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PHASE II STUDIES

A randomized phase II trial of intra-arterial chemotherapy using SM-11355 (Miriplatin) for hepatocellular carcinoma

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Abstract *Background* SM-11355 is a platinum complex developed to treat hepatocellular carcinoma (HCC) via administration into the hepatic artery as a sustained-release suspension in iodized oil. We conducted a multicenter phase II trial in patients with HCC to evaluate the efficacy and safety of SM-11355, using a Zinostatin stimalamer suspension in iodized oil as a reference. *Methods* Patients with unresectable HCC were randomized 2:1 to receive administration of the SM-11355 or Zinostatin stimalamer suspension into the hepatic artery. A second injection was given 4–12 weeks later. Efficacy was evaluated by CT 3 months after treatment and categorized as therapeutic

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effect (TE) V to I, where TE V was defined as disappearance or 100% necrosis of all treated tumors. *Results* A total of 122 patients were evaluated for efficacy and toxicity (SM-11355, n=83; Zinostatin stimalamer, n=39). Baseline characteristics were similar in the two groups. The TE V rates were 26.5% (22/83) and 17.9% (7/39) in the SM-11355 and Zinostatin stimalamer groups, respectively. In the SM-11355 group,the most frequent drug-related adverse events (AEs) of≥grade 3 were elevated AST, elevated ALT, thrombocytopenia, and hyperbilirubinemia. The AEs with the largest difference between the two groups (SM-11355 vs. Zinostatin stimalamer) were hepatic vascular injury (0 vs. 48.4%) and eosinophilia (84.3 vs. 41.0%). The 2-year and 3-year survival rates were 75.9% vs. 70.3% and 58.4% vs. 48.7%, respectively. *Conclusions* The results suggest that SM-11355 in iodized oil has similar efficacy to Zinostatin stimalamer and that repeated dosing of SM-11355 is possible without hepatic vascular injury in cases of relapse.

Keywords Iodized oil · MIRIPLA · Liver cancer · Suspension · Parallel study

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Introduction

International cancer statistics from 2002 indicate that hepatocellular carcinoma (HCC) ranks third behind lung and gastric cancer in the number of deaths [1]. The impact of current standard treatments for advanced HCC, including conventional transcatheter arterial chemoembolization (TACE) using doxorubicin or cisplatin is limited and the prognosis is unsatisfactory [2]. Therefore, there is a clear need for new treatments in management of this disease.

SM-11355, (SP-4-2)-[(1*R*,2*R*)-cyclohexane-1,2-diamine-*N*,*N*']bis (tetradecanoato-*O*) platinum monohydrate (Fig. 1) is a highly lipophilic platinum derivative that can be delivered suspended in iodized oil, an oily lymphographic agent, via injection into the hepatic artery [3]. Following injection into an HCC-feeding artery, iodized oil selectively accumulates in the tumor. Similarly, an iodized oil suspension of SM-11355 accumulates selectively within HCC nodules, allowing continuous release of active platinum compounds into tumor tissues. A phase I dose-finding study using different injection levels indicated a recommended dose of 20 mg/mL and an upper limit of the injection volume of 6 mL [4]. In an early phase II trial , SM-11355 showed a promising anticancer effect with a mild toxicity profile in patients with advanced HCC. Responses were evaluated by computed tomography (CT) three months after treatment, with complete response (CR) defined as disappearance or 100% necrosis of all tumors. Iodized oil accumulation in tumors was taken to indicate necrosis. Of 16 eligible patients, 9 (56%) showed CR [5]. This CR rate was superior to our expectation, because the CR rate in conventional TACE is 15–20% based on the same evaluation criteria [6, 7]. Therefore, the results of the early phase II study

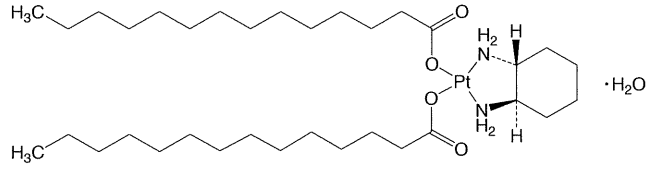

Fig. 1 Structural formula of SM-11355

indicated that SM-11355 has potential as an alternative to TACE in treatment of advanced HCC.

Based on these findings, we conducted a late phase II open-label trial of SM-11355. The aims of the study were to re-evaluate the efficacy, safety and pharmacokinetics of SM-11355 in a larger population, since only 16 eligible patients were included in the previous phase II study, and to confirm the candidacy of SM-11355 as an experimental treatment in a forthcoming clinical study in comparison with conventional TACE. To achieve regulatory approval of SM-11355 in Japan, it was necessary to undertake a parallel study. Therefore, we conducted a randomized phase II trial using Zinostatin stimalamer as a reference, because this agent is the only commercially available lipophilic drug for HCC in Japan and chemolipiodolization of Zinostatin stimalamer has been approved for treatment of advanced HCC in Japan [8, 9]. However, statistical comparisons between the two treatment groups were not planned since the goal of the study was re-evaluation of outcomes for SM-11355, and because the sample size required to conduct a statistical analysis was larger than expected.

Patients and methods

Inclusion criteria

Consecutive patients with HCC were eligible for the study if they had no indication for resection or local ablation therapy. The diagnosis was confirmed histologically and/or clinically using angiography and enhanced CT. Each patient was required to meet the following criteria: at least one measurable intrahepatic lesion that showed tumor staining by CT; tumor stage II or III in the staging system of the Liver Cancer Study Group of Japan [6, 7]; Child-Pugh classification A or B; adequate hematological function (WBC≥3000 /μL, blood platelets≥50000 /μL, hemoglobin≥9.5 g/dL), adequate hepatic function (AST and ALT≤ 5-fold the upper limit of normal, serum bilirubin <3 mg/dL, serum albumin≥3 g/dL), adequate renal function (serum creatinine≤the upper limit of normal); an Eastern Cooperative Oncology Group performance status of 0–2; age 20 to 74 years old; minimum life expectancy≥3 months, and provision of written informed consent. Patients who had undergone hepatic resection, local ablation therapy, and/or TACE were eligible if they showed no evidence of local tumor recurrence in the treated lesions. Patients who had undergone chemolipiodolization with anti-cancer agents other than Zinostatin stimalamer or a platinum-containing agent were also eligible if the treated lesions were resected. The previous anticancer treatment had to have been discontinued for at least 4 weeks before enrollment in this study.

Exclusion criteria

Patients were excluded if they met any of the following criteria: history of allergy to iodine-containing agents and/or contrast material; history of systemic chemotherapy; serious complication such as a cardiac disease or a thyroid disease ; concomitant malignancy; bile duct invasion; pregnant or lactating women and fertile patients who were not using effective contraception; and participation in another trial within 6 months before giving informed consent.

Study treatment

Patients who met the entry criteria were provisionally registered and randomly assigned to the SM-11355 or Zinostatin stimalamer group before undergoing angiography. Each investigator then confirmed registration after establishing that the patient met the following additional requirements based on angiographic findings: intrahepatic lesions that showed tumor staining and were fed by an artery with an appropriate structure for catheter insertion; no evidence of tumor thrombus in the portal or hepatic vein; no evidence of intrahepatic arteriovenous shunting; and no evidence of local tumor recurrence in previously treated lesions. The central random assignment by dynamic allocation to either a SM-11355 group or Zinostatin stimalamer group was stratified according to center and maximun tumor diameter.

A suspension of SM-11355 (MIRIPLA; Dainippon Sumitomo Pharma Co., Japan) or Zinostatin stimalamer (SMANCS; Astellas Pharma Inc., Japan) in iodized oil was injected into the hepatic artery using Seldinger's technique. Patients in the SM-11355 group received SM-11355 suspended in iodized oil (20 mg/mL) in a volume of up to 6 mL according to tumor size. Patients in the Zinostatin stimalamer group received Zinostatin stimalamer suspended in iodized oil (1 mg titer/mL) in a volume of up to 6 mL. When iodized oil accumulation in the treated tumor was insufficient and tumor staining was found in diagnostic imaging 5 weeks (±10 days) after the first injection, a second injection was given within 12 weeks after the first injection.

Efficacy and safety assessment

The antitumor effect was evaluated by CT or MRI 3 months after the last injection according to the response criteria proposed by the Liver Cancer Study Group of Japan [10], which are similar to the criteria proposed by the European Association for the Study of the Liver (EASL) Panel of Experts on HCC [11]. Tumor size was measured using the sum of the products of the perpendicular longest diameters of all measurable lesions. In the response evaluation criteria, iodized oil accumulation in a tumor is regarded as an indication of necrosis because significant positive correlations

have been reported between iodized oil accumulation observed on CT images and necrotic regions in resected tumors examined pathologically after TACE and after intra-arterial chemotherapy with iodized oil [5, 8, 12, 13]. Therapeutic effect (TE) was defined as follows: TE V, disappearance or 100% necrosis of all treated tumors; TE IV, more than 50% reduction in tumor size and/or more than 50% necrosis; TE III, more than 25% reduction in tumor size and/or more than 25% necrosis; and TE I, more than 25% increase in tumor size regardless of the necrotic effect. TE II was defined as a response not qualifying for classification as TE V, IV, III, or I. When a patient assigned to the SM-11355 group and judged to be TE V developed a tumor in a different region and requested SM-11355, the drug was given continuously after the study, provided that this was felt to be necessary by the investigator. The primary endpoint was the TE V rate. The secondary endpoints were the response rate based on the Response Evaluation Criteria in Solid Tumors (RECIST) and on the Japan Society for Cancer Therapy Criteria [14], which are similar to the World Health Organization (WHO) Criteria. The serum α-fetoprotein (AFP) level of each patient was measured before and 5 weeks after each treatment. Survival was evaluated using the Kaplan-Meier method. Toxicity was assessed according to the criteria of the Japan Society for Cancer Therapy [15], which are also fundamentally similar to WHO criteria.

Pharmacokinetics

Pharmacokinetic data were determined in patients in the SM-11355 group who gave written informed consent and were treated at institutions where a pharmacokinetic study could be conducted. Peripheral blood samples (5 ml) were collected 3 weeks after each treatment for determination of the total plasma platinum concentration and the platinum concentration in methanol extracts (SM-11355 metabolite concentration). The total platinum concentration in resected tissue was also determined in a patient who underwent surgery after evaluation of efficacy.

Statistical analysis

We anticipated enrollment of 120 patients at 17 participating hospitals over the study period of 3 years. A 2:1 ratio for SM-11355 to Zinostatin stimalamer randomization was chosen as a balance between the goals of the study, which were to re-evaluate the efficacy, safety and pharmacokinetics of SM-11355 in a larger population than that in the previous phase II study, and the current limited use of Zinostatin stimalamer. The number of subjects was determined based on the feasibility of the study because the sample size required to conduct a statistical analysis was larger than expected. Assuming a baseline 15% TE V rate for conventional TACE [6], the SM-11355 arm would be considered 'favorable' if there was a 10% improvement in this endpoint (to 25%) with an acceptable toxicity profile. A total of 80 patients in the SM-11355 arm is needed to estimate the TE-V rate with an accuracy of ±10%.

This study was not powered to permit formal statistical comparison between the two treatment arms. However, it does allow an initial assessment of SM-11355 in terms of TE-V, response rate, overall survival and toxicity with a view to performance of a follow-on phase III study.

Results

Patient

From April 2002 to October 2004, 131 patients were enrolled in the study, and 126 were assigned randomly at a 2:1 ratio to receive SM-11355 (85 patients) or Zinostatin stimalamer (41 patients) (Fig. 2). Five patients were excluded from the randomization because tumor staining was not observed in angiography and/or an appropriate hepatic artery for selective catheter insertion was not found (n=3), multiple tumors were observed in angiography that required reconsideration of the treatment strategy (n=1), and withdrawal of consent (n=1). After administration, 4 patients were identified as ineligible due to a platelet count <50,000/μL (n=1), esophageal cancer (n=1) in the SM-11355 group, and deviation from correct use of the investigational products (n=2) in the Zinostatin stimalamer group. Therefore, 122 patients (SM-11355 group, n=83; Zinostatin stimalamer group, n=39) were analyzed for efficacy and safety. The baseline demographic and disease characteristics of the patients are listed in Table 1.

Of the 85 original patients in the SM-11355 group, 18 were withdrawn from the study before the planned evaluation of efficacy 3 months after the first injection because of marked progression of the primary disease (n=5), serious adverse events (n=4), use of prohibited concomitant therapeutic agents or a requirement for combination therapy (n=3), and other reasons (duplicated count). Treatment was terminated in 11 patients after evaluation of the the first injection because complete necrosis of tumors (TE V) was obtained. The remaining 56 patients received a second injection.

Of the 41 patients in the Zinostatin stimalamer group, 9 were withdrawn before the planned evaluation of efficacy 3 months after the first injection, due to marked progression of the primary disease (n=2), serious adverse events (n=1), contravention of the protocol (n=1), appearance of hepatic injury (n=1), and other reasons (duplicated count). Treatment was terminated in 7 patients after evaluation of the first injection because complete necrosis of tumors (TE V) was obtained. The remaining 25 patients received a second injection.

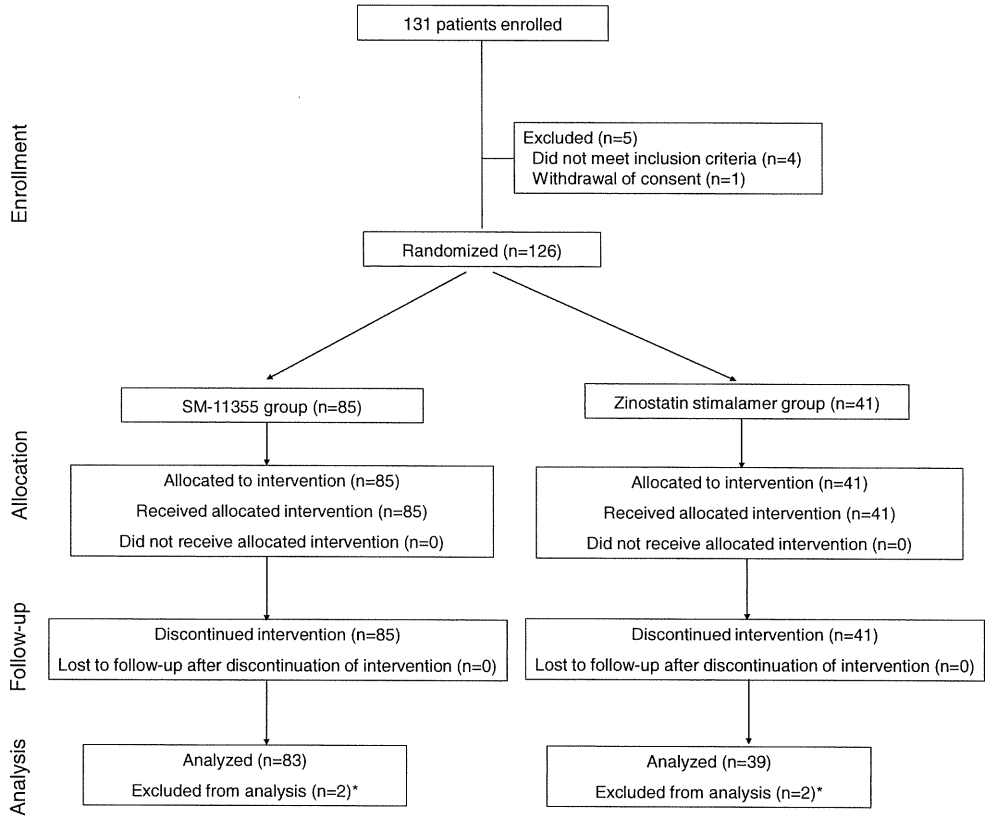

Fig. 2 Study flow diagram

Table 1 Patient background

	SM-11355	Zinostatin stimalamer
Number of patients	83	39
Sex (male:female)	70:13 (84.3%:15.7%)	30:9 (76.9%:23.1%)
Age (median)	67.0 (48–74)	68.0 (52–74)
PS (0:1:2:3:4)	80:3:0:0:0	35:4:0:0:0
HBs antigen positive	9 (13.6%)	1 (3.2%)
HCV antibody positive	55 (83.3%)	30 (96.8%)
HBs antigen · HCV antibody positive	2 (3.0%)	0 (0%)
Tumor stage (I:II:III:IV-A:IV-B)	0:43:40:0:0	0:19:20:0:0
Child-Pugh Classification (A:B:C)	61:22:0	32:7:0
Previously treated	25 (30.1%)	13 (33.3%)
Number of tumors 1	24 (28.9%)	9 (23.1%)
2	19 (22.9%)	11 (28.2%)
3	16 (19.3%)	7 (17.9%)
≥4	24 (28.9%)	12 (30.8%)
Maximum tumor diameter (mm) (Min-Max)	29.0 (10.0–80.0)	29.0 (10.0–94.0)

Table 2 Antitumor efficacy

Group	N	Antitumor efficacy						
"Criteria for Evaluation of Direct Effects on Hepatocellular Carcinoma" of the Liver Cancer Study Group of Japan								
		V	IV	III	II	I	NE	Percentage of TE V (%) [95% CI]
SM-11355	83	22	21	12	7	17	4	26.5 [17.4–37.3]
Zinostatin stimalamer	39	7	14	4	10	1	3	17.9 [7.5–33.5]
Response Evaluation Criteria in Solid Tumors (RECIST)								
		CR	PR	SD		PD	NE	Percentage of CR + PR
SM-11355	83	0	20	52		10	1	24.1 [15.4–34.7]
Zinostatin stimalamer	39	0	10	23		6	0	25.6 [13.0–42.1]
"Clinical Response Evaluation Criteria for Solid Tumor Chemotherapy" of the Japan Society for Cancer Therapy								
		CR	PR	MR	NC	PD	NE	Percentage of CR + PR
SM-11355	83	0	17	10	36	19	1	20.5 [12.4-30.8]
Zinostatin stimalamer	39	0	9	5	19	6	0	23.1 [11.1–39.3]

Efficacy

The antitumor efficacy is shown in Table 2. The percentages of TE V patients were 26.5% (22/83) [95% confidence interval (CI): 17.4–37.3%] in the SM-11355 group and 17.9% (7/39) [95% CI: 7.5–33.5%] in the Zinostatin stimalamer group. In a RECIST assessment, response rates were 24.1% (20/83) [95% CI: 15.4–34.7%] and 25.6% (10/39) [95% CI: 13.0–42.1%] in the respective groups. Based on the Japan Society for Cancer Therapy Criteria, the tumor responses were 20.5% (17/83) [95% CI: 12.4–30.8%] and 23.1% (9/39) [95% CI: 11.1–39.3%] in the respective groups (Table 2).

Of 61 patients with a pre-treatment AFP level above the upper limit of normal in the SM-11355 group, 6 / 60 (10%) had an AFP level within the normal range 5 weeks after the first injection. No data for the AFP level were available for 1 patient in the SM-11355 group at 5 weeks after the first injection. Among the 61 patients, 37 received a second injection and 6 (16%) had a normal AFP level 5 weeks after the second injection. Of the 26 patients in the Zinostatin stimalamer group with a pre-treatment AFP level above the upper limit of normal, none had an AFP level within the normal range 5 weeks after the first injection. Among the 26 patients, 18 received a second injection, but none had a normal AFP level 5 weeks after the second injection.

Cumulative survival rates are shown in Fig. 3. The follow-up period was approximately 3 years after the treatment period. The longest follow-up periods in the SM-11355 and Zinostatin stimalamer groups were both 5.6 years, and the median periods were 3.0 years and 2.8 years, respectively. The one-year survival rates in the SM-11355 and

Fig. 3 Cumulative survival rate

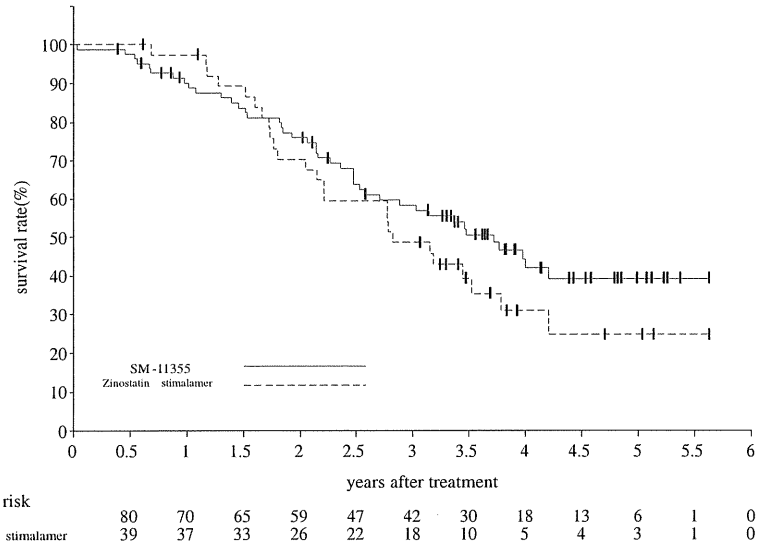

Table 3 Hematological and non-hematological adverse events

	SM-11355			Zinostatin stimalamer		
	No. of patients	All (%)	≥ Grade 3 (%)	No. of patients	All (%)	≥ Grade 3 (%)
Decrease in leukocytes	83	41.0	1.2	39	66.7	0
Decrease in lymphocytes	83	79.5	0	39	79.5	0
Decrease in neutrophils	83	53.0	8.4	39	43.6	2.6
Decrease in platelets	83	50.6	12.0	39	74.4	10.3
Decrease in hemoglobin	83	15.7	0	39	10.3	0
Increase in eosinophils	83	84.3	0	39	41.0	0
Increase in monocytes	83	57.8	0	39	76.9	0
Fatigue	83	39.8	0	39	46.2	0
Fever	83	96.4	3.6	39	97.4	0
Chills	83	39.8	0	39	51.3	0
Vomiting	83	55.4	1.2	39	51.3	0
Pain at injection site	83	43.4	0	39	41.0	2.6
Decrease in albumin	83	50.6	0	39	28.2	0
Increase in ALP	83	30.1	1.2	39	51.3	0
Increase in ALT	83	59.0	24.1	39	66.7	20.5
Increase in AST	83	62.7	26.5	39	79.5	38.5
Increase in bilirubin	83	57.8	12.0	39	71.8	5.1
Decrease in calcium	83	38.6	0	39	51.3	0
Increase in γ-GTP	83	49.4	0	39	61.5	0
Increase in glycemia	83	56.6	12.0	39	56.4	5.1
Increase in LDH	83	60.2	0	39	69.2	0
Increase in CRP	83	95.2	0	39	79.5	0
Prolonged PT time	83	42.2	1.2	39	28.2	0
Decrease in urinary creatinine	83	54.2	0	39	56.4	0
Increase in urinary creatinine	83	49.4	0	39	38.5	0
Increase in urinary NAG	83	89.2	0	39	87.2	0

Adverse events that occurred at a rate of >40% are shown

Zinostatin stimalamer groups were 90.1% and 97.4%, the 2-year survival rates were 75.9% and 70.3%, respectively, and the 3-year survival rates were 58.4% and 48.7%, respectively. The median survival time (MST) was 3.7 years in the SM-11355 group and 2.8 years in the Zinostatin stimalamer group.

Safety

Hematological adverse events were relatively mild and transient in both groups (Table 3). The incidences of neutropenia and decreased hemoglobin were similar in the two groups, but the incidence of eosinophilia was higher in the SM-11355 group, and the incidences of leukopenia and thrombocytopenia were higher in the Zinostatin stimalamer group. Most non-hematological adverse events (Table 3) were also mild and transient in both groups. Major events of grade 3 or higher involved liver dysfunction (including elevations in AST, ALT and hyperbilirubinemia) and hyperglycemia, but these had similar incidences in both groups and most were reversible.

One patient in the SM-11355 group died of esophageal variceal rupture, which occurred 12 days after the first injection, and one patient in the Zinostatin stimalamer group died of hepatic failure 168 days after the second injection. Esophageal variceal rupture was considered not to be related to the treatment because the condition was recognized before initiation of treatment and the event was not classified as a toxicity. Other serious adverse events occurred in 8 patients in the SM-11355 group (increase in AST in 2 patients; and increase in ALT, sepsis, systemic inflammatory response syndrome (SIRS: a syndrome characterized by systemic inflammation and extensive tissue damage associated with serious infection), decrease in neutrophils, acute myocardial infarction (AMI), and hypotension in 1 case each) and in 2 patients in the Zinostatin stimalamer group (respiratory distress and arrhythmia, and abdominal pain in 1 case each). All the patients recovered with appropriate treatment. Most of these events

were considered to be probable or possible drug-related toxicities, except for the cases of SIRS and AMI in the SM-11355 group. SIRS was judged to have no association with the investigational drug based on the results of blood culture and changes in test values. This patient was treated using a urinary catheter, and urinary tract infection is a cause of SIRS. A similar judgment was made for the case of AMI based on the chronological relationship between drug administration and the onset of disease.

In the subsequent angiographic examination before the second administration of SM-11355 or Zinostatin stimalamer or in postprotocol treatment, hepatic artery damage that was probably due to intra-arterial drug administration was observed in 15/31 (48.4%) patients, shunt occurred in 5/31 (16.1%), and disorders of the hepatobiliary system were observed in 3/39 (7.7%) in the Zinostatin stimalamer group. None of these events were observed in patients in the SM-11355 group. Grade 3 hepatic artery damage and a grade 4 disorder of the hepatobiliary system were observed in 1 case each in the Zinostatin stimalamer group. Hepatobiliary damage that may have been caused by arterial damage was found in 3 patients in the Zinostatin stimalamer group (1 case each of liver atrophy and bile duct dilatation, bile duct necrosis, and liver failure and bile duct stricture), whereas there were no such findings in the SM-11355 group.

In the SM-11355 group, the percentages of patients with an increase in Child-Pugh score of one or more points compared to the pre-administration score were 27.7% (23/83) and 17.9% (10/56) in the 5 weeks after the 1st administration and the 5 weeks after the 2nd administration, respectively. In the Zinostatin stimalamer group, these percentages were 35.9% (14/39) and 50.0% (12/24), respectively (Fig. 4).

Pharmacokinetics

Total plasma platinum concentrations and platinum concentrations in methanol extracts (Table 4) were determined in 30 and 24 patients in the SM-11355 group who were given one and two injections, respectively, and received median doses of 85 (Min-max: 24–120) and 120 (10–120) mg, respectively. The mean total platinum concentrations after the first and second injections were 9.6 and 12.9 ng/mL, respectively, and the mean percentages of the concentration in methanol extracts relative to the total plasma platinum concentration were 12.2% and 9.8% after the first and second injections, respectively. In one patient who underwent surgery 172 days after the second injection, the total platinum concentration was determined in the resected liver tissue. The total dose was 200 mg (first injection: 100 mg; second injection: 100 mg) and the concentration in the tumor region of sample S6, which had a 10% necrotic effect, was 62,000 ng/g tissue and that in the non-tumor region was 22,000 ng/g tissue. In contrast, the concentration in the tumor region of sample S8, which showed 50% necrosis, was 260,000 ng/g tissue and that in the non-tumor region was 67,000 ng/g tissue.

Discussion

Most anticancer agents used in TACE are water-soluble and inappropriate for suspension in iodized oil, and are usually administered as a water-in-oil emulsion. Consequently, these agents have reduced sustained release due to poorer retention in the tumor, leading to a limited antitumor effect and adverse effects caused by diffusion of the agents into the blood [16]. In contrast, lipophilic anticancer agents have a high affinity for iodized oil and those injected into the hepatic artery with iodized oil are retained selectively in tumors and exert continuous antitumor effects. SM-11355 is a structurally modified platinum complex with improved affinity for iodized oil due to increased lipophilicity [3]. In an AH109A-transplanted rat liver tumor model, the platinum concentration in the tumor was sustained for longer following administration of a iodized oil suspension of SM-11355 compared to a suspension of cisplatin, with SM-11355 distributed in tumor tissues more selectively than cisplatin [17]. Phase I and early phase II trials

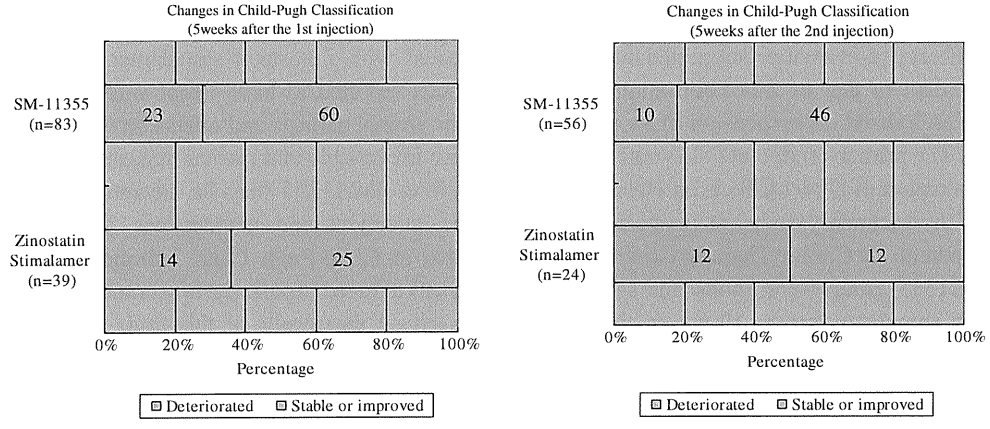

Fig. 4 Changes in Child-Pugh Classification

Table 4 Blood drug concentrations

Administration frequency		Once	Twice
Dose (mg)	Number of patients	30*	24*
	Median (Min-Max)	85.0 (24–120)	120.0 (10–120)
Total plasma platinum concentration (ng/mL)	Number of patients	30	24
	Mean	9.6	12.9
SM-11355 metabolite concentration in methanol extracts (ng/mL)	Number of patients	32	24
	Mean	1.17	1.19
[SM-11355 in methanol-extracted fraction*] / [total plasma platinum concentration] × 100 (%)	Number of patients	30	24
	Mean	12.2	9.8

Number of subjects in whom both the total plasma platinum concentration and SM-11355 metabolite concentration in methanol extracts were measured

* Methanol-extracted fraction: The fraction of SM-11355-derived substances includes components that may exert therapeutic activity as an anticancer agent and excludes components that are irreversibly bound to plasma protein

of SM-11355 have also shown that the total plasma platinum concentration is much lower than that with cisplatin [4, 5, 18]. Our pharmacokinetic data verify these results and suggest that SM-11355 is retained in liver tumors selectively and exerts a continuous effect on the tumor.

In patients in whom the total plasma platinum concentration and the platinum concentration in methanol extracts were determined after the first and second injections, the platinum concentration in methanol extracts 3 weeks after injection (estimated to be the peak of the total plasma platinum concentration) was approximately 10% of the total plasma platinum concentration. Of the platinum components released from the SM-11355 suspension and transferred into the systemic circulation, some are irreversibly bound to plasma proteins and are no longer bioactive. After exclusion of these components, the amount remaining in the plasma is estimated to be up to about 10% of the dose. The total platinum concentrations in several regions of the liver were also determined in one patient. The concentrations in tumors regions were significantly higher than those in non-tumor regions and several thousand-fold higher than the mean total plasma platinum concentration at 3 weeks ±3 days after the second injection (12.9 ng/mL). The total platinum concentration was also higher in tissues in which a higher antitumor effect was observed.

The results of the efficacy re-evaluation suggested that SM-11355 has a similar effect to that of Zinostatin stimalamer following injection of an iodized oil suspension of each drug into the hepatic artery. The primary endpoint (TE V rate based on the Criteria for Evaluation of Direct Effects on Hepatocellular Carcinoma) and the secondary endpoint (response rate based on the Japan Society for Cancer Therapy Criteria and RECIST) in the SM-11355 group were almost the same as those in the Zinostatin stimalamer group. However, the percentage of TE V cases in the SM-11355 group (26.5% [17.4–37.3%]) in this trial was lower than the value of 56% [30–80%] found in the early phase II trial. The discrepancy in the percentage of TE V cases may be due to differences in the tumor burden in the two trials. Eleven (68.8%) of 16 patients in the early phase II study had 3 or less tumors and a longest tumor diameter of 3 cm or less, whereas only 38 (45.8%) of 83 patients in the late phase II study had these characteristics.

The major toxicities of grade 3 or higher involved liver dysfunction, including increases in AST, ALT and bilirubin, and a decrease in platelets in both groups. The incidences were similar in each group and most of the effects were reversible. An increase in eosinophils was found in 84.3% of patients in the SM-11355 group, and was considered to be a SM-11355-specific adverse event. The precise mechanism is unknown, but the finding was not thought to indicate anaphylaxis because the increase in eosinophils showed no marked correlation with an increase in IgE and/or allegic symptoms like wheezing. Renal disorder was transient in patients of the SM-11355 group, except for a patient with sepsis. The incidences and severity of increased blood creatinine and positive urine protein in the SM-11355 group were higher than the respective levels in the Zinostatin stimalamer group (9/83, 10.8% vs. 2/39, 5.1%; and 22/83, 26.5% vs. 2/39, 5.1%, respectively). Based on these data, we consider that the patients were thoroughly followed up.

Injection of SM-11355 did not lead to local vascular damage and had fewer irreversible effects on the hepatobiliary system compared with Zinostatin stimalamer. Zinostatin stimalamer has been reported to have major safety problems, including hepatic arterial damage and effects on the hepatobiliary system that are irreversible and prevent repeated treatment [5, 19, 20] Therefore, SM-11355 may be advantageous for frequent repeated treatment and maintenance of liver function. The changes in Child-Pugh Class indicated a low incidence of treatment-induced hepatic dysfunction in the SM-11355 group.

Based on the results of this trial, we conclude that SM-11355 in iodized oil has similar efficacy to that of Zinostatin stimalamer, which is the only drug currently approved for chemolipiodolization for HCC in Japan. The TE V rate of 26.5% in the SM-11355 group was considered 'favorable'

based on our assumption of a TE V rate of 15% for conventional TACE before the initiation of this study, and was equivalent or superior to the rate of about 20% found in patients receiving current standard TACE treatment in a recent report [7]. Our results also suggest that repeated dosing of SM-11355 in iodized oil is possible without development of hepatic vascular injury in a case of relapse. We are currently conducting a phase III study of intra-arterial treatment with SM-11355 in comparison with conventional TACE with epirubicin, which is designed to detect the superiority of intra-arterial treatment with SM-11355 in overall survival of TACE-naïve patients with advanced HCC (Appendix).

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Appendix

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ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

A novel transcatheter arterial infusion chemotherapy using iodized oil and degradable starch microspheres for hepatocellular carcinoma: a prospective randomized trial

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Abstract
Background We designed a novel transcatheter arterial infusion chemotherapy (TAI) using iodized oil (lipiodol) and degradable starch microspheres (DSM) for hepatocellular carcinoma (HCC) patients. In this study, we investigated the efficacy of TAI using lipiodol and DSM in a prospective randomized trial.
Methods We randomly divided 45 patients with HCC into 3 groups: TAI using lipiodol (lipiodol group, $n = 15$), TAI using DSM (DSM group, $n = 15$), and TAI using lipiodol and DSM (lipiodol + DSM group, $n = 15$). In the lipiodol group, a mixture of cisplatin and lipiodol was administered. In the DSM group, a mixture of cisplatin and DSM was administered. In the lipiodol + DSM group, a mixture of cisplatin and lipiodol was administered, followed by DSM.
Results The response rates were 40% in the lipiodol group, 53.4% in the DSM group, and 80% in the lipiodol + DSM group, respectively. The response rate tended to improve in the lipiodol + DSM group (lipiodol group vs. lipiodol + DSM group, $P = 0.07$). The median progression-free survival time was 177 days in the lipiodol group, 287 days in the DSM group, and 377 days in the lipiodol + DSM group. The progression-free survival in the lipiodol + DSM group was significantly better than those in the DSM group ($P = 0.020$) and the lipiodol group ($P = 0.035$). There were no serious adverse effects among the 3 groups.
Conclusions TAI using lipiodol and DSM was superior to TAI using lipiodol only and TAI using DSM only because of improvements in therapeutic effects and progression-free survival.

Keywords Hepatocellular carcinoma · Transcatheter arterial infusion chemotherapy · Iodized oil · Degradable starch microspheres · Randomized trial

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Introduction

Hepatocellular carcinoma (HCC) is the sixth most common type of cancer in the world [1]. Deaths due to HCC are increasing in almost all countries worldwide, including Japan [2–4]. Recent advancements in several therapeutic techniques such as hepatic resection, percutaneous ethanol injection, radiofrequency ablation (RFA), transcatheter arterial chemoembolization (TACE), sorafenib, and transplantation have improved the prognosis of HCC patients [5–10].

Of these treatments, TACE has become one of the most popular for HCC patients. TACE in Japan has generally used several anticancer agents, iodized oil (lipiodol) and gelatin sponge particles [11]. On the other hand, polyvinyl alcohol (PVA), drug-eluting beads (DEB), and embospheres have been used as embolizing agents in Europe and the United States [12]. Studies prior to 2000 failed to prove a survival benefit of TACE in the treatment of HCC [13, 14]. However, the survival benefit of TACE was proven by meta-analysis in recent reports [15, 16]. In addition, with the development of the microcatheter, the catheter can be inserted in the segmental or subsegmental hepatic artery, and segmental or subsegmental TACE has been reported to be a useful treatment [7, 17]. On the other hand, transcatheter arterial infusion chemotherapy (TAI) using an emulsion of lipiodol and

an anticancer agent (without gelatin sponge particles) has usually been performed for HCC patients in whom the catheter could not be inserted in the targeted segment or a feeding artery was not detected in the tumor. In addition, TAI without gelatin sponge particles has been also used for HCC in high-risk patients (for example, main portal vein occlusion, Child–Pugh B or C) [18]. We have also experienced that repeated TACE therapy is not possible due to obstruction of the hepatic artery in HCC patients. Therefore, we have been performing segmental or subsegmental TACE for selected HCC patients. However, it has been reported that the effect of TAI using lipiodol was lower than that of TACE in local tumor control [19]. Many interventional radiologists desire a novel therapy that is both more effective than TAI using lipiodol in local tumor control and is less damaging to the hepatic artery than TACE.

Degradable starch microspheres (DSM) were developed to provide transient occlusion of small arteries [20, 21]. The duration of occlusion in the hepatic arteries by DSM is limited to 80 min [22]. Several studies of metastatic liver tumors indicate that intra-arterial therapy with DSM and an anticancer agent improves the therapeutic effects compared with therapy using an anticancer agent alone [22–24]. However, few studies have evaluated TAI using DSM in HCC patients [25–27].

Given this background, we designed a novel TAI using lipiodol and DSM for use in HCC patients [28]. After a mixture of an anticancer agent and lipiodol is injected, DSM is administered until stasis or reflux of the arterial flow. We postulate that TAI using two occlusion materials may be beneficial because of the tight interruption of blood supply for HCC. In this study, we investigated the efficacy of a novel TAI using lipiodol and DSM in a prospective randomized trial.

Materials and methods

Patients

The eligibility criteria for inclusion in this study were as follows: (1) age 20–80 years; (2) Child–Pugh score of A or B; leukocyte count $\geq 3000/mm^3$; (3) hemoglobin level ≥ 9.5 g/dL; (4) platelet count $\geq 50000/mm^3$; (5) serum creatinine level <1.2 mg/dL; (6) total bilirubin <3.0 mg/dL; (7) locally nodular disease without extrahepatic metastasis and/or vascular tumor thrombosis (portal vein, hepatic vein, and bile duct); (8) no indication for surgical resection and local ablation, or patients rejected surgical resection; and (9) Eastern Cooperative Oncology Group (EOGG) performance status of 0–1 [29].

We studied 45 patients with HCC who had been admitted to the Department of Gastroenterology and Hepatology, Yamaguchi University Graduate School of Medicine, between February 2006 and May 2008. We randomly divided the patients into 3 groups before the angiography: TAI using lipiodol (lipiodol group, $n = 15$), TAI using DSM (DSM group, $n = 15$), and TAI using lipiodol and DSM (lipiodol + DSM group, $n = 15$). The primary outcome measure was tumor response. Secondary outcome measures included progression-free survival and toxicity (Fig. 1). HCC was diagnosed on the basis of imaging results (hyperattenuation in the arterial phase and hypoattenuation in the portal-venous phase) and elevated serum levels of α-fetoprotein (AFP) and/or des-γ-carboxyprothrombin (DCP).

Patients provided their written informed consent before participating in the study, which was approved by the Institutional Review Board of Yamaguchi University Hospital.

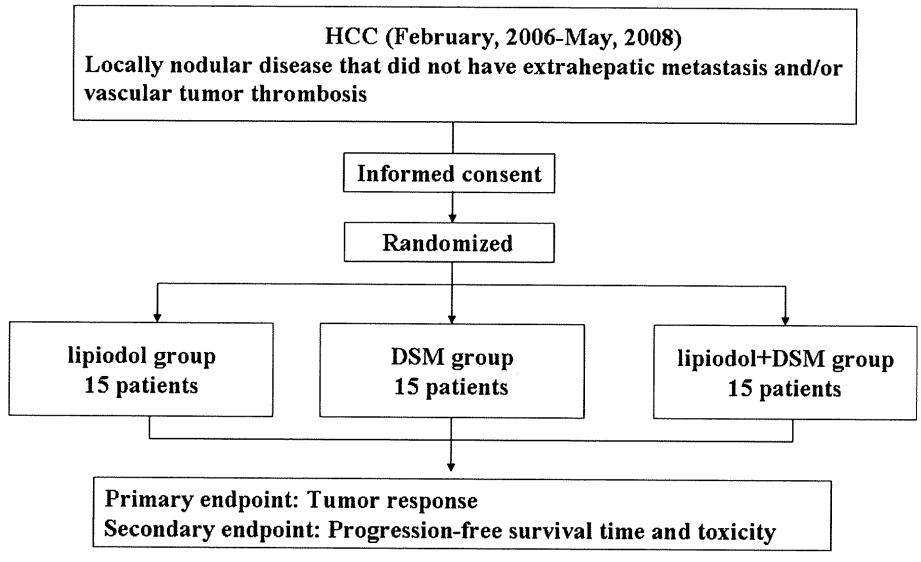

Fig. 1 Study design. We randomly divided patients into 3 groups: transcatheter arterial infusion chemotherapy (TAI) using lipiodol (lipiodol group, $n = 15$), TAI using degradable starch microspheres (DSM) (DSM group, $n = 15$), and TAI using lipiodol and DSM (lipiodol + DSM group, $n = 15$)

Table 1 Clinical profiles of the 45 patients with hepatocellular carcinoma

Clinical characteristics	Lipiodol group ($n = 15$)	DSM group ($n = 15$)	Lipiodol + DSM group ($n = 15$)	P value
Age	69.5 ± 4.4	68.0 ± 7.9	69.3 ± 9.1	NS
Gender (male/female)	12/3	12/3	10/5	NS
HCV Ab(+)/HBs Ag(+)/others	12/2/1	12/2/1	11/3/1	NS
Child–Pugh A/B	11/4	8/7	12/3	NS
Maximum tumor size (mm)	27.1 ± 16.2	33.6 ± 12.8	27.7 ± 15.1	NS
Tumor stage I/II/III[a]	2/4/9	0/2/13	0/7/8	NS
Number of tumors 1/2/3/4/5≦	2/2/3/1/7	1/2/2/2/8	1/3/3/3/5	NS
Previous treatment (yes/no)	15/0	15/0	15/0	NS

DSM degradable microspheres, *NS* not significant

[a] According to the criteria of the Liver Cancer Study Group of Japan

Table 1 summarizes the clinical profiles of the patients in the 3 groups. There were no significant differences between the 3 groups with regard to age, gender ratio, proportion of patients with hepatitis B virus and hepatitis C virus infections, Child–Pugh score, maximum tumor size, tumor stage, number of tumors, or previous treatment. Tumor stage was determined according to the criteria of the Liver Cancer Study Group of Japan [30, 31]. Tumor staging was based on the following 3 parameters (T factor): solitary tumor, <2 cm in diameter and no vessel invasion. Stage I was defined as one fulfilling all of the above 3 criteria (T1); stage II as one fulfilling 2 of the above 3 criteria (T2); stage III as one fulfilling 1 of the above 3 criteria (T3); stage IV A as one fulfilling none of the above 3 criteria (T4) with no distant metastasis or as one with any T factor with lymph node metastasis; and stage IV B as one with any T factor with distant metastasis.

Embolization technique

Hepatic angiography was performed with a 4-French (4-Fr) or 5-Fr angiographic catheter. After digital subtraction angiography (DSA), angiography combined with a computed tomography (angio-CT) [32] system using a Somatom plus 4 (Siemens, Erlagen, Germany) was performed to carefully evaluate HCC tumors. In this study, a fine-powder formulation of cisplatin (IA-call; Nippon Kayaku Co., Tokyo, Japan) was used as the anticancer agent. The dose of cisplatin was limited to 80 mg. According to the tumor vascularization and distribution, TAI was performed by selectively introducing a catheter into the right or left hepatic artery or a segmental branch of the hepatic artery. Gelatin sponge particles were not used in this study.

In the lipiodol group, a mixture of cisplatin and lipiodol (Lipiodol Ultra Fluid; Andre Guerbet, Paris, France) was administered through the tumor-supplying vessels. In the DSM group, a mixture of cisplatin and emulsion obtained by mixing DSM (Spherex; Yakult Honsha Co., Tokyo, Japan) and contrast agent was administered. If this procedure was insufficient, lipiodol or DSM alone was injected until stasis and reflux were achieved.

A mixture of cisplatin and lipiodol was administered in the lipiodol + DSM group. After that point, emulsion obtained by mixing DSM and contrast agent was injected until stasis and reflux were achieved.

The serotonin antagonist ondansetron hydrochloride was administered intravenously as an antiemetic prior to treatment in all 3 groups. To prevent kidney damage, adequate hydration was ensured before and after the treatment by an intravenous drip infusion of 1000–2000 mL of an infusion solution.

After the treatment, a follow-up examination including CT, tumor marker measurement, and serum biochemistry, was performed, first at 1 month after treatment completion and subsequently every 3–4 months. In principle, the same transcatheter arterial treatments were repeated unless the tumors progressed, when a follow-up CT examination showed new lesions in the liver or regrowth of previously treated tumors.

Response and toxicity evaluation

The antitumor effect was assessed by dynamic CT 1 month or more after treatment. The response was classified according to the Liver Cancer Study Group of Japan criteria [30]. In the response evaluation criteria, lipiodol accumulation in the tumors is regarded as an indication of necrosis because significant positive correlations have been reported between lipiodol accumulation observed on CT images and the necrotic regions in the resected tumors examined pathologically after TACE and TAI [33–35]. Therapeutic effect IV (TE IV) is defined as the disappearance or 100% necrosis of all tumors, and TE III as a greater than 50% reduction in tumor size and/or greater than 50% necrosis. TE I is defined as a greater than 25% increase in tumor size. TE II is defined as disease that does not qualify for classification as TE IV, III, or I.

When repeated TAI was performed, the greatest antitumor effect was assessed as the final response.

The severity of adverse reactions was evaluated during the first treatment cycle according to the Common Terminology Criteria for Adverse Events v.4.0 (CTCAE v.4.0) [36].

Statistical analysis

The data are expressed as the mean ± standard deviation (SD). Statistical analyses were performed using the unpaired *t* test and the Mann–Whitney *U* test as appropriate. Progression-free survival and cumulative survival were calculated by the Kaplan–Meier method [37] and significance was determined by the log-rank test. Progression-free survival time was defined as the interval between the first TAI after randomization and death or the progression of the last follow-up period. Survival time was defined as the interval between the first TAI after randomization and death or the last follow-up period. The follow-up period ended on April 30, 2010. Statistical significance was defined as a $P < 0.05$.

Results

Information on the anticancer agent and embolizing agents

The median doses of cisplatin at first TAI in the lipiodol group, the DSM group, and the lipiodol + DSM group were 64.3 ± 22.0 mg (20–80 mg), 59.4 ± 20.0 mg (20–80 mg), and 60.5 ± 20.1 mg (10–80 mg), respectively. There was no significant difference in cisplatin dose among the 3 groups. In the lipiodol group, the dose of lipiodol at first TAI was 4.8 ± 2.0 mL (1–8 mL). In the DSM group, the dose of DSM at first TAI was 1164.6 ± 1013.1 mg (120–3000 mg). In the lipiodol + DSM group, the doses of lipiodol and DSM at first TAI were 4.1 ± 2.0 mL (0.5–8 mL) and 426.6 ± 404.8 mg (60–1500 mg), respectively.

Response to therapy

The total number of treatment courses was 23 with a mean of 1.5 courses per patient (range 1–5 courses) in the lipiodol group, 29 with a mean of 1.9 courses per patient (range 1–6 courses) in the DSM group, and 29 with a mean of 1.9 courses per patient (range 1–6 courses) in the lipiodol + DSM group.

Table 2 shows the final response to therapy. In the lipiodol group ($n = 15$), 4 (26.7%), 2 (13.3%), 4 (26.7%), and 5 (33.3%) patients exhibited TE VI, III, II, and I, respectively [response rate (patients with TE VI and III/all patients) = 40%; complete response (CR) rate (patients with TE VI/all patients) = 26.7%]. In the DSM group ($n = 15$), 4 (26.7%), 4 (26.7%), 7 (46.6%), and 0 (0%) patients exhibited TE IV, III, II, and I, respectively (response rate = 53.4%; CR rate = 26.7%). In the lipiodol + DSM group ($n = 15$), 6 (40%), 6 (40%), 2 (13.3%), and 1 (6.7%) patient exhibited TE IV, III, II, and I, respectively (response rate = 80%; CR rate = 40%). The response rate tended to improve in the lipiodol + DSM group (lipiodol group vs. lipiodol + DSM group, $P = 0.07$; Mann–Whitney *U* test). However, no significant differences were seen between the 3 groups (lipiodol group vs. DSM group, $P = 0.21$; DSM group vs. lipiodol + DSM group, $P = 0.25$; Mann–Whitney *U* test).

Table 2 Response to therapy

Group	TE[a]				Response rate[b] (CR rate[c])
	IV	III	II	I	
Lipiodol group ($n = 15$)	4	2	4	5	40% (26.7%)
DSM group ($n = 15$)	4	4	7	0	53.4% (26.7%)
Lipiodol + DSM group ($n = 15$)	6	6	2	1	80% (40%)

TE therapeutic effect, *CR* complete response, *DSM* degradable microspheres

[a] According to the criteria of the Liver Cancer Study Group of Japan

[b] Response rate, patients with TE IV and III/all patients

[c] CR rate, patients with TE IV/all patients

[#] Lipiodol group versus DSM group, $P = 0.21$

[##] DSM group versus lipiodol + DSM group, $P = 0.25$

[###] Lipiodol group versus lipiodol + DSM group, $P = 0.07$

Progression-free survival

Figure 2 shows the progression-free survival rates for the 3 groups. The 1- and 2-year progression-free survival rates in the lipiodol group were 13 and 13%, respectively. The 1-year progression-free survival rate was 27% in the DSM group. The 1-, 2-, and 3-year progression-free survival rates in the lipiodol + DSM group were 53, 13, and 7%, respectively. The median progression-free survival times were 177 days in the lipiodol group, 287 days in the DSM group, and 377 days in the lipiodol + DSM group. No significant difference in progression-free survival was seen between the lipiodol group and the DSM group ($P = 0.515$). On the other hand, progression-free survival in the lipiodol + DSM group was significantly better than that in the DSM group ($P = 0.020$) and the lipiodol group ($P = 0.035$).

Survival

In the lipiodol group, the 1- and 2-year cumulative survival rates were 80 and 60%, respectively. In the DSM group, they were 87 and 40%, respectively. In the lipiodol +DSM

group, they were 87 and 67%, respectively. No significant differences between the 3 groups were seen in survival (lipiodol group vs. DSM group, $P = 0.377$; lipiodol group vs. lipiodol + DSM group, $P = 0.560$; DSM group vs. lipiodol + DSM group, $P = 0.212$).

By the final follow-up, 21 patients remained alive (lipiodol group, $n = 8$; DSM group, $n = 6$; lipiodol + DSM group, $n = 7$), while the other 24 patients had died (lipiodol group, $n = 7$; DSM group, $n = 9$; lipiodol + DSM group, $n = 8$). In the lipiodol group, the cause of death was cancer progression in 6 patients and hepatic failure in 1 patient. In the DSM group, the cause of death was cancer progression in 7 patients, hepatic failure in 1 patient, and another disease in 1 patient. In the lipiodol + DSM group, the cause of death was cancer progression in 3 patients, hepatic failure in 2 patients, another disease in 2 patients, and rupture of esophageal varices in 1 patient.

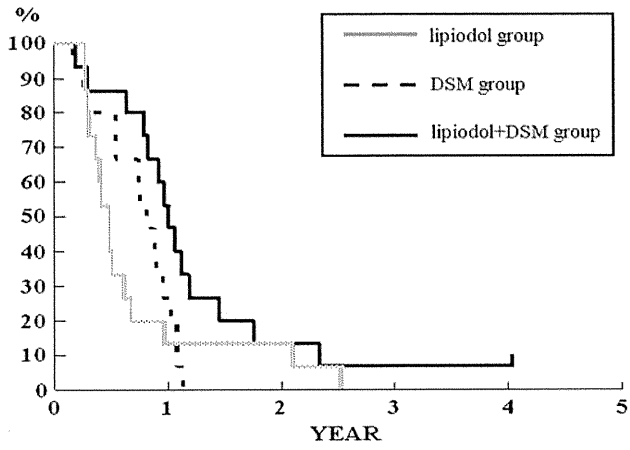

Fig. 2 Progression-free survival rates for the 3 groups. The 1- and 2-year progression-free survival rates in the lipiodol group were 13 and 13%, respectively. The 1-year progression-free survival rate was 27% in the DSM group. The 1-, 2-, and 3-year progression-free survival rates in the lipiodol + DSM group were 53, 13, and 7%, respectively. No significant difference in progression-free survival was seen between the lipiodol group and the DSM group ($P = 0.515$). On the other hand, progression-free survival in the lipiodol + DSM group was significantly better than that in the DSM group ($P = 0.020$) and the lipiodol group ($P = 0.035$)

Adverse effects of therapy

Table 3 shows the adverse effects of therapy. There was no significant difference in thrombocytopenia between the 3 groups, although grade 3 thrombocytopenia occurred in 4 patients of the lipiodol group (26.7%) and grade 3 or 4 thrombocytopenia occurred in 5 patients of the lipiodol + DSM group (33.3%). However, only 1 patient in the lipiodol + DSM group required a blood transfusion. The grade of elevated alanine aminotransferase (ALT) levels was significantly higher in the lipiodol + DSM group than in the lipiodol group ($P = 0.043$), although there were no significant differences in any other adverse effects between the 3 groups. No treatment-related deaths were observed in the 3 groups.

Figure 3 shows the changes in serum ALT or platelets before and after treatment in the lipiodol + DSM group. Transient increases in serum ALT concentration were observed in almost all patients; however, 2 weeks after treatment, concentrations decreased almost to pretreatment levels. Transient decreases in platelets were observed in almost all patients, and platelet counts at 3 days after treatment were the lowest before and after treatment; 2 weeks after treatment, the count increased almost to pretreatment levels.

Table 3 Adverse effects of therapy

Adverse effect	Lipiodol group ($n = 15$)/DSM group ($n = 15$)/lipiodol + DSM group ($n = 15$)				P value
	Grade 1	Grade 2	Grade 3	Grade 4	
Fever	12/5/8	0/1/0	0/0/0	0/0/0	NS
Nausea	0/2/1	0/0/1	0/0/0	0/0/0	NS
Appetite loss	2/5/2	0/0/0	0/0/0	0/0/0	NS
General fatigue	3/5/3	0/0/0	0/0/0	0/0/0	NS
Thrombocytopenia	3/0/0	4/5/5	4/1/3	0/0/2	NS
Creatinine	2/2/1	0/0/0	0/0/0	0/0/0	NS
ALT	12/5/5	3/5/6	0/3/3	0/0/0	0.043[#]
Diarrhea	0/0/1	0/0/0	0/0/0	0/0/0	NS
Ulcer	0/0/0	0/0/1	0/0/0	0/0/0	NS
Pleural effusion	0/0/0	0/0/1	0/0/0	0/0/0	NS
Pulmonary embolism	0/0/0	0/0/0	1/0/0	0/0/0	NS
Ascites	0/1/0	0/0/0	0/0/0	0/0/0	NS
Biloma	0/0/1	0/0/0	0/0/0	0/0/0	NS

According to Common Terminology Criteria for Adverse Events v. 4.0

DSM degradable microspheres, *ALT* alanine aminotransferase, *NS* not significant

[#] Lipiodol group versus lipiodol + DSM group

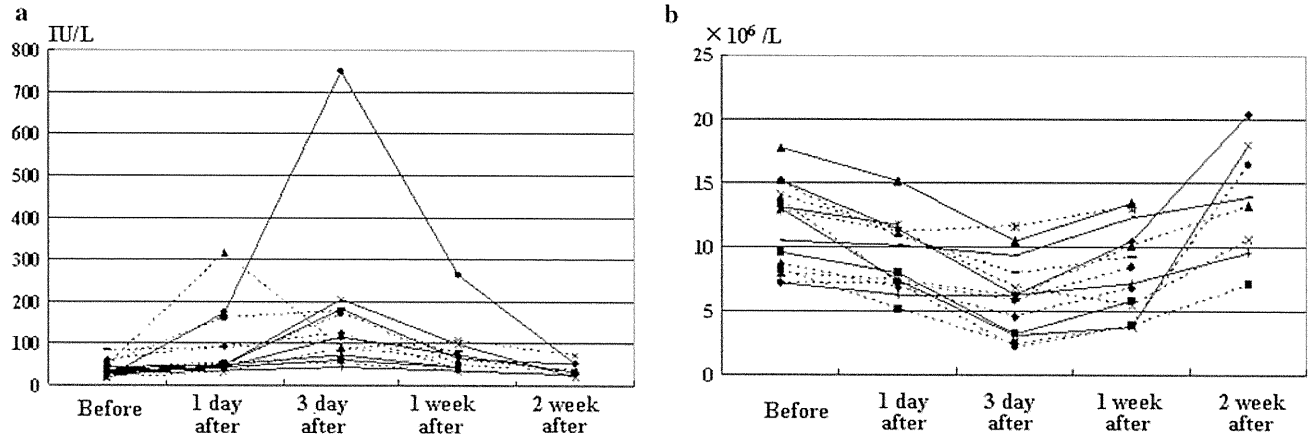

Fig. 3 Changes in serum alanine aminotransferase (ALT) (**a**) or platelet (**b**) levels before and after treatment in the lipiodol + DSM group. Transient increases in serum ALT concentration were observed in almost all patients; however, 2 weeks after treatment, the concentration decreased almost to pretreatment levels. Transient decreases in platelet levels were observed in almost all patients, and platelet counts at 3 days after treatment were lower than before and after treatment; 2 weeks after treatment, the count increased almost to pretreatment levels

Discussion

We designed a novel TAI using lipiodol and DSM for use in HCC patients, and reported the usefulness of this procedure [28]. In this study, we investigated the efficacy of this novel TAI using lipiodol and DSM in a prospective randomized trial (lipiodol vs. DSM vs. lipiodol + DSM).

We used a fine-powder formulation of cisplatin (IA-call; Nippon Kayaku Co., Tokyo, Japan) as the anticancer agent. The most common single-agent anticancer drug was doxorubicin, followed by cisplatin [12]. Although there is no evidence of the superiority of any chemotherapeutic agents [12], only a nonrandomized trial by Ono et al. [38] showed that cisplatin was better than doxorubicin. A Phase II study of hepatic arterial infusion of a fine-powder formulation of cisplatin reported that the response rate was 33.8% [39]. Therefore, we selected IA-call as the anticancer agent.

In our study, the response rates (patients with TE VI and III/all patients) in the lipiodol group, DSM group, and lipiodol + DSM group were 40, 53.4, and 80%, respectively. The CR rate (patients with TE IV/all patients) in particular was 40% in the lipiodol + DSM group. Although no significant differences between the 3 groups were seen due to the small population, the response rate tended to improve in the lipiodol + DSM group (lipiodol group vs. lipiodol + DSM group, $P = 0.07$; Mann–Whitney U test). Because of the response rate results, progression-free survival in the lipiodol + DSM group was significantly better than that in the DSM group ($P = 0.020$) and the lipiodol group ($P = 0.035$). On the other hand, no significant difference in progression-free survival was seen between the lipiodol group and the DSM group ($P = 0.515$).

Previous reports associated with our study are shown in Table 4. The response rate was 51% (CR rate 29%) in TAI using cisplatin and lipiodol [19]. On the other hand, the response rates were 73% (CR rate 32%) [19] and 45% (CR rate 0%) [38] in TACE using cisplatin and lipiodol. Although there is a difference in anticancer drugs, the response rates were 52.9% (CR rate 11.8%) [26] and 26% (CR rate 0%) [27] in TAI using DSM. The present findings showed that the response rates in the lipiodol group and in the DSM group were 40% (CR rate 26.7%) and 53.4% (CR rate 26.7%), respectively. Although it is difficult to compare the response rates of our data with those of previous reports, the response rates of the lipiodol group and the DSM group were similar to those of previous reports. On the other hand, only two clinical studies have evaluated TAI using lipiodol and DSM in HCC patients [40, 41]. However, there were some differences in embolization technique. Although the procedure of Vogl et al. [40] was similar to ours, the DSM dose was low (2–10 mg) compared with our procedure (60–1500 mg; mean, 426.6 ± 404.8 mg). Kirchhoff et al. [41] reported administering a mixture of anticancer drugs, DSM, and lipiodol and seeing a response rate of 36% (CR rate 0%). The particles of the emulsion using anticancer agents and lipiodol (lipiodol emulsion) are <30 μm [42] and those of DSM are 45 ± 7 μm in diameter [43]. Because the DSM particles are larger in diameter than those of the lipiodol emulsion, DSM may cause the occlusion of feeding tumor vessels before the accumulation of lipiodol emulsion by means of a mixture of DSM and lipiodol emulsion. In our study, the response rate was 80% (CR rate 40%). Our response rate is better than that reported by Kirchhoff et al. [41], and is similar to that of TACE reported by Ikeda et al. [19].

Table 4 Previous reports associated with our study

Author and reference	Embolizing agents	Anticancer drugs	Case no.	Response rate (CR rate)	Survival (%)
Ikeda [19]	Lipiodol	Cisplatin	94	51% (29%)	81.6/39.8 (1/3 year)
	Lipiodol, gelform	Cisplatin	74	73% (32%)	87.8/52.2 (1/3 year)
Fruse [26]	DSM	Epirubicin	17	52.9% (11.8%)	64.7/45.3 (1/2 year)
Kirchoff [27]	DSM	Cisplatin, doxorubicin	35	26% (0%)	57/31 (1/2 year)
Kirchoff [41]	Lipiodol, DSM	Cisplatin, doxorubicin	47	36% (0%)	75/59 (1/2 year)
Our study	Lipiodol	Cisplatin	15	40% (26.7%)	80/60 (1/2 year)
	DSM	Cisplatin	15	53.4% (26.7%)	87/40 (1/2 year)
	Lipiodol, DSM	Cisplatin	15	80% (40%)	87/67 (1/2 year)

DSM degradable microspheres

Both animal and clinical studies have reported that lipiodol injected into the hepatic artery occasionally appears in the portal veins through multiple arterioportal communications [44, 45], and that lipiodol can be used to temporarily embolize both the hepatic arteries and the portal veins. We speculate that lipiodol emulsion may be pushed out in the portal vein, the drainage vein of HCC, by DSM. Consequently, we may achieve as tight an interruption of blood supply as TACE for HCC.

There were no significant differences between the 3 groups in adverse effects other than the grade of elevated ALT levels. However, we consider that the high level of ALT in the lipiodol + DSM group reflects the effect of embolization. Transient increases in serum ALT concentration decreased almost to pretreatment levels 2 weeks after TAI using lipiodol and DSM. Because no serious adverse effects were seen in the lipiodol + DSM group, we consider TAI using lipiodol and DSM to be a safe treatment.

In conclusion, our developed TAI using lipiodol and DSM was superior to TAI using lipiodol only and TAI using DSM only because of improvements in therapeutic effects and progression-free survival. This procedure is both a safe and an effective therapy for HCC patients. TAI using lipiodol and DSM may be expected to serve as an alternative to TACE. Since our study examined only a small population, further investigations are necessary.

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