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A Case of Advanced Hepatocellular Carcinoma with Portal Vein Tumor Thrombus Refractory to Epirubicin That Showed Marked Decrease in Tumor Markers after Transcatheter Arterial Infusion with Miriplatin

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Key Words

Miriplatin · Tumor marker · Hepatocellular carcinoma · Epirubicin

Abstract

Miriplatin, a cisplatin derivative with a high affinity for iodized ethyl esters of fatty acids from poppy seed oil, is a novel chemotherapeutic agent designed for use in the transarterial treatment of hepatocellular carcinoma (HCC). Here, we describe transcatheter arterial infusion (TAI) using miriplatin to treat a case of advanced HCC with portal vein tumor thrombus (PVTT) refractory to TAI with epirubicin. A 66-year-old man with advanced hepatitis C virus-related HCC with PVTT in the right lobe of the liver was treated with TAI with epirubicin suspended in iodized oil; however, tumor marker levels (alpha-fetoprotein and des-gamma-carboxy protein) did not decrease. Next, he was treated twice with TAI with miriplatin suspended in iodized oil. The tumor marker levels markedly decreased to a nearly normal range and the size of the main tumor was markedly reduced according to dynamic computed tomography. No serious adverse events occurred during the course of treatment with TAI and miriplatin. Therefore, we suggest that TAI with miriplatin is a safe and effective treatment option for advanced HCCs refractory to TAI with epirubicin.

Introduction

Miriplatin, a cisplatin derivative with a high affinity for iodized ethyl esters of fatty acids from poppy seed oil [1], is a novel chemotherapeutic agent designed for use in the transarterial treatment of hepatocellular carcinoma (HCC). Miriplatin (1) inhibits cell proliferation in a similar manner as cisplatin and has superior solubility in ethyl esters of iodized fatty acids from poppy seed oil; (2) releases its platinum constituent continuously by remaining at local tumor sites together with ethyl esters of iodized fatty acids from poppy seed oil (sustained release); and (3) alleviates adverse effects as it maintains an antitumor effect owing to its sustained release as well as its minimal presence in the general circulation [1–4]. Despite such characteristics, however, many aspects of its antitumor effects are not clear.

We experienced a case of advanced HCC that showed marked decrease in tumor markers following treatment with transcatheter arterial infusion (TAI) with miriplatin, despite being refractory to TAI with epirubicin.

Case Report

The patient, a 66-year-old man, had been diagnosed with chronic hepatitis C and had been followed-up at another hospital for the past 5 years. He had never smoked cigarettes and occasionally drank alcohol. During follow-up for chronic hepatitis C at the other hospital, the levels of tumor markers were found to be elevated, and he was referred to our hospital. An advanced HCC with portal vein tumor thrombus (PVTT) in the right lobe was observed on the dynamic computed tomography (CT) scan, and he was admitted to our hospital for medical treatment in July 2010.

The patient's height was 157 cm, body weight was 46 kg, blood pressure was 134/74 mm Hg, body temperature was 36.6°C, heart rate was 84 bpm, and no significant findings were observed upon physical examination. Laboratory data are shown in [table 1](#). A marked increase in the levels of tumor markers was observed. The patient's Child-Pugh score was 6 points (grade A).

Dynamic CT showed an irregularly shaped tumor, 5.6 × 3.8 cm in size, which was enhanced in the early phase (not enhanced in some areas) and indicated a region of deficiency in the delayed phase, in liver segment 8/7. The tumor had invaded the right anterior branch of the portal vein, and was cut off at the portion indicated by the arrow in [fig. 1](#) (i.e. vp2). In segment 5, adjacent to the gallbladder, a classical HCC 2 cm in size was observed, which was enhanced in the early phase and indicated a region of deficiency in the delayed phase.

As an initial clinical course beginning in late July 2010, abdominal angiography ([fig. 2](#)) was performed. Digital subtraction angiography (DSA) of the superior mesenteric artery showed disruption of the right anterior branch of the portal vein. The lumen of the posterior branch of the portal vein was narrowed. In the DSA of the common hepatic artery, a large irregular tumor stain in the right lobe of the liver and a nodular tumor stain, 2 cm in size, were found in segment 5. An emulsion of epirubicin (50 mg) and lipiodol (8 ml) was infused primarily from the right hepatic artery. After TAI, a transient fever over 38°C was observed; however, the fever was easily managed using only antipyretics, and there were no other adverse events. The patient was discharged in early August 2010.

A blood test conducted in late September revealed a marked increase in tumor marker levels (alpha-fetoprotein [AFP] from 2,116 ng/ml to 4,622 ng/ml, and des-gamma-carboxy protein [DCP] from 373 mAU/ml to 8,394 mAU/ml). Dynamic CT confirmed tumor progression ([fig. 3](#)). Therefore, he was admitted for retreatment in early October 2010.

The second clinical course was begun in early October 2010, during which abdominal angiography was performed. Next, an emulsion of miriplatin (80 mg) and lipiodol (8 ml) was infused primarily from the right hepatic artery because the tumors were refractory to TAI with epirubicin. One month after TAI with miriplatin, the AFP level was 1,507 ng/ml and the DCP level was 9,457 mAU/ml, indicating

that the therapy was not effective. However, 2 months after TAI, the AFP level was 63.9 ng/ml and the DCP level was 64 mAU/ml. A marked decrease in the levels of the tumor markers was observed. Because of the good response to TAI with miriplatin, an emulsion of miriplatin (100 mg) and lipiodol (5 ml) was again infused primarily from the right hepatic artery in early January 2011. One month after the 2nd TAI with miriplatin, the levels of the tumor markers improved to a nearly normal range (AFP, 16.3 ng/ml and DCP, 34 mAU/ml). Dynamic CT performed 3 months after the 2nd TAI with miriplatin showed that the size of the main tumor in segment 8/7 had markedly decreased, resulting in less obstruction of the right branch of the portal vein ([fig. 4](#)). Because the tumor in segment 5 exhibited poor response to the treatment, percutaneous therapy to the nodule is under consideration. The transition of the tumor markers is shown in [fig. 5](#).

Discussion

Several intra-arterial chemotherapy regimens using epirubicin [5], mitomycin [6], adriamycin [7], fluorouracil [8], fluorodeoxyuridine [9], mitoxantrone [10], and cisplatin [11] as treatment for HCC have been reported. However, the optimal regimen for intra-arterial chemotherapy for HCC is still unknown.

In the case described, the patient obtained a marked decrease in tumor marker levels following treatment with TAI and miriplatin, despite being refractory to TAI with epirubicin. There have been no case reports describing this treatment regimen. Considering the clinical courses used, it was thought that the main tumor caused an elevation in the tumor marker levels.

The tumor enhancement pattern seen on the dynamic CT indicated that the main tumor contained an undifferentiated region (irregular enhancement with deficit regions in certain areas) in the early phase. The tumor in segment 5 exhibited classical features of HCC. Considering the effects of the applied treatment (i.e. remarkably effective for the former tumor and ineffective for the latter tumor), TAI with miriplatin may be effective for treating undifferentiated tumors.

It is noteworthy that in the ineffective treatment of the tumor in segment 5 as well as in the markedly effective treatment of the main tumor, most of the administered lipiodol was washed out after treatment with TAI and miriplatin. TAI treatment typically results in tumor necrosis, which is normally evaluated by lipiodol accumulation and CT because lipiodol accumulation in the area of the tumor corresponds to the necrotic area of the tumor [12, 13]. The Liver Cancer Study Group of Japan recommends that the area of lipiodol accumulation should be calculated when evaluating the effects of TAI [14]. However, 1 case has been reported in which sufficient treatment effects were obtained despite washing out of most of the infused lipiodol as was observed for the main tumor in this case. The relationship between the degree of lipiodol accumulation and tumor necrosis should be verified.

In conclusion, TAI with miriplatin is a safe and effective treatment option for advanced HCCs refractory to TAI with epirubicin. Miriplatin can be used as a first-line chemotherapeutic agent for HCC.

Table 1. Laboratory data on admission

Hematology	
White blood cells, / μ l	2,720
Red blood cells, / μ l	354×10^4
Hemoglobin, g/dl	10.5
Platelets, / μ l	8.9×10^4
Coagulation	
Prothrombin time, %	87
APTT, s	36
Virus marker	
HBs antigen	negative
HCV antibody	positive
Tumor marker	
AFP, ng/ml	2,116
AFP(L3), %	67.4
DCP, mAU/ml	373
Chemistry	
Total protein, g/dl	7.5
Albumin, g/dl	3.4
Total bilirubin, mg/dl	0.4
AST, IU/l	52
ALT, IU/l	38
ALP, IU/l	288
γ GTP, IU/l	169
Choline esterase, IU/l	103
LDH, IU/l	200
Na, mEq/l	139
K, mEq/l	4.4
Cl, mEq/l	106
BUN, mg/dl	23.6
Cr, mg/dl	0.93

APTT = Activated partial thromboplastin time; HBs = hepatitis B surface; HCV = hepatitis C virus; AST = aspartate aminotransferase; ALT = alanine aminotransferase; ALP = alkaline phosphatase; γ GTP = γ -glutamyl transpeptidase; LDH = lactate dehydrogenase; Na = sodium; K = potassium; Cl = chlorine; BUN = blood urea nitrogen; Cr = creatinine.

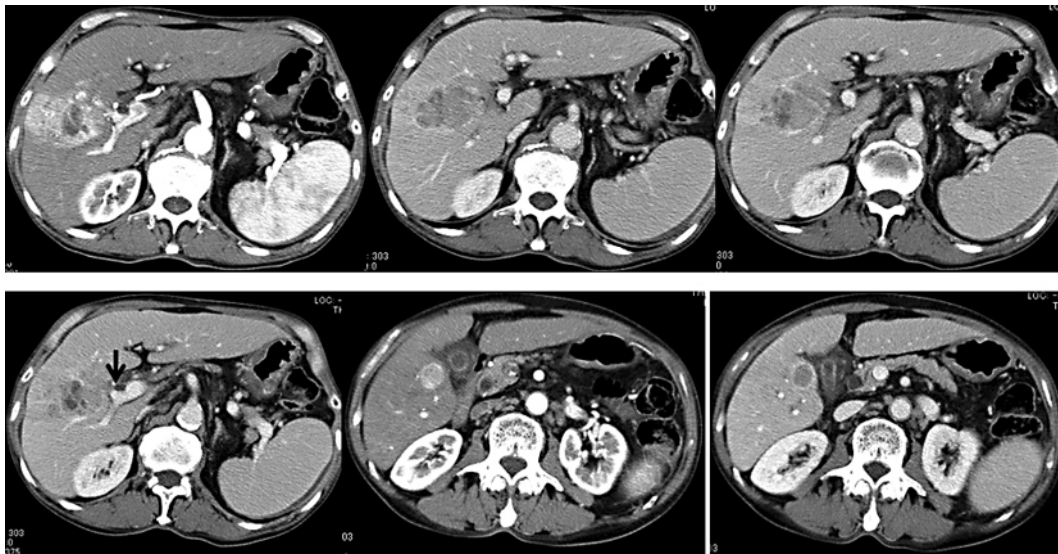


Fig. 1. Dynamic CT findings before treatment. In liver segment 8/7, an irregularly shaped tumor was found, 5.6 cm × 3.8 cm in size, which was irregularly enhanced in the early phase (top left) and indicated a region of deficiency in the delayed phase (top middle, top right, and bottom left). The tumor invaded the right anterior branch of the portal vein (top right and bottom left) and was cut off at the portion indicated by the arrow (i.e. vp2) (bottom left). In segment 5, which is adjacent to the gallbladder, a classical HCC was found, 2 cm in size, which was enhanced in the early phase (bottom middle) and indicated a region of deficiency in the delayed phase (bottom right).



Fig. 2. Abdominal angiography results. Left: trans-superior mesenteric arterial portography (superior mesenteric artery-DSA). The right anterior branch of the portal vein was not enhanced, suggesting the presence of a PVTT. The lumen of the right posterior branch of the portal vein was narrowed (arrow). Right: DSA of the common hepatic artery. A large irregular tumor stain in the right lobe and a small nodular tumor stain were observed.

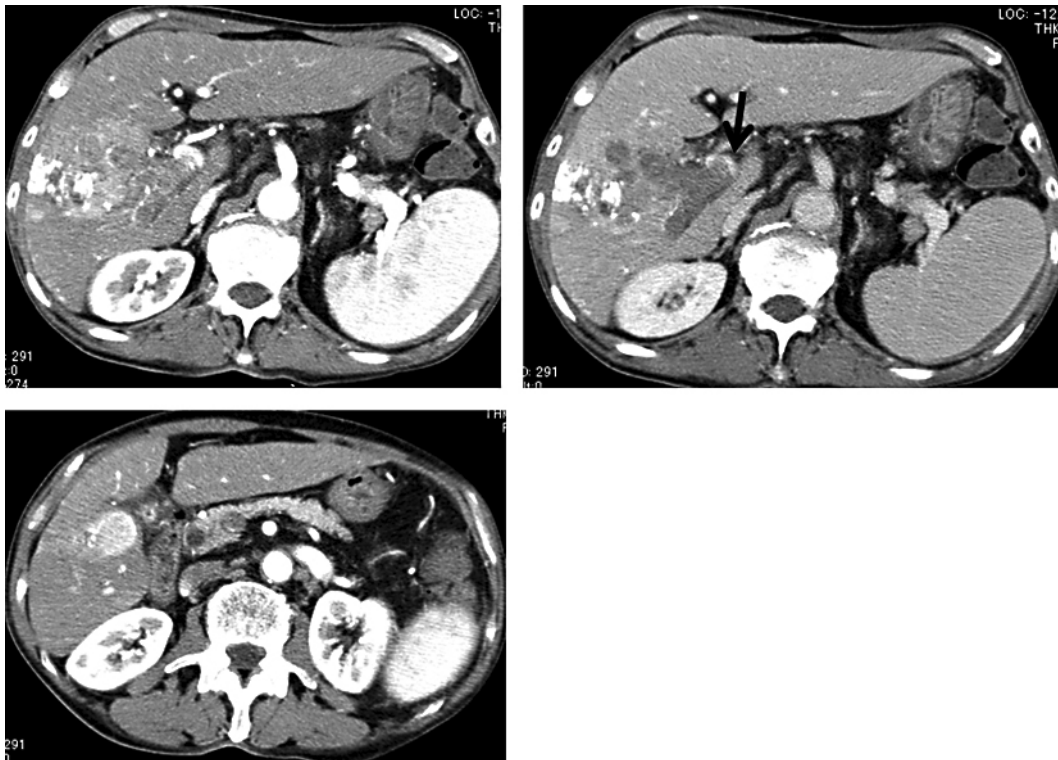


Fig. 3. Dynamic CT findings of tumor progression. In the main tumor, lipiodol accumulation was observed in some areas; however, tumor enhancement indicated progression in size (top left). The PVTT invaded into the main stem of the portal vein (top right; arrow). The tumor in segment 5 also increased in size (from 2 to 2.4 cm).

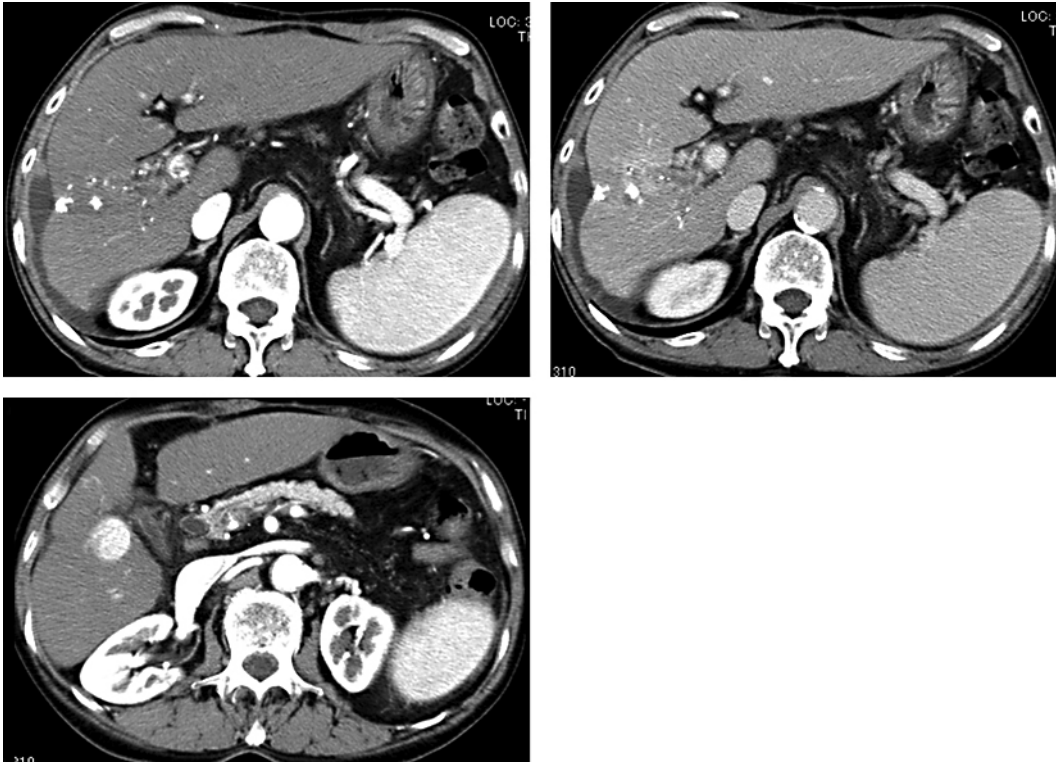
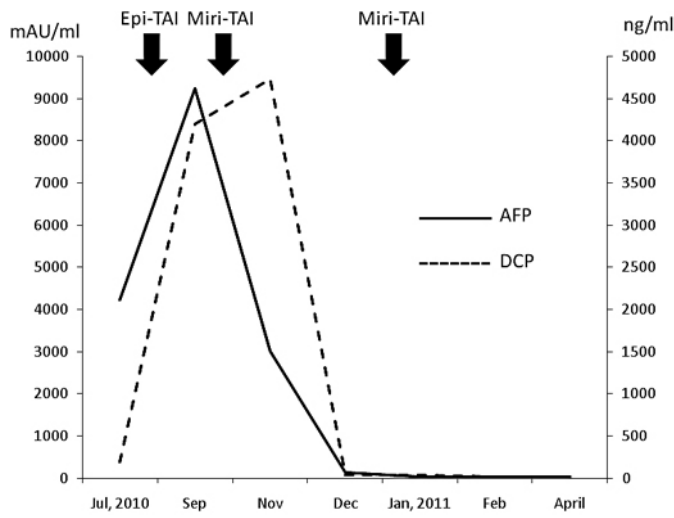


Fig. 4. Dynamic CT 3 months after the 2nd TAI with miriplatin (April 2011). Enhancement of the main tumor was markedly reduced in the remaining area of portal obstruction and most of the administered lipiodol was washed out (top right). The tumor in segment 5 did not change in size.



Epi; epirubicin, Miri; miriplatin, TAI; transcatheter arterial infusion AFP; alpha-fetoprotein, DCP; des-gamma-carboxy protein,

Fig. 5. Transition of tumor markers. After TAI with epirubicin, elevation of the tumor marker levels continued; however, after TAI with miriplatin, tumor marker levels markedly decreased and improved to nearly the normal range.

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