CASE REPORT

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Transcatheter Arterial Chemotherapy with Miriplatin for Hepatocellular Carcinoma Patients with Chronic Renal Failure: Report of Three Cases

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Miriplatin is a novel lipophilic platinum complex that was developed to treat hepatocellular carcinoma (HCC). Although HCC patients frequently have coexisting chronic renal failure, little prospective data are available regarding the clinical toxicity of chemotherapeutic agents used to treat HCC patients with chronic renal failure. In a phase II study, the plasma concentration of total platinum in patients who received miriplatin was very low, and no severe renal toxicity caused by miriplatin injection was reported. Here, we present three cases of HCC with stage 4 chronic renal failure who received transcatheter arterial chemotherapy with miriplatin. All cases were male, ages 72, 84, and 83 years, and had serum creatinine levels of 2.3, 1.6, and 1.9 mg/dL, respectively. Their estimated glomerular filtration rates were 21.9, 20.3, and 22.2 mL/min, respectively. All cases were treated for unresectable HCC with transcatheter arterial chemotherapy with miriplatin. No serious adverse events were observed, and serum creatinine levels did not elevate, even in the patient who experienced renal failure caused by cisplatin administration. These results might suggest that transcatheter arterial chemotherapy with miriplatin can be safely used in HCC patients with chronic renal failure. **(Gut Liver 2013;7:246-251)**

Key Words: Miriplatin; Chronic renal failure; Hepatocellular carcinoma

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common malignant diseases worldwide.[1] Since curative therapies, including resection, liver transplantation, and percutaneous ablation (percutaneous ethanol injection and radiofrequency ablation [RFA]) are applicable in only 30% to 40% of HCC patients, transcatheter arterial chemoembolization (TACE) has been recognized as an effective palliative treatment option for patients with advanced HCC.[2-7] HCC patients frequently have coexisting cirrhosis, which is a predisposing factor for the development of renal dysfunction due to intravascular volume depletion, inadequate renal vasoconstriction, and hyperaldosteronism.[8-13]

Little prospective data are available regarding the clinical toxicity of chemotherapeutic agents used to treat HCC patients with chronic renal failure. Although cisplatin is an effective anticancer drug that is widely used for the treatment of many malignancies, including HCC, it is associated with significant nephrotoxicity, particularly in patients with chronic renal failure.[2,7] Miriplatin is a novel cisplatin derivative containing platinum with a high affinity for the iodized ethyl ester of fatty acids of poppyseed oil (Lipiodol Ultra-fluide; Laboratoire Guerbet, Aulnay-Sous-Bois, France) that is used in TACE. Clinical trials have demonstrated that miriplatin is effective in the treatment of HCC.[14-19]

In a Phase II HCC study, the plasma concentration of total platinum in patients receiving miriplatin was very low, and no severe renal toxicity caused by miriplatin injection was reported.[17] Here we present three cases of HCC with stage 4 chronic renal failure who received transcatheter arterial chemotherapy with miriplatin.[20]

CASE REPORTS

1. Case 1

A 72-year-old man with HCC, liver cirrhosis, and diabetic nephropathy had undergone RFA four times and TACE three times over 5 years. As shown in Fig. 1, a computed tomography (CT) scan of the liver revealed multiple HCCs (tumor size, 15 to 34 mm; tumor number, three; stage, T2N0M0). The serum creati-

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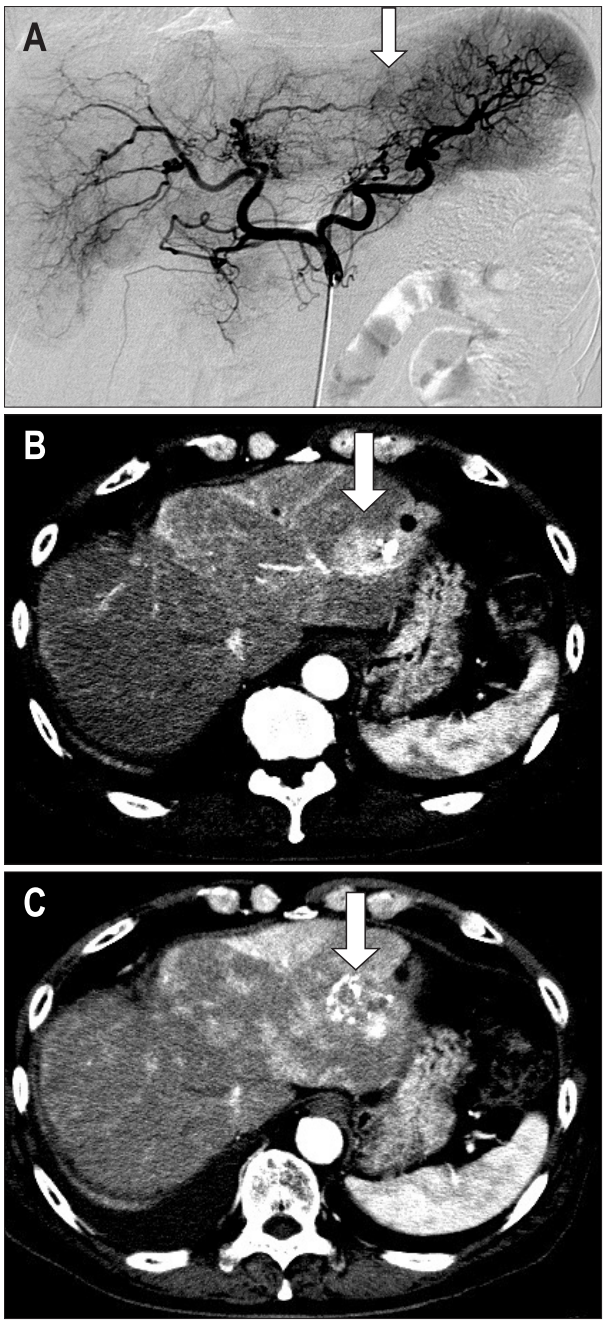

Fig. 1. Case 1. A 72-year-old man with unresectable hepatocellular carcinoma (HCC) who received transcatheter arterial chemoembolization (TACE) with miriplatin. (A) Abdominal angiography showed multiple HCCs (arrow). (B) Computed tomography (CT) showed multiple HCCs (arrow). (C) CT performed 1 month after TACE. The lesions revealed accumulations of lipiodol (arrow). Treatment efficacy was assessed as a partial response.

nine level was 2.3 mg/dL, and the estimated glomerular filtration rate (GFR) was 21.9 mL/min (Table 1).[21]

The patient was hydrated through a peripheral line. The femoral artery was catheterized under local anesthesia, and catheter was inserted superselectively into the hepatic artery that supplied the target tumor, for injection of the miriplatin/lipiodol suspension and 1 mm gelatin particles (1 mm-Gelpart; Nippon Kayaku, Tokyo, Japan). Miriplatin/lipiodol suspension was administrated slowly under careful fluoroscopic guidance. The dose of miriplatin/lipiodol was determined according to tumor size and the degree of liver dysfunction. The patient received TACE with miriplatin (miriplatin 50 mg, lipiodol 2.5 mL, and 1 mm-Gelpart were injected from both the right and left hepatic arteries). Therapy was well tolerated, and the patient's weight and serum creatinine level remained stable after treatment (Fig. 2). Major side effects included grade 1 fever, elevated blood glucose, and grade 1 nausea, which all resolved within 1 week (the National Cancer Institute's Common Terminology Criteria for Adverse Events [CTCAE] version 4.0). Treatment efficacy was assessed 1 month after treatment. Partial response (modified response evaluation criteria in solid tumors, mRECIST) was achieved in all target lesions.[22]

The patient was received two times TACE with miriplatin at intervals of 4 months after the first administration (second and third dosage of miriplatin were 120 mg and dosage of lipiodol were 6 mL). The patient's weight and serum creatinine level still remained stable after repeat injection of miriplatin (serum creatinine level was 2.2 mg/dL after third TACE with miriplatin). Stable disease (mRECIST) was achieved in all target lesions after third TACE with miriplatin.

2. Case 2

An 84-year-old man with HCC, liver cirrhosis, and chronic renal failure had undergone RFA three times and TACE six times over 10 years. As shown in Fig. 3, a CT scan of the liver showed multiple HCCs (tumor size, 12 to 55 mm; tumor number, six; stage, T3N0M0). The serum creatinine level was 1.6 mg/dL, and the estimated GFR was 20.3 mL/min (Table 1).

The patient was hydrated through a peripheral line. The femoral artery was catheterized under local anesthesia, and catheter was inserted superselectively into the hepatic artery that supplied the target tumor, for injection of the miriplatin/lipiodol suspension. Miriplatin/lipiodol suspension was administrated slowly under careful fluoroscopic guidance. The dose of miriplatin/lipiodol was determined according to tumor size and the degree of liver dysfunction.

The patient received transcatheter arterial chemotherapy with miriplatin (miriplatin 50 mg and lipiodol 2.5 mL were injected from both the right and left hepatic arteries). Therapy was well tolerated, and the patient's weight and serum creatinine level remained stable after treatment (Fig. 2). The major side effect of treatment was grade 1 fever, which resolved within 1 week (CTCAE version 4.0). Treatment efficacy was assessed 2 months after therapy. Stable disease (mRECIST) was achieved in all target lesions.

3. Case 3

An 83-year-old man with HCC, liver cirrhosis, hypertension,

Table 1. Patient Characteristics

Characteristic	Case 1	Case 2	Case 3
Age	72	84	83
Gender	Male	Male	Male
Height, cm	159	160	162
Weight, kg	58	47	57
Serum creatinine, mg/dL*	2.3	1.6	1.9
Estimated GFR1, mL/min†	21.9	20.3	22.2
Estimated GFR2, mL/min‡	22.8	32.5	27.0
Etiology	HCV	HCV	HBV
Child-Pugh score	A (6)	A (5)	A (5)
ICG-R15, %	16	13	4
Underlying disease that caused renal failure	Diabetic nephropathy	Chronic glomerulonephritis	Cisplatin induced renal failure
Tumor no.	3	6	40
Maximum tumor size, mm	34	55	39
Cancer stage (TNM)	II (T2N0M0)	III (T3N0M0)	II (T2N0M0)
Dosage of miriplatin, mg	100	100	70
Dosage of lipiodol, mL	5	5	3.5
Use of gelatin sponge particles	Yes	No	Yes
Contrast medium, mL	Iomeprol 60	Iomeprol 50	Iomeprol 190
Use of hydration therapy after miriplatin infusion	Yes	Yes	Yes

GFR, glomerular filtration rate; HCV, hepatitis C virus; HBV, hepatitis B virus; ICG-R15, indocyanine green retention rate at 15 minutes.
*Enzymatic method; †Cockcroft and Gault formula; ‡Japanese equation for estimating GFR.

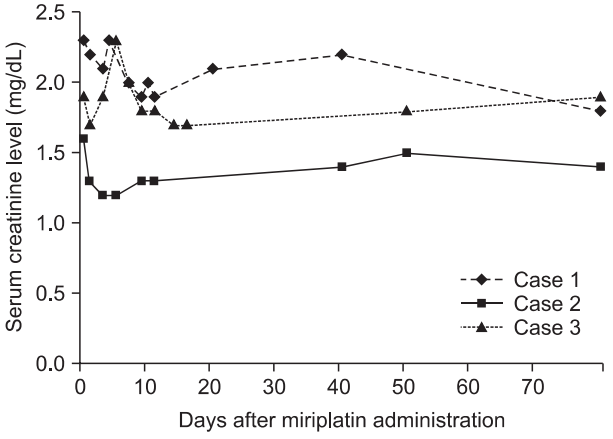

Fig. 2. Serum creatinine level after miriplatin administration in the three cases.

and renal failure that had been caused by cisplatin administration had undergone TACE nine times over 4 years. As shown in Fig. 4, a magnetic resonance imaging scan of the liver revealed multiple HCCs (tumor size, 5 to 39 mm; tumor number, 40; stage, T2N0M0). The patient's serum creatinine level was 1.9 mg/dL, and the estimated GFR was 22.2 mL/min (Table 1).

The patient was hydrated through a peripheral line. The femoral artery was catheterized under local anesthesia, and catheter was inserted superselectively into the hepatic artery that supplied the target tumor, for injection of the miriplatin/lipiodol suspension and 1 mm-Gelpart. Miriplatin/lipiodol suspension was administrated slowly under careful fluoroscopic guidance. The dose of miriplatin/lipiodol was determined according to tumor size and the degree of liver dysfunction.

The patient received TACE with miriplatin (miriplatin 30 mg, lipiodol 1.5 mL, and 1 mm-Gelpart were injected from the right and left hepatic arteries, and miriplatin 10 mg and lipiodol 0.5 mL were injected from the right inferior phrenic artery). Therapy was well tolerated, and the patient's weight and serum creatinine level remained stable after treatment (Fig. 2). Major side effects included grade 1 fever and grade 1 nausea, both of which resolved within 1 week (CTCAE version 4.0). Treatment efficacy was assessed 3 months after therapy. Stable disease (mRECIST) was achieved in all target lesions.

DISCUSSION

Various anticancer drugs, such as doxorubicin hydrochloride, epirubicin hydrochloride, mytomycin C, cisplatin, and neocarzinostatin, have been used at TACE agents for the treatment of HCC. However, the most effective and least toxic TACE protocol for HCC has yet to be identified.

Miriplatin is a novel lipophilic cisplatin derivative that can be suspended in lipiodol and used for transcatheter arterial che-

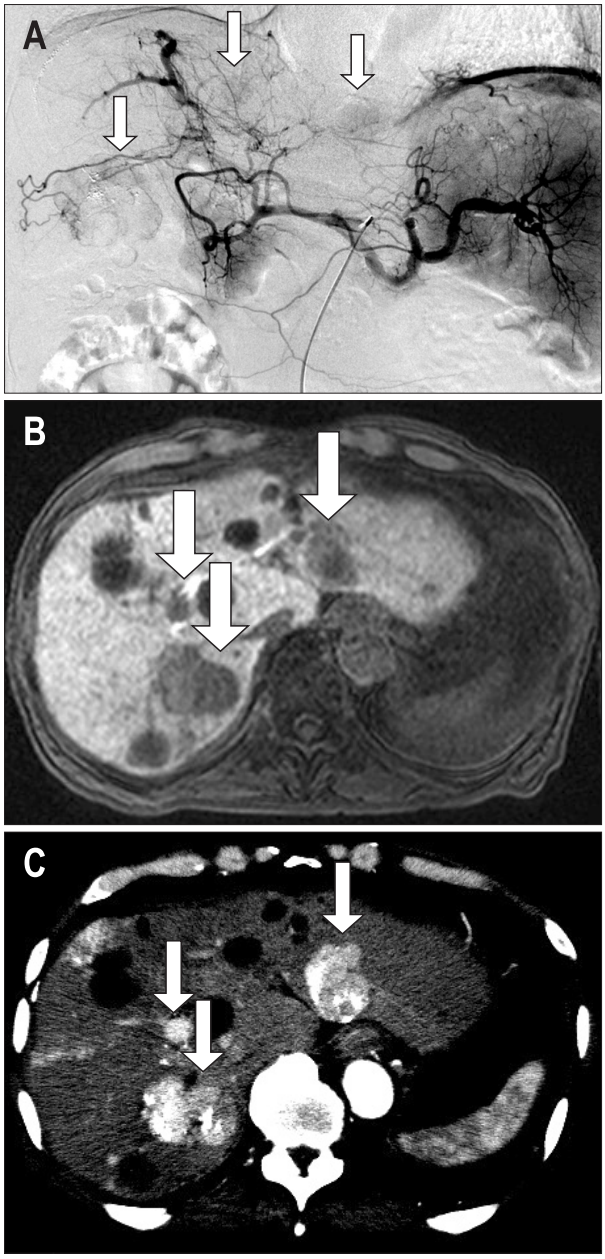

Fig. 3. Case 2. An 84-year-old man with unresectable hepatocellular carcinoma (HCC) who received transcatheter arterial chemotherapy with miriplatin. (A) Abdominal angiography showed multiple HCCs (arrows). (B) Magnetic resonance imaging (hepatobiliary phase) showed multiple HCCs (arrows). (C) Computed tomography performed 2 months after transcatheter arterial chemotherapy with miriplatin. The lesions showed accumulations of lipiodol (arrows). The treatment efficacy was assessed as a stable disease.

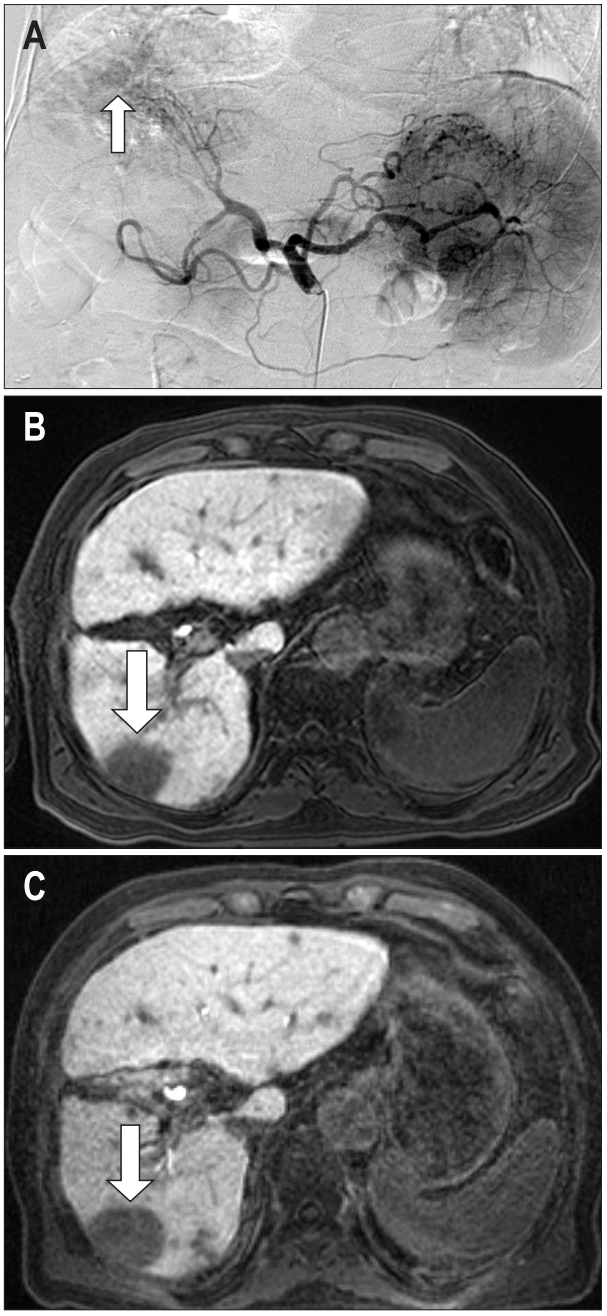

Fig. 4. Case 3. An 83-year-old man with unresectable hepatocellular carcinoma (HCC) who received transcatheter arterial chemoembolization (TACE) with miriplatin. (A) Abdominal angiography showed multiple HCCs (arrow). (B) Gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA) enhanced magnetic resonance imaging (MRI; hepatobiliary phase) showed multiple HCCs (arrow). (C) Gd-EOB-DTPA enhanced MRI performed 3 months after TACE. The lesions showed accumulations of lipiodol (arrow). The treatment efficacy was assessed as a stable disease.

motherapy of advanced HCC. It is one of the platinum agents, although hydration after administration is not necessary of its weak renal toxicity.

Various types of resistance to therapy can occur during repetition of TACE. Platinum derivatives are frequently administered to patients with advanced HCC that is unresponsive to anthracycline and antibiotic drugs.[23]

Miriplatin was developed as a lipophilic platinum complex in an effort to produce a superior antitumor effect in HCC with lower toxicity compared to cisplatin. Miriplatin-lipiodol suspension is a stable colloidal emulsion that is deposited within HCC tumors, where it gradually releases active derivatives of miripla-

tin.

According to pharmacokinetic studies, the plasma concentration of total platinum in patients treated with miriplatin is much lower than that after administration in patients administered intra-arterial cisplatin: the Cmax is approximately 300-fold lower and the Tmax roughly 500-fold longer than the corresponding values for intra-arterial cisplatin.[17] Theoretically, therefore, it can be administered even in patients of advanced HCC patients with chronic renal failure if visceral angiography can be performed.

Clinical trials have shown that miriplatin is effective for the treatment of HCC, but the safety and efficacy of miriplatin has not been evaluated in HCC patients with chronic renal failure.[16,17] Herein we presented three HCC cases with stage 4 chronic renal failure who received transcatheter arterial chemotherapy with miriplatin. In all three cases, no serious adverse events were observed, and serum creatinine level did not increase, even in the patient who had experienced renal failure due to cisplatin administration (Fig. 2). Repeated injection of miriplatin appears to be also safe in HCC patients with chronic renal failure.

The present results might suggest that transcatheter arterial chemotherapy with miriplatin can be safely used in HCC patients with chronic renal failure. A prospective study is required to assess the most effective, least nephrotoxic anticancer agent among the various platinum derivatives. Miriplatin appears to be a promising agent for HCC patients with chronic renal failure.

CONFLICTS OF INTEREST

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