Advanced Hepatocellular Carcinoma with Portal Vein Main Trunk Tumor Thrombosis Successfully Treated by Repeated Hepatic Arterial Cisplatin Infusion Chemotherapy

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Abstract
We report a 75-year-old woman with advanced hepatocellular carcinoma (HCC) with portal vein main trunk tumor thrombosis treated successfully by repeated hepatic arterial infusion chemotherapy (HAIC). She had been diagnosed with hepatitis B virus cirrhosis since 1998 and followed up by a local practitioner. As hepatocellular carcinoma occurrence was suspected on abdominal computed tomography in March 2007, she was referred to our hospital. Although transcatheter arterial chemoembolization (TACE) with emulsion of epirubicin and lipiodol was performed twice, the therapeutic response was poor and temporary. Serum alpha-fetoprotein (AFP) level was elevated, and portal vein tumor thrombosis (PVTT) involving main trunk of portal vein (Vp4) appeared. In January 2008, the treatment was changed to hepatic arterial infusion chemotherapy (HAIC) with a fine-powder formulation of cisplatin (IA-call®). Immediately after HAIC, there was a significant decrease in AFP levels, and we estimated that IA-call® was effective. An arterial infusion reservoir was placed in the right hepatic artery in March 2008, and repeated HAIC of IA-call® was performed 7 times until December 2008. During this period, HCC with PVTT disappeared, and AFP level decreased to normal range. We judged complete remission was obtained, and it persisted for 7 years and 8 months after terminating HAIC. In July 2016, although recurrence was observed, it was controlled by repeated TACE, and she is alive as of December 2020. We encountered a case of advanced HCC with Vp4 who survived for over 13 years owing to the remarkable effect of repeated HAIC of IA-call®.

Key words
Hepatocellular carcinoma, portal vein tumor thrombosis, hepatic arterial infusion chemotherapy, fine-powder formulation of cisplatin, long-term survival

Introduction
For the treatment of advanced hepatocellular carcinoma (HCC), molecular-targeted drugs have been widely administered to patients refractory to transcatheter arterial chemoembolization (TACE). According to the treatment algorithm of the 2017 edition of the Liver Cancer Treatment Guidelines in Japan¹, in cases of liver injury degree A, the treatment policy for advanced HCC associated with vascular invasion was liver resection, TACE, molecular-targeted drugs, and hepatic arterial infusion chemotherapy (HAIC). However, there is no clear evidence of treatment priorities, and therapeutic strategies differ among institutions. Among them, HAIC was not included in the liver cancer treatment algorithms in Europe.

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rope\textsuperscript{2} and the United States\textsuperscript{3}, and it has been mainly developed in Japan and Korea\textsuperscript{4}. We report a case of advanced HCC with portal vein main trunk tumor thrombosis (Vp4) that was treated with repeated HAIC of a fine-powder formulation of cisplatin (diaminedichloroplatinum; IA-call\textsuperscript{16}, Nippon Kayaku Co., Ltd., Tokyo, Japan) and that achieved long-term survival.

### Case Presentation

Our patient was a 75-year-old woman with no subjective complaints. She had no history of drinking and smoking. Her mother was a hepatitis B virus carrier. She had appendectomy when she was young (no other detailed information on that recorded). She had never had blood transfusion and did not have any tattoo on her body. She had acupuncture from approximately 16 years old for several decades.

The patient was identified as chronic hepatitis B during a medical checkup around 1987, and a local practitioner had been conducting follow-up for type B liver cirrhosis since 1998. In March 2007, HCC was suspected on abdominal contrast-enhanced computed tomography (CT), and the patient was referred to our hospital.

The blood test conducted at the first visit in April 2007 revealed a mildly elevated transaminase values and decreased platelet count (Table 1). As no ascites or encephalopathy was noted, the severity of liver disease corresponded to Child-Pugh class A (score of 5). Serum hepatitis B virus (HBV) surface (HBs) antigen was positive and HBV-DNA was 3.4 Log copies/ml. Tumor marker levels were increased, with alpha-fetoprotein (AFP) level of 2020 ng/ml and des-\(\gamma\)-carboxy prothrombin (DCP) of 69 mAU/ml (Table 1). CT revealed an approximately 3-cm ill-defined tumor in segment 8 below the right diaphragm. The tumor showed faint irregular enhancement in the arterial phase and washout in the equilibrium phase (Figure 1). She was admitted to our hospital for a detailed examination and treatment.

Figure 2 shows the course of treatment and changes in tumor marker levels, and Table 1 shows changes in laboratory findings. Hepatic arterial angiography performed in May 2007 (point A in Figure 2), revealed an arterial portal (AP) shunt from the right hepatic artery to the right portal vein. CT during arteriopography (CTAP) and CT during hepatic arteriography (CTHA) revealed thrombosis in the right branch of the portal vein (Vp3) and decreased portal blood flow mainly in the S8 of the liver (Figure 3). Expecting a therapeutic effect on the portal vein tumor thrombosis (PVTT), TACE was performed using 35mg of epirubicin hydrochloride + 5.25 ml of lipiodol (Lip) emulsion. Although AFP and DCP levels further increased, TACE was performed again in July 2008.

### Table 1. Laboratory Findings in the Clinical Course

(at the first visit and point A ~ F in Figure 2)

|          | First visit | A | B | C | D | E | F |
|----------|-------------|---|---|---|---|---|---|
| T. Bil.  | mg/dl       | April 2007 | 0.7 | 0.6 | 0.8 | 0.7 | 0.1 | 1.3 | 2 |
| AST      | U/L         | 43 | 36 | 51 | 38 | 30 | 39 | 57 |
| ALT      | U/L         | 32 | 24 | 32 | 21 | 16 | 20 | 34 |
| \(\gamma\)-GTP | U/L | 45 | 109 | 131 | 38 | 34 | 67 |
| Alb      | g/dl        | 4.5 | 4.1 | 4.5 | 4.2 | 4.3 | 4.3 | 3.7 |
| Cr       | mg/dl       | 0.61 | 0.51 | 0.61 | 0.65 | 0.74 | 1.06 |
| eGFR     | ml/min/1.73m\textsuperscript{2} | 65.8 | 59 | 65.7 | 69 | 58.9 | 39.1 |
| PT(%)    | %           | 104 | 92 | 98 | 93 | 97 | 83 | 45 |
| NH3      | \(\mu\)g/dl | 35 | 61 | 32 | 38 | 30 | 55 | 68 |
| Hb       | g/dl        | 12.8 | 13.1 | 9.8 | 10.8 | 9.6 | 13 |
| PLT      | X10\textsuperscript{4}/\(\mu\)l | 8.5 | 6.6 | 8.3 | 5.6 | 6.8 | 6.6 | 7 |
| AFP      | ng/ml       | 2020 | 7020 | 20000 | 2.4 | 2.5 | 11.8 | 56.9 |
| AFP-L3   | %           | 12.1 | 118 | 11 | 13 | 19 | 379 |
| DCP      | mAU/ml      | 69 | 96 | 118 | 11 | 13 | 19 | 56.9 |

T.Bil., total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; Alb., albumin; Cr, creatinine; eGFR, estimated glomerular filtration rate; PT, prothrombin time; NH3, ammonia; Hb, hemoglobin; PLT, platelet counts; AFP, alpha-fetoprotein; AFP-L3, lens culinaris agglutinin reactiveα-fetoprotein isoform; DCP, des-\(\gamma\)-carboxy prothrombin.
Figure 1. Abdominal CT on admission in April 2007
In liver segment 8, an ill-defined tumor (arrowhead) of approximately 3-cm was observed, which showed faint irregular enhancement in the arterial phase (a) and washout in the equilibrium phase (b).

2007 and then, tumor marker levels showed a transient decrease. However, enlargement of HCC with re-elevation of AFP level to 24900 ng/ml was observed in October 2007. Lipiodol transcatheter arterial infusion therapy (Lip-TAI) was performed using IA-call at the dose of 50 mg followed by 6ml of lipiodol infusion. AFP and DCP levels remarkably decreased, however it was temporary. AFP and DCP levels re-in-
Figure 3. Abdominal angiography, CTAP and CTHA at first TACE in May 2007 (point A in Figure 2)
a, axial image; b, coronal image.

RHA showed AP shunt from an early phase, and CTAP and CTHA showed decreased portal vein blood flow mainly in the S8 and a tumor thrombosis in the right branch of the portal vein (arrowhead).

RHA, right hepatic arteriography; CTAP, computed tomography during arterial portography; CTHA, computed tomography during hepatic arteriography

creased (elevated to 20000 ng/ml and 118 mAU/mL, respectively) in January 2008 (point B in Figure 2) and angiography, CTAP, and CTHA showed PVTT progressing to Vp4 and extensive AP shunts in the right lobe of the liver (Figure 4). As IA-call® was expected to decrease tumor marker levels after Lip-TAI, the treatment was changed to HAIC using IA-call®. Immediately after HAIC with 80mg (65mg/m² body surface area) of IA-call® AFP levels markedly decreased to 8020 ng/ml, and IA-call® was judged to be effective. In March 2008, an arterial infusion reservoir was placed in the right hepatic artery, and IA-call® was administered repeatedly. HAIC with 80mg of IA-call® under sufficient hydration and concurrent administration of antiemetics and corticosteroids was performed eight times in total from January to December 2008, and tumor marker levels decreased to the normal range. During this period, there was no issue related to the catheter, and no major adverse event was observed. In June 2009 (point C in Figure 2), approximately 6 months after the final HAIC, CT showed no residual or recurrence of HCC, and there was no obvious PVTT. The right liver lobe showed atrophic change, which was considered to be due to decreased right portal vein blood flow (Figure 5). We judged complete remission (CR) based on the response evaluation criteria in solid tumors, and the reservoir was removed. Two years later, in July 2011 (point D in Figure 2), CT showed no recurrence of HCC and no tumor thrombosis in right portal vein (Figure 6).

There was no recurrence of HCC until March 2016, which is 7 years after the last HAIC, and levels of AFP and DCP stayed quite low within the normal range. Regarding HBV infection, nucleic acid analogs were administered from January 2009, HBV-DNA levels remained below measurable range, and HBs antigen had become negative since September 2015.

In July 2016 (point E in Figure 2), CT revealed a 1-cm tumor stain under the diaphragm in S7 of the liver, suggesting ectopic HCC recurrence (Figure 7a). A Lip-TAI with CDDP, TACE with CDDP twice, and lipiodol were performed. As of June 2020 (point F in Figure 2), although local residual lesion that was difficult to control accompanied by an increase in DCP levels still existed (Figure 7b), the patient is well, and a new treatment is under consideration.

Discussion

The prognosis of advanced HCC with extensive
Figure 4. Abdominal angiography, CTAP and CTHA in January 2008 (point B in Figure 2)
   a, axial image; b, coronal image
   RHA showed a widespread AP shunt in the right lobe, and CTHA and CTAP showed a tumor
   thrombosis extending to the portal vein main trunk (arrowhead).
   RHA, right hepatic arteriography; CTAP, computed tomography during arterial portography;
   CTHA, computed tomography during hepatic arteriography

Figure 5. Abdominal CT at 6 months after HAIC in July 2009 (point of C in Figure 2)
   a, coronal image; b, arterial phase image; c, arterial phase image.
   CT showed no residual or recurrence of HCC in the liver, and there was no obvious
   tumor thrombosis in the portal vein main trunk. The right lobe showed atrophy.
Figure 6. Abdominal CT at 31 months after HAIC in July 2011 (point D in Figure 2)  
a, coronal image; b, arterial phase image; c, arterial phase image.  
CT showed no recurrence of HCC in the liver and improvement in portal blood flow.

Figure 7. Abdominal CT in follow up for HCC recurrence (point E and F in Figure 2)  
CT in July 2016 (point E in Figure 2) showed a 1-cm tumor stain in S7 of the liver, and  
ectopic HCC recurrence was diagnosed (arrowhead) (a). After three times of TACE, local  
residual lesion showed interval growth (3-cm in diameter) in June 2020 (point F in Figure 2) (b).

PVTT is poor, and the life expectancy is 2–4 months without therapeutic interventions\textsuperscript{6–8}. According to the  
guidelines of European Association for the Study of the Liver and American Association for the Study of  
Liver Diseases, systemic chemotherapies such as sorafenib, which is a molecular-targeted drug, is indi-  
cated for HCC with PVTT in patients with good liver function. Bruix et al.\textsuperscript{9} reported that treatment with  
sorafenib for HCC with cases of vascular invasion showed a significant increase in median survival time  
(MST) of 8.1 months compared to 4.9 months for placebo. In contrast, according to reports from Asia,  
MST is 3.1–5.5 months, and the therapeutic effect is limited\textsuperscript{10,11}.  

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When the patient was admitted to our hospital in 2007, we had no option of treatment with molecular-targeted drugs, because the sorafenib, the first molecular targeted drug against HCC, was applicable to Japanese health insurance only in 2009.

The liver has a dual blood flow with the portal vein and hepatic artery. HAIC is a treatment that utilizes the fact that the feeding blood vessel of the HCC is the hepatic artery. Theoretically, the drug is directly injected into the hepatic artery to increase the concentration of the anticancer drug in the tumor, and a part of the anticancer drug is metabolized in the liver to reduce the transfer of the anticancer drug to the whole body. This suggests that HAIC has the advantage of having fewer side effects than systemic chemotherapy\(^a\). HAIC includes various regimens from the past in Japan: low-dose cisplatin (CDDP) and 5-fluorouracil (5FU); Low-dose FP, 5FU arterial infusion and interferon therapy; FAIT and IA-call\(^a\) as CDDP have been mainly used\(^a\). The above-mentioned HAIC comprise cell-killing anticancer drugs. There are two administration methods: one is a reservoir method in which continuous repeated administration is performed using a hepatic arterial infusion reservoir, and the other is a single bolus injection method in which an angiographic catheter is inserted into the hepatic artery\(^a\).

The treatment results of HAIC for advanced HCC with PVTT are low-dose FP with a response rate (RR) of 30–40% and an MST of 10–16 months, FAIT with an RR of 40–50% and an MST of 7–12 months\(^\text{12–14}\). Conversely, IA-call\(^a\) is reported to have an RR of 20–30% and an MST of 7–10 months\(^\text{15–18}\). However, it is difficult to directly compare the three treatments because the patient's background and number of cases are different. Only in a randomized controlled trial reported by Monden et al.\(^\text{19}\), the FAIT group showed an RR of 26.7% and an MST of 8.4 months. In contrast, the group receiving the best salvage treatment (BST), comprising low-dose FP or IA-call\(^a\) intraarterial infusion, had an RR of 25.8% and an MST of 11.8 months. There was no significant difference between the FAIT and BST groups. The life prognosis for each treatment is limited, with few survivors exceeding 1 year.

In our case, it was judged that the effect of TACE using epirubicin was insufficient because of the extension of PVTT to Vp3 and the increase in tumor marker levels after twice of TACE. The anticancer drug was changed to CDDP, and Lip-TAI was performed. Lip-TAI with IA-call\(^a\) as CDDP seemed to provide obvious antitumor effect. Therefore, a reservoir catheter was placed in the right hepatic artery, and repeated HAIC with IA-call\(^a\) was performed from the reservoir. It was assumed that the high sensitivity of HCC to CDDP contributed to the long-term CR of approximately 7 years. It is difficult to predict whether CDDP is efficacious or not before treatment for HCC. According to a report on the relationship between imaging findings and results of IA-call\(^a\) treatment in Japan\(^\text{20}\), advanced HCCs for which IA-call\(^a\) was effective showed ill-defined borders, faint enhancement and increase of the fine blood vessels. It is interesting that these findings seem to be similar to pretreatment imaging findings of the present case. Another contributing factor to long-term CR should be intensive CDDP administration with sufficient dose via the reservoir. In the present case, the total dose of CDDP administered over a span of 11 months amounted to 690 mg. During this period, there was no issue related to the catheter, and no deterioration of liver function was observed. Neuropathy\(^\text{21}\), which is said to increase in frequency owing to accumulation when the total dose of CDDP exceeds 300–400 mg, and serious side effects such as cytopenia due to myelosuppression were not observed. It might be owing to the direct drug delivery from hepatic artery, not a systemic administration. It should be noted that the use of 5-hydroxytryptamine 3 receptor antagonists and steroids reduced gastrointestinal symptoms and that hydration with sufficient fluid replacement reduced renal damage. It was considered that these procedures enabled intensive CDDP administration with no major adverse event.

More than ten years have passed since the launch of sorafenib, and it has been widely used as a first-line treatment for advanced HCC with good liver function owing to its convenience and safe use. However, as mentioned above, the effect on advanced HCC with Vp4 is limited. In recent years, the treatment of advanced HCC with Vp4 has been reported to prolong prognosis by combined therapy with sorafenib and HAIC\(^\text{22,23}\) and is expected to be a first-line treatment. To improve long-term prognosis, if a marked decrease in tumor marker levels or an apparent regression of PVTT is observed immediately after HAIC, it is necessary to administer a sufficient amount of cell-killing anticancer drugs paying adequate attention to possible side effects.

**Conclusion**

For advanced HCC with Vp4 that occurred in...
type B cirrhosis, repeated hepatic arterial infusion of IA-call® was remarkably effective, and we encountered a case that survived for 13 years after approximately 7 years of CR. The treatment with HAIC for advanced HCC may lead to long-term survival and should be considered for indications continuously in the future.

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Conflicts of Interest
The authors have nothing to disclose.

References
1) The Japan Society of Hepatology. Algorithm of the liver cancer treatment guidelines: The Japan Society of hepatology hepatocellular carcinoma guideline 2017 in Japan, 4th ed, Kanehara Publishers, Tokyo, 2020: 68.
2) European association for the study of the liver. EASL clinical practice guidelines: Management of hepatocellular carcinoma. J Hepatol 2018; 69: 182–236.
3) Bruix J, Sherman M, American association for the study of liver diseases. Management of hepatocellular carcinoma: an update. Hepatology 2011; 53: 1020–1022.
4) Yamashita T, Kaneko S. Hepatic arterial infusion chemotherapy for advanced hepatocellular carcinoma. Journal of Japanese Society of Gastroenterology 2012; 109: 1335–1345.
5) Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. Journal of the National Cancer Institute 2000; 92: 205–216.
6) Llovet JM, Bustamante J, Castells A, et al. Natural history of untreated nonsurgical hepatocellular carcinoma: rationale for the design and evaluation of therapeutic trials. Hepatology 1999; 29: 62–67.
7) Minagawa M, Makuuchi M. Treatment of hepatocellular carcinoma accompanied by portal vein tumor thrombus. World J Gastroenterol 2006; 12: 7561–7567.
8) Schöning HM, Muller C, Kutilek M, et al. Hepatocellular carcinoma in central europe: prognostic features and survival. Gut 2001; 48: 103–109.
9) Bruix J, Raoul JL, Sherman M, et al. Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma: subanalyses of a phase III trial. J Hepatol 2012; 57: 821–829.
10) Jeong SW, Jang JY, Shim KY, et al. Practical effect of sorafenib monotherapy on advanced hepatocellular carcinoma and portal vein tumor thrombosis. Gut Liver 2013; 7: 696–703.
11) Song DS, Song MJ, Bae SH, et al. A comparative study between sorafenib and hepatic arterial infusion chemotherapy for advanced hepatocellular carcinoma with portal vein tumor thrombosis. J Gastroenterol 2015; 50: 445–454.
12) Niizeki T, Sumie S, Torimura T, et al. Serum vascular endothelial growth factor as a predictor of response and survival in patients with advanced hepatocellular carcinoma undergoing hepatic arterial infusion chemotherapy. J Gastroenterol 2012; 47: 686–695.
13) Ueshima K, Kudo M, Takita M, et al. Hepatic arterial infusion chemotherapy using low-dose 5-fluorouracil and cisplatin for advanced hepatocellular carcinoma. Oncology 2010; 78 (suppl 1): 148–153.
14) Ando E, Tanaka M, Yamashita F, et al. Hepatic arterial infusion chemotherapy for advanced hepatocellular carcinoma with portal vein tumor thrombosis: analysis of 48 cases. Cancer 2002; 95: 588–595.
15) Iwasa S, Ikeda M, Okusaka T, et al. Transcatheter arterial infusion chemotherapy with a fine powder formulation of cisplatin for advanced hepatocellular carcinoma refractory to transcatheter arterial chemoembolization. Jpn J Clin Oncol 2011; 41: 770–775.
16) Kondo M, Morimoto M, Numata K, et al. Hepatic arterial infusion therapy with a fine powder formulation of cisplatin for advanced hepatocellular carcinoma with portal vein tumor thrombosis. Jpn J Clin Oncol 2011; 41: 69–75.
17) Yoshikawa M, Ono N, Yodono H, et al. Phase II study of hepatic arterial infusion of a fine-powder formulation of cisplatin for advanced hepatocellular carcinoma. Hepatol Res 2008; 38: 474–483.
18) Kim BK, Park JY, Choi HJ, et al. Long-term clinical outcomes of hepatic arterial infusion chemotherapy with cisplatin with or without 5-fluorouracil in locally advanced hepatocellular carcinoma. J Cancer Res Clin Oncol 2011; 137: 659–667.
19) Monden M, Sakon M, Sakata Y, et al. 5-fluo-
Fluorouracil arterial infusion + interferon therapy for highly advanced hepatocellular carcinoma: A multicenter, randomized, phase II study. Hepatol Res 2012; 42: 150–165.

20) Hayashi T, Kobayashi T, Iwata R, et al. Analysis of transcatheter arterial infusion chemotherapy of cisplatin in advanced hepatocellular carcinoma—relationship between imaging findings (contrast-enhanced CT and angiography) and the results of TAI. Kanzo [in Japanese] 2008; 49: 461–469.

21) Cavaletti C, Marzorati G, Boglium N, et al. Cisplatin-induced peripheral neurotoxicity is dependent on total-dose intensity and single-dose intensity. Cancer 1992; 69: 203–207.

22) Kudo M, Ueshima K, Yokosuka O, et al. Sorafenib plus low dose cisplatin and fluorouracil hepatic arterial infusion chemotherapy versus sorafenib alone in patients with advanced hepatocellular carcinoma (SILIUS): a randomized, open label, phase 3 trial. Lancet Gastroenterol Hepatol 2018; 3: 424–432.

23) Ikeda M, Shimizu S, Sato T, et al. Sorafenib plus hepatic arterial infusion chemotherapy with cisplatin versus sorafenib for advanced hepatocellular carcinoma: randomized phase II trial. Ann Oncol 2016; 27: 2090–2096.