%) with initially unresectable locally advanced PDAC underwent surgical resection after a favorable response to chemo(radio)therapy.[28] Thus, the i.v./i.p. PTX + S-1 combination has shown remarkable performance, both in terms of the conversion rate and outcome of patient who received conversion surgery. This regimen therefore has the potential to control not only peritoneal metastasis but also the primary tumor.

Although 1 treatment-related death due to thrombosis in the superior mesenteric artery and 1 anaphylactic reaction were observed, most of the adverse events observed in this study were similar to those seen in gastric cancer patients with peritoneal metastasis.[8] The median duration of treatment was 8.8 months in the present study, which was relatively longer than the 2.6 to 4.3

TABLE 4. Profile of Adverse Events

Grading by CTCAEv4.0	1	2	3	4	3/4
Leucocytopenia	5	10	4	2	18%
Neutropenia	0	4	8	6	42%
Febrile neutropenia	0	0	1	1	6%
Anemia	12	11	1	0	3%
Thrombocytop enia	4	2	1	1	6%
Liver function	10	1	0	0	0%
General fatigue	5	2	1	0	3%
Appetite loss	10	3	4	0	12%
Nausea	7	1	3	0	9%
Vomiting	1	1	2	0	6%
Diarrhea	5	1	2	0	6%
Skin rash	4	1	0	0	0%
Mucositis oral (stomatitis)	5	1	2	0	6%
Peripheral neuropathy	6	2	0	0	0%
Alopecia	14	4	0	0	0%
Edema	2	1	0	0	0%
Pneumonia	1	1	0	0	0%
Dysgeusia	8	0	0	0	0%
Anaphylaxis	0	0	0	1	3%

months previously reported in the GEST study.[16] Taken together, the i.v./i.p. PTX + S-1 combination was considered relatively safe and feasible.

Even with these highly promising results, this study can only be hypothesis-generating at this time, given the small sample size and the nonrandomized nature. Sustainable efforts are warranted to conduct a decently designed randomized clinical trial to confirm efficacy of this combination in the subset of PDAC patients with high risk of death due to the peritoneal disease.

In conclusion, i.v./i.p. PTX + S-1 provides promising and encouraging clinical efficacy and acceptable tolerability in chemotherapy-naive PDAC patients with peritoneal metastasis.

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