Advanced hepatocellular carcinoma treated effectively with irinotecan via hepatic arterial infusion followed by proton beam therapy

A case of advanced hepatocellular carcinoma treated effectively with irinotecan *via* hepatic arterial infusion followed by proton beam therapy

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ABSTRACT

We report a 48-year-old man with hepatocellular carcinoma (HCC) treated with hepatic arterial infusion (HAI) chemotherapy followed by proton beam therapy. The HCC lesion in this patient was 8.8 cm in diameter with portal vein tumor thrombosis in the right robe of the liver. He was first treated with 5-fluorouracil, cisplatin, and isovorin, combined with interferon-α, and subsequently with epirubicin and mitomycin-C by HAI. However, no definite efficacy was observed. After continuous administration of irinotecan by HAI, the tumor size decreased to 6.8 cm in diameter after 3 weeks. The tumor became enlarged to 10 cm in diameter after 3 months. Angiographic findings indicated that HCC was fed from not only the right hepatic artery, but also the left gastric and right and left subphrenic arteries. After rearrangement of the arteries, the tumor size decreased to 5.0 cm in diameter by continuous HAI chemotherapy with irinotecan and hyperthermia after 4 months. Since the reduction rate

of the main tumor was 43% in Response Evaluation Criteria in Solid Tumors, the efficacy of this case was judged partial response. Although liver tumors showed gradual enlargement during administration of docetaxel instead of irinotecan, almost of the liver tumors resulted in necroses after proton beam therapy. The patient died of hepatic failure and distant metastases 6 years after onset of HCC. As far as we know, this is the first case report of HCC treated effectively with irinotecan by HAI followed by proton beam therapy in which tumor suppression and long-term survival were observed.

Key words: hepatocellular carcinoma, irinotecan, docetaxel, hepatic arterial infusion, hyperthermia, proton beam therapy

INTRODUCTION

The prognosis of patients with advanced hepatocellular carcinoma (HCC), in particular those with portal vein tumor thrombosis (PVTT), remains poor (1, 2). In such cases, therapeutic strategies such as surgery and transarterial or percutaneous interventions have often been avoided because of the intolerable liver function or insufficient curability, and systemic or hepatic arterial infusion (HAI) chemotherapy has often been employed (3–6). From the viewpoint of increases in drug concentrations in HCC and decreases in systemic drug exposure (7), HAI chemotherapy, especially 5-fluorouracil (5-FU)-based regimens, has been used in such cases (4-6). However, such cases seldom receive irinotecan or taxane administered by HAI. Here, we report a case of HCC treated effectively with irinotecan by HAI followed by proton beam therapy in which tumor suppression and long-term survival were observed.

CASE REPORT

A 48-year-old man with liver cirrhosis due to hepatitis C consulted a local hospital for periodic examination in November 2000. Abdominal ultrasonography showed a low echoic mass 2.5 cm in diameter in segment 5 (S_5) of the liver. Therefore, he was referred to our hospital for closer examination and treatment. He underwent local resection of the liver in January 2001, and the lesion was shown to be a moderately differentiated hepatocellular carcinoma. Because of recurrence of HCC, subsegmentectomy in S_5 and local resection in S_8 of the liver were performed in November 2001. However, repeated tumor recurrence was confirmed from January 2002, and he was repeatedly treated with percutaneous ethanol injection and microwave coagulation therapy.

However, HCC 4 cm in diameter with PVTT in the right main branch with intrahepatic metastases was found in November 2003. No definite distant metastases

were confirmed. Surgery or transcatheter arterial chemoembolization (TACE) were not indicated as the hepatic reserve capacity had decreased. Therefore, we planned to perform HAI chemotherapy. The top of the catheter was fixed by coils in the gastroduodenal artery. In addition, the left hepatic and the right gastric arteries were embolized by coils, after which no feeding arteries other than the right hepatic artery were present (Fig. 1). The HCC was rapidly enlarged to 8.8 cm in diameter (Fig. 2a) in January 2004. The results of biochemical and coagulation tests were as follows (normal ranges are shown in parentheses): total protein [TP; 7.3 mg/dL (6.3–7.9 mg/dL)], albumin [Alb; 3.9 mg/dL (3.9–5.2 mg/dL)], aspartate aminotransferase [AST; 59 IU/L (10–48 IU/L)], alanine aminotransferase [ALT; 40 IU/L (3–50 IU/L)], alkaline phosphatase [ALP; 311 IU/L (108–324 IU/L)], γ-glutamyl transpeptidase [γ-GTP; 67 IU/L (11–48 IU/L)], lactate dehydrogenase [LDH; 431 IU/L (120–214 IU/L)], total bilirubin [T.Bil; 0.7 mg/dl (0.2–1.3 mg/dl)], and prothrombin activity [64% (70–130%)].

This case was classified as Child-Pugh grade B because of decreased prothrombin activity. Alpha-fetoprotein (AFP) and protein induced by vitamin K absence or antagonist-II (PIVKA-II) levels in serum were elevated to 482 ng/ml (normal range; <10 ng/ml), and 194 mAU/ml (normal range; <40 mAU/ml), respectively.

The clinical course of this case is shown in Fig. 3. First, continuous administration of 5-FU (500 mg/body/day, later reduced to 300 mg/body/day, days 1–5), cisplatin (5 mg/body/day, days 1–5), and isovorin (20 mg/body/day, days 1–5) were performed by HAI using an infuser (Baxter®) through a subcutaneous injection port implanted into the left forearm, together with interferon-α (300×10^6 U, days 1, 3, 5) injected subcutaneously per week. After 9 weeks, the AFP level in serum was again elevated and intrahepatic metastases showed gradual enlargement. Subsequently, epirubicin (30 mg/body, later reduced to 20 mg/body, day 1) and mitomycin-C (8 mg/body, later reduced to 6 mg/body, day 1) were administered by HAI for 3 weeks. However, the AFP

level in serum was elevated to 5,411 ng/ml in March 2004. Both regimens were judged to show no clinical efficacy.

After informed consent from him and institutional review board (IRB) of Kanazawa university hospital were obtained, low-dose irinotecan by HAI was administered at a dose of 80 mg/body for 96 h, later reduced to 40 mg/body for 48 h due to bone marrow suppression, per week beginning in March 2004. The serum AFP level was decreased to 2,649 ng/ml and the tumor reduced to 6.8 cm in diameter after 3 weeks (Fig. 2b). However, the serum AFP level was again elevated to 14,386 ng/ml and the main tumor became enlarged to 10 cm in diameter and intrahepatic metastases were prominent in July 2004 (Fig. 2c). As angiographic findings indicated that the HCC was fed from not only the right hepatic artery, but also the left gastric and right and left subphrenic arteries, embolization of the left hepatic and right and left subphrenic arteries was performed, after which no feeding arteries other than the right hepatic

artery were present (Fig. 4). After rearrangement of the arteries, irinotecan was administered by HAI at a dose of 40 mg/body per week beginning in August of 2004. In addition, hyperthermia for once or twice per week was performed concurrently. The serum AFP level was decreased to 301 ng/ml, and the main tumor was reduced to 5.0 cm in diameter and intrahepatic metastases were diminished in October 2004 (Fig. 2d). Since the reduction rate of the main tumor was 43% in Response Evaluation Criteria in Solid Tumors (RECIST), the efficacy was judged partial response (PR). Although grade 3 neutropenia was observed in Common Terminology Criteria for Adverse Events (CTCAE) version3.0, toxicity was tolerable.

However, the AFP level in serum was elevated to 1,274 ng/ml in December 2004. After informed consent from him and IRB of Kanazawa university hospital were obtained, low-dose docetaxel was administered by HAI at a dose of 20 mg/body per week beginning in December 2004. Although the tumor increased in size gradually,

AFP level in serum was reduced from 2,000 to 3,000 ng/ml until June 2005. Toxicity was not recognized except for grade 3 anemia in CTCAE version3.0.

However, AFP level was elevated to 18,338 ng/ml in November 2005. Furthermore, abdominal computed tomography (CT) showed two HCCs 6.2 cm and 5.5cm in diameters in the right lobe of the liver. Since no definite tumor was recognized in the left lobe after HAI chemotherapy with irinotecan and docetaxel, the patient underwent proton beam therapy for liver tumors in the right lobe from December 2005 to January 2006. After irradiation with a total of 70 Gy using a proton beam for 35 days, AFP level was markedly decreased to 16 ng/ml, and almost of the liver tumors in the right lobe decreased in size in March 2006. However, multiple bone and lung metastases were verified in July 2006. He died of hepatic failure and distant metastases in March 2007.

DISCUSSION

Patients with HCC have been treated with surgery (resection, liver transplantation), transarterial interventions [transarterial embolization (TAE), chemoperfusion (TAC), and chemoembolization (TACE)], percutaneous interventions (ethanol injection, microwave coagulation, and radiofrequency thermal ablation), radiation therapy, and chemotherapy (8, 9). The prognosis of patients with advanced HCC with PVTT remains poor (1, 2). In such cases, the choices of therapy have been limitted, and therapeutic approaches such as surgery and transarterial or percutaneous interventions are often avoided because of the intolerable liver function or insufficient curability. In this case, we did not choose hepatic resection or liver transplantation because of intolerable hepatic reserve capacity or discordance with the blood type of the donor, respectively. In addition, transarterial and percutaneous interventions were avoided because of PVTT in the right main branch and insufficient curability, respectively. Therefore, the patient was

treated with HAI chemotherapy.

There have been few reports of randomized studies comparing HAI with systemic chemotherapy for advanced HCC (10). However, the response rate of HAI (4-6) has been shown to be higher than that of systemic chemotherapy (3). In addition, HAI chemotherapy has been performed in cases of advanced HCC with PVTT (4-6). In comparison with systemic drug administration, HAI can increase drug concentrations at hepatic tumor sites and reduce systemic drug exposure (7). Therefore, we chose HAI rather than systemic chemotherapy. 5-FU-based chemotherapy by HAI combined with cisplatin or interferon-α has been reported with a response rate of approximately 40–50% (4-6). In the present case, 5-FU, cisplatin, and isovorin were administered by HAI, together with interferon-α injected subcutaneously. However, no definite efficacy was observed. Subsequently, administration of epirubicin and mitomycin-C by HAI was performed, which resulted in no improvement.

Systemic chemotherapy using irinotecan has been employed in the treatment of colon, gastric, and lung cancers. However, there has been relatively little research into the use of systemic chemotherapy for HCC, and the response rate is only 0–7% (11, 12). Although cases with liver metastases from colon cancer in which irinotecan was administered by HAI have been reported, there have been no previous reports of such cases with HCC. The results of pharmacokinetic studies showed that the metabolic ratio, a measure for the conversion of irinotecan into its metabolite SN-38, was higher with prolonged than with short infusion (13, 14). Irinotecan has been suggested to act in a time-dependent manner. Therefore, in this case, irinotecan at 80 mg/body, later reduced to 40 mg/body, was administered by HAI using an infuser for 48–96 h weekly. Although the tumor reduction was observed at the beginning, the tumor was enlarged to the size of the initial state after 4 months of administration of irinotecan. Angiographic findings indicated that HCC was fed from not only the right hepatic artery, but also the left

gastric and right and left subphrenic arteries. Therefore, we plugged the left gastric and right and left subphrenic arteries using metallic coils. After rearrangement of the arteries, continuous administration of irinotecan by HAI at a dose of 40 mg/body weekly was again effective and the efficacy was judged PR. If resistance to treatment is confirmed during HAI chemotherapy, angiographic examination is necessary. In addition, if the feeding arteries other than the main artery can be confirmed, rearrangement of the arteries should be performed, because resistance to treatment was not due to drug resistance, but to a decrease in drug concentration caused by the increase in feeding arteries.

Systemic chemotherapy using docetaxel has been used in breast, lung, and gastric cancers. However, there have been relatively few surveys of systemic chemotherapy using docetaxel or paclitaxel for HCC, which have shown response rates of only 7% (15) and 0–6% (16,17), respectively. There have been no previous reports of treatment

of HCC with taxane by HAI. In the present case, low-dose docetaxel was administered by HAI. Although HCC increased in size gradually, AFP levels in serum were suppressed from 2,000 up to 3,000 ng/ml for 6 months. Therefore, it was suggested that tumor progression was inhibited by docetaxel administered by HAI.

Concurrent treatment with hyperthermia was performed with irinotecan or docetaxel by HAI. Hyperthermia combined with transcatheter arterial embolization, radiotherapy, immunotherapy, and chemotherapy has been reported in cases of liver tumors (18). It has been reported that moderate hyperthermia increases the cytotoxicity of irinotecan, docetaxel, and gemcitabine on mouse fibrosarcoma (19). In the present case, hyperthermia may have enhanced the effect of irinotecan or docetaxel administration by HAI.

Proton beam therapy for patients with HCC is effective, safe, well tolerable, and repeatable (20～22). The therapy is useful for patients with HCC irrespective of tumor

size, tumor location, presence of vascular invasion, and impaired hepatic function. In this case, although intrahepatic metastases were observed before HAI chemotherapy, the tumors in the left lobe have disappeared after HAI chemotherapy with irinotecan and docetaxel. Therefore, the patient underwent proton beam therapy for HCCs in the right lobe. After proton beam therapy, AFP level was markedly decreased, and almost of the liver tumors in the right lobe decreased in size and probably became necroses. Although multiple bone and lung metastases were confirmed 6 months after proton beam therapy, the therapy would contribute the local control of HCCs.

In conclusion, irinotecan administered by HAI may be recommended in cases with advanced HCC showing resistance to 5-FU-based chemotherapeutic regimens. In addition, angiographic examination and embolization of the feeding arteries other than the main artery should be performed if tumor growth is confirmed again. This is the first report of a case of HCC treated effectively with irinotecan administered by HAI

followed by proton beam therapy in which tumor suppression and long-term survival were observed.

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FIGURE LEGENDS

Fig. 1

Abdominal angiography injected from the common hepatic artery (CHA; white arrow) showing the tumor (black arrow). The top of the catheter was fixed by coils in the gastroduodenal artery (GDA; white arrow). No feeding arteries other than the right hepatic artery (RHA; white arrow) were present after embolization of the left hepatic (LHA; white arrow) and right gastric arteries (RGA; white arrow).

Fig. 2

a. Abdominal CT showing a low-density mass 8.2 cm in diameter (arrow) with PVTT in the right robe of the liver.

b. Abdominal CT showing tumor reduction to 6.8 cm in diameter (arrow) 3 weeks after continuous administration of irinotecan by HAI.

c. Abdominal CT showing tumor enlargement to 10 cm in diameter (black arrow) and intrahepatic metastatic lesion (white arrow) after 3 months.

d. Abdominal CT showing tumor reduction to 5.8 cm in diameter (arrow) 4 months after rearrangement of the left gastric and right and left subphrenic arteries.

Fig. 3

The clinical course of this case. The diameters of the main tumor are shown in parentheses under the AFP levels in serum.

Fig. 4

Abdominal angiography injected from the common hepatic artery (CHA; white arrow) showing the tumor (black arrow) after embolization of the left hepatic (LHA; white arrow), left gastric (LGA; white arrow) and right and left subphrenic arteries (LSPA;

white arrow). No feeding arteries other than the right hepatic artery (RHA; white arrow) were present.