ANTICANCER RESEARCH *25*: 477-482 (2005)

Continuous Hepatic Arterial Infusion Chemotherapy for Liver Metastasis from Biliary Tract and Pancreatic Cancers

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Abstract. *Background: The efficacy of intrahepatic arterial chemotherapy for liver metastasis from biliary tract or pancreatic cancer remains uncertain. Patients and Methods: Five patients with bilio-pancreatic liver metastasis underwent continuous hepatic arterial infusion chemotherapy. One treatment course basically consisted of a 14-day infusion period during which continuous infusions of 5-fluorouracil and intermittent bolus injections of cisplatin were given, and a subsequent 14-day intermission. After two consecutive courses, these drugs were administered bi-weekly. Results: One complete and three partial responses were observed (response rate, 80%). In responders, the responses persisted until or even after the cessation of chemotherapy. The median survival was 15 months after the start of chemotherapy. The longest survivor has been disease-free for 46 months since a liver tumour remaining despite chemotherapy was eradicated by further treatment. Toxicity was acceptable. Conclusion: 5-Fluorouracil and cisplatin-based continuous hepatic arterial infusion chemotherapy may serve as a promising treatment for bilio-pancreatic liver metastasis.*

The prognosis of biliary tract and pancreatic cancers (BPC) with liver metastasis is extremely poor (1-3), but effective treatments for them have not been established (4). Surgical resection has been attempted for a solitary metachronous metastasis (5, 6), but is rarely performed for synchronous or multiple tumours. Systemic chemotherapy does not appear to confer significant benefits in locally far advanced and metastatic BPC (4, 7, 8).

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Key Words: Hepatic arterial infusion chemotherapy, reservoir port, liver metastasis, biliary tract and pancreatic cancer, 5-fluorouracil, cisplatin.

Intrahepatic arterial chemotherapy has been accepted as a feasible treatment option for several liver tumours. This mode of chemotherapy may have such advantages as the potential to control occult intrahepatic metastases and low-grade systemic toxicity (9). Although this treatment has been attempted for unresectable BPC (8, 10-14), its efficacy and optimal regimens are not defined because each study was small and varied in the applied regimens. On the other hand, continuous hepatic arterial infusion chemotherapy (HAI) is an established modality for the treatment of colorectal liver metastasis, improving the rates of recurrence and survival (15, 16). Benefits of HAI have increasingly been reported in inoperable and recurrent hepatocellular carcinoma (17, 18). 5-Fluorouracil (5-FU), fluorodeoxyuridine (FUdR), cisplatin and mitomycin-C (MMC) are suggested to be effective agents in HAI for colorectal metastasis and hepatocellular carcinoma (15, 19, 20).

In view of the above findings, we used 5-FU and cisplatin-based HAI to treat five patients with multiple simultaneous or metachronous liver metastases from BPC. The applied HAI regimen, its results, and the patients' outcomes are reported in detail, and the roles of HAI in the treatment of bilio-pancreatic liver metastasis are discussed.

Patients and Methods

Patients' clinical courses before HAI and tumour characteristics. The profiles of five patients and features of their primary and metastatic tumours are summarised in Table I. In patient 1, radical surgery for the primary ampullary cancer was rejected because concomitant multiple liver metastases were detected intraoperatively. In patient 2, the primary pancreatic cancer was treated by extracorporeal radiation (50 Gy), and the synchronous liver metastasis by HAI. Patients 3 and 4 experienced metachronous liver metastasis following curative resections of primary cancers. Patient 5, with a massive gall bladder cancer, had undergone non-curative liver resection for alleviation of symptoms, despite the presence of a tiny peritoneal metastasis. Primary tumours were typical adenocarcinomas in patients 1, 3, 4 and 5, and a pancreatic anaplastic adenocarcinoma in patient 2. None of the

Table I. *Characteristics of patients and their primary cancers and liver metastases.*

Case	Age/Sex	Primary site	Treatment for primary cancer	Timing (interval)	Tumour number	Tumour size
1	57 / M	ampulla of Vater	resection (LRx)	S	4	15mm
2	54 / F	pancreas	radiation	S	>10	30mm
3	51 / M	ampulla of Vater	resection (PDx)	M (12 mo)	5	30mm
4	60 / M	CBD	resection (PDx)	M (13 mo)	4	15mm
5	72 / M	gall bladder	resection (Hx)	M (2 mo)	3	12mm

Age, age at the diagnosis of metastatic liver tumours; CBD, the common bile duct; LRx, local resection of the tumour; PDx, pancreatodudenectomy; Hx, hepatectomy; S, synchronous liver metastasis; M, metachronous liver metastasis following treatment of primary cancers; interval, the time interval between the primary resection and hepatic recurrence; Tumour number, number of metastatic liver tumours confirmed intraoperatively and/or radiologically; Tumour size, the maximum size of liver tumours.

patients had received chemotherapy prior to HAI, or had haematological or hepatic dysfunction before the start of treatment. All the patients were in a World Health Organization (WHO) performance status of 0 or 1 (21).

HAI regimen. HAI was started within a month after the diagnosis of liver metastasis in all cases. The chemotherapy agents were administered *via* an implantable reservoir port connected with a catheter, the tip of which was radiologically placed inside the proper hepatic artery. One course of the inpatient chemotherapy regimen consisted of a 2-week infusion period and a subsequent 2-week intermission period. The infusion schedule consisted of 24-hour continuous infusions of 5-FU (500 mg/day) on days 1 to 5 and 8 to 12 and bolus injections of cisplatin (10 mg/day) on days 1, 3, 5, 8, 10 and 12 for biochemical modulation of 5-FU (22). No drugs were administered on days 6, 7, 13 and 14. In patient 5, bolus injections of MMC (10 mg/day) were given on days 5 and 10 instead of cisplatin. After two consecutive courses, the patients were given bi-weekly 5-hour infusions of 5-FU (1000 mg/day) and bolus injections of cisplatin (20 mg/day) in outpatient until a decision to stop HAI was made.

Evaluation of tumour response. The tumour response to HAI was evaluated in terms of the size and number of hepatic lesions estimated by serial computed tomography (CT) or magnetic resonance imaging (MRI) studies. Extrahepatic lesions were not subjected to the response evaluation, since HAI is almost exclusively effective for liver tumours. The first and second time points for evaluation were set at the final week of the first and second courses of HAI, respectively. Thereafter, the patients underwent several radiological checkups on a regular basis. The tumour response classification [complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD)] was derived from the standard WHO criteria (21).

Patient outcome and evaluation of recurrence. The survival period was determined from the day of the start of HAI and from that of the treatment for primaries until the last observation day. Organs in which a recurrence had occurred were confirmed by radiological imaging near the time of death or by autopsy.

Results

Tumour response to HAI and further treatment. Table II shows the results of HAI therapy. The durations of HAI varied among patients depending on their medical conditions and social circumstances. We obtained one CR (patient 4), three PRs (patients 1 to 3) and one PD (patient 5), and the overall response rate (CR+PR) was 80% (4/5 patients). All the responders attained their responses as early as 2 months after the start of HAI. Furthermore, in all of them, the responding liver tumours showed no regrowth and, thus, the responses were well maintained during the course of HAI.

In patient 1, HAI was discontinued after 9 months when he underwent a pancreatoduodenectomy for a locally recurrent tumour causing obstructive jaundice and a concomitant partial hepatectomy for the partially responding liver tumours. In patient 2, the PR lasted for 2 months of a 4-month infusion, after which HAI was switched to systemic chemotherapy according to the patient's wish. In patient 3, the PR lasted for 6 months of an 8-month HAI, but one of five original hepatic lesions was radiologically diagnosed as containing residual viable cells (Figure 1, B-b). HAI was discontinued at that point, and

Table II. *Results of HAI and patients' outcome.*

Case	Duration of HAI	Total dose (mg) (5-FU/CDDP)	Side-effects	Hepatic response (duration)	Further treatment	Survival (mo)	Recurrent site at the death
1	9 mo	20500 / 350	–	PR (7 mo)	Resection (PDx + Hx)	Dead (16* / 19**)	liver, LN pancreas
2	4 mo	7500 / 90	GI BM	PR (2 mo)	CTx (gemcitabine + CDDP)	Dead (6* / 6**)	liver, lung LN pancreas#
3	8 mo	16375 / 560	BM	PR (6 mo)	RFA	Alive, NER (56* / 69**)	–
4	11 mo	15000 / 320	GI	CR (9 mo)	CTx (5-FU+CDDP)	Dead (15* / 29**)	lung peritoneum
5	4 mo	10000 / 200	–	PD (4 mo)	–	Dead (6* / 9**)	liver, lung LN peritoneum

Further treatment; treatment following HAI; survival*, interval after the start of HAI; survival**, interval after treatment of primary cancers; GI, gastrointestinal side-effects; BM, bone marrow suppression; CTx, systemic chemotherapy; NER, no evidence of recurrence; LN, lymph node; pancreas#, regrowth of the primary pancreatic cancer. The listed organs involved by recurrence at death were confirmed radiologically near the time of death in patients 1, 4 and 5, and by autopsy in patient 2.

radiofrequency ablation (RFA) was performed to treat the single liver lesion. In patient 4, despite the CR lasting for 9 months, the aggressive progression of extrahepatic metastases led us to discontinue HAI and to provide systemic chemotherapy. In patient 5, HAI was discontinued after 4 months because the patient's general condition deteriorated due to aggressive recurrence.

Agent toxicity. The adverse effects of the chemotherapeutic agents included gastrointestinal symptoms, like nausea or appetite loss during periods of infusion, and a mild degree of bone marrow suppression characterized by thrombocytopenia (Table II). No significant liver dysfunction was recorded. All adverse effects were considered acceptable, and no special treatments, including the cessation of infusion, were necessary.

Patients' outcome and recurrence patterns. The outcome and the recurrence pattern in each patient are shown in Table II. Survival after the start of HAI and the primary treatment ranged from 6 to 56 and 6 to 69 months, respectively. The median survival was 15 and 19 months, respectively. In patients 1, 2, 4 and 5, intra- and/or extra- hepatic recurrence ultimately caused their deaths. In patient 2, liver metastases did not show any notable progress even after the cessation of HAI until the patient's death. An autopsy revealed that the majority of more than 10 liver nodules were histologically exhibited chemotherapy-induced necrosis or fibrosis. In patient 3, RFA following HAI resulted in complete disappearance of the liver tumours, and the patient has currently been disease-free for 46 months since the RFA (Figure 1, A-c and B-c). In patient 4, CR in the liver persisted after the cessation of HAI until the patient's death.

Discussion

This report was compiled from uncommon cases in which multiple BPC liver metastases were treated by 5-FU and cisplatin-based HAI. Although based on a small number of patients, the current study has addressed the efficacy and safety of this modality. Our result, showing a response rate of 80%, may suggest that liver metastasis from BPC is responsive to HAI under the present regimen. Furthermore, the responses persisted during the entire course of HAI in all the responders. In two patients, the responses were well maintained even after the cessation of HAI until their deaths, suggesting long-lasting effects of HAI, though the systemic chemotherapy following HAI might have exerted some additive effects. Metachronous liver metastasis without extrahepatic involvement appeared to be a good indication for HAI, while synchronous diseases also responded to it in our series. In patients 3 and 4, whose postoperative recurrence was confined to the liver, HAI or HAI followed by RFA attained long-lasting complete disappearance of

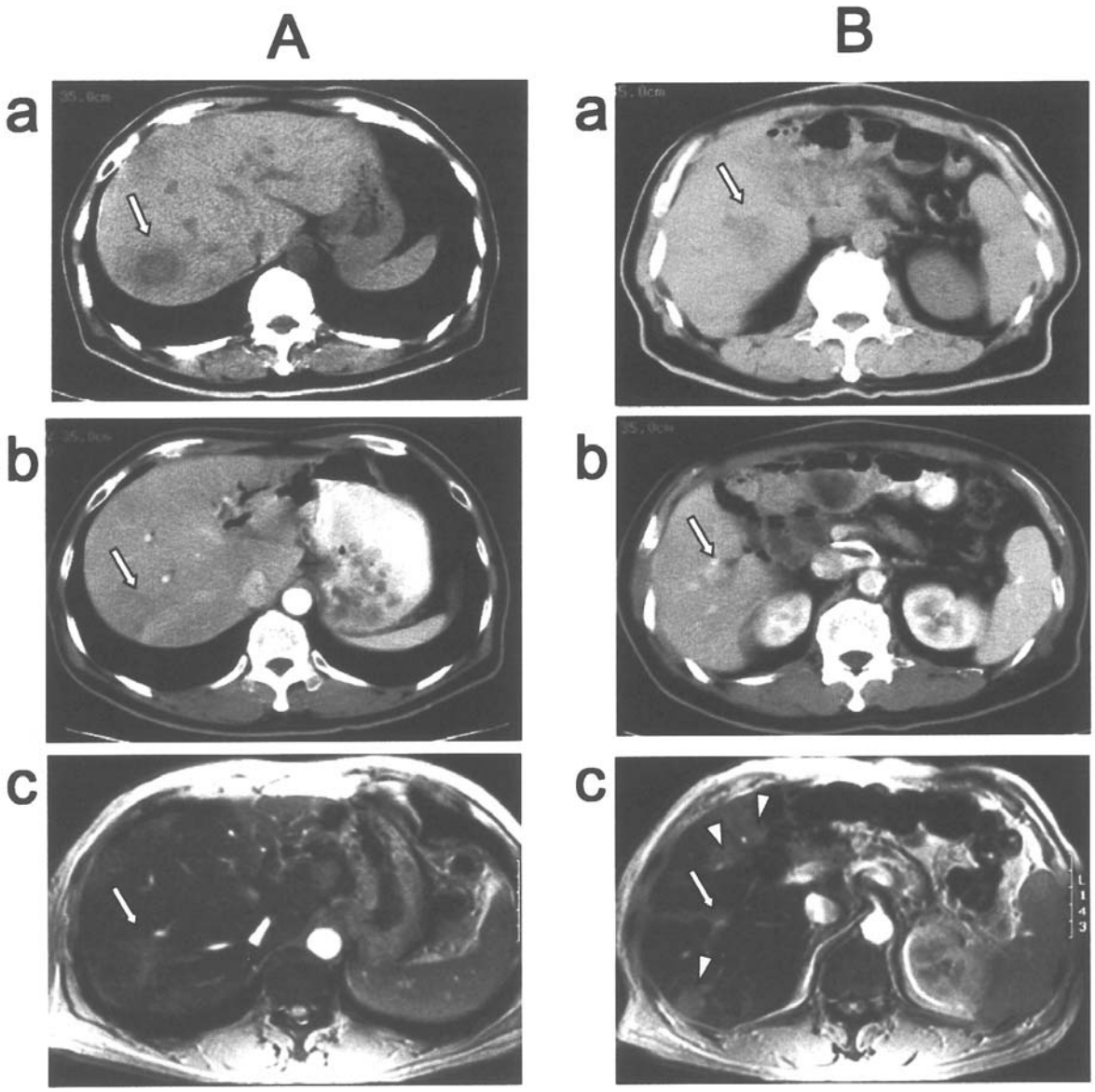

Figure 1. *Serial changes in radiological findings of the two major liver metastases (arrows) in patient 3. A and B demonstrate metastatic tumours located at the segments VII and V/VI of the liver, respectively. A-a and B-a: CT findings before the start of HAI, indicating the tumours as low density areas. A-b and B-b: CT findings at 8 months after the start of HAI. A-b shows a vague low density area without contrast enhancement at a tumour site, suggesting no or minimal viability of the mass. B-b demonstrates an enhanced area within the shrinking tumour, suggesting its remaining viability. A-c and B-c: MRI findings at 18 months after the start of HAI, showing asterisk-shaped scars without viable tumours. Note the chemotherapy-induced fatty deposits in some areas of the liver (B-c, arrowheads).*

liver tumours. These are, to our knowledge, the first documented cases in which HAI-based therapy achieved a CR of multiple liver metastases from BPC.

Several small studies and case reports on HAI for unresectable BPC have addressed its efficacy for BPC liver metastasis (8, 10, 12-14, 23-25). The overall response rates in unresectable biliary tract cancers treated by HAI have been reported to be 20 to 78% (8, 11-13, 25). However, the rates did not directly reflect the efficacy of HAI for liver metastasis because these studies consisted of intermingled cases of locally advanced and metastatic tumours. Furthermore, these studies did not include cases of metachronous liver metastasis. Only anecdotal case reports have documented HAI-induced PRs of metachronous

multiple liver metastases from biliary tract cancers (23-25). On the other hand, reports on the efficacy of HAI for pancreatic liver metastasis are rare. In two previous reports, HAI using FUdR (10) and 5-FU (14) achieved a response rate of 50 % (2/4) and 8% (1/13), respectively.

This study is obviously insufficient to establish survival benefits of HAI in BPC patients with liver metastasis because of the small patient sample and the lack of a control group. Furthermore, the survival data were modulated by the influences of additional treatments following HAI. However, it is noteworthy that the median survival was 15 months after the start of HAI, and that one patient has been disease-free for nearly 4 years since the eradication of five tumours of maximum 30 mm. These results may be encouraging in view of the previous results that the median survival in inoperable BPC patients who underwent HAI rarely exceeded 15 months (8, 10-12).

The progression or new development of extrahepatic metastasis during HAI is an oncologically unavoidable problem because HAI targets, almost exclusively, intrahepatic lesions. In our series, extrahepatic involvement may actually be a major factor influencing the patients' prognosis. The four patients who ultimately died of recurrence had sustained extrahepatic disease prior to HAI or developed it during the course of HAI. Particularly in patients 2 and 4, the progression of the extrahepatic disease appeared to determine their short survival period, because their liver tumours were highly responsive to HAI. To treat BPC patients with both intra- and extra- hepatic metastases, a combined systemic and intrahepatic arterial chemotherapy could be a tempting option, but little evidence to support its benefits is available at the moment (26). Large studies are necessary to clarify whether HAI or HAI combined with other modalities has any survival benefit in BPC patients with liver metastasis.

In previous studies, agents such as 5-FU, FUdR, MMC and cisplatin have been used alone or in various combinations for systemic chemotherapy or HAI for the treatment of BPC, with response rates of 20-78% (8). In our results, HAI using 5-FU biochemically modulated by cisplatin attained a promising response rate, and the toxicity level was acceptable despite long-term treatment. Similar favourable results for HAI using 5-FU plus cisplatin have been reported in a study on patients with unresectable gall bladder cancers, where a response rate of 62.5% was obtained (25).

In summary, we applied 5-FU and cisplatin-based HAI for the treatment of multiple liver metastases in five BPC patients. Based on our response rates, their lasting durations and survival data, HAI under the present regimen may serve as a promising modality for the control of multiple liver metastases from BPC, imparting a survival benefit. Further studies are warranted to explore the survival benefit of HAI and to identify the optimal chemotherapy regimens.

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Received August 23, 2004
Accepted October 29, 2004