

# Pilot study of hepatic arterial infusion chemotherapy with gemcitabine and 5-fluorouracil for patients with postoperative liver metastases from pancreatic cancer

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**Abstract.** Hepatic metastasis is a common cause of treatment failure after curative resection of pancreatic cancer. We report a pilot study of hepatic arterial infusion (HAI) chemotherapy with gemcitabine and 5-fluorouracil (5-FU) for postoperative liver metastases from pancreatic cancer. Five patients who had undergone curative resection of liver metastases from pancreatic cancer received HAI of gemcitabine and 5-FU between October 2008 and September 2010 at Kanazawa University Hospital. Gemcitabine at a dose of 800 mg was infused over 30 min via a bedside pump. After gemcitabine administration, 250 mg of 5-FU was infused continuously over 24 h on days 1-5, comprising one cycle of therapy. These treatment cycles were continued biweekly. In the evaluation according to RECIST criteria, a partial response was obtained in 2 of the 5 cases, with stable disease being achieved in the remaining 3 cases (response rate, 100%). In 4 of the 5 cases, a decrease in serum tumor marker CA19-9 was observed after 10 HAI treatment cycles. The median time to treatment failure was 10 months (range 3-17). As to adverse events, leukocytopenia was grade 3 in 1 of 4 affected cases and all 5 were anemic, although 4 of the 5 cases had anemia prior to HAI therapy. Grade 2 thrombocytopenia was observed in 2 cases. No non-hematologic events, such as nausea, diarrhea, liver injury and neuropathy, occurred. There were no life-threatening toxicities, but 4 cases (80%) developed catheter complications, and the HAI catheter and subcutaneous implantable port system

had to be removed. HAI delivers high doses of chemotherapeutic agents directly into tumor vessels, producing increased regional levels with greater efficacy and a lower incidence/severity of systemic side effects. In conclusion, HAI chemotherapy is useful and safe for the treatment of malignancies confined to the liver.

## Introduction

Pancreatic cancer is one of the major causes of cancer-related death globally, with a 5-year survival rate of less than 5% (1,2). For patients with localized disease, radical surgery may provide long-term benefits. However, even in patients who undergo resection, the reported 5-year survival rate remains in the range of 7-24%, and median survival is only approximately 1 year in most series, indicating that surgery alone is generally inadequate. Even after curative resection, patients with pancreatic cancer face a 50-80% local recurrence rate and a 25-50% chance of developing distant metastases (3).

Gemcitabine, a deoxycytidine analogue that competes for incorporation into DNA thereby inhibiting its synthesis, is the key drug employed in the treatment of pancreatic cancer. Adjuvant chemotherapy with gemcitabine improves, although to a limited degree, the survival of patients with resectable pancreatic adenocarcinoma as compared to resection alone (4). However, a major drawback of adjuvant therapy for pancreatic cancer is that 20-30% of patients cannot receive the designated therapy as a result of postoperative complications, delayed surgical recovery and/or early disease recurrence (5,6).

Hepatic arterial infusion (HAI) of chemotherapeutic agents is a treatment option in patients with primary or metastatic hepatic malignancies that are confined to the liver. The use of HAI chemotherapy is soundly based on physiological and pharmacological factors. First, liver metastases that grow beyond 2-3 mm depend on the hepatic artery for vascularization, whereas normal liver tissues are perfused by the portal vein (7,8). Second, HAI therapy allows for drug delivery to

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Table I. Patient characteristics.

Case no.	1	2	3	4	5
Age	61	62	69	71	60
Gender	F	M	M	M	F
Performance status	0	0	0	0	0
Tumor location	H	H	BT	BT	BT
Stage at surgery	IV A	III	II	III	IV A
Resection	0	0	0	0	0
Preoperative chemotherapy	+	+	-	-	-
Postoperative chemotherapy	-	+	-	+	+
Interval between surgery and liver metastasis (months)	5	10	3	10	5
No. of liver metastases	2	4	4	7	12
Body surface area (m <sup>2</sup> )	1.60	1.7	1.84	1.51	1.27
Standard liver volume (liters)	1.13	1.2	1.30	1.07	0.90

hepatic metastases not achievable by systemic administration, particularly for drugs with a high systemic clearance rate (9). Third, first-pass hepatic extraction of certain drugs results in lower systemic concentrations and hence, few systemic toxicities (10). Phase I studies of HAI chemotherapy with gemcitabine in patients with liver malignancies have recently been reported (8-10).

We recently described a patient with pancreatic head cancer with postoperative liver metastases, judged to be an unsuitable candidate for systemic chemotherapy due to leukocytopenia, who was safely treated with gemcitabine plus 5-fluorouracil (5-FU) HAI (11). It was suggested that HAI chemotherapy is useful and safe for the treatment of postoperative metastatic tumors confined to the liver, even in patients in poor general condition. To improve the therapeutic results of resected pancreatic cancer, it is vital to optimize the postoperative management of liver metastases, which frequently constitute the major factor determining prognosis. We designed a pilot study for patients with postoperative liver metastases from pancreatic cancer in which an arterial infusion of gemcitabine and 5-FU was delivered directly to the liver, and report our experience herein.

## Patients and methods

**Patient eligibility.** Five patients with postoperative liver metastases from pancreatic cancer underwent HAI with gemcitabine and 5-FU between October 2008 and September 2010 at Kanazawa University Hospital. The baseline characteristics of the patients are listed in Table I. The patients selected for this study had metastases confined to the liver after curative (R0) resection of the pancreatic primary adenocarcinoma. The male-to-female ratio was 3:2. The median patient age was 64.6 years (range 60-71). The Eastern Cooperative Oncology Group performance status was 0 in all patients in this study. Two patients had received preoperative chemotherapy with gemcitabine and oral S-1, and adjuvant chemotherapy with gemcitabine had been administered to 3 of the 5 patients before

the appearance of liver metastases. The interval between surgery and the appearance of liver metastases was 6.6 months (range 3-10). The median standard liver volume [SLV (ml) = 706.2 x body surface area (BSA) + 2.4] of our patients was 1.12 liters (range 0.9-1.30) (12).

Written informed consent was obtained from each patient prior to enrollment in the study, and the treatment was undertaken with the approval of the local medical ethics committee.

**Catheter placement and treatment regimen.** An intrahepatic arterial catheter was percutaneously implanted after hepatic arteriography via a right femoral puncture. The catheter tip was placed at the proper hepatic artery by a radiologist. The catheter was then connected to a subcutaneous implantable port system, located in the right lower abdominal area. Then, an 800 mg dose of gemcitabine was dissolved in 50 ml of saline for administration over a 30-min period using a bedside pump. After gemcitabine infusion, a 250-mg dose of 5-FU dissolved in 50 ml of saline was infused continuously over 24 h on days 1-5, comprising one cycle of therapy. In Case 1, only 400 mg of gemcitabine was administered because of the presence of leukocytopenia (11). Each treatment cycle was continued biweekly from hospital days 1-6.

**Assessment of response.** Physical examination, complete blood counts, biochemical tests, chest and abdominal X-rays were obtained before the start of each cycle. Serum CA19-9 was measured monthly and changes in this tumor marker were determined as the serum CA19-9 level before and after 10 HAI cycles. Follow-up contrast-enhanced CT scans were conducted upon completion of each 5 cycles, or earlier in cases showing clinical deterioration. The response rate was evaluated in accordance with Response Evaluation Criteria in Solid Tumors (RECIST) criteria (13). A complete response (CR) was defined as the disappearance of all evidence of disease and normalization of tumor markers persisting for at least 2 weeks. A partial response (PR) was defined as a >30% reduction on uni-dimensional tumor measurements, without

Table II. Treatments and responses.

Case no.	1	2	3	4	5
GEM administration (cycles)	13	40	23	10	8
5-FU administration (cycles)	10	10	10	10	6
Response	SD	PR	PR	PR	SD
TTF (months)	15	17	7	8	3
Another metastatic lesion	L, N	N	Lg	L, Lg	N
Another chemotherapy	Tx	S-1	S-1	S-1	S-1
Another therapy	RT	-	-	-	-
Prognosis	D	A	A	A	A
Survival after HAI (months)	23	24	13	13	9
Catheter problems	+	+	-	+	+
CA19-9 before HAI (U/ml)	138	14	311	2,073	43,460
CA19-9 after 10 HAI cycles (U/ml)	33	65	221	811	32,200

GEM, gemcitabine; TTF, time to treatment failure; L, local recurrence; N, lymph node metastasis; Lg, lung metastasis; Tx, taxane; RT, radiation therapy; D, dead; A, alive.

the appearance of any new lesions or progression in any existing lesion. Progressive disease (PD) was defined as any of the following: i) a 20% increase in the sum of the products of all measurable lesions, ii) the appearance of any new lesion, or iii) the reappearance of any lesion that had previously disappeared. Stable disease (SD) was defined as a tumor response that did not fulfill the criteria for CR, PR or PD.

After 10 cycles, HAI of 5-FU was terminated and administration of oral S-1 was initiated. S-1 is an oral fluorinated pyrimidine developed by Taiho Pharmaceutical Co., Ltd. (Tokyo, Japan). Patients received gemcitabine HAI and administration of oral S-1 in the outpatient clinic for as long as possible, i.e., so long as they showed neither tumor re-growth nor the appearance of any new lesions, and were free of HAI catheter-related problems.

## Results

The median follow-up duration was 15.6 months (range 8-23). In 4 cases, more than 10 cycles of HAI chemotherapy were administered. In a single case (Case 5), after the 8th cycle, the HAI catheter and subcutaneous implantable port system had to be removed because of a complication with the tube.

In the evaluation according to RECIST criteria, PR was obtained in 2 of the 5 cases, and SD was achieved in the other 3 cases (100% response rate). Neither CR nor PD was observed. In 4 of the 5 cases, decreases in the serum tumor marker CA19-9 were observed after 10 cycles of HAI treatment.

The median time to treatment failure was 10 months (range 3-17). The initial disease progression factor was nodal metastasis in 3 cases and local recurrence plus lung metastasis in 2 cases (Table II). The overall median survival time was 22.4 months (range 9-24). In Case 1, the cause of death was progression of local recurrence, nodal metastases and re-growth of liver metastases after termination of HAI due to arterial thrombosis.

Adverse events are listed in Table III. Grade 3 leukocytopenia was observed in Case 1, who could not receive

Table III. Treatment toxicities (NCI-CTC grade).

Case no.	1	2	3	4	5
Anemia	2	2	1	1	2
Leukocytopenia	3 <sup>a</sup>	0	0	0	0
Thrombocytopenia	2	1	0	2	0
Nausea	0	0	0	0	0
Diarrhea	0	0	0	0	0
Liver injury	0	0	0	0	0
Neuropathy	0	0	0	0	0

<sup>a</sup>Grade 2 before HAI was started.

adjuvant systemic chemotherapy because of grade 2 leukocytopenia prior to HAI. Leukocytopenia was not observed in any other cases. All cases were anemic, but 4 of the 5 had been anemic prior to HAI therapy. Grade 2 thrombocytopenia was observed in 2 cases. There were no non-hematologic events, such as nausea, diarrhea, liver injury (AST/ALT increase) and neuropathy. No life-threatening toxicities developed, but in 4 cases (80%) catheter complications (arterial thrombosis or catheter dislocation) occurred, and the HAI catheter and subcutaneous implantable port system had to be removed.

## Discussion

Pancreatic cancer is nearly always a fatal disease, with a 5-year survival rate of less than 5% (1,2). Surgery remains the only curative option. Therefore, we usually perform radical pancreatic resection, including wide lymph node dissection and complete removal of the extra-pancreatic nerve plexus of the superior mesenteric artery or celiac axis, in patients with carcinoma of the pancreas in hopes of improving the prognosis (14,15). Adjuvant chemotherapy improves, although

to a limited degree, the survival of patients with resectable pancreatic adenocarcinoma as compared to resection alone (4). However, a major drawback of adjuvant therapy for pancreatic cancer is that 20-30% of patients cannot receive the designated therapy due to postoperative complications, delayed surgical recovery and/or early disease recurrence (5,6). Theoretically, these drawbacks may be overcome by employing the neoadjuvant approach, so that more patients can receive potentially beneficial adjuvant treatment. Clinical studies of neoadjuvant chemo-(radio)-therapy in pancreatic cancer have recently been reported (16-22).

HAI chemotherapy, using fluorodeoxyuridine or 5-FU, has been studied most extensively in patients with liver metastases from colorectal cancer. Despite the significantly higher response rates to HAI than to intravenous infusion, most of these studies did not document a significant prolongation of survival, even in meta-analyses (23,24). Arterial infusion chemotherapy with gemcitabine and 5-FU was recently reported for locally advanced pancreatic cancer and liver metastases from pancreatic cancer (10,25,26). Moreover, in some phase I studies, HAI chemotherapy with gemcitabine was well tolerated up to 1,000 mg/m<sup>2</sup> infused over 400 min (8,9).

According to the pharmacokinetics of gemcitabine, when 1,000 mg/m<sup>2</sup> of gemcitabine is administered via intravenous infusion over 30 min, the average maximum plasma concentrations reach 21,865±4,165 ng/ml by 15 min. The flow volume of the proper hepatic artery is reportedly approximately 330 ml/min (27). When an 800-mg dose of gemcitabine is infused into the proper hepatic artery over a 30-min period, the local plasma concentration in the liver reaches approximately 80,000 ng/ml by 30 min. Vogl *et al* reported that the maximum tolerated dose of HAI chemotherapy with gemcitabine was 1,400 mg/m<sup>2</sup> (8). On the other hand, the plasma concentration of 5-FU with a 250 mg infusion into the proper hepatic artery over a 24-h period was 0.5 µg/ml. This concentration is equal to that obtained following administration of 30 mg/kg (1,350 mg in the reported patient) of 5-FU over a 24-h period (28). Maruyama *et al* reported that when 1,000-1,500 mg of 5-FU was infused into the hepatic artery over a period of 5 h, the maximum plasma concentration was 0.48 µg/ml, on average, and no grade 3 adverse effects developed (29).

Super-selective HAI delivers high doses of chemotherapeutic agents into tumor vessels, producing increased regional levels with more effectiveness and a lower incidence/severity of systemic side effects. In this study, the response rate was 100%, despite 4 of the 5 cases having received systemic chemotherapy with gemcitabine before HAI. Moreover, no severe toxicity developed with this therapy. Thus, HAI chemotherapy is safe and effective for postoperative liver metastasis from pancreatic carcinoma. The drawbacks of HAI chemotherapy include problems with the tube and the appearance of new lesions outside of the liver. In this study, 4 of 5 cases required removal of the HAI catheter and the subcutaneous implantable port system because of problems with the tube, and new lesions outside of the liver appeared in all 5 patients.

In a previous study, the amounts of chemotherapeutic agents to be delivered were determined based on BSA. However, SLV is more suitable than BSA for determining the

drug amount to be administered in HAI chemotherapy. We advocate that in HAI the amounts of chemotherapeutic agents are determined based on SLV. A phase I study of HAI chemotherapy with gemcitabine and 5-FU is underway in patients with pancreatic cancer with postoperative metastases confined to be liver. In conclusion, HAI chemotherapy is useful and safe for the treatment of postoperative metastases from pancreatic cancer confined to the liver.

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