Safety and Short-term Therapeutic Effects of Miriplatin–Lipiodol Suspension in Transarterial Chemoembolization (TACE) for Hepatocellular Carcinoma

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Abstract. *Aim: To determine the safety and usefulness of a novel anticancer drug, miriplatin, in transarterial chemoembolization (TACE) for unresectable hepatocellular carcinoma. Patients and Methods: Patients (n=115) who underwent TACE with miriplatin–lipiodol suspension (miriplatin group), and control patients (n=131) who underwent TACE with cisplatin–lipiodol suspension (CDDP group) took part in this study. Results: The overall incidence of adverse events was significantly lower in the miriplatin group. The percentage of patients attaining treatment effect 4 in both groups was not significantly different. The proportion exhibiting a >50% decrease in positive tumor markers following TACE was significantly greater in the CDDP group for alpha-fetoprotein, but not significantly different for des-gammma-carboxy prothrombin. Conclusion: Miriplatin–lipiodol suspension was associated with reduced intensity of adverse events and had comparable short-term therapeutic effects to cisplatin–lipiodol suspension, thereby indicating its usefulness in TACE.*

In the treatment of unresectable hepatocellular carcinoma (HCC), transarterial chemoembolization (TACE) is widely known to improve the prognosis (1, 2), but the agents used in the procedure vary between institutions. In our department, a suspension of fine powdered cisplatin (IA call®; Nippon Kayaku, Tokyo, Japan) in lipiodol (an ethyl ester of iodinated poppyseed oil fatty acids) has been mainly used, based on reports describing the favorable antitumor effects of this preparation in TACE (3-12). However, with prolonged survival and repeated TACE sessions, some problems, such as drug resistance and anaphylactic reactions, have been encountered (13).

In January 2010, miriplatin (Miripla®; Dainippon Sumitomo Pharma, Co. Ltd., Osaka, Japan) in suspension in lipiodol was approved for coverage by health insurance and released commercially in Japan, with the drug expected to offer greater safety with comparable therapeutic effects. Miriplatin is a third-generation platinum compound and a potent inhibitor of tumor growth. Cisplatin-resistant tumor cell lines showed sensitivity to miriplatin, and the compound forms a stable suspension in lipiodol (14-18). The present study was conducted to determine the short-term therapeutic effects and adverse event profile associated with the use of miriplatin–lipiodol suspension in TACE, using a cisplatin–lipiodol suspension as a control.

Patients and Methods

The study included 115 patients with HCC who underwent TACE with miriplatin–lipiodol suspension between January and August 2010 (the miriplatin group), as well as 131 comparative patients with HCC who underwent TACE with cisplatin–lipiodol suspension between January 2007 and August 2010 (the CDDP group). Data were compared between the two groups.

HCC was diagnosed by the distinctive findings on ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI), and angiography. The eligibility criteria of the patients for this study were as follows: i) No indication for surgical resection or local ablation therapy such as radiofrequency ablation (RFA) or percutaneous ethanol injection (PEI) therapy; ii) no evidence of active renal disease meeting the contraindications for miriplatin and cisplatin therapy; iii) Eastern Cooperative Oncology Group (ECOG) performance status (PS) (19) level 0-2; iv) no uncontrolled ascites or

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Table I. *Characteristics of patients taking part in the study.*

	Miriplatin group (n=115)	CDDP group (n=131)	*P*-value
Gender (male/female)	82/33	97/34	N.S.
Age (years) (mean) (range)	71.0 (48-85)	71.8 (49-90)	N.S.
Etiology (B/C/B+C/nonB nonC)	12/81/3/19	20/101/0/10	0.029
Number of tumor (1/2/3/≥4)	24/12/15/64	20/24/18/69	N.S.
Maximal tumor diameter (mean±SD) (mm)	30.6±30.7	28.1±21.1	N.S.
(≤20/20-30/30-50/≥50)	44/49/12/10	48/53/12/18	N.S.
HCC stage* (I/II/III/IV)	14/37/46/18	9/40/48/34	N.S.
Child-Pugh classification (A/B/C)	62/53/0	71/60/0	N.S.
TACE sessions (1/2-3/≥4)	20/45/50	27/48/56	N.S.
Amount of drug-suspended lipiodol, ml (mean±SD) (20 mg/ml)	2.3±1.5	1.9±1.1	0.045
Amount of gelatin sponge, ml (mean±SD)	0.6±1.2	0.8±1.2	N.S.

N.S., Not significant; *HCC stage was classified according to The General Rules of Primary Liver Cancer, 5th edition (20).

pleural effusion; and v) total serum bilirubin less than 3 mg/dl. Informed consent was obtained from all of the patients. The study protocol was approved by the Ethics Committee of NTT West Kyusyu Hospital and the study was conducted in accordance with the Declaration of Helsinki.

TACE was performed through the femoral artery using the Seldinger technique. In both groups, administration of the lipiodol suspension was followed by administration of gelatin sponge particles (Gelpart®; Nippon Kayaku, Tokyo, Japan) as an embolization material. Patients were excluded from the study if they concomitantly received hepatic arterial infusion of 5-fluorouracil (5-FU). Administration of the lipiodol suspension was terminated when tumor vessels were filled with the suspension and tumor stain disappeared on imaging. Both miriplatin and cisplatin were prepared as suspensions at a concentration of 20 mg/ml in lipiodol, and the maximum amount administered per session of TACE was limited to 120 mg for miriplatin and 100 mg for cisplatin. One vial of Gelpart® 1 mm gelatin sponge was used as a suspension in 10 ml of a contrast agent.

The incidence of post-procedural adverse events (nausea, vomiting, pain, diarrhea, fever, fatigue, anorexia, anaphylaxis, and hypotension) was compared between the groups according to the Common Terminology Criteria for Adverse Events (CTCAE, ver. 4.0). Changes in laboratory data detailing white blood cell count, eosinophil percentage, hemoglobin level, platelet count, total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and creatinine were also examined. In both groups, the observation period was either for two weeks following TACE, or until discharge from hospital.

Treatment effect (TE) at one month following TACE was assessed based on the extent of necrosis on contrast-enhanced abdominal computed tomography (CT), and was graded into four categories according to the Response Evaluation Criteria in Cancer of the Liver (RECICL), developed by the Liver Cancer Study Group of Japan (20). Specifically, the areas on the CT showing lipiodol uptake were regarded as necrotic areas, and the four grades of TE were defined as follows: TE4, 100% necrosis or size reduction of tumor; TE3, 50-99% necrosis/size reduction; TE2, up to 50% necrosis/size reduction, or less than 25% tumor enlargement; and TE1, tumor enlargement by 25% or more, irrespective of the extent of necrosis. For patients with positive values for the tumor markers alpha-fetoprotein (AFP) or *des*-gamma-carboxy prothrombin (DCP), the percentage decrease in these values at one week following TACE was calculated.

The differences in the groups were tested using the chi-square test and *t*-test. A statistically significant difference was regarded as $p<0.05$. The software used for statistical analyses was JMP 7.0.1 for Macintosh (SAS institute Inc., Cary, NC, USA).

Results

Clinical characteristics. Table I shows the baseline characteristics of both patient groups. There were no significant differences between the groups in terms of gender distribution and mean age. Virus marker tests showed non-hepatitis B non-hepatitis C disease in a significantly greater number of patients in the miriplatin group (16.5%) than in the CDDP group (7.6%). In both groups, the number of tumors was four or more in >50% of patients. Many patients in both groups had advanced HCC and the number of patients with HCC of stage III (21) or higher was not significantly different, accounting for 55.6% and 62.6% in the miriplatin and CDDP groups, respectively. With regard to hepatic reserve, patients in both groups were split almost evenly between Child-Pugh classes A and B, without significant differences between the groups. No patients in either group were in Child-Pugh class C.

The amount of miriplatin/cisplatin-suspended lipiodol used in TACE was significantly less in the CDDP group, but the amount of geratin sponge suspension did not differ significantly between the groups.

Incidence of adverse events. Table II shows the incidence of adverse events. The overall incidence of adverse events

Table II. *Adverse events of TACE experienced by patients in this study.*

	Miriplatin group (n=115)	CDDP group (n=131)	*P*-value
Overall	46.5%	67.9%	0.00069
Nausea (Gr 1/2/≥3)	7.0% (8/0/0)	21.4% (25/3/0)	0.0015
Vomiting (Gr 1/2/≥3)	5.2% (6/0/0)	6.9% (8/1/0)	N.S.
Pain (Gr 1/2/≥3)	20.0% (22/1/0)	28.2% (36/1/0)	N.S.
Diarrhea (Gr 1/2/≥3)	10.4% (10/2/0)	3.8% (4/1/0)	0.039
Fever (Gr 1/2/≥3)	23.5% (24/3/0)	31.3% (38/2/1)	N.S.
Fatigue (Gr 1/2/≥3)	9.6% (11/0/0)	19.1% (24/1/0)	0.038
Anorexia (Gr 1/2/≥3)	5.3% (6 / 0 / 0)	19.8% (24/2/0)	0.0007
Anaphylaxis (Gr 1/2/≥3)	0.0% (0/0/0)	3.1% (0/0/4)	N.S.
Hypotension (Gr 1/2/≥3)	0.0% (0/0/0)	1.5% (0/2/0)	N.S.

N.S., Not significant; Gr, grade.

Table III. *Changes in laboratory data for patients undergoing TACE in this study.*

	Miriplatin group		CDDP group		*P*-value
	Pre TACE	Post TACE	Pre TACE	Post TACE	
WBC (/μl)	3877±1344	3717±1348	3924±1530	3832±1727	N.S.
Neutrophils (%)	58.4±11.0	58.7±9.9	55.3±12.2	56.7±12.1	N.S.
Eosinophils (%)	3.9±3.1	7.1±4.7	4.8±3.9	6.5±5.4	0.0053
Hemoglobin (g/dl)	12.1±2.2	11.2±2.2	12.0±1.9	11.0±1.9	N.S.
Platelets ($\times 10^4$/μl)	10.1±5.9	8.6±5.4	10.7±6.0	8.1±5.1	0.00011
Prothrombin time (PT) (%)	76.5±15.0	70.4±14.4	78.8±15.0	77.8±17.7	0.000045
Total bilirubin (mg/dl)	1.2±0.7	1.5±1.4	1.2±0.6	1.7±1.0	N.S.
Albumin (g/dl)	3.4±0.5	3.0±0.4	3.4±0.5	3.2±0.4	0.000001
AST (IU/l)	60.7±34.1	101.1±102.7	51.2±28.4	115.9±104.2	N.S.
ALT (IU/l)	44.9±30.1	75.2±68.3	35.4±22.6	89.8±75.2	0.0074
ALP (IU/l)	435±307	435±323	413±275	442±328	N.S.
Creatinine (mg/dl)	0.9±0.5	1.0±0.5	0.9±0.6	0.9±0.6	N.S.

AST, Aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; WBC, white blood cell; N.S., not significant.

following TACE was significantly lower in the miriplatin group than in the CDDP group, as was the specific incidence of nausea, fatigue, and appetite loss. Treatment site pain and fever was slightly lower in the miriplatin group but these differences were not significant. Anaphylactic reactions (3.1% in the CDDP group) were absent from the miriplatin group. However, the miriplatin group suffered significantly more frequently from diarrhea than did the CDDP group.

Changes in laboratory data. Table III summarizes changes in parameters measured using laboratory tests. Maximal pre- and post-procedural values were analyzed. Thrombocytopenia was significantly less in the miriplatin group. Conversely, decreases in PT and increases in eosinophils were more prominent in the miriplatin group. In biochemical tests, the increase in ALT was significantly greater in the CDDP group. No apparent increase in creatinine was observed in either group, suggesting no renal dysfunction was caused by these treatments.

Comparison of short-term therapeutic effects. Table IV shows the treatment effects on target nodules as assessed by CT at one month following TACE. Tumors assessed as TE4 (100% necrosis or size reduction) on the CT image accounted for 47.0% and 43.3% of all observable tumors in the miriplatin and CDDP groups, respectively, but this difference was not significant.

Various markers exist for HCC. Before TACE, AFP was positive in 88 and 104 patients in the miriplatin and CDDP groups, respectively, and DCP was positive in 73 and 87 patients, respectively, in these groups. At one week following TACE, the percentage of patients whose AFP levels

Table IV. *Treatment effects of TACE.*

	Treatment effect (TE) on the target nodule					*P*-value
	4	3	2	1	TE 4 ratio	
Miriplatin group (n=115)	54	33	28	0	47.0%	N.S.
CDDP group (n=120)	52	42	26	0	43.3%	

N.S., Not significant.

Table V. *Patients whose tumor marker decreased to less than 50% one week after TACE.*

	Miriplatin group	CDDP group	*P*-value
AFP (cut-off value: 10 ng/ml)	9.1% (8/positive: 88)	24.0% (25/positive: 104)	0.0062
DCP (cut-off value: 40 mAU/ml)	23.3% (17/positive: 73)	31.0% (27/positive: 87)	N.S.

N.S., Not significant; AFP, alfa-fetoprotein; DCP, *des*-gamma-carboxy prothrombin.

decreased to less than 50% of their pre-treatment values was 9.1% and 24.0% in the miriplatin and CDDP groups, respectively, showing that decreased AFP was observed in a significantly higher percentage of patients in the CDDP group. For DCP, a decrease to less than 50% was observed in 23.3% in the miriplatin group and 31.0% in the CDDP group, showing that the percentage was relatively but not significantly higher in the CDDP group (Table V).

Discussion

In TACE for the treatment of unresectable HCC, the current common procedure is to use an oily contrast agent, lipiodol (an ethyl ester of iodinated poppyseed oil fatty acids), as a vehicle for localized delivery of anticancer drugs to tumors. However, there are no drugs available that can be stably suspended in lipiodol, and epirubicin and cisplatin have been used as suspensions obtained by ultrasonic mixing. In the 1990s, zinostatin stimalamer (SMANCS) was released commercially but has been associated with problems, such as vascular and liver damage, and thus may not be suitable for repeated use in TACE.

Miriplatin is a novel anticancer drug specifically developed for use in TACE as a suspension in lipiodol. It is lipid soluble and thus simply mixing with lipiodol can lead to an even suspension which is characteristically stable over prolonged periods and does not separate over time. Miriplatin is anticipated to exert antitumor effects with prolonged retention along with lipiodol locally at the tumor site (14-18). In addition, this third-generation platinum compound does not produce cross-resistance to cisplatin, presumably owing at least partly to activation of different DNA mismatch repair mechanisms in response to the two drugs (22).

Because cisplatin–lipiodol suspension also has remarkable antitumor effects in TACE (3-12), our department has been using the suspension as the agent of choice in TACE. However, because prolonged survival in some individuals is associated with an increased number of TACE sessions, there has been an increased need for measures against drug resistance and hypersensitivity reactions including anaphylaxis. Furthermore, it has also been reported that the risk of hypersensitivity reactions is increased from the third session of TACE using cisplatin-lipiodol suspension (13), so consideration of drug rotation is warranted. Given that safe conduct of repeated TACE sessions is the key to prolonged survival, particularly in patients with decreased hepatic reserve associated with progression of tumors, liver cirrhosis or patients with complications of other organs, it is necessary to select appropriate drugs for individual cases.

In this study, miriplatin–lipiodol caused apparently minor adverse events following TACE using this treatment compared with conventional TACE using cisplatin–lipiodol suspension. Occurrence of gastrointestinal symptoms, such as nausea and appetite loss, was suppressed, and fever was also less likely to occur in the miriplatin group. Thrombocytopenia was significantly suppressed and liver function showed no apparent decrease. Renal dysfunction is a typical problem with cisplatin use. However, the miriplatin group demonstrated no decrease in renal function, irrespective of any periprocedural hydration, indicating that miriplatin can be used safely even in patients with decreased hepatic reserve or complications of other

organs. With regard to the concomitant use of the embolization material, this study indicated that serious complications can be avoided by rigorously selective treatment of only the vessels supplying the tumors.

The therapeutic effects, although based only on short-term evaluation with a limited post-procedural observation period, were not significantly different between the two groups when measured as the percentage of patients who attained TE4 on CT at one month, indicating comparable efficacy of miriplatin and cisplatin. For tumor markers, a significantly higher percentage of patients in the CDDP group exhibited decreased AFP (to less than 50% of pre-TACE levels) at one week following TACE, while the corresponding percentage for DCP did not significantly differ between the groups. Nevertheless, because miriplatin can be retained locally for a prolonged time along with lipiodol and exert prolonged antitumor effects, long-term evaluation of the therapeutic effects is required to confirm the safety of this preparation.

The present study demonstrated that miriplatin–lipiodol suspension in TACE was associated with reduced intensity of adverse events overall and had comparable short-term therapeutic effects, compared with cisplatin–lipiodol suspension. Miriplatin broadens the range of available drugs for selection for TACE in the treatment of unresectable HCC, and should contribute to further improvement of prognosis.

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