Phase I/II study of adding intraperitoneal paclitaxel in patients with pancreatic cancer and peritoneal metastasis

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**Background:** Intraperitoneal chemotherapy using paclitaxel is considered an experimental approach for treating peritoneal carcinomatosis. This study aimed to determine the recommended dose, and to evaluate the clinical efficacy and safety, of the combination of intravenous gemcitabine, intravenous nab-paclitaxel and intraperitoneal paclitaxel in patients with pancreatic cancer and peritoneal metastasis.

**Methods:** The frequencies of dose-limiting toxicities were evaluated, and the recommended dose was determined in phase I. The primary endpoint of the phase II analysis was overall survival rate at 1 year. Secondary endpoints were antitumour effects, symptom-relieving effects, safety and overall survival.

**Results:** The recommended doses of intravenous gemcitabine, intravenous nab-paclitaxel and intraperitoneal paclitaxel were 800, 75 and 20mg/m² respectively. Among 46 patients enrolled in phase II, the median time to treatment failure was 6.0 (range 0–22.6) months. The response and disease control rates were 21 of 43 and 41 of 43 respectively. Ascites disappeared in 12 of 30 patients, and cytology became negative in 18 of 46. The median survival time was 14.5 months, and the 1-year overall survival rate was 61 per cent. Conversion surgery was performed in eight of 46 patients, and those who underwent resection survived significantly longer than those who were not treated surgically (median survival not reached versus 12.4 months). Grade 3–4 haematological toxicities developed in 35 of 46 patients, whereas non-haematological adverse events occurred in seven patients.

**Conclusion:** Adding intraperitoneal paclitaxel had clinical efficacy with acceptable tolerability.

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**Introduction**

Pancreatic cancer has a poor prognosis, particularly for disseminated disease1. The presence of peritoneal metastasis is often associated with ascites and intestinal obstruction, leading to malnutrition and poor performance status, which could deprive patients of the opportunity to receive chemotherapy2. Intraperitoneal chemotherapy appears advantageous owing to higher drug concentrations achieved in the peritoneal cavity, compared with systemic chemotherapy1–6.
of the enrolled patients\textsuperscript{8}. Recently, nab-paclitaxel combined with gemcitabine was shown to be the standard treatment option for patients with pancreatic cancer and distant metastasis\textsuperscript{9}.

The aims of this phase I/II study were to determine the recommended dose for the combination of intravenous nab-paclitaxel with gemcitabine and intraperitoneal paclitaxel in patients with pancreatic cancer and peritoneal metastasis, and to evaluate its clinical efficacy and safety.

**Methods**

The eligibility and exclusion criteria are shown in Fig. 1. 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 for this clinical trial is UMIN000018878. The last follow-up date was 31 December 2019.

**Treatment**

If peritoneal dissemination or positive peritoneal cytology was detected during staging laparoscopy or open laparotomy, a peritoneal access port was implanted in the lower abdomen. Intravenous nab-paclitaxel combined with gemcitabine was administered along with intraperitoneal paclitaxel on days 1, 8 and 15, followed by 1 week of rest. The treatment course was repeated every 4 weeks until unacceptable toxicity had developed, disease progression or surgery (Fig. 1). The criteria for surgical resection (conversion surgery) were: an Eastern Cooperative Oncology Group performance status of 0 or 1; marked tumour shrinkage; decrease or normalization of tumour marker levels; washing cytology via peritoneal access port turned negative (twice in a row); and disappearance of peritoneal deposits on staging laparoscopy\textsuperscript{8}. To obtain a sufficient clinical effect with this regimen and avoid early peritoneal recurrence, the decision to proceed to conversion surgery was based on an interval exceeding 8 months between the initial treatment and surgical resection, which was associated with favourable prognosis in patients with initially unresectable pancreatic cancer in a previous study\textsuperscript{10}.

**Primary and secondary endpoints**

The primary endpoint of phase II of the study was the 1-year overall survival rate. The secondary endpoints were antitumour effects, symptom-relieving effects, safety and overall survival.

Objective tumour responses were classified according to Response Evaluation Criteria in Solid Tumours (RECIST) guidelines version 1.1\textsuperscript{11}. To evaluate antitumour effects on peritoneal metastases, peritoneal washing cytology specimens were examined every 2 months.

Toxicity was monitored weekly and graded according to the National Cancer Institute–Common Terminology Criteria for Adverse Events (CTCAE) version 4.0\textsuperscript{12}.

**Definition of dose-limiting toxicities and determination of recommended dose**

The frequencies of dose-limiting toxicities were evaluated, and the recommended dose was determined during phase I of the study. Dose-limiting toxicities were determined during the first two cycles of chemotherapy. Dose-limiting toxicities were defined according to CTCAE version 4.0\textsuperscript{12} based on the presence of one or more of the following events: grade 4 leucopenia or neutropenia; grade 3 neutropenia complicated by fever of at least 38°C; grade 3–4 anaemia, thrombocytopenia or non-haematological toxicities; and more than 2 weeks of drug withdrawal within one cycle. The maximum tolerated dose was determined, and the previous level was set as the recommended dose\textsuperscript{13}.

**Statistical analysis**

The sample size was calculated for an estimated overall survival rate at 1 year after treatment initiation for patients with metastatic pancreatic cancer of 25 per cent. Assuming a null hypothesis of 25 per cent and an alternative hypothesis of 45 per cent with a one-sided type I error of 0.05 and power of 0.8, enrolment of 24 patients was required.

Continuous variables are expressed as median (range). Overall survival was defined as the interval from the start of treatment to death from any cause. Survival analysis was based on the Kaplan–Meier method, with evaluation of differences using the log rank test. A binary logistic regression model using the backward method was employed to predict the use of conversion surgery. The level of statistical significance was set at $P < 0.050$. All statistical analyses were done using JMP\textsuperscript{®} Pro version 14.2.0 (SAS Institute, Cary, North Carolina, USA).

**Results**

A total of 50 patients diagnosed with pancreatic cancer and peritoneal metastasis were enrolled in this phase I/II study from seven Japanese centres; ten patients participated in phase I and 46 (including 6 patients from phase I) in phase II (Fig. 1).
**Eligibility criteria**

- Histologically or cytologically proven pancreatic cancer
- Peritoneal metastasis in patients with otherwise resectable cancer or the presence of cancer cells in patients with unresectable locally advanced cancer
- No prior receipt of chemotherapy or chemotherapy started within 2 months
- Eastern Cooperative Oncology Group performance status of 0 or 1
- Adequate bone marrow function (leucocyte count $\geq 3500/mm^3$ and $< 12000/mm^3$, neutrophil count $\geq 2000/mm^3$)
- Haemoglobin $\geq 8.0\, g/dL$ and platelet count $\geq 100000IU/L$
- Adequate liver function (serum total bilirubin $\leq 1.25 \times$ of the institutional upper limit and serum transaminase $\leq 150IU/L$)
- Adequate renal function (serum creatinine $\leq 1.2\, mg/dL$ and creatinine clearance $\geq 50\, mL/min$)
- Possible oral intake
- Receipt of informed consent
- Age $\geq 20$ years and $< 80$ years

**Exclusion criteria**

- Presence of distant metastasis excluding the ovaries
- Positive peritoneal cytology in patients without peritoneal deposits in otherwise resectable pancreatic cancer
- Contraindication for gemcitabine, nab-paclitaxel or paclitaxel
- Infection or inflammation
- Severe medical conditions
- Massive ascites
- Bleeding in the alimentary tract with repetitive blood transfusion
- Severe diarrhoea
- Other active concomitant malignancies
- Interstitial pneumonia
- Invasion of more than half of the alimentary tract by the primary tumour or peritoneal deposits

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**Determination of recommended dose**

Dose levels and dose-limiting toxicities in phase I are shown in Table S1 (supporting information). At dose level 1, three of four patients experienced dose-limiting toxicities. Therefore, the next six patients were enrolled at level 0; only one patient experienced a dose-limiting toxicity (grade 4 neutropenia) at this level. Based on these results, the recommended doses for intravenous gemcitabine, intravenous nab-paclitaxel and intraperitoneal paclitaxel were 800, 75 and 20 mg/m$^2$ respectively.

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**Patient characteristics**

A total of 46 patients were enrolled in phase II, and drugs were administered at the recommended dose (level 0). The tumour was located in the pancreatic head in 13 patients and the body/tail in 33. Median tumour diameter was 36 (range 18–64) mm. Primary tumours were categorized as resectable in 12 patients, borderline resectable in 11, and unresectable and locally advanced in 23 patients. Malignant ascites was observed in 30 of the 46 patients on laparoscopy or laparotomy. All patients had positive...
Fig. 2 Tumour response and survival

**a** Waterfall plot of tumour shrinkage response. Median primary tumour shrinkage was 20 per cent (red line). **b** Spider plot showing tumour response over time. The dotted line indicates no change. **c** Overall survival of 46 patients with pancreatic ductal adenocarcinoma and peritoneal metastasis. The shaded area represents the 95 per cent confidence interval. **d** Comparison of survival between patients who underwent conversion surgery and those who did not. \( P = 0.004 \) (log rank test). OS, overall survival.

intraperitoneal cytology, and 29 had pathological confirmation of peritoneal dissemination. The median duration of treatment was 6.0 (range 0–22.6) months (Table S2, supporting information).

**Clinical responses and survival by treatment type**

During treatment, median primary tumour shrinkage was 20 (range 0–100) per cent (Fig. 2a,b). CA19-9 levels decreased by a median of 84.4 (range 16.9–99.1) per cent, and normalized in 12 patients. The response and disease control rates were 21 of 43 and 41 of 43 respectively.

Peritoneal washing cytology turned negative in 18 of 46 patients, and malignant ascites disappeared in 12 of 30 (Table 1).

All eligible patients were followed up for at least 12 months. Median overall survival was 14.5 (range 11.5–19.2) months, and 1- and 2-year overall survival rates were 61 and 32 per cent respectively (Fig. 2c).

**Conversion surgery**

Eight of the 46 patients underwent conversion surgery (Table 2). The tumour was located in the pancreatic body...
Table 1 Clinical responses to treatment

| Clinical response | No. of patients (n = 46) |
|-------------------|--------------------------|
| **Tumour shrinkage (%)‡** | 20 (0–100) |
| CA19-9 | |
| Minimum (units/ml)† | 72 (4–23 700) |
| Decreased ratio (%)† | 84-4 (16-9–99-1) |
| Normalization | 12 |
| **Objective tumour responses** | |
| Best RECIST category | |
| Complete response | 2 |
| Partial response | 19 |
| Stable disease | 20 |
| Progressive disease | 2 |
| Response | 21 |
| Disease control | 41 |
| **Peritoneal cytology turned negative** | 18 |
| **Disappearance of ascites** | 12 of 30 |
| **Conversion surgery** | 8 |

*Unless indicated otherwise; †values are median (range). CA19-9, carbohydrate antigen 19-9; RECIST, Response Evaluation Criteria in Solid Tumours.

and tail in seven patients. Six patients had peritoneal dissemination at diagnosis, and two patients had positive peritoneal washing cytology plus unresectable locally advanced cancer before surgery. The median time to surgery was 8.8 (range 4.1–12.2) months after the initiation of chemotherapy. Seven patients underwent R0 resection. The Evans (tumour regression) grade was IIA in three patients, IIB and III in two patients each, and IV in one patient.

Concerning overall survival, patients who underwent conversion surgery survived significantly longer than those who did not (median survival not reached versus 12.4 (range 11.0–18.1) months; P = 0.004) (Fig. 2d).

Adverse event profile

The adverse events data are summarized in Table S3 (supporting information). Grade 3–4 haematological adverse events occurred in 35 of 46 patients, including leucocytopenia (22), neutropenia (32), febrile neutropenia (4), anaemia (8) and thrombocytopenia (6). Grade 3–4 non-haematological adverse events occurred in seven patients, including appetite loss (4) and nausea (2). A grade 3–4 peritoneal port problem was observed in one patient.

Prediction of conversion surgery in patients with peritoneal dissemination

Univariable analysis identified a shift to negative peritoneal cytology and normalization of CA19-9 levels as significant predictors of survival. In multivariable analysis, age (odds ratio 1.29, 95 per cent c.i. 1.04 to 1.59; P = 0.020) and a shift to negative peritoneal cytology (odds ratio 32.73, 2.71 to 395.30; P = 0.006) were significant predictors of eligibility for conversion surgery (Table S4, supporting information).

Discussion

This trial demonstrated the clinical efficacy of a chemotherapy regimen comprising intravenous gemcitabine, intravenous nab-paclitaxel and intraperitoneal paclitaxel, with acceptable tolerability, in patients with peritoneal metastasis from pancreatic cancer. Although the clinical response and survival data did not exceed those of an S-1-based regimen in a previous study, this strategy represents an option for treating peritoneal disease in countries where S-1 is not available. Intraperitoneal chemotherapy enables peritoneal deposits to be exposed to high concentrations of drugs without increasing the systemic concentration to toxic
levels. The duration of effectiveness after intraperitoneal administration is determined by the molecular characteristics of the drug. In this regard, paclitaxel is a large-molecule lipophilic drug that is absorbed slowly. In addition to this pharmacokinetic advantage, combination with systemic chemotherapy is a key variable in intraperitoneal chemotherapy. Ishigami and colleagues established the use of intravenous/intraperitoneal paclitaxel combined with S-1 therapy in patients with gastric cancer, and conducted the phase III PHOENIX-GC trial to compare this regimen with standard therapy. The present study may be considered encouraging. Conversely, no significant improvement was noted compared with the effects of a previous S-1-based regimen, despite the use of state-of-the-art systemic therapy in combination with intraperitoneal paclitaxel.

Recently, multidisciplinary treatment combining chemotherapy and surgery has been used widely and regarded as a promising strategy. In particular, conversion surgery for metastatic disease has an advantage in that chemotherapy is administered to patients with a better performance status. The combination therapy used in the present study enabled eight of 46 patients to be eligible for conversion surgery. The median survival time was not reached in patients who underwent conversion surgery, which is a considerable achievement given the generally poor outcomes of patients with pancreatic cancer and peritoneal disease. Median survival time after conversion surgery for pancreatic cancer has generally been reported in the range 30–52 months. The present combination therapy has performed remarkably in terms of both conversion rate and survival outcome, and its potential to control both peritoneal metastasis and the primary tumour was proven. However, this investigation was conducted as a phase I/II study with a single-arm design; the bias in its clinical implications must be recognized. A phase III study is being planned to compare survival outcomes between the intraperitoneal therapy used here and standard chemotherapy.

Regarding adverse events, grade 3–4 haematological toxicities occurred in 35 of 46 patients and non-haematological adverse events in seven. In particular, the rate of haematological toxicities was high, but the incidence and severity were comparable to those of standard chemotherapy regimens and previous findings. In the phase II analysis, grade 4 neutropenia was noted in seven of 40 patients (18 per cent); however, these events were well managed and tolerable. Intraperitoneal port-related adverse events were less frequent than in the authors’ initial experience, which was a meaningful result for this intraperitoneal therapy.

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**Supporting information**

Additional supporting information can be found online in the Supporting Information section at the end of the article.