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Case report

Extensive liver metastasis of gastric cancer effectively treated by hepatic arterial infusion of 5-fluorouracil/cisplatin

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Abstract

Most gastric cancer patients with jaundice caused by extensive liver metastasis show no tumor shrinkage response to systemic chemotherapy, while often showing severe adverse reactions. Their prognosis is very poor. We experienced two patients for whom hepatic arterial infusion (HAI) of 5-fluorouracil (5-FU) and cisplatin through an implantable port was effective for treating extensive liver metastasis. One patient had jaundice (serum bilirubin level before HAI therapy, 12.4 mg/dl) caused by metachronous liver metastasis, and prior systemic chemotherapy with 5-FU and irinotecan had not been effective. The other patient had gastric cancer with synchronous liver metastasis and also exhibited jaundice (serum bilirubin level before HAI therapy, 11.8 mg/dl). Both patients were treated with HAI of cisplatin, 20 mg/m² for 30 min on day 1, and continuous intraarterial infusion of 5-FU, 300 mg/m², from day 1 to day 4 every week. Their metastatic liver tumors were significantly reduced in volume and the jaundice disappeared. They survived for 30 and 27 weeks, respectively. A pharmacokinetic study conducted during the period of partial remission revealed that the extraction ratios of 5-FU and cisplatin in the liver were 0.89 and 0.024, respectively, suggesting a favorable first-pass effect of 5-FU. Although our findings here suggest that the successful local control of liver metastasis could improve the deteriorated condition and prolong the survival in some patients with far advanced cancer, it is essential to pay much attention to possible adverse effects during the treatment.

Key words Gastric cancer · 5-Fluorouracil · Cisplatin · Hepatic arterial infusion · Pharmacokinetics

Introduction

Advanced gastric cancer tends to extend widely into the peritoneal cavity, with the accumulation of carcinomatous ascites, observed as peritoneal dissemination, or to form metastatic foci in the liver, bone, and other organs. It is generally accepted that these patients should receive systemic chemotherapy. Some active new anticancer drugs and effective combination regimens have been reported recently [1–4]. Because liver involvement is one of the critical factors determining prognosis, hepatic arterial infusion (HAI) therapy has occasionally been used against hepatic metastasis in Japan [5–9]. However, extensive liver metastasis with jaundice has been considered to be a contraindication for chemotherapy, and such affected patients have received palliative care only.

We performed HAI therapy of 5-fluorouracil (5-FU) and cisplatin in two gastric cancer patients with extensive liver metastasis, and observed a significant reduction in the metastatic tumor volume. Their survival time reached 7 months, which corresponded to the median survival time achieved with systemic chemotherapy for patients with gastric cancer with moderate metastatic lesions [1–4].

Case reports

Case 1

A 56-year-old man was diagnosed with advanced gastric cancer in February 1997, and underwent subtotal gastrectomy and postoperative chemotherapy with 5-FU in another hospital. Histological diagnosis was moderately-to-poorly differentiated adenocarcinoma. Recurrence, of multiple hepatic metastases, was observed in December 1997. Because the administration of irinotecan was not effective, he visited our hospital with a strong desire for aggressive treatment, and was hospitalized in March 1998. Physical examination revealed jaundice and hepatic tumors. His Eastern Cooperative Oncology Group (ECOG) performance status (PS) was

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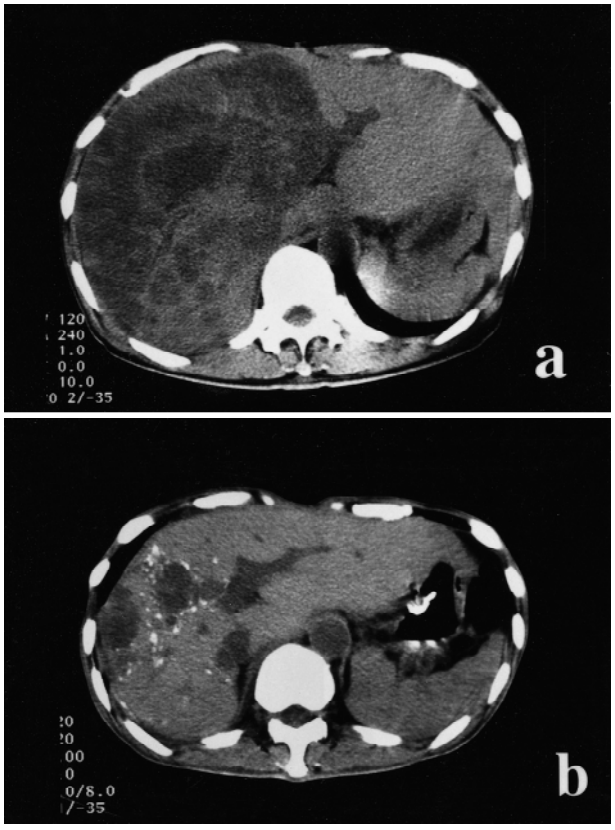

Fig. 1. CT images of case 1 before (**a**) and after (**b**) hepatic arterial infusion. Almost all the right lobe was occupied by metastatic tumors (**a**). The reduction of tumor lesions was more than 90% 4 months after initiation of the therapy. High-density spots suggesting calcification were seen around the residual tumors (**b**)

3. His laboratory findings, including GOT, 317 IU/l; GPT, 125 IU/l; and total bilirubin (T. Bil), 3.2 mg/dl, suggested severe hepatic injury. Abdominal computed tomography (CT) revealed an extremely enlarged right hepatic lobe with diffusely expanding tumors, and also several nodules in the left lobe (Fig. 1a). Bone scintigraphy showed no evidence of bone metastasis.

The gastroduodenal artery was embolized with a metal coil, and a catheter was inserted from the right femoral artery, with its tip located in the proper hepatic artery. An arterial implantable port, inserted subcutaneously in the abdomen, was used for the intraarterial administration of cisplatin, at a dose of 20 mg/m^2 for 30 min on day 1, and continuous intraarterial infusion of 5-FU, at a dose of 300 mg/m^2 per day, from day 1 to day 4 every week. Although his serum T. Bil level had already been elevated, to 12.4 mg/ml, before the HAI therapy, the jaundice rapidly resolved, and disappeared after the HAI therapy (Fig. 2). Tumor marker levels also decreased dramatically. The patient's PS returned to a level of 1. Partial response was observed after 1 month, and maximum effect (more than 90% reduction) was achieved 4 months after the initiation of HAI therapy (Fig. 1b). The only notable adverse effects of the HAI therapy were mild stomatitis and nausea.

Two months after initiation of the HAI therapy he developed left shoulder pain and back pain. Bone scintigraphy revealed hot spots in the ribs, the lumbar vertebrae, the femur, and other locations, suggesting the development of bone metastasis. He subsequently developed disseminated intravascular coagulation (DIC) syndrome, and the main therapy was changed from HAI to systemic therapy with methotrexate/5-FU and 5-FU/cisplatin. He recovered once from DIC, but died of carcinomatous myelosis in the 30th week of the therapy.

Case 2

In July 1998, a 70-year-old man was referred to our hospital because of edema of the lower extremities. Physical examination revealed jaundice, anemia, and enlarged liver. His PS was 1. Laboratory examination suggested severe hepatic injury (GOT, 128 IU/l; GPT, 98 IU/l; and T. Bil, 3.1 mg/dl). Gastroendoscopy confirmed an advanced gastric cancer of type 3 extending from the angle to the antrum of the stomach. This tumor was histologically diagnosed as well differentiated adenocarcinoma. Abdominal CT revealed numerous tumors in both lobes of the liver and slight retention of ascites (Fig. 3a).

Because this patient had both the primary tumor and liver metastasis, probably with peritoneal dissemination, we started treatment with the systemic administration of cisplatin, at a dose of 20 mg/m^2 for 30 min on day 1, and 5-FU, at a dose of 300 mg/m^2 per day, as a continuous intravenous infusion from day 1 to day 4 every week. Despite this treatment, his serum bilirubin level rose to 11.8 mg/dl, suggesting further deterioration of liver function (Fig. 4). In this situation, urgent suppression of tumor expansion in the liver appeared to be necessary. Therefore, the method of administration was changed to HAI, using the same regimen as in case 1, in order to deliver high-dose intensities of the drugs to the liver. His serum T. Bil level decreased to 4.7 mg/ml after 4 weeks of the HAI therapy. The patient then received systemic and hepatic intraarterial therapy on alternate weeks to suppress the extrahepatic tumor progression. Significant improvements were observed in the levels of serum bilirubin and tumor markers (Fig. 4). Partial response was achieved in the second month, and the maximum effect was achieved in the fifth month (Fig. 3b). No toxicity was found during HAI therapy.

Approximately 22 weeks after the initiation of the initial HAI therapy, jaundice and ascites developed again, and the patient died in the 27th week of treat-

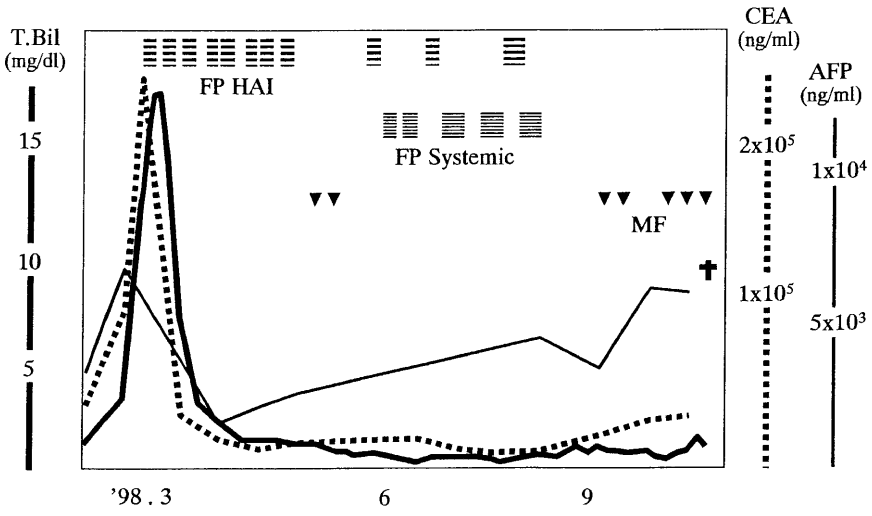

Fig. 2. Changes in serum parameters in case 1. *T. Bil*, total bilirubin; *FP*, 5-fluorouracil + cisplatin; *HAI*, hepatic arterial infusion; *MF*, methotrexate + 5-fluorouracil; *CEA*, carcinoembryonic antigen; *AFP*, alpha-fotoprotein

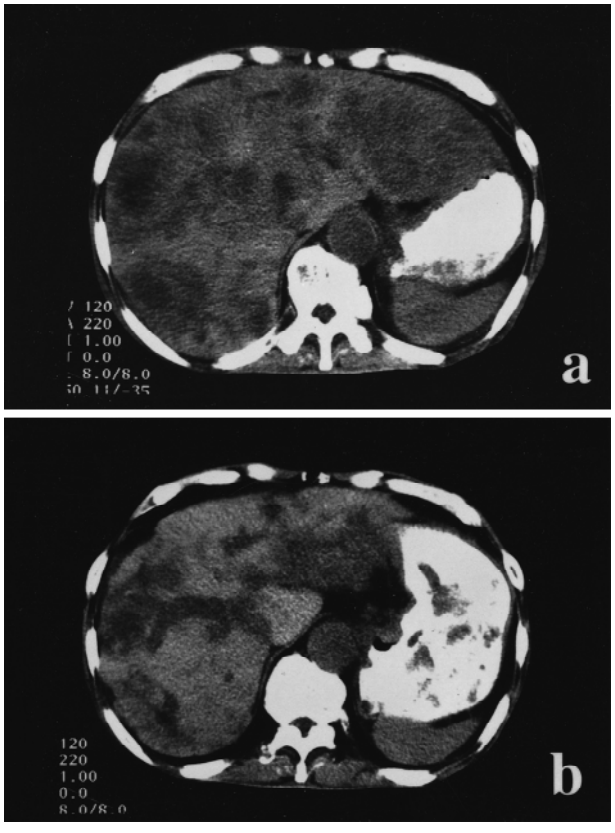

Fig. 3. CT images of case 2 before (**a**) and after (**b**) hepatic arterial infusion. Multiple low-density areas were observed throughout the liver before hepatic arterial infusion (**a**), and they markedly decreased 5 months after initiation of the therapy (**b**)

ment. Autopsy showed that the cause of death was cachexia, caused by systemic metastasis, and obstructive jaundice caused by peritoneal dissemination around the bile duct. There were numerous metastatic nodules with scar formation in the liver, and few of them remained viable.

Pharmacokinetic study

In case 2, a pharmacokinetic study of both cisplatin and 5-FU was performed during the period of partial remission, on December 17 (systemic administration), and on December 24 (hepatic intraarterial infusion), 1998 (Fig. 5). For cisplatin, serum total platinum was measured using atomic absorption spectrophotometry. Plasma 5-FU concentration was measured by high-performance liquid chromatography. Pharmacokinetic parameters were calculated using computer software (MultiStaff ver. 5.74). There was little difference in the maximum plasma concentration (Cmax) or the area under the plasma concentration-time curve (AUC_{0-24}) of platinum between intraarterial and intravenous infusions, and the extraction ratio in the liver was 0.024. The steady state concentration (Css) and AUC_{0-24} of 5-FU after intraarterial infusion were about one-tenth of the levels after intravenous infusion, and the extraction ratio of 5-FU in the liver was 0.89, suggesting a favorable first-pass effect (Table 1).

Discussion

In patients with advanced gastrointestinal cancer, metastatic lesions are often more important than the primary tumor in determining prognosis. HAI therapy for the local control of hepatic metastatic lesions has commonly been performed in patients with colorectal cancer [10,11]. However, few reports are available on HAI therapy for the hepatic metastasis of gastric cancer; one reason for this is that there are fewer patients with

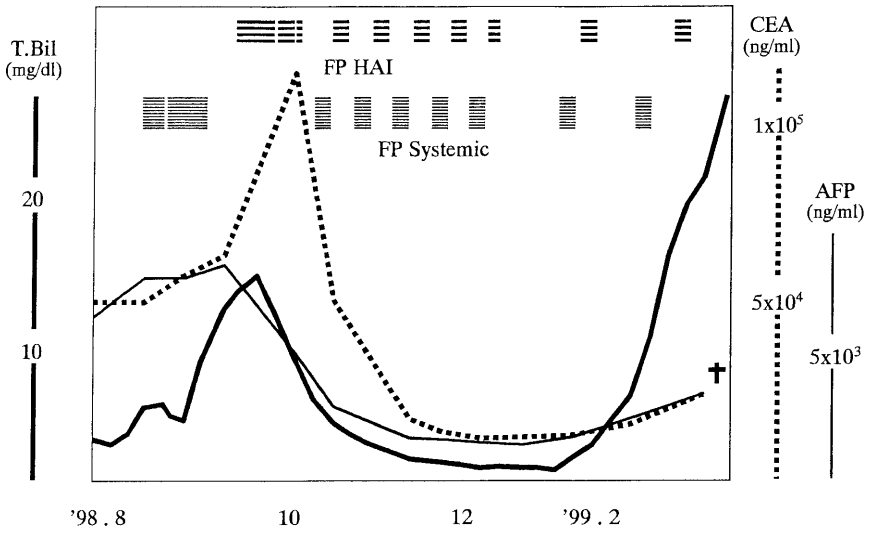

Fig. 4. Changes in serum parameters in case 2. *T. Bil*, total bilirubin; *FP*, 5-fluorouracil + cisplatin; *HAI*, hepatic arterial infusion

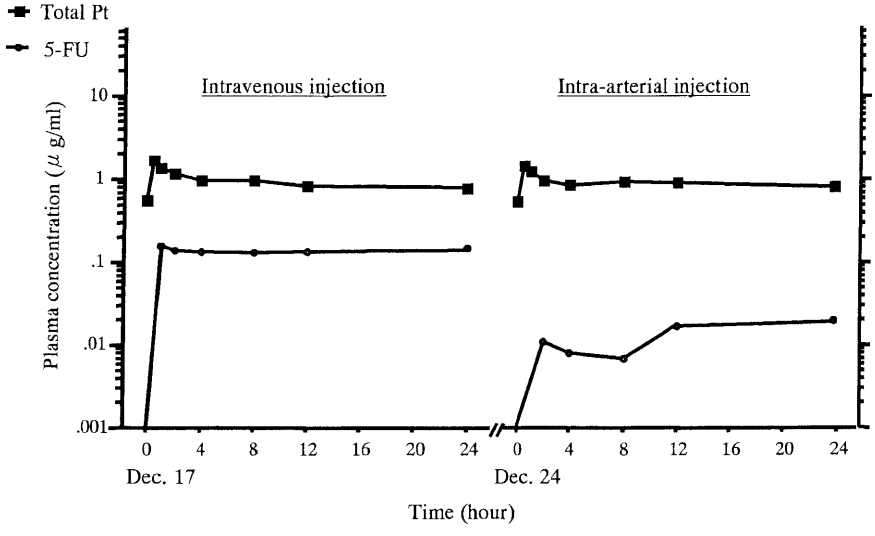

Fig. 5. Plasma concentrations of 5-FU and total platinum following intravenous infusion or hepatic arterial infusion of 5-FU and cisplatin. The same regimen (cisplatin 20 mg/m² per day, 30 min, day 1 and 5-FU 300 mg/m² per day, 24 h, day 1–4) was used for intravenous infusion and hepatic arterial infusion

Table 1. Pharmacokinetic profile of cisplatin and 5-fluorouracil in case 2

Administration schedule and route	*Cmax* (μg/ml)	$t_{1/2}$ α/β (hour)	*Css* mean ± SD (μg/ml)	AUC_{0-24} (μg·hr/ml)	Extraction Ratio
Cisplatin: 20 mg/m² per day, 30 min, day 1					
Intravenous	1.70	0.9/76.3	—	22.5	0.024
Intraarterial	1.46	0.6/106	—	22.0	
5-FU: 300 mg/m² per day, 24 h, day 1–4					
Intravenous	—	—	0.138 ± 0.004	3.27	0.89
Intraarterial	—	—	0.012 ± 0.005	0.37	

Extraction ratio = 1 − (AUC after intraarterial administration)/(AUC after intravenous administration)
Cmax, maximum plasma concentration; $t_{1/2}$, half-life of the apparent elimination phase; *Css*, plasma concentration at steady-state; AUC, area under the concentration–time curve

gastric cancer in Western countries than in Japan. To our knowledge, only a few retrospective studies and case reports on HAI therapy have been published in Japan [5–9], and no prospective study with a large number of patients has yet been conducted. It has been reported in these studies and case reports that hepatic metastasis of gastric cancer was controlled as easily as that of colorectal cancer. However, the development of extrahepatic lesions during HAI therapy could be an important factor in determining the prognosis.

The advantages of HAI are that direct infusion into the hepatic artery enables the regional delivery of higher doses of cytotoxic agents and that the lower level of distribution of the drugs into organs other than the liver can reduce adverse effects of the drugs. In both patients presented here, the size of the metastatic lesions was significantly reduced, and the general condition of the patients improved with the disappearance of jaundice. Moreover, the autopsy in case 2 revealed that, although the extrahepatic metastatic lesions were not suppressed, the reduction of hepatic metastasis had lasted as long as the HAI therapy had been continued. In our two patients, myelotoxicity, which can often be a dose-limiting toxicity during the systemic administration of 5-FU and cisplatin therapy, did not develop. On the other hand, the disadvantages of HAI are that the extrahepatic growth of tumor cannot be suppressed because of the concentrated effects on the liver, that drug-induced liver injury often develops, and that dislocation or occlusion of a catheter can occur [12,13]. Fortunately, there were no complications related to the inserted catheter and there was little anticancer drug hepatotoxicity in our patients. However, bone metastasis developed during HAI therapy in case 1 and the additional early systemic chemotherapy with HAI therapy in case 2 did not prevent the progression of extrahepatic lesions.

Among many anticancer drugs, we selected 5-FU and cisplatin, which are key drugs for chemotherapy against gastric cancer. It has been reported that 5-FU is more effective when used in continuous infusion than as a bolus injection [14], and that the combination with a small amount of cisplatin produces biochemical modulation providing high therapeutic efficacy [15,16]. Our pharmacokinetic study of cisplatin revealed a negligible first-pass effect on the liver after HAI of cisplatin. The internal dynamics of 5-FU have been reported to vary according to the dose and duration of administration [17]. The extraction ratio of 5-FU was 0.89 with our infusion dose and schedule, and about 90% of 5-FU administered by the HAI therapy was metabolized as a first-pass effect. Therefore, in our alternating weekly administration by the systemic and hepatic intraarterial routes in case 2, the dose intensity of 5-FU against extrahepatic lesions could possibly have been too low.

In general, gastric cancer patients with hepatic metastasis often have peritoneal dissemination and lymph node metastasis at the same time. Therefore, it seems unlikely that the patients' survival would be prolonged by the local control of the hepatic tumors. We experienced another patient with extensive hepatic and peritoneal metastasis whom we treated with this HAI therapy. In fact, he died of cancer progression with massive ascites 2 months after the initiation of the therapy, and did not show a benefit of the HAI therapy. The prognosis of cancer patients with extensive hepatic metastasis and obvious jaundice has been considered to be less than 1 or 2 months, and the best supportive care has been the only choice for these patients. However, the survival time in our patients presented here reached about 7 months, and their general condition improved. This would imply the possibility of symptom relief and survival benefit in some of such patients. However, the chemotherapy often causes severe adverse drug reactions in these patients. It is essential to obtain adequate informed consent before this treatment, and to pay much attention to possible adverse effects during this treatment.

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