A Phase I Trial of Arterial Infusion Chemotherapy with Gemcitabine and 5-Fluorouracil for Unresectable Advanced Pancreatic Cancer after Vascular Supply Distribution via Superselective Embolization

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Background: We previously reported that arterial infusion chemotherapy improved the response rate and survival of the patients with pancreatic cancer at advanced stages in an open trial. We conducted a Phase I trial of arterial infusion chemotherapy with gemcitabine and 5-fluorouracil for advanced pancreatic cancer after vascular supply distribution via superselective embolization.

Methods: Patients were treated after arterial embolization for hemodynamic change to restrict the blood flow into the pancreas (mainly to the great pancreatic artery and the caudal pancreatic artery). Arterial infusion chemotherapy consisted of gemcitabine in doses that were increased from 600 to 1000 mg/m² in subsequent cohorts on Day 1 plus continuous infusion of 5-fluorouracil 300 mg/m²/day on Days 1–5 every 2 weeks.

Result: Twelve patients were enrolled. The maximum tolerated dose of gemcitabine was determined to be Level 3 (1000 mg/m²). Only very mild hematological and non-hematological toxicities were noted. The overall response rate was 33.3%. The median survival time was 22.7 (95% CI; 9.5–24.5) months and the 1- and 2-year overall survival rates were 83.3 and 25.0%, respectively.

Conclusion: Arterial infusion chemotherapy using 1000 mg/m² gemcitabine on Day 1 and 300 mg/m²/day 5-fluorouracil on Days 1–5 every 2 weeks warrants a Phase II study.

Key words: chemo-phase I-II-III – GI-pancreas – GI-pancreas-med – GI-pancreas-radoncol – radiology-angio

INTRODUCTION

Pancreatic cancer is rarely curable, and the highest cure rate occurs when the tumor is truly localized to the pancreas (Stages I–III). However, these stages of the disease account for less than 20% of cases, and until quite recently, the prognosis of patients at advanced stages (IVa and IVb) was dismal with a less than 1% overall survival (OS) rate at 5 years (1).

In 1997, the introduction of gemcitabine improved the prognosis of Stage IV pancreatic cancer (median survival time (MST) 5.7 months) when compared with that of fluorouracil (5-FU, MST 4.4 months) (2). Since then, systemic gemcitabine therapy has been accepted as a standard therapy for unresectable advanced pancreatic cancer (Stages IVa and IVb). Further, several Phase II studies of gemcitabine combined with 5-FU, cisplatin, irinotecan, or oxaliplatin in patients at Stages IVa and IVb have been conducted with some improvement of efficacy compared with that of gemcitabine alone (3–8). However, Phase III studies of these combinations did not confirm the survival advantage over that of gemcitabine therapy alone (9–11), though patients with good Karnofsky performance scores (PSs) showed significant improvement of survival when gemcitabine was combined with capecitabine (MST 10.1 months).
as compared with gemcitabine therapy alone (MST 7.4 months) in a Phase III study (12). With regard to prognosis of patients with disease limited at Stage IVa, MST with gemcitabine alone was 11.3 months, almost equivalent to that observed with 5-FU-based concurrent chemoradiotherapy (CCRT) (MST 10.4 months), which is accepted as a standard therapy for locally advanced disease (13).

One plausible explanation for poor response of advanced pancreatic cancer is that systemic chemotherapy is extremely insufficient for delivery of anticancer drugs to the tumor because of the hypovascularity of pancreatic cancer (14). We previously reported that arterial infusion chemotherapy (5-FU + cisplatin) after hemodynamic change to restrict the blood flow into the pancreas (mainly to the great pancreatic artery (GPA) and the caudal pancreatic artery (CPA)) improved the response rate (73.9%) and survival (MST 18.3 months) of the disease at Stages IVa and IVb with metastasis limited to the liver in an open trial (15). Since then, similar arterial embolization therapy employing the combination of gemcitabine and 5-FU or gemcitabine and mitomycin-C have proven to be highly effective both in terms of response rate and survival (16,17). However, these previous reports were not based on phase studies, but open trials. In the present study, we conducted a Phase I trial of selective arterial embolization with a combination of gemcitabine and 5-FU for Stages IVa and IVb with metastasis limited to the liver.

PATIENTS AND METHODS

Eligibility

Patients were considered eligible for this study based on following criteria: histologically or cytologically proven adenocarcinoma of the pancreas; advanced unresectable pancreatic cancer; clinical stage IVa or IVb (International Union Against Cancer tumor-node-metastasis system, 1997); no prior chemotherapy or radiation therapy; an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; age ≥20 years; adequate baseline bone marrow function (hemoglobin level >10 g/dl, white blood cell count >4000/mm² and <12 000/mm², neutrophil count >2000/mm³ and platelet count >100 000/mm³); adequate hepatic function (total bilirubin level <2.0 mg/dl, aspartate aminotransferase and alanine aminotransferase levels two times the upper limit of normal); adequate renal function (serum creatinine level ≤1.5 mg/dl); adequate respiratory and cardiac function; no complete obstruction of either celiac artery, common hepatic artery (CHA) or splenic artery (SPA); no metastatic lesion except for liver; and life expectancy at least 2 months. Written informed consent was obtained from all patients. This study was approved by the review boards at Sapporo Medical University.

PRETREATMENT EVALUATION AND FOLLOW-UP STUDIES

History and physical examination were performed prior to registration and before each subsequent course of chemotherapy. Studies carried out at the time of registration included peripheral blood examination, biochemistry and renal and hepatic function tests. All patients underwent peripheral blood examination, biochemistry and renal and hepatic function tests before each course of arterial infusion chemotherapy. Testing for tumor maker (CEA) was conducted every 4 weeks.

EMBOLIZATION OF ARTERIES

In general, the arterial system in the head of the pancreas consists of the anterior or posterior superior pancreaticoduodenal artery (ASPDa or PSPDa) that arises from the gastroduodenal artery (GDA) and inferior pancreaticoduodenal artery (IPDA) that branches out of the superior mesenteric artery (SMA). These arteries combine to form a pancreaticoduodenal arcade that surrounds the pancreatic head. Regarding the arterial system in the pancreatic body and cauda, the dorsal pancreatic artery (DPA), the GPA and CPA that directly branch out of the SMA or the SPA combine with the pancreatic parenchyma to form the transverse pancreatic artery (TPA). In this treatment, the pancreatic arteries were embolized superselectively, leaving only the DPA, GPA and CPA that branch off the SPA for the purpose of simplifying the numerous potential branches that flow into the pancreatic parenchyma, as described previously (Figs 1 and 2). After completion of these hemodynamic changes, the tip of the catheter used for infusion of chemotherapy into the primary tumor was placed in the SPA proximal to the branching of the DPA on the side of the celiac artery. The tip of the catheter used for infusion into the liver in order to prevent or treat the liver metastasis was placed in the CHA.

Figure 1. Hemodynamics of pancreatic arteries. (a) Angiogram and (b) schema. The arterial system in the head of the pancreas consists of the anterior or posterior superior pancreaticoduodenal artery (ASPDa or PSPDa) that arises from the gastroduodenal artery (GDA) and inferior pancreaticoduodenal artery (IPDA) that branches out of the superior mesenteric artery (SMA). The dorsal pancreatic artery (DPA) that directly branches out of the SMA or splenic artery (SPA) combines with the pancreatic parenchyma to form the transverse pancreatic artery (TPA). CPA, caudal pancreatic artery; CHA, common hepatic artery.
Then, the catheters were connected with the port to be embedded in the medial femoral region. The catheters used were a 4.2Fr catheter (Goodtec; Goodman Co. Ltd., Nagoya, Japan) for angiography and a 3Fr microcatheter (prograde; Termo Co. Ltd., Tokyo, Japan).

**TREATMENT PROTOCOL**

Treatment consisted of two cycles of gemcitabine (Eli Lilly Japan K.K, Kobe, Japan; gemcitabine doses were increased to 600, 800 and 1000 mg/m² in subsequent cohorts) on Days 1 and 15 plus continuous infusion of 5-fluorouracil (5-FU, 300 mg/m²/day) on Days 1–5 and 15–19 during a course consisting of 4 weeks. Gemcitabine was diluted in 50 ml saline and infused over a period of 30 min via an injected reservoir port (port). 5-FU was diluted in saline up to 240 ml and infused continuously using intermate LV2 (Baxter Healthcare Co. Ltd., Irvine, CA, USA) over a period of 120 h via the port.

**STUDY DESIGN AND TOXICITY CRITERIA**

Three patients were initially enrolled at each dose level. If none of the patients experienced dose limiting toxicity (DLT) during two courses, the next cohort of patients was treated at the next higher dose level. If one of the three patients experienced DLT, then three additional patients were enrolled at the same dose level. If two or more DLTs occurred at a given dose level, that level was considered to be the maximum tolerance dose (MTD) and the dose escalation was stopped. If less than two patients of the six experienced DLT at the maximum dose level, that level was considered to be the maximum administered dose (MAD), i.e. recommended dose (RD). DLT was defined as the occurrence of any one of the following during treatment: Grade 4 neutropenia, any febrile neutropenia, Grade 4 thrombocytopenia, or Grade 3 nonhematologic toxicity. Any event resulting in treatment discontinuation for longer than 10 days was also considered to be a DLT. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC), version 2.0. Prophylactic granulocyte-stimulating factor (G-CSF) was not given with the treatment. However, when Grade 4 neutropenia persisted more than 7 days or if febrile neutropenia was noted, 50 μg/m²/day of G-CSF was optionally given subcutaneously starting the following day and continued until symptoms recovered to Grade 2. Any patient who required more than 4 weeks for recovery from adverse reactions was taken off the study.

**DISEASE ASSESSMENT**

Computed tomography scanning of the chest, abdomen and pelvis was performed for all patients every 4 weeks. Patients were considered to have a complete response (CR) to therapy if evidence of the tumor disappeared. A partial response (PR) was defined as a ≥50% reduction in the sum of the products of the largest perpendicular diameters of the indicator lesions, single or multiple sites, chosen prior to therapy. A regression was defined as a reduction in the size of an evaluable tumor that did not fit the definition of either a CR or PR. A response to therapy was accepted if it persisted for two or more consecutive scans at least 4 weeks apart.

**PHARMACOKINETIC ASSESSMENT**

The pharmacokinetic assessments in this study were designed to explore the possibility of a change in metabolism of gemcitabine by 5-FU. Serum samples for these analyses were obtained at time 0, 15, 30, 60 and 120 min after infusion of gemcitabine.

**RESULTS**

**PATIENT CHARACTERISTICS**

Between April 2003 and March 2006, a total of 12 patients entered this trial. All patients were treated in sequential cohorts of three to six patients per dose level. They were considered evaluable for toxicity and response assessment. A summary of patient characteristics is given in Table 1. There were three female and nine male patients, and their median age was 63 years old. Only one patient had an ECOG PS of 1, and the remaining patients had good performance statuses. Seven patients had tumors of the pancreas head and five patients had tumors of the pancreas body. All patients had histologically or cytologically proven adenocarcinoma. Two patients had lymph node metastasis (N3) and one patient had liver metastasis. Sixty-seven percent of the patients were diagnosed as being in Stage IVa. The characteristics of each dose level before treatment were similar except for the tumor location.
DLTS and RD Level

All patients were administered one of three dose levels of gemcitabine combined with 5-FU 300 mg/m². The various dose levels, the number of patients and the DLTS that were observed during the arterial infusion chemotherapy in determination of MTD are summarized in Table 2. At level 1 to level 3, no Grade 3 non-hematological toxicity or Grade 4 hematological toxicity was observed in the nine patients treated. However, one Grade 3 anemia was observed at level 3, thus, an additional three patients were recruited for dose level 3. However, DLTS did not occur among these last patients. Therefore, this dose level was identified as the MAD for this study. We concluded that dose level 3 should be considered as the RD for this treatment.

SAFETY PROFILE

Tables 3 and 4 list the treatment-related clinical adverse events experienced by patients treated at each dose level throughout the treatment period. Treatment toxicities were very slight. Grade 3 anemia was detected in only one patient (8.3%). Grade 3–4 leucopenia, neutropenia and thrombocytopenia were not observed. Non-hematological side effects were manageable. Grade 1 fatigue was observed in five patients. Grade 1 anorexia, nausea and vomiting were observed in only two patients.

### Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Gemcitabine (mg/m²)</th>
<th>600</th>
<th>800</th>
<th>1000</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>3</td>
<td>3</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>Age-years</td>
<td>Median 63</td>
<td>63</td>
<td>67</td>
<td>63</td>
</tr>
<tr>
<td>Male/female</td>
<td>3/0</td>
<td>2/1</td>
<td>4/2</td>
<td>9/3</td>
</tr>
<tr>
<td>Performance status</td>
<td>0/1–2</td>
<td>3/0</td>
<td>3/0</td>
<td>5/1</td>
</tr>
<tr>
<td>Tumor location</td>
<td>Head/body/tail</td>
<td>3/0</td>
<td>1/2/0</td>
<td>3/0</td>
</tr>
<tr>
<td>Node 0/1–2/3</td>
<td>2/0/1</td>
<td>2/0/1</td>
<td>9/0/0</td>
<td>10/0/2</td>
</tr>
<tr>
<td>RP +/-</td>
<td>3/0</td>
<td>2/1</td>
<td>4/2</td>
<td>9/3</td>
</tr>
<tr>
<td>Liver meta. +/- –</td>
<td>0/3</td>
<td>0/3</td>
<td>1/5</td>
<td>1/11</td>
</tr>
<tr>
<td>Clinical stage IVa/IVb</td>
<td>2/1</td>
<td>2/1</td>
<td>4/2</td>
<td>8/4</td>
</tr>
</tbody>
</table>

RP, retroperitoneum.

### Table 2. Dose-escalation schedule and results

<table>
<thead>
<tr>
<th>Dose level</th>
<th>Gemcitabine (mg/m²)</th>
<th>No. of patients</th>
<th>DLTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>600</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>800</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>1000</td>
<td>6</td>
<td>0</td>
</tr>
</tbody>
</table>

DLT, dose limiting toxicity.

### Table 3. Hematological toxicities

<table>
<thead>
<tr>
<th>Toxicities</th>
<th>Level 1 (n = 3)</th>
<th>Level 2 (n = 3)</th>
<th>Level 3 (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leucopenia</td>
<td>0/3/0/0</td>
<td>1/1/0/0</td>
<td>1/1/0/0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>0/0/0/0</td>
<td>0/1/0/0</td>
<td>1/2/0/0</td>
</tr>
<tr>
<td>Anemia</td>
<td>1/2/0/0</td>
<td>1/2/0/0</td>
<td>0/2/1/0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0/0/0/0</td>
<td>0/0/0/0</td>
<td>0/2/0/0</td>
</tr>
</tbody>
</table>

Grade, grade.

Other treatment-associated symptoms were infrequent or negligible. During the arterial infusion chemotherapy, no case required administration of insulin or oral hypoglycemic agents. No case presented diarrhea at Grade 2 or higher nor showed a decrease in exocrine and endocrine capacities of the pancreas. There was no treatment-related death that occurred during arterial infusion chemotherapy.

### Table 4. Non-hematological toxicities

<table>
<thead>
<tr>
<th>Toxicities</th>
<th>Level 1 (n = 3)</th>
<th>Level 2 (n = 3)</th>
<th>Level 3 (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anorexia</td>
<td>1/0</td>
<td>1/0</td>
<td>3/0</td>
</tr>
<tr>
<td>Nausea</td>
<td>0/0</td>
<td>1/0</td>
<td>1/0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0/0</td>
<td>0/0</td>
<td>2/0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>Mucositis</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2/0</td>
<td>2/0</td>
<td>1/0</td>
</tr>
<tr>
<td>AST/ALT elevation</td>
<td>1/0</td>
<td>1/0</td>
<td>1/0</td>
</tr>
</tbody>
</table>

AST, asparate aminotransferase; ALT, alanine aminotransferase.
diagnosed by needle biopsy before treatment, but autopsy revealed that most of the tumor was adenosquamous carcinoma.

Of the 10 patients who had an elevated CEA level before treatment, seven patients demonstrated a 50% or greater reduction in CEA. Three patients showed complete normalization of their CEA value.

Eleven of the 12 patients enrolled in this study died. One patient was still alive at the time of this report. The median time to progression (MTTP) was 9.1 (95% CI: 5.4–12.8) months (Fig. 3). The breakdown of the disease progression was enlargement of the primary and/or liver metastatic lesions, five cases (treatment was stopped in all cases); lung metastasis, one case (treatment was changed to systemic chemotherapy using the same regimen); newly found lymphatic metastasis, three cases (after radiation therapy, arterial infusion chemotherapy was continued); and carcinomatous peritonitis, three cases (gemcitabine alone was intraperitoneally infused and arterial infusion chemotherapy was continued).

The MST was 22.7 (95% CI: 18.3–27.1) months (Fig. 4). The 1- and 2-year OS rates were 83.3 and 25.0%, respectively.

**DISCUSSION**

In this study, the dose of 5-FU was fixed at the amount we had previously used in a pilot study on arterial infusion chemotherapy with 5-FU plus CDDP. A report showed that the \( C_{\text{max}} \) value of systemic administration of gemcitabine alone at 1000 mg/m\(^2\)/30 min was 15.0 \( \mu \text{g/ml} \) and the AUC was 493 \( \mu \text{g/ml} \) (18). Similarly to our study, a previous report demonstrated a detailed analysis of pharmacokinetics and the observation of adverse events in cases of arterial infusion of gemcitabine alone after hemodynamic changes. Compared with systemic gemcitabine administration, it was reported that the peak gemcitabine concentration in the blood (30 min after 1000 mg/m\(^2\) administration) was reduced to \( \sim 1/7 \) of that observed in topical arterial infusion. Further, adverse events occurred less frequently and they were milder. No severe adverse events were observed, even in the pancreas, liver and gastrointestinal tract where the local concentration became high. As a whole, no toxicity at Grade 3 or higher was recognized (19).

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**Table 5. Best overall response**

<table>
<thead>
<tr>
<th>Dose level</th>
<th>Patients</th>
<th>Response</th>
<th>Response rate (%)</th>
<th>Baseline increased CEA</th>
<th>CEA50% decrease</th>
<th>Normalized CEA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CR</td>
<td>PR</td>
<td>SD</td>
<td>PD</td>
<td>33.3</td>
<td>2</td>
</tr>
<tr>
<td>1</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>33.3</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>33.3</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>0</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>33.3</td>
</tr>
<tr>
<td>Total (%)</td>
<td>12</td>
<td>0</td>
<td>4</td>
<td>6</td>
<td>2</td>
<td>33.3</td>
</tr>
</tbody>
</table>

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; CEA, carcinoembryonic antigen.

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**PHARMACOKINETICS**

The maximum concentration in plasma (\( C_{\text{max}} \)) was observed at 30 min. \( C_{\text{max}} \) values for the 800 and 1000 mg/m\(^2\) administrations were 5.06 \( \pm \) 1.02 and 8.20 \( \pm \) 2.29 \( \mu \text{g/ml} \), respectively. The areas under the concentration curve (AUC) of gemcitabine were 307.33 \( \pm \) 94.11 and 207.82 \( \pm \) 60.45 \( \mu \text{g/ml} \), respectively.
However, the possibility of a change in metabolism by arterial infusion of 5-FU and its MTD has not been determined yet. Therefore, in the present study, safety of the treatment was ensured by beginning at a low dose of 600 mg/m² and defining the maximum dose as 1000 mg/m², which was recommended for systemic chemotherapy and approved by the insurance in Japan as the optimal dose. Furthermore, pharmacokinetics of gemcitabine was also examined.

As a result, three cases were enrolled at each level, and neither Grade 4 hematological nor Grade 3 or higher non-hematological toxicity was observed. Since Grade 3 anemia was observed in one of three cases at the maximum dose, three new cases were enrolled and safety was continuously examined. However, Grade 3 or higher hematological toxicity was not observed in these additional cases, and 1000 mg/m² of gemcitabine was determined as the optimal dose for the scheduled Phase II study. Compared with systemic administration in the previous report (18), the maximum concentration in the blood and AUC of gemcitabine were reduced to about as low as 1/2 and 3/4, respectively. In the present study, their concentrations by systemic administration were not measured and they were compared strictly. However, we concluded that there was no large metabolic change associated with the administration of a combination of 5-FU and gemcitabine.

The factor limiting the maximum dose of gemcitabine monotherapy for systemic administration is bone marrow suppression. At the optimal dose of 1000 mg/m² for monotherapy, the following frequencies of adverse effects were reported in Phase III studies: Grade 3 or higher levels of neutropenia, 5–9%; anemia, 2–10%; and thrombocytopenia, 5–11% (20–22). In this study, anemia at Grade 3 occurred in one case at level 3 (7.9 g/dl), but there was no Grade 3 or higher reduction in neutrophils, leukocytes, or platelets.

The low gemcitabine concentration in the bone marrow was presumed to be the main reason why bone marrow suppression rarely occurred in this regimen. On the other hand, topical drug concentrations in the liver, spleen and pancreas increased, and the appearance of non-hematological toxicity was a concern.

Most of the non-hematological toxicities in systemic administration of gemcitabine alone were gastrointestinal tract symptoms. Anorexia, nausea and vomiting at Grade 3 or higher were observed in less than 10% of cases (20–22). In this study, however, no symptoms at Grade 3 or higher were observed, and Grade 1 toxicity was observed only in two of six cases at the maximum dose.

In this method, drugs were directly flowed into the gastric cardia/upper part of the body via the short gastric artery branched from the SPA, and it was demonstrated that adverse events rarely occurred at the designated dose. Upper gastrointestinal endoscopy was performed after two cycles of treatment in all cases, and no case showed gastric mucosal lesions. As to the reason for low frequencies of gastrointestinal symptoms, low drug concentrations in the blood and in the whole body were presumed to be one reason. No case exhibited duodenal mucosal lesions due to embolization of the pancreatic artery arcade. In terms of liver disorder, adverse events were recognized only at Grade 2 or lower, and generally adverse events due to the increase in focal drug concentrations were not observed. No case developed interstitial pneumonitis.

In the present method, 5-FU was arterially infused continuously for five of 14 days. During this period, activities such as heavy labor and hard exercise were strictly restricted, but regular daily life activities such as taking a shower, light labor (desk work and housework), and driving a car were fully feasible. There was no drop-out case due to impaired QOL by continuous arterial infusion.

Taken together, safety at the regular dose was confirmed in this study, but it is necessary to further increase the dose to determine DLT. However, the dose of gemcitabine was approved at 1000 mg/m² by the Japanese Ministry of Health, Labor and Welfare (formerly, the Ministry of Health and Welfare), and for practical reasons, it is impossible to further increase the dose. As the reference data for the Phase I study, treatment efficacy such as treatment response (33.3%), MST (22.7 months; average, 18.9 months), 1-year survival (83.3%) and 2-year survival (25.0%) was markedly excellent. The maximum dose (level 3) employed in this study was determined to be the RD for the Phase II study.

Cases with distant metastasis other than to the liver, carcinomatous peritonitis and occlusion by tumor infiltration in the hepatic and splenic arteries where a catheter is placed were not indicated for the treatment used in this study. Since a selection bias is present due to the limitation of the subjects indicated for the treatment of advanced pancreatic cancer, it is not appropriate to simply compare the results with those observed after gemcitabine monotherapy in patients with unresectable advanced pancreatic cancer (Stages IVa and IVb). However, results of a comparative trial on 5-FU-based CCRT and gemcitabine alone in cases with unresectable advanced pancreatic cancer without distant metastasis or carcinomatous peritonitis were reported in 2006 (13), and the efficacy was concluded to be comparable between the two regimens. When the treatment efficacy (MST, 10.4 and 11.3 months, respectively) was compared with that of the current study, treatment efficacy by the method employed in this study was considered excellent. Further, the treatment used in this study was more beneficial compared with the CCRT because the efficacy was confirmed in the subjects, including those with liver metastasis, the most frequent metastatic pattern for distant metastasis.

Single-agent gemcitabine remains the standard treatment for advanced pancreatic cancer because recent Phase III trials using gemcitabine in combination with other agents have failed to show a clinically significant prolongation of survival. Therefore, as the strategy for treating pancreatic cancer, gemcitabine combinations with cytotoxic drugs have been superseded by other treatments such as the combination of gemcitabine with drugs that target molecular abnormalities.
By this treatment, the local concentration of anticancer agents can be increased. Recently, the SPECT/CT system demonstrated excellent drug delivery to lesions by the same arterial infusion system as used in the present study (23). Additionally, it is possible that decrease of the interstitial pressure in the tumor by shutting down the major arterial blood flow into the pancreas (except for the GPA and the CPA branched off from the SPA) contributes to this advantage.

As shown in Fig. 2, embolization of arteries around the pancreas changed the blood flow in the TPA, which had flowed from the tumor in the pancreatic head to the upstream pancreatic tail, to the direction from the pancreatic tail and flowed from the tumor in the pancreatic head to the upstream advantage.

Additionally, it is possible that decrease of the interstitial pressure in cancer tissues and results implicate that embolization of arteries around the pancreatic tail, to the direction from the pancreatic tail and flow into the pancreas (except for the GPA and the CPA) contributes to this advantage.


Conflict of interest statement
None declared.

References