

Comparison of Therapeutic Effect of Miriplatin Suspension Versus Miriplatin Emulsion in Transcatheter Arterial Chemoembolization of Hepatocellular Carcinoma: A Prospective Evaluation

Hiroki Sanda, Nobuyuki Kawai, Morio Sato, Hiroki Minamiguchi, Motoki Nakai, Hinako Sakaguchi, Kouhei Nakata, Akira Ikoma, Fumihiko Tanaka, Hirotatsu Sato, Tetsuo Sonomura

Hiroki Sanda, Nobuyuki Kawai, Morio Sato, Hiroki Minamiguchi, Motoki Nakai, Hinako Sakaguchi, Kouhei Nakata, Akira Ikoma, Fumihiko Tanaka, Hirotatsu Sato, Tetsuo Sonomura, Department of Radiology, Wakayama Medical University, 811-1 Kimiidera, Wakayamashi, Wakayama 641-8510, Japan

Correspondence to: Morio Sato, MD, Department of Radiology, Wakayama Medical University, 811-1 Kimiidera, Wakayamashi, Wakayama 641-8510, Japan. morisato@mail.wakayama-med.ac.jp

Telephone: +81-73-444-3110

Fax: +81-73-441-0604

Received: May 23, 2013

Revised: July 2, 2013

Accepted: July 3, 2013

Published online: September 21, 2013

with no significant difference. There was no significant difference in adverse events between the groups.

CONCLUSION: There was no significant difference between the miriplatin suspension and miriplatin emulsion groups regarding Lp accumulation, TE, overall tumor response at 3 months, and adverse events.

© 2013 ACT. All rights reserved.

Key words: Hepatocellular carcinoma; Lipiodol; Miriplatin emulsion; miriplatin suspension; Overall tumor response; Prospective study; Transcatheter arterial chemoembolization

ABSTRACT

AIM: To compare miriplatin plus lipiodol (viscous mixture; miriplatin suspension) with miriplatin plus lipiodol with contrast medium (less-viscous mixture; oil-in-water miriplatin emulsion), in terms of lipiodol (Lp) accumulation in hepatocellular carcinoma (HCC) nodules immediately after transcatheter arterial chemoembolization, adverse events, treatment effect (TE), and overall tumor response.

METHODS: This study was designed as a single-center, prospective, randomized controlled trial. Patients with unresectable hypervascular HCC confined to the liver were assigned to either the miriplatin suspension group or miriplatin emulsion group. We evaluated radiographic response (modified Response Evaluation Criteria in Solid Tumors) at 3 months as the primary endpoint; secondary endpoints were Lp accumulation immediately after (Grade I, lipiodol accumulation of 100% or greater), lesion TE (Liver Cancer Study Group of Japan), and safety (Common Terminology Criteria for Adverse Events v4.0).

RESULTS: Twenty-nine patients with 71 nodules were randomized to the suspension group and 32 patients with 84 nodules to the emulsion group. No significant difference in HCC patient background was found between the groups. Grade I Lp accumulation immediately after, TE4, and overall tumor response (partial response plus complete response) of the suspension vs. emulsion groups were 70% vs. 66.7%, 39.4% vs. 39.3%, and 51.7% vs. 46.9%, respectively,

Sanda H, Kawai N, Sato M, Minamiguchi H, Nakai M, Sakaguchi H, Nakata K, Ikoma A, Tanaka F, Sato H, Sonomura T. Comparison of Therapeutic Effect of Miriplatin Suspension Versus Miriplatin Emulsion in Transcatheter Arterial Chemoembolization of Hepatocellular Carcinoma: A Prospective Evaluation. *Journal of Gastroenterology and Hepatology Research* 2013; 2(9): 774-779 Available from: URL: <http://www.ghrnet.org/index.php/joghr/article/view/481>

INTRODUCTION

Anticancer drugs associated with transcatheter arterial chemoembolization (TACE) for hepatocellular carcinoma (HCC) include water-soluble drugs such as doxorubicin, mitomycin C, epirubicin, cisplatin, and zinostatin^[1-11]. Doxorubicin, mitomycin C, and epirubicin are generally dissolved with contrast medium and used in the form of an emulsion^[1,5-7,11], while cisplatin and zinostatin particles are mixed directly with lipiodol as a suspension^[2-11]. Because these particles exist on the surface of the lipiodol, the viscosity of the suspension is almost the same as pure lipiodol.

Miriplatin has been commercially available for use in TACE for HCC since 2010. Miriplatin has a myristic acid molecular chain for lipid-affinity^[12,13]. When miriplatin is mixed with lipiodol, the miriplatin particles penetrate the lipiodol, leading to the continuous release of active platinum compounds into tumor nodules^[12-15], but causing the mixture to have a greater viscosity than the lipiodol itself. It is possible that the increased viscosity could cause proximal

embolization of the hepatic branch artery, preventing the miriplatin from reaching the HCC nodule and/or having an effect on the therapeutic response. de Baere *et al.* and Demachi *et al* reported that the viscosity of the emulsion changes with the ratio of contrast medium, and that lesser (water-in-oil emulsion) and greater (oil-in-water emulsion) ratios of contrast medium result in viscosities higher and lower, respectively, than that of pure lipiodol^[16,17].

When miriplatin suspension became available (after it was covered by insurance in Japan), we realized that for TACE, miriplatin suspension was more viscous than the anticancer-drug emulsion that had been used previously for TACE. Accordingly, we considered that it was important to investigate whether the viscosity had any effect on tumor response.

The purpose of this study is to prospectively compare miriplatin plus lipiodol (miriplatin suspension) and TACE with miriplatin plus lipiodol with contrast medium (oil-in-water miriplatin emulsion) in terms of accumulation of lipiodol in HCC nodules immediately after TACE, therapeutic effect, and overall response.

METHODS

Definitions of suspension and emulsion

When miriplatin is mixed with lipiodol, the miriplatin particles are contained within the lipiodol because of their affinity with oil. In the present study, the term ‘suspension’ is used as in previous manuscripts, and the term ‘emulsion’ is used to describe a mixture of contrast medium and lipiodol with the addition of miriplatin particles. When the ratio of lipiodol to contrast medium is 1:1 or greater, the mixture is termed an ‘oil-in-water emulsion’^[17].

Study design

This clinical investigation was approved by the Ethics Committee of our institute, and all patients were informed that the use of miriplatin was primarily a clinical requirement for TACE and secondarily a part of clinical research; all provided written consent. The study was a single-center prospective randomized controlled trial. The treatment goal was to target all hypervascular HCC nodules. The primary endpoint of the study was radiographic response at 3 months, and the secondary endpoint was lipiodol accumulation in HCC nodules immediately after TACE, treatment effect on the target nodules, and adverse events.

Eligibility criteria were as follows: (1) patients with unresectable hypervascular HCC that was diagnosed within 1 month before TACE by dynamic contrast-enhanced computed tomography (CT) or dynamic contrast-enhanced magnetic resonance imaging (MRI), which revealed a pattern of early enhancement in the arterial phase and washout pattern in the portal or equilibrium phase; (2) patients who were scheduled to undergo TACE following assessment by surgeons, hepatologists, and interventional radiologists and who had four or more HCC nodules that were not suitable for radiofrequency ablation (RFA); (3) absence of ascites or under medical control of ascites; (4) Child-Pugh score (CPS) of 5-10; (5) Eastern Cooperative Oncology Group performance status of between 0 and 2; and (6) previous treatments including TACE with epirubicin and mitomycin C, and radiation treatment were allowed.

Exclusion criteria were as follows: (1) confirmed macroscopic vascular invasion or the presence of extrahepatic metastases; (2) total bilirubin level >3 mg/dL, creatinine >2 mg/dL, platelet count <50000/mm³; (3) having received treatment for HCC within the previous month; (4) the presence of massive arterio-portal shunt or complete hepato-fugal blood flow; (5) the presence of another malignancy.

At our outpatient clinic, patients received dynamic CT or MRI

and a plain chest X-ray, and were scheduled for enrolment based on the findings of the imaging studies and the eligibility criteria. After admission to hospital, the patients were immediately enrolled in the study. An independent doctor assigned patients to either the suspension group or emulsion group via random sampling using an envelope registration system. Thereafter, patients received CTA and CTAP in the angiography room, immediately before TACE.

Sample size calculation for evaluating the radiographic response was designed to enable detection of a 50% difference between the two groups. The estimated sample size was 51 patients, with α and β errors of 0.05 and 0.20, respectively.

TACE procedure

Each procedure was conducted by an interventional radiologist with at least 5 years’ experience in TACE. Each patient received CT during angiography at an angio-CT (Toshiba Medical, Tokyo, Japan) facility. The facility utilizes a common tabletop that enables angiography or CT to be obtained without transferring the patient.

The site of the HCC and the feeding artery were reconfirmed in all patients by angiography of the celiac artery and the superior mesenteric artery, and by CT during hepatic arteriography and during arterio-portography, in which a 4 F catheter (Rosch 2 type; Medikit, Tokyo, Japan) was inserted through a 4 F sheath (Supersheath; Medikit). To obtain complete occlusion of the feeding arteries and to preserve liver function, highly selective catheterization was performed prior to TACE, using a 2.5 F microcatheter (Microferret; Cook, Bloomington, IN) through a 4 F catheter. If multiple tumors were present in both the right and left lobes, the catheter was advanced as close as possible to each tumor after TACE, to at least the level of the segmental hepatic artery peripherally. If an inferior phrenic artery was identified as the feeding vessel, this was also catheterized as close as possible to the tumor, using a 4 F catheter (Mikaelsson, Medikit) and a 2.5 F microcatheter.

TACE using lipiodol (Guerbet, Roissy CDG, France) with gelatin sponge particles (GSP) (Gelpart; Nihonkayaku, Tokyo, Japan) was scheduled for each patient. For the suspension group, the mixture of miriplatin plus lipiodol suspension was prepared by mixing 6 mL of lipiodol with 120 mg of miriplatin (Dainippon Sumitomo, Osaka, Japan). To achieve maximum possible accumulation of miriplatin suspension in the tumor nodule, we injected the mixture in small increments, slowly and intermittently. If during TACE the viscosity of the mixture caused it to stall in the hepatic branch artery, we waited for a few minutes until the hepatic branch artery re-opened.

According to the data of Demachi *et al.*, adding contrast medium to lipiodol at a ratio of 1:1 (i.e., as an oil-in-water emulsion) decreases the viscosity of the emulsion, compared with pure lipiodol.¹⁷ Accordingly, a mixture of 6 ml lipiodol plus 120 mg miriplatin plus 6 ml contrast medium (Iopamidol 370; Bracco, Milano, Italy) was prepared for use in the emulsion group. The mixture was injected in small increments into the hepatic branch artery. Total lipiodol volume was calculated according to total HCC volume: for an HCC nodule 1 cm in diameter, we used approximately 1 mL of lipiodol. The maximum lipiodol dose was limited to 10 mL to avoid liver damage.

To preserve liver function, we performed TACE as selectively as possible, using 1- or 2-mm GSPs. When the 10 mL lipiodol dose limit was reached in the initial procedure before all tumors were treated, a second procedure was performed 7 to 10 days later, to cover all the tumors, in which case the total volume of lipiodol in two procedures was limited to 20 mL. Tumor response terms were calculated from the time of the second procedure.

Prior to TACE, 5-HT₃ (serotonin) antagonists were given as

an antiemetic. Prophylactic antibiotics (cefazolin, CEZ) were administered in all patients for 3 days after the procedure.

Evaluation of lipiodol accumulation, adverse events, and treatment efficacy

Lipiodol accumulation in tumor nodules was evaluated on plain CT obtained immediately after TACE. CT images were viewed with window level of 200 Hounsfield units (HU) and window width of 400 HU; any area in a nodule having a CT number of 400 HU or greater was considered to be lipiodol accumulation. The degree of lipiodol accumulation in each tumor nodule was classified using a three-grade system: Grade I, lipiodol accumulation in the tumor of 100% or greater; Grade II, lipiodol accumulation in the tumor of 50% to less than 100%; Grade III, lipiodol accumulation in the tumor of less than 50%.

Physical examination, blood tests, and liver function tests were conducted routinely during the hospital stay, before and at least 2, 5, and 10 days after TACE, and at 3 months after discharge. Adverse events related to TACE were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v4.0.

In CT imaging assessment of treatment efficacy, multi-phase CT was obtained at 3 months and the images were reviewed by two radiologists, each with more than 6 years' experience in abdominal image diagnosis. Multi-phase CT was conducted using an MDCT scanner (LightSpeed VCT 64, General Electric Healthcare, Milwaukee, WI) with a 64×0.625 mm detector configuration. The four-phase acquisition included unenhanced CT and three phases (arterial, portal, and equilibrium) of contrast-enhanced CT. Axial images (thickness, 5 mm; reconstruction interval, 5 mm) were sent to the picture archiving and communication system, and to workstations.

The following MDCT protocol was used to obtain scans for examining the upper abdomen, including the whole liver. Using an automatic injector (Dual Shot GX, Nemoto Kyorindo, Tokyo, Japan), each patient was administered an intravenous bolus of 580 mg I/kg of patient body weight of nonionic contrast medium, containing 300 mg I/mL [Omnipaque (iohexol), Daiichisankyo Pharmaceutical, Tokyo, Japan] for a duration of 25 sec, through a 20-gauge angiocatheter placed in the antecubital vein. Tumor enhancement on the arterial phase, the extent of lipiodol accumulation in the HCC nodules, and three-dimensional reduction in tumor size were determined.

Direct treatment effect (TE) on the target nodule was graded into four levels based on the findings on the follow-up CT at 3 months, according to the criteria of the Liver Cancer Study Group of Japan^[18]: TE4, 100% tumor-necrotizing effect or 100% tumor size reduction rate; TE3, tumor-necrotizing effect or tumor size reduction rate of 50%-100%; TE2, effects other than TE3 and TE4; TE1, tumor growth by 25% regardless of the necrotizing effect. Overall response was evaluated at 3 months after TACE in accordance with modified Response Evaluation Criteria in Solid Tumors (mRECIST)^[19].

Statistical analyses

Student's *t*-test was used to compare the continuous variables of age, body weight, HCC size, lipiodol volume, and miriplatin volume between patients in the suspension and emulsion groups. The Mann-Whitney U test was used to compare the number of previous TACE procedures for the ordinal scale of discrete variables between patients in the suspension and emulsion groups. Fisher's exact test or Pearson's χ^2 test was used to compare the categorical variables of gender, Child-Pugh classification, hepatitis, clinical stage, α -fetoprotein (AFP) value, protein induced by vitamin K absence or antagonist (PIVKA)

II value, number of previous treatments, number of HCC nodules, grade of lipiodol accumulation immediately after, treatment effect on the HCC target nodules, overall tumor response, and adverse events between patients in the two groups. For each analysis, $p < 0.05$ was considered statistically significant.

RESULTS

Applicability

Sixty-six consecutive patients (33 in the suspension group, 33 in the emulsion group) who underwent TACE between March 2011 and March 2012 were enrolled prospectively. Four patients in the suspension group and 1 patient in the emulsion group were excluded based on differences between the findings of dynamic CT or MRI obtained at the outpatient clinic and those of CTA and CTAP obtained immediately before TACE; and also in the event of RFA following TACE after requesting RFA for lesions numbering four or more, despite agreeing to the terms of the study. In short, the causes for exclusion in the suspension group were as follows: in 2 patients, portal tumor thrombi were observed on CTAP prior to TACE; in 1 patient, marked arterio-portal shunt was observed on CTA; 1 patient underwent RFA following TACE. The causes for exclusion in the emulsion group were as follows: one patient had portal tumor thrombus on CTAP. Twenty-nine patients were randomized to TACE with miriplatin suspension, and 32 patients were randomized to TACE with miriplatin emulsion. The data were analyzed in March 2012. None of the patients was lost to follow-up.

The TACE protocol was successfully completed in all cases. Arterial blood supply was confirmed as occluded by angiography. Lipiodol accumulation to the tumor was confirmed on CT immediately after TACE in each case.

Characteristics of patients with HCC

The following clinical characteristics of the patients prior to commencement of the study are listed in Table 1: age, gender, body weight, virus infection, Child-Pugh classification, AFP and PIVKA II levels, and clinical stage according to The General Rules for the Clinical and Pathological Study of Primary Liver Cancer (ver.5) of the Liver Cancer Study Group of Japan, and previous curative treatment^[18]. We found no statistically significant differences in these characteristics between the two groups.

The number, size, and location of HCC nodules are presented in Table 2. There were 71 HCC nodules in 29 patients of the suspension group and 84 HCC nodules in 32 patients of the emulsion group. No statistically significant difference was found between the two groups in terms of these tumor characteristics.

The mean lipiodol volume used in the suspension and emulsion groups was 4.9 ± 2.5 and 5.0 ± 2.9 mL, respectively (no significant difference, $p = 0.903$). The mean dose of miriplatin was 77.8 ± 31.7 mg in the suspension group and 70.2 ± 29.6 mg in the emulsion group (no significant difference, $p = 0.337$) (Table 2).

Lipiodol accumulation immediately after TACE

Table 3 shows lipiodol accumulation in the tumor nodules immediately after TACE, as evaluated by CT. Grade I lipiodol accumulation was observed in 50 nodules (70.0%) in the suspension group and in 56 nodules (66.7%) in the emulsion group. There was no significant difference between the groups in terms of lipiodol accumulation.

Treatment effect on the target nodules

Table 4 shows treatment effect on the target nodules by CT at 3 months. Either TE4 or TE3 was achieved in 39 nodules (54.9%) in

the suspension group and in 43 nodules (51.2%) in the emulsion group. There was no significant difference between the groups in terms of treatment effect.

Table 1 Patient backgrounds.

	Suspension group <i>n</i> =29	Emulsion group <i>n</i> =32	<i>P</i> -value
Age mean±SD (range)	76.5 ± 8.7 (58–89)	75.7 ± 8.4 (61–89)	0.730 ¹
Gender (male/female)	15/14	23/9	0.121 ²
Body weight (kg) mean±SD (range)	54.2±8.5 (44.0–74.5)	58.9±12.4 (39.0–87.5)	0.091 ¹
Hepatitis (C/B/non B non C)	21/3/5	25/3/4	0.855 ³
Child–Pugh classification (A/B/C)	21/8/0	21/11/0	0.567 ³
AFP (ng/mL) median (range)	116.9 (4.2–12246.2)	50.7 (3.9–9811.5)	0.525 ⁴
PIVKA (mAU/mL) median (range)	394 (14–13402)	190 (11–22894)	0.398 ⁴
Clinical stage (I/II/III)	5/16/8	4/18/10	0.859 ³
Past treatment			
Surgical hepatectomy	4	6	0.735 ²
RFA	15	17	1.000 ²
PEIT	4	6	0.735 ²
TACE	23	26	1.000 ²
Frequency of TACE mean±SD (range)	3.3 ± 2.7 (0–7)	3.8 ± 3.4 (0–11)	0.838 ⁴

AFP: alpha fetoprotein; PIVKA: protein induced by vitamin K absence; RFA: radiofrequency ablation; PEIT: percutaneous ethanol injection; TACE: transcatheter arterial chemoembolization; ¹: Student's *t*-test; ²: Fisher's test; ³: χ^2 test; ⁴: Mann-Whitney U test.

Table 2 Injected lipiodol volume and miriplatin dose to tumor nodules.

	Suspension group <i>n</i> =29	Emulsion group <i>n</i> =32	<i>P</i> -value
No. of tumors			
1	12	9	
2	5	5	
3	3	10	0.249 ¹
4 ≤	9	8	
Mean tumor size (mm)	21.2±18.5 (6.0–103)	19.4±18.6 (5.0–110)	0.712 ²
Lp volume (mL)	4.9±2.5 (1.5–10)	5.0±2.9 (1–12)	0.903 ²
Miriplatin dose (mg)	77.8±31.7	70.2±29.6	0.337 ²

No.: number; Lp: lipiodol; ¹: χ^2 test; ²: Student's *t*-test.

Table 3 Lipiodol accumulation in tumor nodules immediately after TACE as evaluated by CT.

Grade	Suspension group <i>n</i> =71	Emulsion group <i>n</i> =84	<i>P</i> -value
I	50 (70.0%)	56 (66.7%)	
II	19 (26.8%)	20 (23.8%)	0.235 ¹
III	2 (2.8%)	8 (9.5%)	

I: accumulation of 100% or more; II: accumulation of 50 to 100%; III: accumulation of less than 50%; ¹: χ^2 test.

Table 4 Treatment effect (TE) on the target nodule at 3 months.

	Suspension group <i>n</i> =71	Emulsion group <i>n</i> =84	<i>P</i> -value
TE4	28 (39.4%)	33 (39.3%)	
TE3	11 (15.5%)	10 (11.9%)	0.923 ¹
TE2	25 (35.2%)	32 (38.1%)	
TE1	7 (9.9%)	9 (10.7%)	

¹: χ^2 test.

Overall tumor response

Table 5 shows the overall tumor response at 3 months (mRECIST). Either PR or CR was achieved in 15 patients (51.7%) in the suspension group and in 15 patients (46.9%) in the emulsion group. There was no significant difference between the groups in terms of radiographic response using mRECIST^[19].

Adverse events

Table 6 lists adverse events after TACE for the two groups. Major complications or toxicity of Grade 4 or higher were not observed in either group. Grade 3 fever, pain, or nausea was not observed in either group. Blood and laboratory data revealed Grade 3 glutamic oxaloacetic transaminase (GOT) elevation in three patients (10%) in the suspension group and in nine patients (28%) in the emulsion group ($p=0.107$), and Grade 3 glutamic pyruvic transaminase (GPT) elevation in one patient (3%) in the suspension group and in two patients (6%) in the emulsion group ($p=0.117$). Grade 3 bilirubin or creatinine elevation did not occur in either group. These abnormalities resolved within 10 days and did not show any relevant deterioration.

Table 5 Overall response evaluation (mRECIST) at 3 months.

	Suspension group <i>n</i> =29	Emulsion group <i>n</i> =32	<i>P</i> -value
CR	4 (13.8%)	7 (21.9%)	
PR	11 (37.9%)	8 (25.0%)	0.673 ¹
SD	10 (34.5%)	13 (40.6%)	
PD	4 (13.8%)	4 (12.5%)	
CR+PR	15 (51.7%)	15 (46.9%)	

mRECIST: modified Response Evaluation Criteria in Solid Tumors; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; ¹: χ^2 test.

Table 6 Adverse events (CTCAE v4.0).

	Suspension group <i>n</i> =29					Emulsion group <i>n</i> =32					<i>P</i> -value ¹	
	Grade	1	2	3	4	Grade	1	2	3	4		5
Fever		12	7	0	0	0	16	9	0	0	0	0.547
Pain		8	0	0	0	0	7	0	0	0	0	0.605
Nausea		2	0	0	0	0	3	0	0	0	0	0.725
GOT		12	12	3	0	0	8	9	9	0	0	0.107
GPT		17	7	1	0	0	9	12	2	0	0	0.117
T.Bil		4	3	0	0	0	6	7	0	0	0	0.354
PLT		5	0	0	0	0	5	1	0	0	0	0.627
Cr		2	0	0	0	0	1	0	0	0	0	0.496

CTCAE v4.0: Common Terminology Criteria for Adverse Events v4.0; GOT: glutamic oxaloacetic transaminase; GPT: glutamic pyruvic transaminase; T.Bil: total bilirubin; PLT: platelets; Cr: creatinine; ¹: χ^2 test.

DISCUSSION

Two methods of lowering the viscosity of miriplatin suspension are warming the miriplatin suspension or creating an oil-in-water emulsion^[17,20]. If the miriplatin suspension is heated, its temperature falls as soon as it is exposed to room temperature and/or body temperature. Because of the difficulty of keeping the miriplatin suspension warm until the embolization is finalized, we chose to lower the viscosity of the miriplatin lipiodol using the oil-in-water emulsion method.

We conducted this study based on the hypothesis that the higher viscosity of miriplatin suspension could reduce the accumulation of lipiodol, thus decreasing the effectiveness of miriplatin emulsion in terms of tumor response, compared with that of less viscous miriplatin emulsion. The results of the present study, however, clarified that in terms of tumor response there was no significant difference between the two preparations, which can be considered equally therapeutically effective. However, in the case of a fine feeding artery to the tumor, miriplatin emulsion was preferable to miriplatin suspension because of its lower viscosity. When miriplatin suspension is used for TACE, incremental infusion of small volumes is necessary to obtain sufficient accumulation. Further, in the miriplatin suspension group, we attempted to achieve maximum accumulation of suspension in the tumor nodule by injecting the mixture slowly and intermittently

via a microcatheter advanced as selectively as possible. In practice, stasis of the suspension in the hepatic branch artery was relieved and the suspension gradually moved to the tumor nodule with time, after which we could inject additional miriplatin suspension to obtain maximum accumulation. This explains why no significant difference was observed between the miriplatin suspension and emulsion groups regarding CT lipiodol accumulation immediately after injection.

Lipiodol accumulation of 100% or more immediately after (Grade I) and at 3 months (T4) was 70.0% and 39.4% in the suspension group, respectively; and 66.7% and 39.3% in the emulsion group, respectively, with no significant difference between the groups. The incidence of lipiodol accumulation of 100% or more decreased in both groups as time lapsed. We consider that the causes for the decrease of accumulation were lipiodol washout in completely necrosed tumor nodules, and/or recurrence of viable tumor within regions of lipiodol accumulation. These findings indicate that the effect of time is crucial in evaluating treatment effect.

Regarding treatment effect, Okusuka *et al.*^[15] reported TE4 of 26.5% at 3 months following intra-arterial miriplatin chemotherapy, while Okabe *et al.*^[21] reported TE4 of 47.0% at 1 month after TACE with miriplatin suspension. In the present study, TE4 at 3 months was 39.4% in the emulsion group and 39.3% in the suspension group. Because Okusuka *et al.*^[15] did not use gelatin sponge particles, we consider that the difference in treatment effect between their results and those of the present study can be attributed to the degree of stagnation of arterial blood flow.

In agreement with the results of previous reports regarding overall response for TACE with lipiodol plus cisplatin or miriplatin, Sahara *et al.*^[7] documented overall response of CR plus PR of 50.0% at 6 months in a prospective study of TACE with cisplatin suspension. Regarding miriplatin, Imai *et al.*^[22] reported overall response of CR plus PR of 58% at 1 to 3 months for TACE with miriplatin suspension. Aramaki *et al.* reported overall response of CR plus PR of 85.7% at 1-2 months following TACE with miriplatin suspension^[23]. Araki *et al.*^[24] reported CR plus PR of 52% at 3 months following TACE with miriplatin suspension. Miyayama *et al.*^[25] reported no difference in local recurrence between miriplatin suspension and emulsion groups. These reports documenting TACE with miriplatin are from retrospective studies. In the present prospective study, CR plus PR at 3 months was 51.7% and 46.9% in the suspension and emulsion groups, respectively, with no significant difference. Although comparison with the previous studies is not meaningful because of differences in the backgrounds of the patients, overall response in our study was at least not inferior to those in previous studies.

Regarding adverse events, TACE with miriplatin suspension is known to cause relatively minor side effects compared with TACE with cisplatin suspension. Because of its affinity with lipiodol, miriplatin is released gradually to the tumor nodules^[20-23], while contrast-medium-soluble cisplatin is released quickly, to flow into the systemic vessels^[26,27]. There were no cases of Grade 2 or worse creatinine elevation in either of the present groups, even though the patients were not hydrated prior to TACE. We did observe transient fever, pain, and nausea, and transient elevation of GOT, GPT, and total bilirubin values. No Grade 4 or 5 adverse events were observed in either group. The incidence and grade of adverse events were similar in both groups, with no significant difference between the groups. These findings indicate that TACE with either miriplatin suspension or emulsion is tolerable for HCC patients.

A limitation of the present study is that although we injected miriplatin suspension in small increments, slowly and intermittently,

we have no data for miriplatin suspension injected continuously, as is conducted in conventional TACE. Further, we merely clarified the HCC nodule response and overall tumor response at 3 months after TACE. However, the fact that there was no significant difference in tumor response between the two groups is crucial when deciding whether to conduct further studies to explore survival rates. Another limitation is that our investigation was a prospective study conducted at a single institution, rather than a randomized study at multiple institutions.

In conclusion, although limitations exist, no significant difference was found regarding HCC nodule response, overall tumor response at 3 months, or adverse events between the miriplatin suspension and the miriplatin emulsion groups.

REFERENCES

- 1 Kawai S, Tani M, Okamura J, Ogawa M, Ohashi Y, Monden M, Hayashi S, Inoue J, Kawarada Y, Kusano M, Kubo Y, Kuroda C, Sakata Y, Shimamura Y, Jinno K, Takahashi A, Takayasu K, Tamura K, Nagasue N, Nakanishi Y, Makino M, Masuzawa M, Yumoto Y, Mori T, Oda T. Prospective and randomized trial of lipiodol-transcatheter arterial chemoembolisation for treatment of hepatocellular carcinoma: a comparison of epirubicin and doxorubicin (second cooperative study). The Cooperative Study Group for Liver Cancer Treatment of Japan. *Semin Oncol* 1997; **24**: 38-45
- 2 Sasaki Y, Imaoka S, Kasugai H, Fujita M, Kawamoto S, Ishiguro S, Kojima J, Ishikawa O, Ohigashi H, Furukawa H. A new approach to chemoembolization therapy for hepatoma using ethiodized oil, cisplatin, and gelatin sponge. *Cancer* 1987; **60**: 1194-1203
- 3 Kasugai H, Kojima J, Tatsuta M, Okuda S, Sasaki Y, Imaoka S, Fujita M, Ishiguro S. Treatment of hepatocellular carcinoma by transcatheter arterial embolization combined with intraarterial infusion of a mixture of cisplatin and ethiodized oil. *Gastroenterology* 1989; **97**: 965-971
- 4 Konno T, Maeda H, Iwai K, Tashiro S, Maki S, Morinaga T, Mochinaga M, Hiraoka T, Yokoyama I. Effect of arterial administration of high molecular weight anticancer agent SMANCS with lipid lymphographic agent on hepatoma: A preliminary report. *Eur J Cancer Clin Oncol* 1983; **19**: 1053-1065
- 5 Kamada K, Nakanishi T, Kitamoto M, Aikata H, Kawakami Y, Ito K, Asahara T, Kajiyama G. Long-term prognosis of patients undergoing transcatheter arterial chemoembolization for unresectable hepatocellular carcinoma: Comparison of cisplatin lipiodol suspension and doxorubicin hydrochloride emulsion. *J Vasc Interv Radiol* 2001; **12**: 847-854
- 6 Ono Y, Yoshimasu T, Ashikaga R, Inoue M, Shindou H, Fuji K, Araki Y, Nishimura Y. Long-term results of lipiodol-transcatheter arterial embolization with cisplatin or doxorubicin for unresectable hepatocellular carcinoma. *Am J Clin Oncol* 2000; **23**: 564-568
- 7 Sahara S, Kawai N, Sato M, Minamiguchi H, Nakai M, Takasaka I, Nakata K, Ikoma A, Sawa N, Sonomura T, Shirai S. Prospective comparison of transcatheter arterial chemoembolization with lipiodol-epirubicin and lipiodol-cisplatin for treatment of recurrent hepatocellular carcinoma. *Jpn J Radiol* 2010; **28**: 362-368
- 8 Maeda S, Shibata J, Fujiyama S, Tanaka M, Noumaru S, Sato K, Tomita K. Long-term follow-up of hepatic arterial chemoembolization with cisplatin suspended in iodized oil for hepatocellular carcinoma. *Hepatogastroenterology* 2003; **50**: 809-913

- 9 Uyama N, Hatano N, Maetani Y, Isoda H, Shibata T, Taura K, Oe S, Naito M, Yasuchika K, Fujii H, Ikai I, Uemoto S. Efficacy and toxicity of transcatheter arterial chemoembolization with Cisplatin suspended in lipiodol for unresectable hepatocellular carcinoma. *Jpn J Cancer Chemother* 2008; **35**: 775-780
 - 10 Chang JM, Tzeng WS, Pan HB, Yang CF, Lai KH. Transcatheter arterial embolization with or without cisplatin treatment of hepatocellular carcinoma. A randomized controlled study. *Cancer* 1994; **74**: 2449-2453
 - 11 Sahara S, Kawai N, Sato M, Tanaka T, Ikoma A, Nakata K, Sanda H, Minamiguchi H, Nakai M, Shirai S, Sonomura T. Prospective evaluation of transcatheter arterial chemoembolization (TACE) with multiple anti-cancer drugs (epirubicin, cisplatin, mitomycin C, 5-fluorouracil) compared with TACE with epirubicin for treatment for hepatocellular carcinoma. *Cardiovasc Intervent Radiol* 2012; **35**: 1363-1371
 - 12 Maeda M, Uchida NA, Sasaki T. Liposoluble platinum (II) complexes with antitumor activity. *Jpn J Cancer Res* 1986; **77**: 523-525
 - 13 Kishimoto S, Fukui M, Fukushima S, Nakano M. Application of a lipophilic platinum derivative contained in an oily lymphographic agent to intrahepatic arterial chemotherapy. *Reg Cancer Treat* 1992; **1**: 25-29
 - 14 Fujiyama S, Shibata J, Maeda S, Tanaka M, Noumaru S, Sato K, Tomita K. Phase I clinical study of a novel lipophilic platinum complex (SM-11355) in patients with hepatocellular carcinoma refractory to cisplatin/lipiodol. *British J Cancer* 2003; **89**: 1614-1619
 - 15 Okusaka T, Okada, Nakanishi T, Fujiyama S, Kubo Y. Phase II trial of intra-arterial chemotherapy using a novel lipophilic platinum derivative (SM-11355) in patients with hepatocellular carcinoma. *Invest New Drugs* 2004; **22**: 169-176
 - 16 de Baere T, Zhang X, Aubert B, Harry G, Lagrange C, Ropers J, Dufaux J, Lumbroso J, Rougier P, Ducreux M, Roche A.K. Quantification of tumor uptake of iodized oils and emulsions of iodized oils: experimental study. *Radiology* 1996; **201**: 731-735
 - 17 Demachi H, Matsui O, Abo H, Tatsu H. Simulation model based on non-newtonian fluid mechanics applied to the evaluation of the embolic effect of emulsions of iodized oil and anticancer drug. *Cardiovasc Intervent Radiol* 2000; **23**: 285-290
 - 18 Liver Cancer Study Group of Japan, The general rules for the clinical and pathological study of primary liver cancer. Third English edition, revised version. 2010
 - 19 Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. *Semin Liver Dis* 2010; **30**: 52-60
 - 20 Takara S, Higashihara H, Urakawa H, Masima S, Nou A, Yosimitu K. Thermo-effect of miriplatin-lipiodol emulsion. *J New Rem & Clin* 2011; **60**: 994-998
 - 21 Okabe K, Beppu T, Haraoka K, Oh-Uchida Y, Yamamura S, Tomiyasu S, Yamanaka T, Sano O, Masuda T, Chikamoto A, Fujiyama S, Baba H. Safety and short-term therapeutic effects of miriplatin-lipiodol suspension in transarterial chemoembolization (TACE) for hepatocellular carcinoma. *Anticancer Res* 2011; **31**: 2983-2988
 - 22 Imai N, Ikeda K, Kawamura Y, Sezaki H, Hosaka T, Akuta N, Kobayashi M, Saitoh S, Suzuki F, Suzuki Y, Arase Y, Kumada H. Transcatheter arterial chemotherapy using miriplatin-lipiodol suspension with or without embolization for unresectable hepatocellular carcinoma. *Jpn J Clin Oncol* 2012; **42**: 175-182
 - 23 Aramaki T, Moriguchi M, Bekku E, Asakura K, Sawada A, Endo M. Comparison of epirubicin hydrochloride and miriplatin hydrate as anticancer agents for transcatheter arterial chemoembolization of hepatocellular carcinoma. *Hepatol Res* 2012 Sep 3
 - 24 Araki T, Okada T, Kimura K, Sawada E, Sano K, Araki T. Adverse events and therapeutic efficacy associated with TACE for hepatocellular carcinoma with a miriplatin-lipiodol suspension in comparison with a cisplatin-lipiodol suspension. *IVR* 2012; **27**: 33-40
 - 25 Miyayama S, Yamashiro M, Shibata Y, Hashimoto M, Yoshida M, Tsuji K, Toshima F, Matsui O. Comparison of local control effects of superselective transcatheter arterial chemoembolization using epirubicin plus mitomycin C and miriplatin for hepatocellular carcinoma. *Jpn J Radiol* 2012; **30**: 263-270
 - 26 Ikoma A, Kawai N, Sato M, Minamiguchi H, Nakai M, Nakata K, Tanaka T, Sonomura T. Comparison of blood dynamics of anticancer drugs (cisplatin, mitomycin C, epirubicin) in treatment groups of hepatic arterial infusion, hepatic arterial infusion with lipiodol, hepatic arterial chemoembolization with lipiodol plus gelatin sponge particles in a swine model. *Hepatol Res* 2012 May 8
 - 27 Sahara S, Tanihata H, Sato M, Kawai N, Takasaka I, Minamiguchi H, Nakai M, Sonomura T. Effects of hepatic artery chemoembolization using cisplatin-lipiodol suspension with gelatin sponge particles on swine liver. *J Vasc Interv Radiol* 2009; **20**: 1359-1364
- Peer reviewers:** Yong-Fang Jiang, PhD, Associate Professor, Liver Diseases Research Center, The Second Xiangya Hospital, Central South University, No.139 Middle Renmin Road, Changsha, Hunan, China; Changsong Zhang, PhD, Clinical Oncology Laboratory, Soochow University Affiliated Changzhou Tumor Hospital, No.1 Huai De North Rd. Changzhou, 213001 P. R. China.