

A Case of Hepatocellular Carcinoma with Pulmonary Metastases Treated Successfully with a Combination of Repeated Hepatic Arterial Infusion Epirubicin and Cisplatin Chemotherapy and Systemic Low-Dose Infusion of 5-Fluorouracil

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We report a case of hepatocellular carcinoma (HCC) with pulmonary metastases treated with repeated hepatic arterial infusion chemotherapy (HAIC) comprising epirubicin and cisplatin, and systemic infusion of 5-fluorouracil (a modified EC/F protocol), which led to complete remission. A 49-year-old man with compensated liver cirrhosis experienced intrahepatic recurrence of HCC with extensive lung metastases. The modified EC/F therapeutic protocol, which was applied at the tenth cycle every 4-5 weeks, resulted in disappearance of the pulmonary metastases and normalization of serum α -fetoprotein levels. A single small HCC lesion was found in the left lobe of the liver 13 months after the final chemotherapy session. HAIC with the same regimen was conducted again, followed by percutaneous intratumoral chemoinjection therapy with 5-fluorouracil and interferon- γ . Thereafter, there was no evidence of recurrence in either the liver or the lung, as evidenced by image analysis and expression of tumor markers. The disease-free intervals for the liver and lung were 41 and 54 months, respectively. (*Gut and Liver* 2009;3:343-348)

Key Words: Carcinoma, Hepatocellular; Lung metastasis; Hepatic arterial infusion chemotherapy; Drug therapy

INTRODUCTION

Hepatocellular carcinoma (HCC) is the one of the most

common malignant cancers that occurs in worldwide. HCC is the third most common cause of cancer-related death in South Korea, where the death rate from HCC is 22.5/100,000 of the population.¹ Although recent progress in therapeutic modalities for HCC has improved the prognosis of HCC to some degree,² the majority of patients are diagnosed with inoperable multiple intrahepatic and/or extrahepatic metastases, and no more than 30% of patients are suitable to undergo curative resection.²

The lung (55%) is the most common site of extrahepatic spread from an HCC, followed by the abdominal lymph nodes (41%) and bone (28%), as shown in studies performed in the U.S.³ The most common site of extrahepatic spread from an HCC is the lung (67%), followed by the bone (12%), the adrenal gland (9%) and the peritoneum (5%) in South Korea.⁴ Although HCC has a poor prognosis mostly, several studies about the treatment of HCC with pulmonary metastases have been reported; however, there has been no standard therapeutic strategy determined for HCC with pulmonary metastases.⁵⁻⁷

In this report, we describe the case of a recurrent HCC with extensive lung metastases that was rapidly aggravated, despite of undergoing conventional transarterial chemoembolization (TACE) with adriamycin. Both the intrahepatic HCC and pulmonary metastases were successfully treated with the combined therapeutic protocol of monthly hepatic arterial infusion chemotherapy (HAIC) with epirubicin, cisplatin, and systemic infusion of 5-fluo-

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rouracil (5-FU).

CASE REPORT

A 49-year-old man was admitted to our department due to extensive pulmonary metastases of HCC with intra-

hepatic recurrence. The patient was initially treated with radiofrequency ablation therapy 15 months prior for a single HCC that was 4 cm in diameter and located in segment 7 of the liver. It was found 3 months prior that a 6.9 cm sized- single HCC recurred locally, with a few pulmonary metastases. The patient was underwent conventional TACE

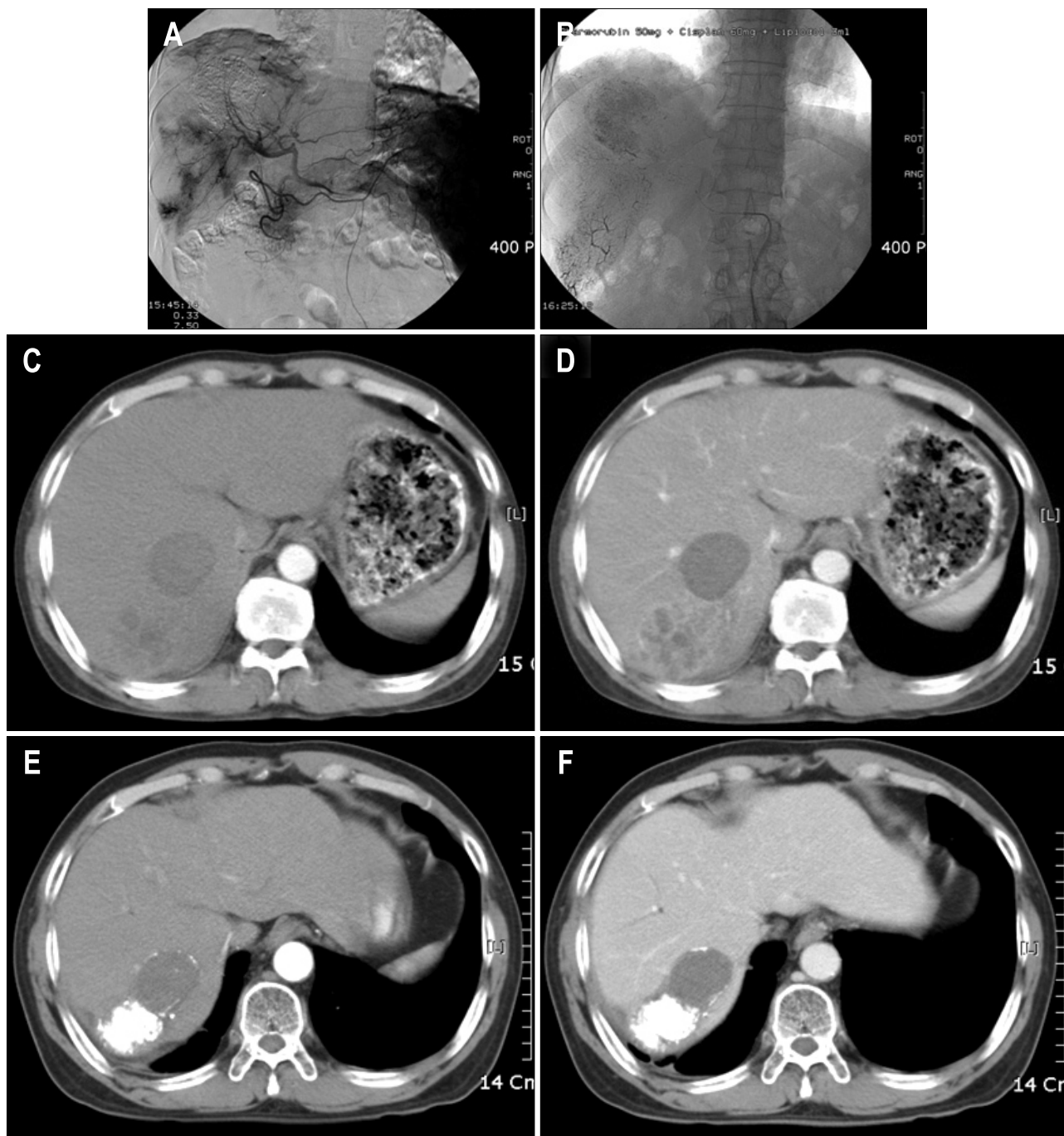


Fig. 1. Ill-defined hypervascular tumor staining is observed in the right lobe on celiac angiography (A, B). Abdominal computed tomography (CT) revealed a 6.8-cm irregular-margined recurrent hepatocellular carcinoma (HCC) and a 4.4-cm low-density necrotic lesion that was attributable to prior radiofrequency ablation in the right lobe of liver (C, D). There was no evidence of intrahepatic tumor recurrence on arterial- (E) and portal-phase (F) dynamic CT images after completion of chemotherapy.

with adriamycin alone twice during a one-month period. However, the pulmonary metastatic lesions were extensively aggravated. The patient had alcohol drinking history of 80 to 150 g ethanol content by U.S. standard daily and the patient was chronically infected with hepatitis B virus.

On admission, general physical examinations showed unremarkable findings. The laboratory findings showed leukocyte count of $3,200/\text{mm}^3$, hemoglobin level of 12.5 g/dL and platelet count of $104,000/\text{mm}^3$. The levels of aspartate aminotransferase (AST, 36 IU/L), alanine aminotransferase (ALT, 20 IU/L) and alkaline phosphatase

(ALP, 188 IU/L) were normal. The total bilirubin level (0.5 mg/dL; normal range, 0.2-1.4 mg/dL), albumin level (4.4 g/dL; normal range, 3.3-5.2 g/dL), prothrombin time 13.7 sec (80.5%; INR, 1.25) demonstrated adequate hepatic reserve, and then the Pugh-Child classification was class A. Elevation of the serum α -fetoprotein (AFP) level (202,530 ng/mL; normal range, 0-8.1 ng/mL) was found. Serum hepatitis B surface antigen (HBsAg) was positive, hepatitis B e antigen (HBeAg) was negative and HBV DNA was not detectable in serum, indicating a non-infective HBV carrier status. Reaction with anti-HCV (hepa-

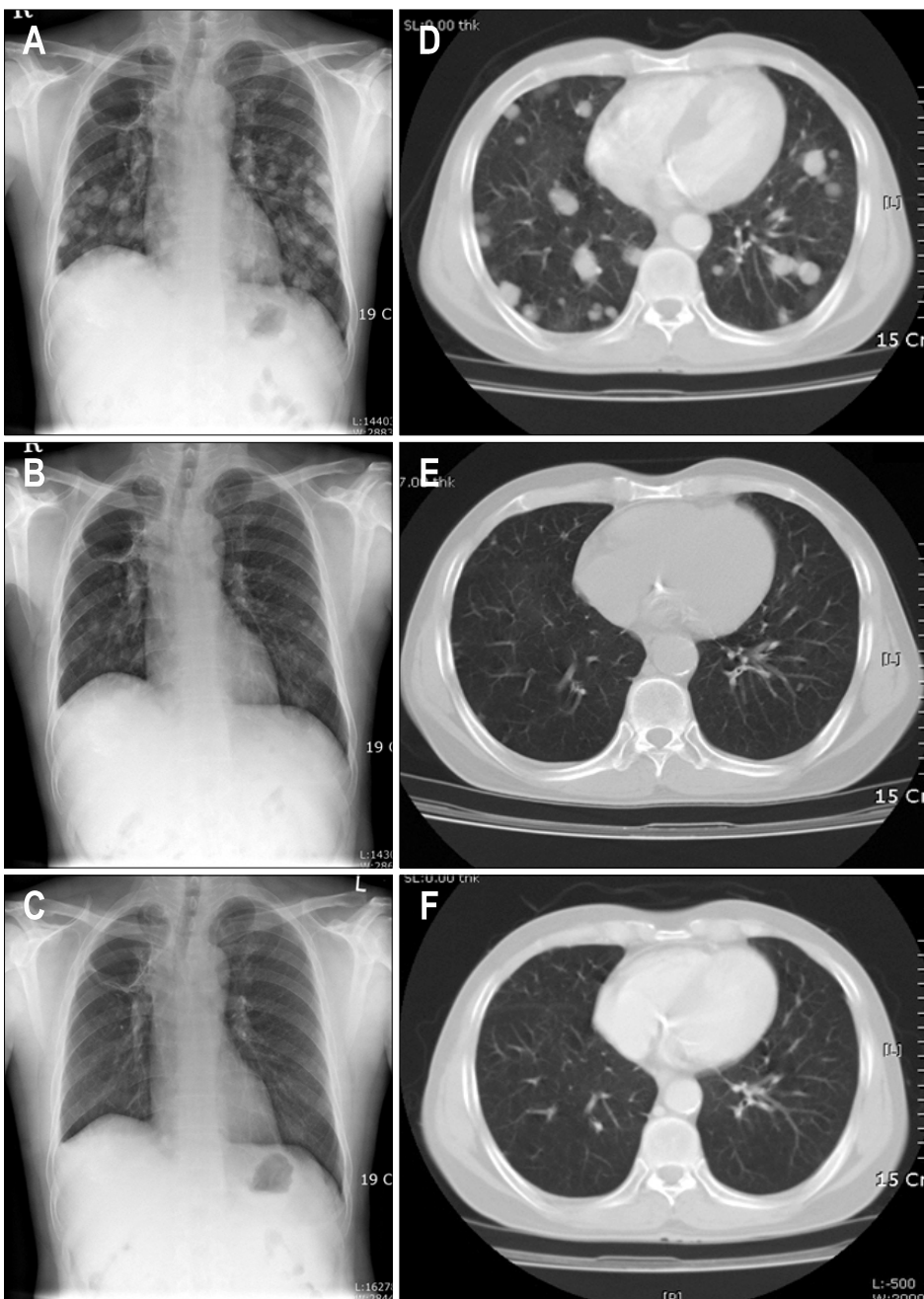


Fig. 2. Serial chest X-rays reveal the reduction in the size and number of lung nodules between before (A), during (B), and after (C) chemotherapy. Serial CT revealed the dramatic improvement in pulmonary metastases between before (D), during (E), and after (F) chemotherapy.

titis C virus) was negative.

Considering both the occupation of the patient and HCC status, which was TNM 4b stage and CLIP score 1, we modified the intrahepatic arterial infusion of epirubicin and cisplatin and systemic intravenous infusion of 5-fluorouracil (EC/F) protocol for HCC that Jang *et al.*⁸ had reported. This protocol consisted of hepatic arterial infusion chemotherapy (HAIC) with the use of 50 mg/m² epirubicin and 60 mg/m² cisplatin and systemic 12-hour infusion of 200 mg/m² 5-FU. Dose modification for the use of epirubicin and cisplatin was calculated as follows: calculated dose=(dose per BSA [body surface area]) \times (leukocyte count/4000) \times (1-(Pugh-Child score-5)/10) \times (1-(age-45)/100). The patient underwent a three-day admission course each cycle. Every 4 to 5-week modified EC/F-based treatment was performed for 10 times repeatedly. The total accumulation doses of epirubicin and cisplatin were 502 mg and 600 mg, respectively. There was neither significant cytopenia nor decline of hepatic function with

the use of this protocol. After the end of the second cycle of treatment, the serum AFP level was dramatically decreased from 462,704 ng/mL to 575 ng/mL. At the end of the sixth cycle, the serum AFP level was normalized to 4.47 ng/dL, and also the pulmonary metastatic nodules had nearly disappeared (Figs. 1 and 2). The treatment was continued until tenth cycle as a 0.7 cm-sized isolated nodule was still observed in the left lower lung field in a dormant state. After 13 months of the disease-free interval (DFI), another 1 cm-sized HCC was found in the left hepatic lobe. To identify another tumors that were possibly missed on CT images, we performed HAIC with the same regimen and added the use of percutaneous intra-tumoral chemo-injection therapy with a mixture of 500 mg 5-FU and 4 MU interferon gamma to the target tumor (Fig. 3). No evidence of recurrence in both liver and lung was found, which was based on image analysis and expression of tumor markers up to December 2008. For liver and lung, the DFIs were 41 months and 54

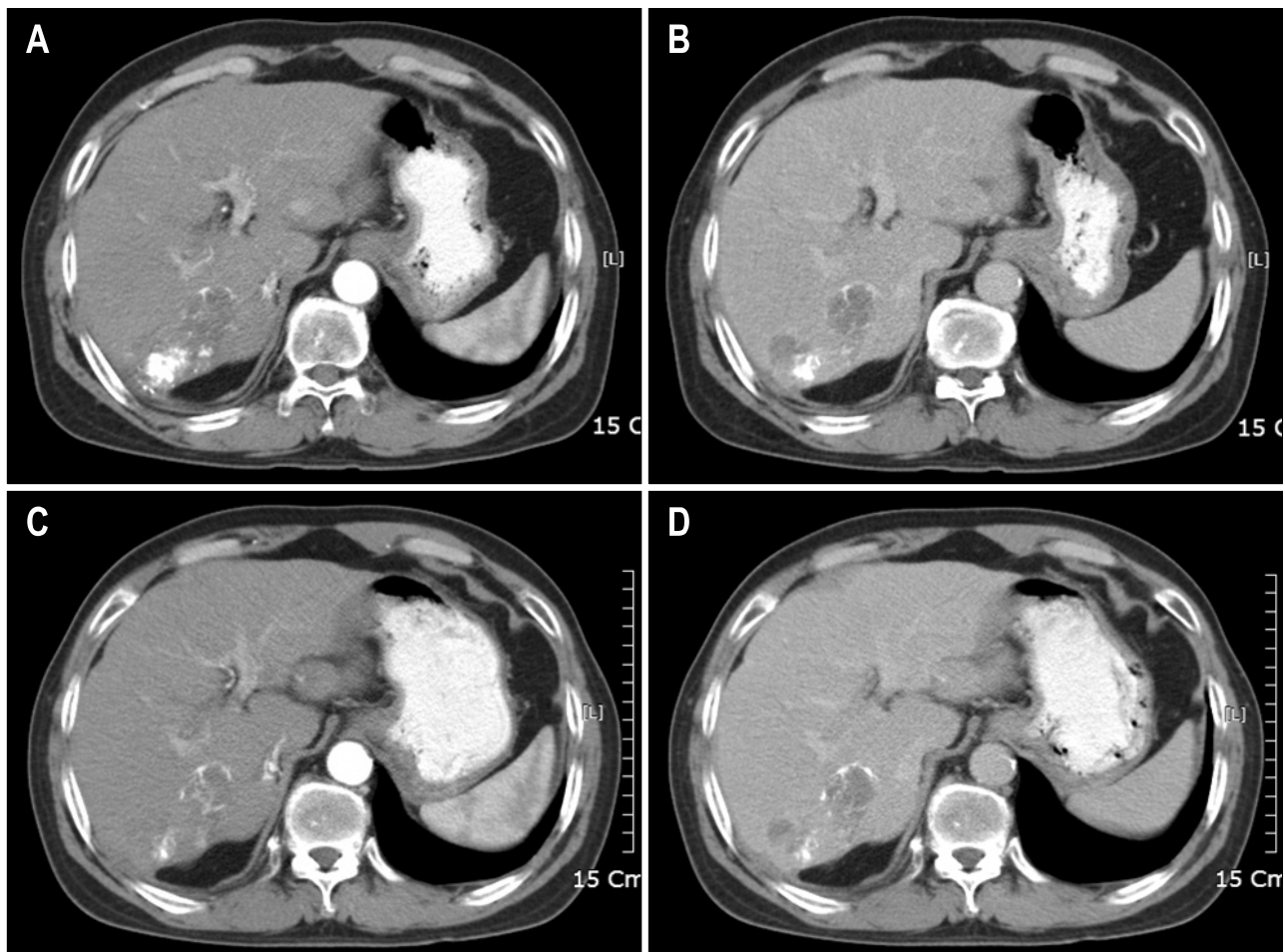


Fig. 3. Abdominal arterial-phase CT showing the new, 1-cm, enhanced HCC in the left lobe of the liver (A, B). The CT scan performed during the follow-up period after further chemotherapy shows complete atrophy of the hepatic tumor (C, D).

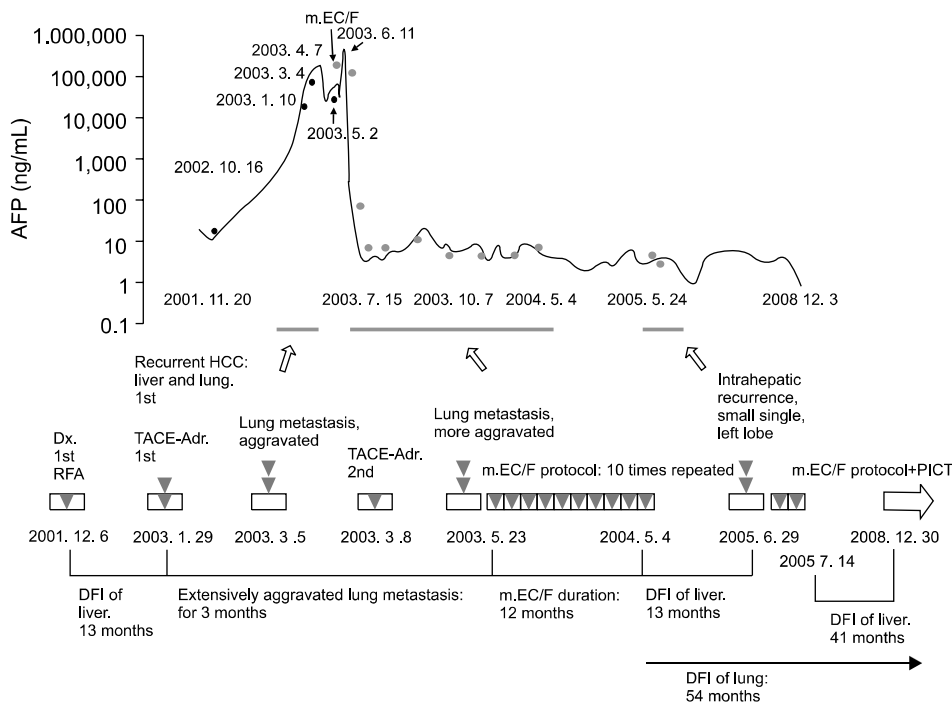


Fig. 4. Summary of the clinical course of the patient. The red circle indicates transarterial chemoembolization (TACE) and the blue circle indicates hepatic arterial infusion chemotherapy (HAIC) with the modified epirubicin, cisplatin/5-fluorouracil protocol. The blue inverted triangle inside the quadrangle indicates treatment performance for HCC, and the inverted triangle above the quadrangle implies changed disease status (i.e., recurrence or metastasis). AFP, α -fetoprotein; Dx, diagnosis; RFA, radiofrequency ablation therapy; m. EC/F, modified EC/F protocol; PICT, percutaneous intra-tumoral chemo-injection therapy; DFI, disease-free interval.

months, respectively (Fig. 4).

DISCUSSION

Although systemic chemotherapy has been used for advanced HCC, the disease has been reported to have a low response rate and the use of systemic chemotherapy has been unable to demonstrate a significant survival improvement.^{9,10} Because most HCC patients have liver cirrhosis with limited hepatic reserve, the patients are not adequate candidates for chemotherapy and are likely to have more side effects associated with the cytotoxic effects of anti-cancer drugs.¹¹

As almost all HCC obtain the blood supply from the hepatic artery, HAIC was developed as a therapeutic option for advanced HCC. Intra-arterial infusion provides a high concentration of drug to the tumors¹² and efficient delivery of drugs to tumors occurs by the use of angiography or by the use of an implanted chemoport subcutaneously. Administration of anti-cancer drugs is divided into several sessions and can lower the dose of one-shot arterial chemoinfusion, so that the systemic cytotoxicities of drugs can be minimized and the risk of hepatic dysfunction associated with chemotherapy can be reduced. A number of studies have shown a superior results for the use of intra-arterial chemotherapy as compared to the use of systemic chemotherapy.¹³⁻¹⁵

Drugs such as cisplatin, 5-FU, epirubicin and mitomycin C have been tried as single or combination agents for

HAIC.^{8,16-18} The deoxynucleotide 5-fluoro-2'-deoxyuridine-5'-monophosphate derived from 5-FU blocks DNA synthesis by inhibiting thymidylate synthase. Cisplatin enhances 5-FU cytotoxicity by inhibiting intracellular L-methionine metabolism and by consequently increasing the reduced folate pool.¹⁹ Based on these effects, studies with combination chemotherapy with cisplatin and 5-FU have been attempted. Toyoda *et al.*¹⁶ reported that the objective response (OR) rate of continuous local arterial infusion with cisplatin and 5-FU for severe advanced HCC was 14.3%. Ando *et al.*¹⁷ showed that the OR rate of arterial infusion chemotherapy with 5-FU and cisplatin for HCC with tumor thrombosis of the main trunk of the portal vein was 44.4%. Jang *et al.*⁸ reported that the OR rate and median survival time for patients undergoing combination therapy comprised of transarterial infusion of epirubicin and cisplatin, systemic infusion of 5-FU and additional percutaneous ethanol injection was higher as compared to the use of conventional TACE with adriamycin and gelfoam in patients with unresectable HCC. In addition, Kogure *et al.*¹⁸ reported a case of a patient with an HCC with tumor invasion to the inferior vena cava and multiple pulmonary metastases who was treated with the administration of epirubicin, cisplatin and mitomycin C by hepatic artery and bronchial artery infusion, which led to complete remission.

In the present case, we modified an original protocol reported by Jang *et al.*⁸ to reduce the admission period because of the occupational situation for the patient and used

calculated doses of epirubicin and cisplatin for intrahepatic arterial infusion and one-day low fixed dose systemic infusion of 5-FU. Although the HCC did not respond to adriamycin alone, which was used just before visiting our department, the modified EC/F protocol showed a dramatic treatment effect after the second cycle of administration. After the end of the sixth cycle of treatment, both liver and pulmonary metastases had the nearly completely responds and the serum AFP level was normalized, as shown in Fig. 4.

A question arises why the HCC in this case responded completely to the modified EC/F therapy despite both the non-responsiveness to adriamycin, which belongs to the same pharmacological group as epirubicin and the use of the one-day low dose 5-FU in the protocol. It may be considered that cisplatin played the main therapeutic role in this protocol. Several case reports have suggested that the use of cisplatin sometimes leads to a complete remission of advanced HCC with pulmonary metastases.²⁰⁻²² As the original EC/F therapeutic protocol demonstrated efficiency in the treatment of advanced HCC, it is possible that combination treatment might contribute to a good result.

In conclusion, this case indicates that chemosensitivity plays a more important role in HCC treatment than any other clinical prognostic factors, such as the AFP level, tumor volume, presence of metastases, vascular invasion, the type of administration and dosage.

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