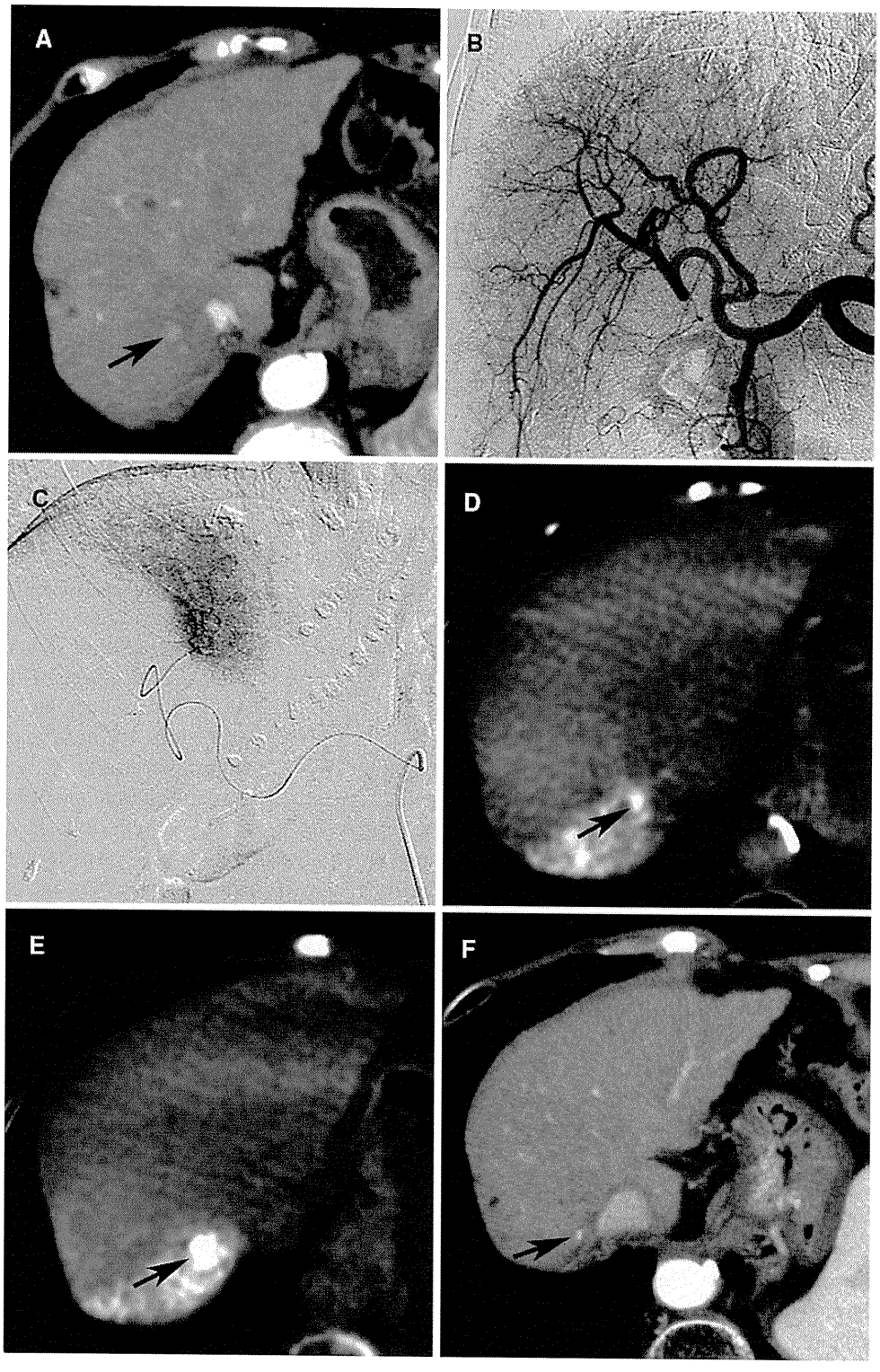

Fig. 3 A small tumor in segment VII in a 74-year-old woman. **A** Arterial-phase CAT shows a hyperatteunating tumor in segment VII (*arrow*). **B** Celiac arteriogram does not show any tumor stains. **C** Selective arteriogram of the branch of the posterior superior subsegmental artery also does not show any obvious tumor stains. **D** CBCTHA at the branch shows enhancing tumor (*arrow*). **E** LipCBCT shows a dense iodized oil accumulation in the tumor more clearly than CBCTHA images. **F** Arterial-phase CAT 12 months after TACE shows that the tumor has decreased in size without any evidence of local recurrence (*arrow*). Atrophy of the surrounding liver parenchyma is also seen

LipCBCT demonstrated 29 (100%) of 29 tumors (Figs. 1 through 3). In 25 tumors that underwent both selective CBCTHA and LipCBCT, all tumors were depicted more clearly by LipCBCT than by selective CBCTHA (Fig. 3), although artifacts from densely accumulated iodized oil were observed in several tumors.

Technical Success Rates and Local Effects of Ultraselective TACE

Ultraselective TACE was performed in all 33 tumors. A single branch was embolized in 28 tumors (Figs. 1 and 3) (84.6%), and 2 branches were embolized in 5 tumors

(15.4%) after confirmation of additional supply from another branch by selective CBCTHA and/or LipCBCT (Fig. 2).

Complete success was achieved in 27 tumors (81.8%) (Figs. 1 through 3), and adequate success was achieved in 6 tumors (18.2%). No tumors demonstrated incomplete embolization. All 33 tumors were followed-up during the mean follow-up period of 13.1 ± 6.0 months. Twenty-five tumors (75.8%) had not recurred during 4 to 25 months (mean 12.0 ± 6.2) after the procedure (Figs. 1 through 3). In the remaining 8 tumors (24.2%), 5 (18.5%) of 27 had complete success, and 3 (50%) of 6 had adequate success; local recurrence was observed from 2 to 20 months (mean 10.1 ± 6.2) after TACE. Additional TACE was performed in 5 tumors in 5 patients, and the recurrent tumor was supplied by another feeding artery. The remaining 3 tumors were followed-up because the recurrent tumors were small. Two patients died during follow-up. One patient died from rapid tumor progression at other sites 16 months after TACE, and another died from arrhythmia 8 months after TACE without tumor recurrence.

Discussion

TACE is one of the effective therapeutic options for inoperable HCC lesions, and it is widely performed throughout the world [1–5]. With advancement of imaging modalities, such as the MDCAT scanner, smaller HCC lesions are being detected [11]. Despite advances in the angiography unit, these tumors frequently cannot be demonstrated by angiography because the lesions are small and have a less hypervascular nature. A combined CAT-angiography system (Interventional radiology-CAT) is useful to detect these small lesions; however, the system is expensive and requires a large room [12, 13].

CBCT is a new technology to obtain CAT-like images using a C-arm system that rotates around the patient [14, 15]. A C-arm system equipped with a large FPD can obtain high image quality and large FOV compared with that obtained by the image-intensified system. Recently, this technology has been introduced into several interventional procedures [6–10]. CAT-like images can be easily obtained during the procedure simply by lifting the patients' hands without causing other movement.

We combined CBCT technology with TACE for HCC lesions that could not be demonstrated on angiography. CBCT demonstrated sufficient ability to detect small HCC lesions, although these images were slightly noisy. In the present study, the ability of CBCTAP to detect HCC lesions was 93.9%, and two tumors measuring 1 cm in diameter could not be detected. In our previous report [9], CBCTAP depicted approximately 89% of HCC nodules, including eight suboptimal lesions, compared with conventional CTAP. CBCTHA and LipCBCT also showed sufficient detection ability, being able to detect 96.7% and 100% of tumors, respectively. In addition, selective CBCTHA and LipCBCT at the TACE point were also useful for not only depicting the tumor but also for monitoring the embolized area. Observations on optional cross-sections can easily provide information on whether the embolized area includes the entire target tumor with an appropriate safety margin. LipCBCT can depict the tumor as a hyperattenuating lesion more clearly compared with CBCTHA because of the high contrast of iodized oil, although artifacts from densely accumulated iodized oil infrequently may decrease the image quality.

Histopathologically, even small HCC lesions have microsatellite lesions. Sasaki et al [16]. reported that microsatellites were observed in 7 (29.2%) of 24 tumors <25 mm in diameter, and all but 1 microsatellite were located within 5 mm from the main tumor. Therefore, we supposed that a safety margin of the embolized area around a small tumor was at least 5-mm wide. In contrast, the embolized area should be minimized considering the risk of adverse effects. This is the dilemma of ultraselective TACE. The smaller the area embolized, the more likely TACE will be insufficient without an adequate safety margin. Especially in a tumor located at the boundary between different small branches, a safety margin around the tumor frequently may not be obtained. Therefore, intraprocedural monitoring of the embolized area is necessary to achieve the complete success of TACE. In the present study, however, a safety margin around the entire tumor was not obtained in 18.2% of tumors. This limitation of TACE therapy is dependent on the vascular territory of the selected branch. Peritumoral recurrence may occur during long-term follow-up in such tumors without a safety margin. In fact, 50% of tumors with insufficient safety margins recurred during follow-up in the present study.

There are several limitations to the present study. First, all tumors were diagnosed based on imaging findings without being histologically proven. In addition, serum levels of tumor markers were not elevated in 39.2% of patients because of small tumor size and/or early-stage HCC. However, we consider that advances in imaging modalities can facilitate establishment of an HCC diagnosis without biopsy. Second, the "gold standard" for diagnosis of HCC in this study was dynamic CAT and CBCTAP or conventional CTAP findings. This means that any HCC nodules that were not detected by these CAT or CAT-like images were not evaluated in the present study. However, we consider that a combination of dynamic CAT obtained by MDCAT scanner and CBCTAP or conventional CTAP has sufficient ability to detect small HCC lesions that require treatment [9, 11]. Third, the

present study mainly evaluated the technical aspects of TACE for HCC lesions that were undetectable on angiography, and follow-up has not yet been sufficient to conclude the efficacy of ultraselective TACE for such small tumors. Fourth, the indications and timing of TACE for such small tumors may be controversial. However, adverse effects, such as impairment of hepatic function reserve and hepatic arterial damage, can be minimized if complete treatment is performed in a small focus. In addition, ultraselective TACE has stronger therapeutic effects on early-stage HCC lesions compared with those of conventional TACE [17]. We consider that ultraselective TACE in a highly limited area and assisted by CBCT technology for small tumors may improve the prognosis of patients with HCC. Finally, local tumor recurrence was judged by CAT alone in almost all patients. Hyperattenuating iodized oil in the tumor impairs assessment of residual tumor enhancement on contrast-enhanced CAT [18]. In a report by Kim et al. [19], MR had higher sensitivity for small HCC lesions ($\leq$1 cm) compared with MDCAT. In addition, Kamel et al. [20] reported that the amount of iodized oil deposition alone could not be used as a consistent predictor of tumor response and that dynamic contrast-enhanced and diffusion-weighted MR imaging could potentially provide effective markers of treatment response and tumor cell death after TACE. Periodic MR imaging should be necessary to improve tumor response interpretation.

CBCT technology is also useful in all TACE procedures for HCC lesions, although we only evaluated its usefulness for small HCC lesions that could not be demonstrated by angiography in the present study. As indicated previously, intraprocedual monitoring of the embolized area by CBCT may improve the success rates and therapeutic effects of TACE, and we have routinely performed CBCT during approximately 760 TACE procedures for HCC lesions since May 2006. In the future, selective CBCTHA may be performed instead of selective angiography at the minute feeding branch of small tumors because the information about whether the entire tumor is included in the vascular territory of the selected branch is more important than whether the selected branch is fed by the tumor. Two-dimensional angiography cannot provide this information in small tumors. Further technical advances, such as improvement of image quality (improvement of soft tissue contrast and reduction of artifacts), shortening of acquisition and reconstruction times, and advances in the image display console may be needed to more easily perform several CBCT sessions during a single TACE procedure. In addition, the patients' hands are unstable during CBCT acquisition. We now employ a hand-fashioned grip above the patients' heads to keep their hands lifted during the procedure.

In conclusion, CBCT technology during TACE was useful in detecting and treating small HCC lesions that could not be demonstrated on angiography. This technology may make possible ultraselective TACE for these HCC lesions. In addition, it may improve the success rates and therapeutic effects of ultraselective TACE for small HCC lesions.

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ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

Usefulness of miriplatin as an anticancer agent for transcatheter arterial chemoembolization in patients with unresectable hepatocellular carcinoma

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Abstract
Background Injection of a suspension of miriplatin into the hepatic artery has been employed for the treatment of hepatocellular carcinoma (HCC). The efficacy and safety of transcatheter arterial chemoembolization (TACE) using miriplatin were evaluated.
Methods A total of 236 patients with unresectable HCC received miriplatin administration through the hepatic artery, followed by embolization with porous gelatin particles. The efficacy of this treatment modality was evaluated by contrast-enhanced computed tomography performed 1 month later and its safety based on the Common Terminology Criteria for Adverse Events (CTCAE).
Results Miriplatin was used at a median dose of 66 mg. The therapeutic efficacy was evaluated in 130 patients, and the overall and complete response rates were 70.0 and 37.7%, respectively. The efficacies differed depending on the staging and Japan integrated staging (JIS) scores of the HCCs, with the overall and complete response rates being 87.7 and 66.7% for stage I and stage II HCC, and 56.2 and 15.1% for stage III and stage IV HCC, respectively; the corresponding rates were 93.2 and 70.5%, respectively, for HCCs with score 0 and score 1, and 58.1 and 20.9%, respectively, for those with scores 2–4. The stage of HCC was a significant independent factor associated with curative effects of TACE using miriplatin. Grade 3 elevation of serum transaminase levels was found in 23.4% of the patients; however, the values returned to the baseline levels.
Conclusions Miriplatin is a useful and safe agent for TACE in patients with HCC stage I or II and/or JIS score 0 or 1 only when radiofrequency ablation and liver resection cannot be performed.

Keywords Miriplatin · Hepatocellular carcinoma · Transcatheter arterial chemoembolization · Lipiodol

Introduction

In Japan, more than 30,000 people die of hepatocellular carcinoma (HCC) each year, and HCC ranks third and fifth, respectively, in men and women as a cause of death due to malignant neoplasms [1]. Surgical resection and radiofrequency ablation (RFA) of tumors, chemotherapy through the hepatic artery with or without embolization of the feeding arteries, molecular-targeted therapy, or cadaveric or living-donor liver transplantation have been selected as therapeutic procedures for HCC depending on three factors: degree of liver damage, number of tumors, and the diameter of the tumors [2].

Surgical resection may be the most preferable therapeutic procedure for HCC in suitable candidates. However, it can be performed as the initial treatment in only about 30% of the patients, according to a report by the Liver Cancer Study Group of Japan [3]. Hepatectomy is precluded in the large number of HCC patients with decreased liver function due to underlying cirrhosis and/or the presence of multiple tumors in the liver. Even when curative hepatectomy is performed, recurrent HCC develops in about 80% of the patients within 5 years after the resection

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because of intrahepatic metastasis from the primary tumors or the multicentric carcinogenesis of HCC [4]. RFA therapy has been employed as an alternative procedure to surgical resection for the treatment of HCC [5]. Although RFA therapy has been revealed to show almost equivalent therapeutic efficacy to hepatectomy in cases of HCC with small tumors (tumor diameter of 3 cm or less) [6], the procedure is not suitable for the treatment of HCC patients with three or more tumors and/or tumors measuring more than 3 cm in diameter [2, 6]. On the other hand, liver transplantation is recommended for HCC patients with class C liver damage when the number of tumors is 3 or less and the tumor diameters do not exceed 3 cm, or a single tumor is present, with a diameter not exceeding 5 cm (Milan's criteria) [2, 7].

According to the guideline for treatment of HCC proposed by the Japan Society of Hepatology in 2009, transcatheter arterial chemoembolization (TACE) is recommended for HCC patients with class A and B liver damage when the number of tumors is 2 or 3 and the tumor diameter is greater than 3 cm [2, 8]. Also, both TACE and hepatic arterial infusion chemotherapy are recommended for HCC patients with 4 or more tumors [2, 9]. Thus, chemotherapy through the hepatic artery with or without subsequent arterial embolization plays a central role in the treatment of HCC patients with large and/or multiple tumors. Miriplatin is a novel lipophilic platinum complex that was approved in Japan for use as a transhepatic arterial chemotherapeutic agent in the treatment of HCC in 2010 [10]. In general, miriplatin is suspended in an oily contrast medium and injected through the hepatic artery without successive embolization with porous gelatin particles. It has been reported, however, that the tumor necrosis is more extensive in cases receiving TACE than in those receiving transarterial infusion chemotherapy, and that the former procedure yields superior survival rates as compared with the latter [11, 12]. These observations prompted us to postulate that the therapeutic efficacy of transhepatic arterial injection of miriplatin may be increased when the intra-arterial administration is followed by embolization of the tumor feeding arteries. Thus, we performed an open trial to evaluate the therapeutic efficacy and safety of TACE therapy using miriplatin in patients with unresectable HCC.

Patients and methods

Patients

The subjects were 236 consecutive patients with unresectable HCC who underwent TACE therapy using miriplatin at Saitama Medical University Hospital between February and December 2010. Written informed consent was obtained from each patient, and the study was conducted with the approval of the hospital's institutional review board. The diagnosis of HCC was confirmed by means of at least two of the following imaging modalities: ultrasonography with or without contrast medium, contrast-enhanced computed tomography (CT), and gadolinium-EOB-enhanced magnetic resonance imaging (MRI).

The demographic and clinical characteristics of the patients are shown in Table 1. The patients consisted of 160 males and 76 females, ranging in age from 48 to 91 years. All patients had underlying chronic hepatitis or liver cirrhosis, and the degree of liver damage (Child–Pugh classification) was grade A, B, and C in 149, 86 and 1 patients, respectively. The extent of HCC progression was as follows: (1) the number of tumors was 2 or more in 144 patients (61.0%), (2) the diameter of the largest tumor was greater than 2 cm in 138 patients (58.5%), and (3) portal vein thrombosis was found in 17 patients (7.2%). Thus, 119 patients (50.4%) were classified as having stage III HCC, characterized by the absence of distant metastasis and fulfillment of two of the three above intrahepatic conditions, based on the staging system of the Liver Cancer Study Group of Japan [13]. On the other hand, 101 (42.8%) patients were diagnosed as having stages I and II HCC, and TACE with miriplatin was performed in these patients on the basis of the following reasons: (1) RFA therapy cannot be done because of the locations of tumors, where ablation may provoke insufficient therapeutic efficacy and/or adverse effects against neighborhood organs; (2) the number of tumors was 3 or more; (3) surgical resection was not performed because of liver damage or refusal by the patients. Also, 17 patients (7.2%) were assigned a JIS score of 0, and 65 (27.5%), 87 (36.9%), and 67 patients (28.4%) were assigned scores of 1, 2, and 3–4, respectively, according to the JIS scoring system proposed by the same group [14].

Therapeutic procedures

A 3-Fr or 4-Fr Shepherd Hook catheter (FansacIV or Angiomaster, Terumo Clinical Supply, Gifu, Japan) was inserted via the right femoral artery, and portography through the superior mesenteric artery and celiac arteriography were performed according to Seldinger's method. Then, a 2.0-Fr or 2.1-Fr microcatheter (Sniper 2, Terumo Clinical Supply or Tangent, Boston Scientific Japan, Tokyo, Japan) was advanced into the feeding arteries of each tumor, and miriplatin (Miripla, Dainippon-Sumitomo Pharmaceutical Co. Ltd., Osaka, Japan) suspended in lipiodol solution (Lipiodol Ultra-Fluid, Dainippon-Sumitomo Pharmaceutical Co. Ltd) was injected into the hepatic artery at a concentration of 20 mg/mL. The dose of

Table 1 Demographic and clinical characteristics of patients with unresectable HCC treated by TACE using miriplatin

	No. of patients (%)
Age [median (minimal–maximal)]	71 (48–91)
Sex	
Male	160 (67.8)
Female	76 (32.2)
Child–Pugh class	
A	149 (63.1)
B	86 (36.4)
C	1 (0.4)
Etiology	
HBV	17 (7.2)
HCV	172 (72.9)
Alcohol	21 (8.9)
Others	26 (11.0)
Stage[a]	
I	27 (11.4)
II	74 (31.4)
III	119 (50.4)
IV	16 (6.8)
JIS score[a]	
0	17 (7.2)
1	65 (27.5)
2	87 (36.9)
3–4	67 (28.4)
Portal vein invasion	
Absent	219 (92.8)
Present	17 (7.2)
Tumor multiplicity	
Solitary	92 (39.0)
Double	36 (15.3)
Multiple	108 (45.8)
Maximum tumor size (cm)	
≤2.0	98 (41.5)
2.1–3.0	74 (31.4)
3.1–5.0	41 (17.4)
>5.0	23 (9.7)
Previous TACE	
Absent	70 (29.7)
Present	166 (70.3)
Previous administration of miriplatin	
Absent	153 (64.8)
Present	83 (35.2)

Values represent the number of patients, with the mean percentage of patients indicated within parentheses

HBV hepatitis B virus, *HCV* hepatitis C virus

[a] Staging and JIS scoring of HCCs as proposed by the Liver Cancer Study Group of Japan

miriplatin was determined depending on the size of the tumors, but the injection was discontinued immediately before the flow ceased completely. In cases of treatment for multiple tumors, the injection was repeated through the corresponding feeding arteries; however, the total dose of miriplatin per session of the procedure was limited to 120 mg. Thereafter, the feeding arteries to the tumors were embolized with porous gelatin particles (Gerpart, Nippon Kayaku, Tokyo, Japan). The extent of embolization was determined depending on the number and location of the tumors and the degree of liver damage. A 5-HT_3 antagonist was administered before the miriplatin injection, whereas hydration by intravenous administration of fluids was not undertaken before the TACE procedure.

Evaluation of the therapeutic efficacy

The therapeutic efficacy was evaluated by contrast-enhanced CT performed 1 month after the TACE procedures, according to the criteria proposed by the Liver Cancer Study Group of Japan [13]. According to these criteria, the percentages of necrotic areas in the tumors are 100%, between 50 and 99%, and less than 50%, respectively, in cases classified as showing TE4, TE3, and TE2, and the extent of tumor progression is less than 25 and at least 25%, respectively in cases showing TE2 and TE1.

The patients receiving additional therapies, such as surgical resection and RFA, within 1 month after the procedure were excluded from the analysis of the therapeutic efficacy of TACE. Also, patients with a history of previous TACE or transarterial infusion chemotherapy using miriplatin were excluded from the evaluation. In contrast, the safety of the TACE was evaluated in all patients for 90 days following the procedures. Adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0, published by the National Cancer Institute [15], except for peripheral blood cells counts and serum levels of albumin and bilirubin, because derangement of these parameters was found frequently even before the TACE procedures in HCC patients with underlying chronic liver disease. For these latter parameters, the severity of the adverse effect was classified according to the gradient of increase of the CTCAE grade after the TACE procedure as compared with that at the baseline, after adaptation of the values for CTCAE grading. The serum creatinine level was also excluded from the evaluation of adverse effects in patients under maintenance hemodialysis for chronic renal failure.

Statistical analysis

The Fisher's exact test and chi-square test were used to analyze the relation between the tumor response rates and

the demographic and clinical characteristics of the patients. Multivariate logistic regression analysis was done to elucidate significant factors influencing the therapeutic efficacy of TACE using miriplatin. p values of less than 0.05 were considered as indicating statistical significance.

Results

Miriplatin was used at the median dose of 66 mg (range 10–120 mg) for a single TACE procedure. Among the 236 patients who underwent TACE using miriplatin, the therapeutic efficacy was evaluated in 130 patients, because 16 patients required RFA therapy or surgical resection within 1 month after the TACE procedure, and 83 patients had a previous history of undergoing TACE and/or transarterial infusion chemotherapy using miriplatin. The reasons for exclusion of the remaining 7 patients from the efficacy evaluation were that 2 of the patients died within 1 month after the TACE procedure, and imaging examinations were not performed in 5 patients.

As shown in Table 2, the overall response rate (TE3 and TE4) and complete response rate (TE4) for the TACE procedures were 70.0 and 37.7%, respectively. When the therapeutic efficacy was assessed according to the stage of the HCC, the overall and complete response rates were 87.7 and 66.7%, respectively, in patients with stages I or II HCC, and 56.2 and 15.1%, respectively, i.e., significantly lower, in patients with stage III or IV HCC. Furthermore, both the overall and complete response rates in the HCC patients differed significantly depending on the JIS scores; the overall and complete response rates were 93.2 and 70.5%, respectively, in cases with a score of 0 or 1, and 58.1 and 20.9%, respectively, in cases with scores of 2–4. Moreover, both the response rates were significantly higher in patients without a previous history of TACE than in those who had undergone TACE using antitumor agents other than miriplatin. As shown in Table 3, multivariate analysis revealed that the stage of HCC (stages I and II vs. III and IV) was a factor associated with the curative effect of TACE using miriplatin with odds ratio of 4.87 ($p = 0.001$), whereas previous TACE with anticancer agents other than miriplatin was not selected as an independent factor that influenced the curative effect (odds ratio = 2.30, $p = 0.063$).

The adverse effects observed following TACE with miriplatin are shown in Table 4. Fever and nausea were found transiently in most patients, but both symptoms were mild; the percentages of patients showing fever and nausea of grade 2 or more were 4.7 and 7.7%, respectively. Also, the serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels increased after the TACE procedures in most of the patients, and grade 2, 3, and 4 elevations were found in 56 (23.8%), 53 (22.6%), and 2 patients (0.8%), respectively. The serum AST and ALT levels returned to the baseline levels within a month in all patients. Elevation of the serum total bilirubin concentrations up to CTCAE grade 3 (greater than 3.6 mg/dL) was observed in 6 patients. Among them, serum total bilirubin level concentrations corresponding to CTCAE grade 2 (between 1.8 and 3.6 mg/dL) and grade 1 (between 1.3 and 1.7 mg/dL) were already present in 4 and 2 patients, respectively, before the TACE procedures. Thereby, the extent of elevation of the total serum bilirubin concentration was classified as grade 2 and grade 3 in 33 (14.0%) and 0 patients, respectively. Derangements of the blood cell counts and serum albumin and creatinine concentrations were found in only a few patients; the percentages of patients showing grade 2 or more severe derangements were 2.1% for neutropenia, 0% for anemia, 1.7% for thrombocytopenia, 0.4% for decrease of the serum albumin concentration, and 3.0% for elevation of the serum creatinine concentration.

As shown in Table 5, 6 patients (2.5%) of this study died between 10 and 56 days after the TACE procedures. The extension of HCC progression was stage III or IV in all of these patients, and there were no treatment-related deaths; the cause of death was HCC progression in 2 patients, HCC rupture in 3 patients, and complicating pneumonia in 1 patient.

Discussion

HCC tumors receive their blood supply from the hepatic artery. Thus, TACE and transarterial infusion chemotherapy are performed to induce necrosis and apoptosis of HCC cells through the action of anticancer agents, as well as through the ischemia induced by embolization with porous gelatin particles and/or lipiodol, an oily contrast medium. Several anticancer agents have been used for these procedures, e.g., epirubicin, doxorubicin, mitomycin C, carboplatin, and cisplatin. These agents are injected into the hepatic artery after being suspended in lipiodol. Lipiodol is distributed and retained in the microcirculation of HCC tumors for long periods of time [16], suggesting that the anticancer agents concomitantly injected with lipiodol may accumulate in HCC tissues and exert their anticancer effects exclusively on the tumors for prolonged periods of time. However, all of these agents are water soluble, and not stable in suspension in lipiodol. Zinostatin stimalamer, a lipophilic anticancer agent, approved for transhepatic arterial administration, has been used for the therapy of HCC in Japan since 1994 [17]. However, zinostatin stimalamer is not suitable for TACE, because this agent frequently produces vascular damage, necessitating discontinuation of the

Table 2 Therapeutic efficacy of TACE using miriplatin in patients with unresectable HCC

	Number of patients (%)					*p* value
	Total	TE4	TE3	TE2	TE1	
Total	130	49 (37.7)	42 (32.3)	29 (22.3)	10 (7.7)	
Stage[a]						
I	14	10 (71.4)	4 (28.6)	0	0	<0.0001
II	43	28 (65.1)	8 (18.6)	7 (16.3)	0	
III	69	11 (15.9)	29 (42.0)	21 (30.4)	8 (11.6)	
IV	4	0	1 (25.0)	1 (25.0)	2 (50.0)	
JIS score[a]						
0	8	6 (75.0)	2 (25.0)	0	0	<0.0001
1	36	25 (69.4)	8 (22.2)	3 (8.3)	0	
2	51	15 (29.4)	17 (33.3)	15 (29.4)	4 (7.8)	
3–4	35	3 (8.6)	15 (42.9)	11 (31.4)	6 (17.1)	
Previous TACE						
Absent	59	26 (44.1)	21 (35.6)	9 (15.3)	3 (5.1)	0.028
Present	71	23 (32.4)	21 (29.6)	20 (28.2)	7 (9.9)	

[a] Staging and JIS scoring of the HCCs as proposed by the Liver Cancer Study Group of Japan

Table 3 Factors associated with the curative efficacy of TACE using miriplatin in patients with unresectable HCC

Factors	*n*	Odds ratio	95% confidence interval	*p* value
Age (year)				
≥70	76	1		
<70	54	0.97	0.41–2.29	0.937
Sex				
Female	45	1		
Male	85	1.33	0.55–3.24	0.527
HCV				
Negative	35	1		
Positive	95	1.69	0.66–4.31	0.274
Child–Pugh class				
B, C	50	1		
A	80	1.31	0.55–3.08	0.543
Stage[a]				
III, IV	73	1		
I, II	57	4.87	1.86–12.79	0.001
Dose of miriplatin (mg)				
<70	63	1		
≥70	67	0.81	0.34–1.93	0.633
Previous TACE				
Present	71	1		
Absent	59	2.30	0.96–5.53	0.063

[a] Staging of the HCCs as proposed by the Liver Cancer Study Group of Japan

procedures. Thus, a novel lipid-soluble anticancer agent for the treatment of HCC patients that would not produce vascular damage has been awaited.

Miriplatin, (*SP*-4-2)-[(1*R*,2*R*)-cyclohexane-1,2-diamine-*N*,*N*′]-bis(tetradecanoato-*O*) platinum, is a novel lipophilic platinum complex reported by Maeda et al. [18]. Miriplatin can easily be suspended in lipiodol and releases active platinum compounds into the aqueous phase gradually [19]. This agent was approved for use in chemolipiodolization therapy through the hepatic artery for HCC in 2010. Hanada et al. [20] reported that the concentrations of platinum compounds were greater in the tumors than in the non-tumor regions of the liver, when miriplatin suspension in lipiodol was injected into the hepatic artery of rats bearing hepatoma AH109A tumors in the liver. They also found that the concentrations of the platinum compounds in

Table 4 Adverse effects of TACE using miriplatin in patients with unresectable HCC

Characteristics	Number of patients (%)				
	Total	Grading (CTCAE version 4)			
		1	2	3	4
Fever	107 (45.5)	96 (40.9)	10 (4.3)	1 (0.4)	0
Anorexia	101 (43.0)	83 (35.3)	17 (7.2)	1 (0.4)	0
Vomiting	18 (7.7)	10 (4.3)	8 (3.4)	0	0
Abdominal pain	60 (25.5)	31 (13.2)	29 (12.3)	0	0
Leukocytopenia[a]	53 (22.5)	36 (15.3)	17 (7.2)	0	0
Neutropenia[a]	56 (23.7)	51 (21.6)	5 (2.1)	0	0
Anemia[a]	56 (23.7)	56 (23.7)	0	0	0
Thrombocytopenia[a]	74 (31.4)	70 (29.7)	4 (1.7)	0	0
Elevation of total bilirubin concentration[a]	114 (48.3)	81 (34.3)	33 (14.0)	0	0
Elevation of AST and/or ALT levels	225 (95.7)	114 (48.5)	56 (23.8)	53 (22.6)	2 (0.8)
Decrease of serum albumin[a]	117 (49.6)	116 (49.2)	1 (0.4)	0	0
Elevation of serum creatinine[b]	57 (24.3)	50 (21.3)	7 (3.0)	0	0
Ascites	4 (1.6)	2 (0.8)	2 (0.8)	0	0

AST aspartate aminotransferase, *ALT* alanine aminotransferase

[a] The extent of derangement after the TACE procedure is shown as a gradient of grade increase from baseline, after adaptation of each value to a CTCAE grade

[b] Patients receiving hemodialysis were excluded from the analysis

Table 5 Demographic and clinical features of patients with HCC who died after TACE using miriplatin

Patient no.	Age/sex	Child–Pugh class	Stage[a]	Survival period after TACE (days)	Cause of death
1	70/F	B	III	41	Tumor progression
2	78/M	B	IV	49	Rupture of tumor
3	48/M	B	IV	56	Rupture of tumor
4	77/M	B	III	10	Pneumonia
5	41/M	A	III	51	Rupture of tumor
6	68/M	B	IV	12	Tumor progression

[a] Staging of HCC proposed by the Liver Cancer Study Group of Japan

the tumors decreased more slowly in cases administered miriplatin than in those administered cisplatin similarly suspended in lipiodol [20]. Also, a randomized phase II trial revealed that miriplatin was more effective as an agent for transarterial infusion chemotherapy against HCC as compared with zinostatin stimalamer; the complete response rate was 26.5% in miriplatin-treated patients, whereas it was 17.9% in zinostatin stimalamer-treated patients, 48.4% of whom developed drug-induced vascular damage [10]. Considering these observations, miriplatin would seem to be among the most useful of anticancer agents currently available for TACE as well as transarterial infusion chemotherapy in the treatment of unresectable HCC.

Thus, the efficacy and safety of TACE using miriplatin were evaluated in patients with unresectable HCC. The majority of patients had underlying liver cirrhosis due to hepatitis C virus infection, and the extent of liver damage was classified as Child–Pugh class A or class B in 99.6% of the patients. In contrast, the patients showed marked divergence in respect of the stage of progression of the HCC; the percentages of patients with stage I, II, III, and IV disease were 11.4, 31.4, 50.4, and 6.8%, respectively, according to the staging criteria proposed by the Liver Cancer Study Group of Japan, and those with JIS scores of 0, 1, 2, and 3–4 were 7.2, 27.5, 36.9, and 28.4%, respectively, as shown in Table 1. The doses of miriplatin and the extent of embolization by the porous gelatin particles were determined depending on both the extent of liver damage and the stage of HCC progression in each patient.

In the present study, the overall response rate and complete response rate were 70.0 and 37.7%, respectively, both of which were greater than those obtained in a randomized phase II trial performed to evaluate the efficacy of

transarterial infusion chemotherapy using miriplatin [10]. Ikeda et al. [21] reported that the overall response rate was 73%, with complete response rate of 32%, in a clinical trial conducted to evaluate the therapeutic efficacy of TACE using cisplatin suspended in lipiodol. These data are almost equivalent to those obtained in our study. The ratios of TE3 and/or TE4 may be altered depending on the time points of evaluation with CT after TACE procedures. The response rates might be decreased when the therapeutic efficacy was evaluated later than 1 month after the TACE procedure with miriplatin. These matters should be investigated in the future. Also, the percentages of patients with stages I and II HCC may influence the therapeutic efficacies of TACE procedures. Thus, a randomized controlled study is warranted to compare therapeutic efficacy of TACE using miriplatin with that using cisplatin especially in patients with advanced HCC.

It is noteworthy that the therapeutic efficacy of TACE using miriplatin was excellent in patients with stage I or II HCC; the overall response rates in patients with stage I and stage II disease were 100 and 83.7%, respectively. Similar excellent therapeutic efficacy was found in HCC patients with a JIS score of 0 and 1, who showed overall response rates of 100 and 91.7%, respectively. However, it should be noted that TE4 therapeutic efficacy, characterized by complete necrosis of HCC, was not obtained in 28.6% of patients with stage I HCC and 34.9% of those with stage II HCC. TACE with miriplatin should be done in patients with stage I or II HCC only when RFA and liver resection cannot be performed because of medical and personal reasons.

In contrast, both the response rates were low in HCC patients with stage III or IV disease and those with JIS scores of 2–4. Thus, the optimal doses of miriplatin and optimal technique of embolization for the treatment of advanced HCC should be investigated further. Also, the usefulness of TACE with miriplatin for patients receiving TACE with anticancer agents other than miriplatin should be further investigated, because the previous TACE was not selected as an independent factor influencing the overall response rate ($p = 0.063$).

TACE therapy using miriplatin produced elevations of the serum AST and ALT levels up to CTCAE grade 3 or grade 4 in 23.4% of the patients, although the elevation was only transient in all of the patients. Transient elevations of the serum transaminase levels are commonly observed following TACE using other anticancer agents, such as epirubicin, doxorubicin, and cisplatin [21–24]. Elevation of the serum total bilirubin concentration up to CTCAE grade 2 was found in 14.0% of the patients, and the values eventually returned to the baseline in all patients. There were no cases who showed progression of liver failure following the TACE procedures. Also, there were no treatment-related deaths. Thus, TACE therapy using miriplatin is considered to be safe when embolization procedures are performed completely or partially, depending on the number and size of tumors and the degree of liver damage. In the present study, anorexia and vomiting of CTCAE grade 3 were observed in only 0.4 and 0% of the patients, respectively. Even though hydration was not undertaken before the TACE procedures in the present study, elevation of the serum creatinine concentration of CTCAE grade 3 or more was not found in any patients. In contrast, in a phase II study of transarterial infusion chemotherapy using a fine-powder formulation of cisplatin, anorexia, vomiting, and elevation of the serum creatinine concentration of CTCAE grade 3 were found in 22.5, 6.3, and 2.5% of the enrolled patients, respectively [25]. It would seem that miriplatin, which is stable in lipiodol and is retained in the tumors for prolonged periods of time, evokes fewer adverse effects derived from toxicity to the extrahepatic organs.

In conclusion, miriplatin appears to be a useful agent for TACE in patients with unresectable HCC. Therapeutic modifications to improve the treatment efficacy for patients with advanced HCC as well as those with a previous history of TACE need to be further investigated, because TACE using miriplatin may be associated with fewer adverse reactions derived from toxicity to the extrahepatic organs.

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Conflict of interest The authors declare that they have no conflict of interest.

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