Table 2. Outcomes of Patients Undergoing One-Step Biliary Stent Placement with Transhepatic Tract Embolization

Pt. No.	Clinical Success	Total Bilirubin (mg/dL)		Complications	Stent Occlusion (d)	Survival (d)	Cause of Death
		Before	After				
1	Yes	4.5	0.7	None	NA	61	Progression
2	Yes	5.4	2.7	None	NA	74	Progression
3	Yes	10.8	0.9	None	NA	39	Progression
4	Yes	1.1	0.7	None	NA	86	Progression
5	Yes	4.8	0.7	Right pleural effusion	NA	153	Progression
6	Yes	13.4	2.3	None	NA	66	Progression
7	No	6.4	17.4	Cholangitis	NA	19	Complication
8	Yes	2.7	0.5	Right pleural effusion	159	175	Progression
9	Yes	12.7	3.5	Bloody bowel discharge	NA	43	Progression
10	Yes	5.1	0.3	Self-limiting hemobilia	NA	169	Progression
11	Yes	7.3	3.4	Cholangitis	NA	33	Progression
12	Yes	8.8	0.8	None	NA	56	Progression
13	Yes	7.1	0.7	Right pleural effusion	NA	93	Progression
14	Yes	4.1	1.6	Right pleural effusion	NA	128	Progression
15	Yes	4.3	0.8	None	NA	66	Progression
16	No	8.7	16.4	None	NA	24	Progression

Note.—NA = not applicable.

12) or postdilation (n = 8) with 6–10-mm balloon catheters (Synergy [Boston Scientific, Natick, Massachusetts] or Powerflex [Cordis/Johnson and Johnson, Oosteinde, The Netherlands]).

After stent placement, the introducer sheath was replaced by a 6.5-F catheter, confirming good flow of contrast material through the biliary system (**Fig 1c**). The biliary access point and distal end of the transhepatic tract were carefully determined by injecting contrast material. Tract embolization was performed by advancing and tightly packing one to three 0.035-inch metallic coils (5 mm × 5 cm, 4 mm × 3 cm, 3 mm × 4 cm; MReye embolization coil; William Cook Europe) through a 6.5-F catheter. The coils were pushed by using a 0.035-inch wire, and the 6.5-F catheter was gently removed (**Fig 1d**).

Study Endpoints and Definitions

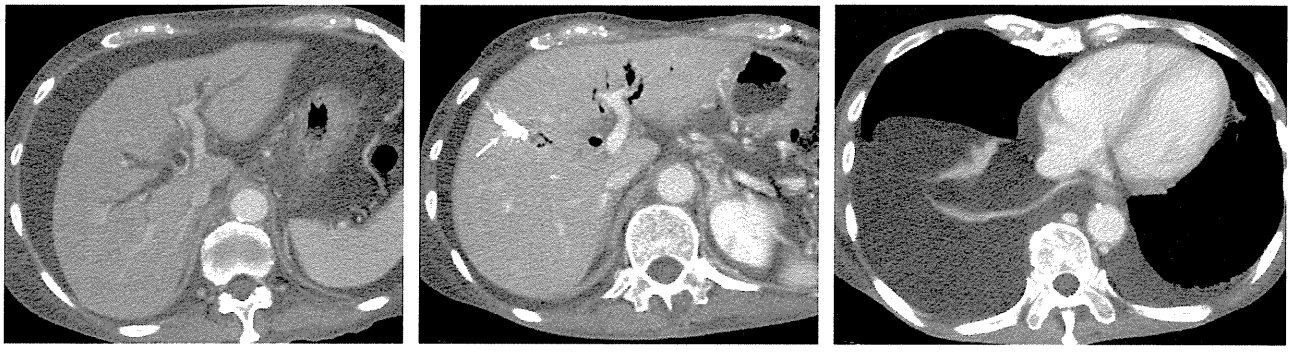
Technical success, clinical success, complications, stent patency, and duration of survival were retrospectively assessed. Technical success was defined as percutaneous transhepatic stent placement in the expected position and successful embolization of the tract without an external drainage catheter left in place. Clinical success was defined as a decrease in serum total bilirubin levels within 30 days of stent placement compared with levels recorded before the procedure. All complications arising from the procedure were divided into major and minor categories according to the reporting standards of the Society of Interventional Radiology (20).

Follow-up, which consisted of clinical examination and laboratory testing, including serum total bilirubin, serum liver enzyme levels, and complete blood count, was performed as needed until the time of death. US examination was performed to assess postprocedural biloma, ascites, and pleural effusion. When total serum bilirubin levels were increased and stent occlusion was suspected, CT or US examination was performed to confirm stent malfunction by dilation of the intrahepatic bile ducts. Stent patency was judged based on the absence of increased total serum bilirubin levels or the absence of dilation of intrahepatic bile ducts on CT or US examination even if total serum bilirubin level was increased. If there was no evidence of stent malfunction during the patient's life, the stent patency period was considered to be equal to the survival period.

RESULTS

Technical Success

Stent placement and tract embolization were successful in all patients without leaving an external drainage catheter, and the technical success rate was 100% (**Table 2**). All 16 patients received stent placement via the left (n = 4) or right (n = 12) hepatic lobe approach. Two patients received multiple stent placements through two puncture sites on the right, and one patient received three punctures on the right. In each of the remaining 13 patients, stents were placed through one puncture site. One patient received bilateral stent placement through one puncture site on the right in a "T" configuration. Consequently, a total of 20 transhepatic tracts were embolized. A total of 28 expandable metallic stents were inserted according to availability and operator preference. A total of 21 uncovered stents (Zilver; William Cook Europe) were placed in 11 patients, and seven cov-



a. b. c.

Figure 2. Gastric cancer with nodal metastasis in a 57-year-old man (patient 5). **(a)** Contrast-enhanced CT before the procedure shows dilated intrahepatic biliary ducts and massive ascites. **(b)** Contrast-enhanced CT after the procedure revealed improvement of obstructive jaundice and decreased ascitic fluid. Note that the transhepatic tract was tightly packed with metallic coils (arrow). **(c)** Contrast-enhanced CT also showed significantly increased right pleural effusion.

ered stents (VIABIL; W.L. Gore and Associates, Flagstaff, Arizona) were placed in five patients in the common bile duct.

Clinical Success

Reduction of the total serum bilirubin level compared with the preprocedural level was achieved in 14 of 16 patients, yielding a clinical success rate of 87.5%. The mean total serum bilirubin level before the stent placement was 6.7 mg/dL ± 3.5 (SD) (median, 5.9 mg/dL; range, 1.1–13.4 mg/dL), and that after the stent placement was 3.3 mg/dL ± 5.4 (median, 0.9 mg/dL; range, 0.3–17.4 mg/dL). The mean total serum bilirubin levels after the procedure were significantly lower than those before the procedure ($P = .009$).

Clinical success could not be achieved despite the procedure in two patients (12.5%). In one patient who had a Bismuth type IV obstruction, an additional stent was inserted into another intrahepatic biliary duct 6 days after the initial procedure to achieve drainage of the entire liver; however, the patient died 24 days after the procedure without showing any decrease of serum bilirubin level as a result of hepatic insufficiency caused by multiple liver metastases. The other patient, who had a distal bile duct obstruction, died of cholangitis 19 days after the procedure.

Complications

Major complications occurred in seven patients (43.7%), and included postprocedural cholangitis with fever and leukocytosis treated by administration of antibiotic therapy in two patients (12.5%), bloody bowel discharge requiring blood transfusion in one patient (6.2%) who had undergone balloon dilation of a biliary stricture, and right pleural effusion in four patients (25.0%). In one patient who died of cholangitis 19 days after stent placement, the death was judged to be a procedure-related mortality. The patient had distal bile duct occlusion and also had distal intestinal obstruction caused by peritoneal dissemination, and developed reflux cholangitis complicated by sepsis after the procedure, resulting in death. All four patients in whom right pleural effusion occurred received stent placement via the right hepatic lobe approach without paracentesis during the procedure. CT examination after stent placement showed increased right pleural effusion and decreased ascites (Fig 2). The pleural effusions were treated successfully by percutaneous drainage and aspiration over a period of 3–5 days. A diagnostic pleural tap from the right chest did not reveal bile, and laboratory testing of pleural effusion did not show increased total bilirubin levels. No peritonitis caused by bile leakage or intraperitoneal hemorrhage occurred in any of the 16 patients.

A minor complication was seen in one patient (6.2%). Self-limited hemobilia was caused by balloon dilation of biliary stricture and confirmed by cholangiography during the procedure. The patient did not require blood transfusion.

Follow-up

Complete follow-up until death was carried out for all patients. The survival period after stent placement ranged from 19 to 175 days (median, 66 d; mean, 80.3 d ± 50.5). Two patients died within 30 days after the procedure: one accounting for the procedure-related mortality mentioned earlier and another who died 24 days after the procedure because of hepatic insufficiency resulting from multiple liver metastases. The remaining 14 patients died of disease progression.

Of the 14 patients who survived for longer than 30 days after stent placement, three patients (21.4%) showed increased total serum bilirubin levels 37, 46, and 151 days after the procedure. One of these three patients showed stent occlusion, which was confirmed by US examination 159 days after stent placement, and died 175 days after the procedure without any repeat intervention. In the other two patients, no stent occlusion was evident on CT and/or US examination, and the patients died of hepatic insufficiency caused by disease progression 33 and 66 days after stent

placement. Overall, primary stent patency was achieved in 14 of 16 patients (87.5%), and secondary patency was achieved in an additional patient, for a total patency rate of 93.7%.

DISCUSSION

This study demonstrates that tract embolization for percutaneous biliary metallic stent placement in patients with massive ascites is technically feasible and clinically effective, with a limited number of severe complications. These findings indicate that percutaneous biliary stent placement may be considered as a treatment option even in patients with massive ascites when the endoscopic approach is not feasible or has failed.

In this study, adequate stent placement to cover the stricture was successfully performed in all patients, and tract embolization with metallic coils was also successfully carried out in all patients. Our results also show no evidence of bile peritonitis, subcapsular biloma, or intraperitoneal hemorrhage. These findings suggest that tract embolization is quite useful for preventing bile leakage and bleeding into the peritoneal cavity even in patients with massive ascites, as described in some previously published studies (10–13). Conversely, Thornton et al (18) found that a few patients (5.6%) who received primary metallic biliary stent placement had symptoms of bile peritonitis after catheter removal. The discrepant findings may have come about because most of their patients did not undergo tract embolization (three of 52 patients received primary biliary stent placement), and it was not revealed whether these three patients developed bile peritonitis (18). Although Lammer et al (21) also reported simultaneous deposition of compressed gelatin sponge into the transhepatic tract in uncomplicated cases, they documented no precise number of patients who underwent tract embolization. Nevertheless, Thornton et al (18) speculated that immediate removal of the biliary access facilitated by tract embolization might be desirable, and this would have mandated a new biliary drainage procedure for patients with ascites. The present results clarify their speculation.

We used metallic coils to embolize transhepatic tracts because they can be delivered precisely and placed tightly in the appropriate location, although other embolic materials, including gelatin sponges (10), n-butyl cyanoacrylate (11,12,14), AMPLATZER Vascular Plugs (15), and metallic coils (13) have also been used. The use of gelatin sponge or n-butyl cyanoacrylate poses a risk of material migration into the biliary tree, possibly resulting in biliary obstruction, and incomplete embolization of the tract. The AMPLATZER Vascular Plug is reasonable to use in the transhepatic tract but is comparably expensive. In addition to complete tract embolization, optimization of bile flow by full expansion of the stents is crucial in the authors' opinion for the prevention of bile reflux; however, this could not be definitively proven by the present study.

By contrast, a significant right pleural effusion developed in four of 12 patients who were treated by a right hepatic lobe approach without paracentesis. We assume that transpleural puncture associated with the use of a right hepatic lobe approach leads to the leakage of ascites into the pleural cavity. This may have been prevented by a left hepatic approach or large-volume paracentesis before the procedure. In addition, we encountered one patient who died of postprocedure cholangitis. A possible reason is that all the patients in the present study had more advanced disease and were in poorer general condition than patients in other published reports, and this condition predisposed them to lethal complications. This possibility indicates that early infection potentially leads to death in such patients who have advanced disease.

The 87.5% clinical success rate of biliary stent placement in the present study is comparable to those of others (2–5,8). It should be noted that, despite successful drainage of the entire liver, one of two patients who showed clinical failure died of hepatic insufficiency caused by multiple liver metastases. This outcome highlights the fact that biliary intervention does not always lead to clinical improvement in patients with extremely advanced disease, even if adequate drainage can be achieved.

The median and mean survival durations after stent placement in the present study were 66 days and 80.3 days, respectively. This may be attributable to the poor clinical status of the patients in the study. These patients had extremely advanced malignancies, most of which not of hepatobiliary/pancreatic origin. These results are consistent with those reported by Thornton et al (18) and Meller et al (21), who reported poorer survival after biliary stent placement in non–hepatobiliary/pancreatic malignancies than in hepatobiliary/pancreatic malignancies. We consider that primary stent placement with tract embolization might have been beneficial for patients with ascites and a limited survival period, because it provides 100% catheter-free survival and eliminates lifestyle limitation and potential complications such as insertion-site pain, catheter dislodgment, and pericatheter leakage of bile or ascites related to the presence of an external drainage catheter (18). It would be difficult to assess the true stent patency rate because of the short observation of the limited survival period.

The present study has limitations. First, the study design was retrospective, and the sample size was small. However, we are aware of no published that have investigated the efficacy of primary percutaneous biliary stent placement in patients with massive ascites except for one case report (11). The second limitation was the lack of long-term follow-up as a result of the patients' short life expectancies, which limited assessment of long-term stent patency. Finally, no real evaluation of the tract for bile leakage was undertaken in any sort of systemic manner; only a diagnostic tap of ascites and patient-reported abdominal pain were assessed. Despite these limitations and the slightly higher rate of complications than in other studies, we believe percutaneous stent placement with tract embolization in a single session may be an important treatment

option for patients with obstructive jaundice that cannot relieved by endoscopic intervention, in addition to massive ascites.

In conclusion, we report that primary biliary stent placement with coil embolization of the tract is technically safe in patients with massive ascites. It offers an effective palliative treatment option for malignant biliary obstruction when endoscopic intervention is not possible.

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CLINICAL STUDY

Phase I/II Multicenter Study of Transarterial Chemoembolization with a Cisplatin Fine Powder and Porous Gelatin Particles for Unresectable Hepatocellular Carcinoma: Japan Interventional Radiology in Oncology Study Group Study 0401

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ABSTRACT

Purpose: A multicenter phase I/II study of transarterial chemoembolization with a fine cisplatin powder and gelatin particles (GPs) for multifocal hepatocellular carcinoma (HCC) was conducted. Primary endpoints were dose-limiting toxicity (DLT) and recommended dose (RD). Secondary endpoints were the incidence and severity of adverse events and tumor response.

Materials and Methods: Nonselective transarterial chemoembolization was performed until all tumor enhancement disappeared. Lipiodol was not used. In the phase I study, the cisplatin dose was escalated from 35 mg/m^2 to 65 mg/m^2 in 15-mg/m^2 increments to determine DLT and RD. In the phase II study, 40 patients were treated with the RD. Toxicity was assessed by Common Toxicity Criteria for Adverse Effects (version 3.0), and tumor response was evaluated by Response Evaluation Criteria in Solid Tumors (RECIST; version 1.0) and European Association for the Study of the Liver (EASL) criteria.

Results: A total of 46 patients were enrolled. As no DLT occurred at any dose level in the phase I study, RD was determined as 65 mg/m^2. In the phase II study, the treatment was discontinued in one patient as a result of vasovagal response. Toxicities of grade 3 or higher included nausea (2.2%), pancreatitis (2.2%), cholecystitis (2.2%), thrombocytopenia (8.7%), hyperbilirubinemia (2.2%), and increased aspartate aminotransferase (28.3%) and alanine aminotransferase (21.7%) levels. Tumor response rates under RD were 25.6% and 64.1% by RECIST and EASL criteria, respectively.

Conclusions: Nonselective transarterial chemoembolization with fine cisplatin powder and GPs was well tolerated and effective in patients with multifocal HCC at the RD of 65 mg/m^2.

ABBREVIATIONS

ALT = alanine aminotransferase, AST = aspartate aminotransferase, CR = complete response, DEB = drug-eluting bead, DLT = dose limiting toxicity, EASL = European Association for the Study of the Liver, GP = gelatin particle, HAIC = hepatic arterial infusion chemotherapy, HCC = hepatocellular carcinoma, MTD = maximum tolerated dose, RD = recommended dose, RECIST = Response Evaluation Criteria in Solid Tumors, NE = not evaluable, PR = partial response

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Hepatocellular carcinoma (HCC) is one of the leading causes of cancer mortality worldwide (1). In patients with HCC who are not eligible for curative therapies such as surgical resection or radiofrequency ablation, transarterial chemoembolization has been the prevailing treatment and has proven survival benefits (2). Conventionally, a mixture of chemotherapeutic agents and lipiodol has been used for transarterial chemoembolization. However, the choice of chemotherapy regimen has not been standardized, and use of lipiodol chemoembolization in both liver lobes can increase liver damage (3,4). For localized tumors of small number or size, selective lipiodol chemoembolization has been safely performed by using a segmental or subsegmental approach (5), whereas, for bilobar multifocal tumors, multistaged lipiodol chemoembolization may be considered. Newer technologies such as chemoembolization with drug-eluting beads and radioembolization with yttrium-90 (^{90}Y) microspheres have been increasingly applied to treat unresectable HCC. Although these techniques have been investigated in clinical trials (6–8), neither are approved in Japan. Recently, two commercial products, a fine cisplatin powder and porous gelatin particles (GPs), have been specifically approved for transarterial treatment of HCC in Japan. The cisplatin powder was originally designed for use in hepatic arterial infusion chemotherapy (HAIC). However, the indication for HAIC with the fine cisplatin powder remains unclear, because the role of HAIC for HCC has not been well established (9). Therefore, this fine powder is being used for transarterial chemoembolization in situations in which lipiodol chemoembolization may be inappropriate, such as nonselective embolization of multifocal HCC. However, the dose of cisplatin fine powder for transarterial chemoembolization has not been optimized. The purpose of the present study was to evaluate the safety and efficacy of nonselective transarterial chemoembolization for multifocal HCC with the use of a combination of fine cisplatin powder and porous GPs. This study was conducted as a multicenter phase I/II study by the Japan Interventional Radiology in Oncology Study Group (study code 0401).

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MATERIALS AND METHODS

Study Endpoints

The primary endpoints were dose-limiting toxicity (DLT) and recommended dose (RD) of fine cisplatin powder used for nonselective transarterial chemoembolization in multifocal HCC. Secondary endpoints were incidence and severity of adverse events and tumor response to therapy.

Patient Eligibility

Patients were considered for enrollment if they had (i) unresectable bilobar multifocal HCC (or multifocal recurrent HCC in the remnant liver after surgery) confirmed by histologic examination or diagnostic imaging; (ii) measurable hypervascular lesions confined to the liver that showed early enhancement on contrast-enhanced dynamic computed tomography (CT); (iii) no tumor thrombus in the first branch or main trunk of the portal vein; (iv) no extrahepatic metastases; (v) Eastern Cooperative Oncology Group performance status of 0, 1, or 2; (vi) Child–Pugh classification of A or B; (vii) no lingering effect of any previous treatment (at least a 4-wk interval from most recent treatment); (viii) adequate bone marrow, renal, and cardiac function demonstrated by laboratory test results obtained within 2 weeks of signing the study consent (ie, leukocyte count $\geq$ 3,000 mm^2, platelet count $\geq$ 50,000/mm^3, hemoglobin level $\geq$ 9.5 g/dL, serum creatinine level no greater than the upper limit of normal range, blood urea nitrogen level $\leq$ 25 mg/dL, and no abnormality on electrocardiogram); (ix) age at least 20 years and younger than 75 years; and (x) life expectancy of at least 8 weeks. Patients were excluded from the study if they had (i) previous transarterial chemoembolization with a platinum-containing drug; (ii) an extrahepatic collateral tumor supply suspected or confirmed by contrast-enhanced CT or previous angiography; (iii) previous surgical bile duct reconstruction or endoscopic sphincterotomy; (iv) lymph node or other distant metastases; (v) severe comorbidity including cardiac failure, myocardial infarction, pulmonary fibrosis, interstitial pneumonia, intractable diabetes mellitus, or renal failure; (vi) an active infection except for viral hepatitis; (vii) another concurrent malignancy; (viii) a known allergy to iodinated contrast media, platinum-containing drugs, or gelatin-containing drugs or foods; (ix) pregnancy or lactation; or (x) any condition judged by the investigators to potentially jeopardize patient safety or compliance with the study protocol.

The study protocol was approved by the ethics committee of the Japanese Society of Interventional Radiology and the institutional review boards of each participating hospital. All patients signed an informed consent document for the research protocol and the procedure.

Chemotherapeutic and Embolic Agents

Cisplatin fine powder (IA Call; Nippon Kayaku, Tokyo, Japan) was the first platinum-containing drug specifically approved for HAIC for HCC. The mean size of the fine-powder granules is 28.5 μm, and the dissolution rate of the

fine powder in saline solution is 1.43 mg/mL, approximately three times higher than that of conventional cisplatin (0.5 mg/mL). To prepare the cisplatin fine-powder solution for use in transarterial chemoembolization, 70 mL of saline solution warmed to 50°C was added to a vial containing 100 mg of fine cisplatin powder according to the manufacturer's instructions for use.

Porous GPs (Gelpart; Nippon Kayaku) were also specifically approved for transarterial chemoembolization of HCC. GPs are sterilized and packaged in a ready-to-use vial containing 80 mg of dry particles (10). Although two particle sizes (1 and 2 mm) are available, only 1-mm particles were used to achieve maximum distal vessel occlusion in the present study. To prepare the GP suspension, 10 mL of nonionic iodinated contrast medium (300 mgI/mL) was added to the sterile vial according to the manufacturer's instructions for use.

Treatment Protocol

Hepatic angiography was performed via a femoral approach, and tumor enhancement and vessels supplying the tumors were identified. The planned dose of cisplatin solution was infused through a microcatheter placed nonselectively in the proper hepatic artery for 20–40 minutes to allow for full exposure of all tumors to the drug. If necessary to account for anatomic variations, the drug was injected separately from the right or left hepatic artery. Injection could be performed by power injection, infusion pump, or manual injection. After cisplatin infusion, all hepatic arteries were embolized with GPs. Particle injection into the cystic artery and other nonhepatic arteries such as the right gastric artery was avoided, and coil embolization of those arteries was allowed if necessary. Lipiodol was not used in any patient. To prevent renal damage, 1,000–2,000 mL and 1,500–3,000 mL of electrolytes were administered over a period of 4 hours before and 6 hours after the procedure, respectively. To reduce nausea and vomiting, antiemetic agents (including a 5-HT_3 antagonist and steroids) were administered prophylactically. Completion of therapy was defined as the administration of the total planned dose of cisplatin and the disappearance of all tumor enhancement on postembolization arteriograms of the proper hepatic artery. Subsequent treatment was withheld during the observational period needed for tumor assessment unless obvious tumor progression was seen. After the observational period, subsequent treatment for residual or recurrent tumors was not restricted.

Study Design

The phase I dose-escalation study included cisplatin doses of 35, 50, and 65 mg/m^2. Cohorts of three to six patients were given the assigned dose of cisplatin until the maximum tolerated dose (MTD) was reached. If DLT occurred in one of three patients in a dose group, an additional three patients were enrolled. If DLT occurred in two of three patients or three of six patients in a dose group, that dose was defined as the MTD. If the MTD was reached in the 35-mg/m^2 dose group, the dose would be lowered to 20 mg/m^2. If DLT occurred even at 20 mg/m^2, the study was to be ceased. The phase II study enrolled additional patients at the RD until a total of 40 patients were treated at this dose. The RD was determined based on the phase I MTD results, or, if no MTD was reached, the RD would be considered to be 65 mg/m^2.

The number of patients needed to all judgment of tumor response under an α value of 0.1 and a β value of 0.1 was calculated based on the assumption that the threshold tumor response rate and the expected efficacy rate were 30% and 50%, respectively, based on European Association for the Study of the Liver (EASL) criteria.

Analysis of Study Endpoints

The primary endpoints, DLT and RD, were determined by the toxicities observed in the phase I study. DLT was defined as follows: (i) grade 4 leukopenia or neutropenia; (ii) grade 4 thrombocytopenia; (iii) grade 4 increase of AST or ALT levels for 7 days; (iv) hyperbilirubinemia exceeding 5.0 mg/dL or remaining greater than 3.0 mg/dL for 2 weeks; (v) liver abscess, cholangitis, or cholecystitis requiring interventional radiologic, endoscopic, or surgical procedures; and (vi) grade 3 or higher nonhematologic toxicities except for elevation of ALT or ALT, also excluding those from progression of disease, fatigue, fever, nausea/vomiting, abdominal pain, and alopecia.

The incidence and severity of adverse events were assessed for all treated patients. Adverse events were graded according to the Common Toxicity Criteria for Adverse Events (version 3.0). Severe adverse events were defined as follows: (i) any death within 30 days of treatment; (ii) any death more than 31 days after treatment that could possibly be related to treatment; and (iii) grade 4 nonhematologic toxicity.

Tumor response rates were calculated for all treated patients and for patients treated at the RD. Tumor response was evaluated based on centrally reviewed CT findings. All patients underwent a contrast-enhanced dynamic CT study in which 5-mm axial images were obtained. Tumor assessment was performed by using pre- and postcontrast arterial and portal venous phases. CT images obtained within 2 weeks before and 1 month after chemoembolization were reviewed and simultaneously interpreted by three independent radiologists; discrepancies were resolved by consensus. The best overall response was categorized as complete response (CR), partial response (PR), stable disease, progression of disease, or not evaluable (NE) according to the Response Evaluation Criteria in Solid Tumors (RECIST; version 1.0), in which the maximum diameter of the entire lesion is measured, including tumor necrosis induced by chemoembolization. CR or PR was confirmed by repeat CT imaging at intervals of more than 4 weeks. Because tumor necrosis is not always correlated with tumor size reduction, tumor response was also evaluated based on the change in

Table 1. Patient Numbers at Collaborative Institutions

Hospital	No. of Pts.
Nara Medical University Hospital	14
National Cancer Center Hospital	10
Shizuoka Cancer Center Hospital	6
Osaka Medical Center for Cancer and Cardiovascular Disease	3
Aichi Cancer Center Hospital	2
Tochigi Cancer Center Hospital	2
Okinawa Prefectural Nanbu Medical Center	2
Niigata Cancer Center Hospital	1
Jikei University Hospital	1
Ryugasaki Saiseikai Hospital	1
Ishikawa Prefectural Central Hospital	1
Teine Keijinkai Hospital	1
The University of Tokyo Hospital	1
Mie University Hospital	1

bidimensional diameters of the viable part of the lesion according to EASL criteria.

Considering that it was an exploratory study, the interim analysis was performed when 20 patients were treated at the RD. Based on the threshold tumor response rate, if more than three of the 20 patients were categorized as showing CR or PR by EASL criteria, an additional 20 patients were enrolled.

RESULTS

Fourteen hospitals participated in the study (Table 1). A total of 46 patients (nine in phase I and 37 in phase II) were enrolled between July 2005 and December 2008. At the interim analysis, three patients were categorized as showing CR and eight patients were categorized as showing PR. Therefore, the phase II study continued.

Baseline patient characteristics and clinical data are shown in Table 2. The dominant etiology of HCC was hepatitis C virus infection (n = 25; 54.3%), and most patients (n = 43; 93.4%) were classified as having Child–Pugh class A disease. The baseline bilirubin level ranged from 0.3 to 2.7 mg/dL (mean, 0.95 mg/dL) . Thirty-four patients (73.9%) had recurrent HCC. Of previously treated patients, 17 had undergone surgery and 27 patients had undergone an average of 2.4 transarterial chemoembolization sessions (range, 1–6), predominantly with epirubicin. Thirty-three patients (71.7%) had more than five tumors at baseline. The mean maximum tumor diameter was 37.2 mm, and the mean sum of maximum diameters of measurable target lesions was 94.0 mm.

Treatment was fully completed in all patients except for one phase II patient who experienced hypotension (i.e., vasovagal response) during gelatin embolization. As the

Table 2. Demographics and Clinical Data

Characteristic	Value
Age (y)	
Mean	64.6
Range	27–74
Sex	
Male	42
Female	4
ECOG performance status (0 / 1 / 2)	
0	45
1	0
2	1
Etiology	
HCV	23
HBV	9
HCV and HBV	2
Other	12
Child–Pugh class	
A	43
B	3
Previous therapy	
Surgery	17
Ablation	13
Transarterial chemoembolization	27
Radiation	1
Chemotherapy	2
HCC status	
New	12
Recurrent	34
No. of tumors	
2	1
3	3
4	4
5	5
> 5	33
Maximum tumor diameter (mm)	
Mean	37.2
Range	14–146
Measurable targeted lesions (mm)*	
Mean	94.0
Range	28–256
Portal invasion factor†	
0	44
1	1
2	1
Tumor stage†	
II	18
III	25
IVa	3

ECOG = Eastern Cooperative Oncology Group, HBV = hepatitis B virus, HCV = hepatitis C virus.
* Sum of maximum diameter of measurable targeted lesions.
† Factors of portal invasion and tumor stages were categorized according to the classification proposed by the Liver Cancer Study Group of Japan.

Table 3. Adverse Events: Clinical Symptoms and Signs

	Grade					
Event	1	2	3	4	Total	3/4
Anorexia	24	8	0	0	32 (69.6)	0
Nausea	16	10	1	0	27 (58.7)	1 (2.2)
Fatigue	21	3	0	0	24 (52.2)	0
Fever without neutropenia	18	3	0	0	21 (45.7)	0
Vomiting	10	7	0	0	17 (37.0)	0
Abdominal pain	12	5	0	0	17 (37.0)	0
Hypertension	1	1	0	0	2 (4.3)	0
Esophageal varix rupture	1	1	0	0	2 (4.3)	0
Gallstone-induced pancreatitis*	0	0	1	0	1 (2.2)	1 (2.2)
Cholecystitis	0	0	1	0	1 (2.2)	1 (2.2)
Suspected liver abscess*	0	1	0	0	1 (2.2)	0
Vasovagal episode†	0	1	0	0	1 (2.2)	0
Hypotension	1	0	0	0	1 (2.2)	0
Reflux esophagitis	1	0	0	0	1 (2.2)	0
Hiccups	1	0	0	0	1 (2.2)	0
Constipation	1	0	0	0	1 (2.2)	0

Values in parentheses are percentages.
* Not considered to be treatment-related.
† The procedure was discontinued in this patient.

dose escalation study did not reach MTD without DLT at any dose level, the RD was determined to be 65 mg/m^2.

Adverse Events

Adverse events were related to clinical symptoms/signs or laboratory findings. There were no severe adverse events except for transient grade 4 increase of AST or ALT levels in two patients (4.3%). Symptoms of postembolization syndrome, such as anorexia, nausea, fatigue, fever, vomiting, and abdominal pain, were all grade 1 or 2 in severity, except in one patient (2.2%) with grade 3 nausea (Table 3). Grade 3 adverse clinical symptoms/signs occurred in two additional patients. Grade 3 pancreatitis developed in one patient (2.2%) on postoperative day 43. Endoscopy demonstrated gallstone pancreatitis, which was successfully treated by endoscopic biliary drainage and pancreatic duct stent placement. However, this event was not considered to be treatment-related because it occurred more than 30 days after treatment. One patient (2.2%) had grade 3 cholecystitis caused by inadvertent particle embolization of the cystic artery, which was demonstrated on postembolization angiography. This patient was successfully treated with percutaneous gallbladder drainage. Additionally, a grade 2 liver abscess was suspected in one patient 1 week after treatment, as a CT scan revealed marked gas formation in the large main tumor. The patient was treated with antibiotic agents and had an uneventful clinical course; therefore, the CT findings were more likely related to acute extensive tumor necrosis. Grade 3 or higher adverse laboratory events included thrombocytopenia in four patients (8.7%), hyperbilirubinemia in one patient (2.2%), increased AST level in 13 patients (28.3%), and increased ALT level in 10 patients (21.7%; Table 4).

Tumor Response

Tumor response rates in all treated patients were 23.9% (95% CI, 14.0%–36.5%) and 65.2% (95% CI, 52.1%–76.8%) by RECIST and EASL criteria, respectively. Tumor response rates at the RD were 25.6% (95% CI, 14.6%–39.6%) and 64.1% (95% CI, 49.7%–76.8%) by RECIST and EASL criteria, respectively (Table 5). The case in which treatment was discontinued was categorized as NE in evaluation of all treated cases, and was excluded from evaluation of the response at the RD. In three cases, some lesions were difficult to differentiate from pseudolesions, and they were categorized as NE. In addition, one case was categorized as NE because only a noncontrast CT scan was obtained at 1-month follow-up.

Follow-up and Survival

The mean follow-up period was 22.4 months (range, 1.0–53.2 mo). Forty-two patients (91.3%) underwent one or more of the following subsequent treatments: transarterial chemoembolization (n = 37), HAIC (n = 11), systemic chemotherapy (n = 8), radiofrequency ablation (n = 5), and/or radiation therapy (n = 1). Thirty patients (65.2%) died as a result of cancer progression. Additional deaths were related to hepatic failure (n = 7), variceal rupture (n = 2), and other causes (n = 2). Survival was calculated by using a Kaplan–Meier analysis in which patients lost to follow-up or alive at the time of analysis were censored (Fig). One- and 2-year survival rates were 75.3% and

Table 4. Adverse Events: Laboratory Data

	Grade					
Event	**1**	**2**	**3**	**4**	**Total**	**3/4**
Leukopenia	16	8	0	0	24 (52.2)	0
Anemia	26	4	0	0	30 (65.2)	0
Thrombocytopenia	24	13	4	0	41 (89.1)	4 (8.7)
Hypoalbuminemia	28	13	0	0	41 (89.1)	0
Hyperbilirubinemia	11	20	1	0	32 (69.6)	1 (2.2)
Elevated AST	15	17	12	1	45 (97.8)	13 (28.3)
Elevated ALT	16	20	8	2	46 (100)	10 (21.7)
Elevated creatinine	14	2	0	0	16 (34.8)	0

Values in parentheses are percentages. ALT = alanine aminotransferase, AST = aspartate aminotransferase.

Table 5. Tumor Response According to RECIST and EASL Criteria

Criteria	**CR**	**PR**	**SD**	**PD**	**NE**	**Total**	**OR (95% CI)**
All treated cases							
RECIST	0	11	29	2	4	46	23.9% (14.0–36.5)
EASL	3	27	11	0	5	46	65.2% (52.1–76.8)
RD cases only*							
RECIST	0	10	27	0	2	39	25.6% (14.6–39.6)
EASL	3	22	11	0	3	39	64.1% (49.7–76.8)

CR = complete response, EASL = European Association for the Study of the Liver, NE = not evaluable, OR = objective response, PD = progressive disease, PR = partial response, RD = recommended dose, RECIST = Response Evaluation Criteria in Solid Tumors (version 1.0), SD = stable disease.
* Excludes the patient in whom treatment was discontinued.

51.3%, respectively. The median survival time was 27.8 months.

DISCUSSION

Cisplatin has been the second most common drug for transarterial chemoembolization, after anthracyclines such as doxorubicin and epirubicin (11–15). In retrospective comparative studies, transarterial chemoembolization with cisplatin showed greater therapeutic effects than transarterial chemoembolization with anthracyclines, and HCC has been considered to be relatively sensitive to cisplatin (11,14,15). However, conventional cisplatin used in previous studies was prepared in a liquid form (0.5 mg/mL) for intravenous use. It takes a long time to infuse a large volume of cisplatin solution into the hepatic artery, and it is difficult to mix conventional cisplatin with lipiodol. To solve these problems, a fine-powder formulation of cisplatin has been developed, which can be easily dissolved in saline solution at a higher concentration (1.43 mg/mL).

In a phase II study by Yoshikawa et al (16), the RD of fine cisplatin powder for HAIC was 65 mg/m^2. Grade 3 or higher adverse events included anorexia (22.5%), vomiting (6.3%), thrombocytopenia (25%), neutropenia (13%), and increased serum AST levels (32.5%). However, the toxicity and optimal dose of fine cisplatin powder remained unknown when embolization was added to HAIC. Therefore, the present study primarily aimed to determine the DLT and the RD, and secondarily evaluated the safety and efficacy of transarterial chemoembolization with fine cisplatin powder. Nonselective transarterial chemoembolization was performed for multifocal HCC in both liver lobes simultaneously to unify the intervention and toxicity among subjects. Patients with suspected or previously confirmed extrahepatic collateral tumor supply were excluded from the study, because part of the liver and/or tumors would not receive the treatment. Selective transarterial chemoembolization could have been performed in separate sessions to reduce the possibility of liver damage; however, nonselective transarterial chemoembolization was performed to minimize the heterogeneity of treatment among subjects. In addition, we avoided use of lipiodol because: (i) the method of mixing fine cisplatin powder with lipiodol is not standardized and varies among investigators (ie, suspension or emulsion) (17); (ii) dose adjustment according to tumor volume would be necessary; (iii) lipiodol could increase the risk of ischemic biliary injury (18); and (iv) a large volume of lipiodol delivered to both liver lobes could lead to liver failure.

In the present study, no DLT was observed at any dose level in the phase I study, and the RD was determined as 65 mg/m^2. We identified the same RD as Yoshikawa et al.

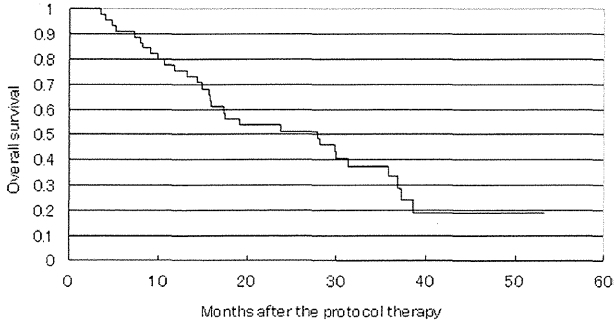

Figure. Kaplan–Meier curve shows the overall survival after protocol therapy. The 1- and 2-year survival rates were 75.3% and 51.3%, respectively. The median survival time was 27.8 months.

(16). Addition of embolization may account for the relatively higher incidence of increased ALT and AST levels among grade 3 or higher toxicities than observed by Yoshikawa et al (16). However, despite embolization of both liver lobes, toxicity remained mild. Investigators may have performed limited embolization to avoid proximal hepatic artery occlusion and to minimize liver damage.

The tumor response rate at the RD was 64.1% by EASL criteria, which exceeded the estimated efficacy rate of 50%. The response rate decreased to 25.6% per RECIST, but more than two thirds of the patients (27 of 39; 69.2%) were classified as having stable disease. By Kaplan–Meier analysis, overall survival rates were 75.3% at 1 year and 51.3% at 2 years, and the median survival time was 27.8 months. These were lower than the results of a large prospective cohort study from Japan (19), in which 1- and 2-year overall survival rates were 82% and 63%, respectively, and the median survival after chemoembolization was 34 months. The less favorable results may be because the present study enrolled patients with only multifocal HCC and included a high proportion of patients with recurrent HCC (74%).

A mixture of fine cisplatin powder and lipiodol has been studied in two recent prospective clinical trials (20,21). Yamashita et al (20) reported on a phase I/II study of HAIC using a lipiodol mixture with fine cisplatin powder with or without embolization with gelatin sponge particles. In their study (20), the powder was directly suspended in lipiodol. The DLT was identified by grade 3 vomiting, and the RD was lowered to 35 mg/m^2. The tumor response rate was as high as 57.1% per RECIST, because the area of lipiodol retention was regarded as equivalent to the area of tumor necrosis and was therefore excluded from the tumor size measurement. Moriguchi et al (21) also reported on a phase I/II study of transarterial chemoembolization with fine cisplatin powder emulsified in lipiodol. All patients also underwent embolization with gelatin sponge particles. There was no DLT, and the RD was 65 mg/m^2. Grade 3 or higher adverse events were thrombocytopenia (8%) and increased AST or ALT levels (44%). The tumor response rate was 21% per RECIST, which is similar to our result (25.6%). However, in these two studies (20,21), treatment was limited to the tumor burden area, and the dose of lipiodol was adjusted according to the tumor size; therefore, local toxicity may vary among patients.

Recently, drug-eluting beads (DEBs) containing doxorubicin have been used in transarterial chemoembolization (6,7). In a randomized controlled trial (6), the DEB chemoembolization group showed a trend toward fewer side effects than the conventional chemoembolization group; however, there was no significant difference in objective tumor response under EASL criteria between the two groups (51.6% vs 43.5%, respectively) (6). In a retrospective study (7), 237 patients with HCC underwent as many as three sessions of DEB chemoembolization within a 2-month interval, and the objective 6-month response per EASL criteria was 62.9% (CR, 22.4%; PR, 40.5%) (7). To date, DEB chemoembolization has shown no impact on patient survival compared with conventional chemoembolization with or without lipiodol. Radioembolization with ^{90}Y microspheres has also been applied to treat intermediate- to advanced-stage HCC, including diffuse disease with or without portal vein thrombosis. Median survival reported with this technique ranged from 20 to 26 months and from 11 to 14 months with Okuda stage I and II disease, respectively (8). However, neither of these new materials has been approved in Japan, and it is difficult to compare our transarterial chemoembolization regimen with these trials as a result of the heterogeneity of the study populations. Nevertheless, our nonselective transarterial chemoembolization regimen with fine cisplatin powder and GPs resulted in good tolerability and early tumor response in patients with bilobar multifocal HCC. Scheduled repeat treatment may improve tumor control and prolong the time to disease progression.

There are limitations to the present study. First, our results were specific to bilobar multifocal HCC. In addition, more than 70% of enrolled patients had recurrence of previously treated HCC. Therefore, the results may not be able to be generalized to patients who have localized or treatment-naive HCC. Third, tumor response was judged as NE in some cases as a result of the inability to distinguish lesions from pseudolesions. Therefore, the response rates may have some errors. Fourth, as a center effect, 65% of patients were enrolled in three institutions. Thus, the procedure and angiographic endpoints could still remain operator dependent, despite all attempts at uniformity. Finally, parameters of duration of treatment response, such as time to disease progression, were not evaluated.

In conclusion, the present study demonstrates that nonselective transarterial chemoembolization with fine cisplatin powder and porous GPs has a favorable safety and efficacy profile for patients with bilobar multifocal HCC. No DLT was observed, and the RD was 65 mg/m^2. This dose can be safely recommended in a clinical setting or in future comparative studies.

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Phase I/II Study of Radiologic Hepatic Arterial Infusion of Fluorouracil Plus Systemic Irinotecan for Unresectable Hepatic Metastases from Colorectal Cancer: Japan Clinical Oncology Group Trial 0208-DI

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ABSTRACT

Purpose: Treatment of patients who have metastatic colorectal cancer (CRC) by using a combination of hepatic arterial infusion chemotherapy (HAIC) and systemic chemotherapy has resulted in promising clinical outcomes. Additionally, image-guided HAIC is reported to be less invasive and distribute drugs more accurately than surgical HAIC. The purpose of this study was to assess the combination of image-guided delivery of fluorouracil through HAIC and systemic irinotecan in a multicenter phase I/II study.

Materials and Methods: Twenty-five patients with unresectable liver metastases from CRC were fitted with hepatic arterial catheter and port systems by using image-guided methods. Intraarterial fluorouracil (1,000 mg/m^2) was administered on days 1, 8, and 15 of each treatment cycle. The dose of systemic irinotecan on days 1 and 15 was escalated from 75 mg/m^2.

Results: No dose-limiting toxicity was encountered during phase I, and the recommended dose of irinotecan was set at 150 mg/m^2. Grade 3 or higher adverse events included hyperglycemia (15%), elevated γ-glutamyl transpeptidase levels (15%), and neutropenia (9%). The response rate and median survival time were 72% and 49.8 months (95% CI, 27.5–78.1 mo), respectively.

Conclusions: The combination of image-guided delivery of fluorouracil through HAIC and systemic irinotecan yielded favorable safety, response rate, and survival results. This combination should be evaluated in a large study.

ABBREVIATIONS

AE = adverse event, CRC = colorectal cancer, DLT = dose-limiting toxicity, DSA = digital subtraction angiography, HAIC = hepatic arterial infusion chemotherapy, MTD = maximum tolerated dose, OS = overall survival, RD = recommended dose, WBC = white blood cell

Modern chemotherapy with the use of active agents, such as irinotecan, oxaliplatin, and molecular-targeted therapies, has significantly prolonged the survival of patients with metastatic colorectal cancer (CRC) (1,2). However, achieving complete response and long-term survival is still rare, even with intensive therapy with combinations of these agents.

Although hepatic arterial infusion chemotherapy (HAIC) with fluorinated pyrimidines has demonstrated high local response rates for CRC liver metastases, 10 of 11 randomized

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Table 1. Eligibility Criteria

Inclusion criteria

1. Histologically documented colorectal cancer
2. Unresectable liver-limited metastases as determined by imaging studies
3. Previous resection of primary tumor with D1 or D2 lymph node dissection
4. No previous chemotherapy except adjuvant chemotherapy with fluoropyrimidines completed > 3 mo before study
5. At least one measurable tumor in the liver per RECIST (version 1.0)
6. Between 20 and 70 y of age
7. ECOG performance status of 0–2
8. Adequate hematological, hepatic, renal, and cardiac functions
9. Written informed consent

Exclusion criteria

1. Massive ascites or pleural effusion
2. Active gastrointestinal bleeding
3. Active infection
4. Watery diarrhea
5. Severe comorbid conditions
6. Other untreated cancers
7. Previous abdominal radiotherapy
8. Positive serum hepatitis B antigen or hepatitis C antibody
9. Allergy to iodinated contrast material
10. Severe mental disorder
11. Previous catheter placement into the hepatic artery
12. Pregnancy or nursing

ECOG = Eastern Cooperative Oncology Group, RECIST = Response Criteria in Solid Tumors.

controlled trials published before 2006 did not find any survival benefit of HAIC greater than that of systemic chemotherapy (3–13). Metaanalyses of HAIC studies have also demonstrated that HAIC does not improve survival in patients with CRC (14–16). Consequently, HAIC is not generally considered a first-line treatment or a component of standard treatment regimens.

Laparotomy was employed for HAIC catheter and pump placement in all previous randomized controlled trials of HAIC in Western countries. In Japan, on the contrary, a percutaneous technique for hepatic arterial catheter and port placement was developed in the 1980s and was established in the 1990s as an image-guided interventional radiologic procedure, with drug distribution evaluated by using contrast-enhanced computed tomography (CT) via the indwelling catheter–port system (17–20). The advantages of this technique are that it is minimally invasive and provides accurate periodic evaluation of drug delivery. In addition, HAIC treatment outcomes with this technique are favorable; phase II studies (17,21–23) of intermittent HAIC with fluorouracil in patients with CRC liver metastases with or without extrahepatic metastasis had median survival times of 18.6–26 months. HAIC treatment success requires monitoring of drug distribution to ensure that the administered drug is delivered directly to all liver tumors without reaching extrahepatic organs (20).

Kemeny et al (24) reported a phase I study of HAIC with floxuridine and dexamethasone combined with systemic irinotecan that was or was not followed with cryosurgery. The study demonstrated a response rate of 74% and a median survival time of 17 months in patients who did not undergo cryosurgery. In their study, however, surgical laparotomy was used for implantation instead of a radiologic intervention (24), and the drug and administration schedules were different from those of Japanese phase II studies. Thus, we conducted a multicenter phase I/II study to assess the feasibility, safety, and preliminary efficacy of image-guided delivery of fluorouracil through HAIC combined with systemic irinotecan.

MATERIALS AND METHODS

Patients

Inclusion and exclusion criteria are listed in **Table 1**. A Consolidated Standards of Reporting Trials diagram of this study is shown in **Figure 1**. The study protocol was approved by the institutional review boards of all participating institutions. All patients provided written informed consent. This study was registered to UMIN-CTR (UMIN C000000051, 2005/08/08).

Treatment

Placement of Intraarterial Catheter and Port System. A catheter and port system was implanted within 2 weeks of enrollment in the study. Details of the procedure are described elsewhere (19,25). In brief, percutaneous implantation of a catheter and port system was performed under local anesthesia by using an interventional radiologic technique. Before each cycle of chemotherapy, drug delivery was evaluated by digital subtraction angiography (DSA) and CT angiography through the implanted catheter and port system (**Fig 2**).

Chemotherapy Administration. After implantation of the catheter and port system, chemotherapy was started when the patient's laboratory values were as follows: white blood cell (WBC) count of at least 4,000/mm^3 and no greater than 12,000/mm^3, platelet count of at least 100,000/mm^3, aspartate aminotransferase and alanine aminotransferase levels no greater than three times the upper limit of normal, bilirubin level no greater than 1.5 mg/dL, and serum creatinine level no greater than 1.5 mg/dL. Patients received concurrent systemic chemotherapy and HAIC in 4-week cycles, and the treatment protocol was considered to be complete after five cycles of this regimen. In each cycle, 1,000 mg/m^2 of fluorouracil in saline solution plus 100 mg of hydrocortisone were administered on days 1, 8,

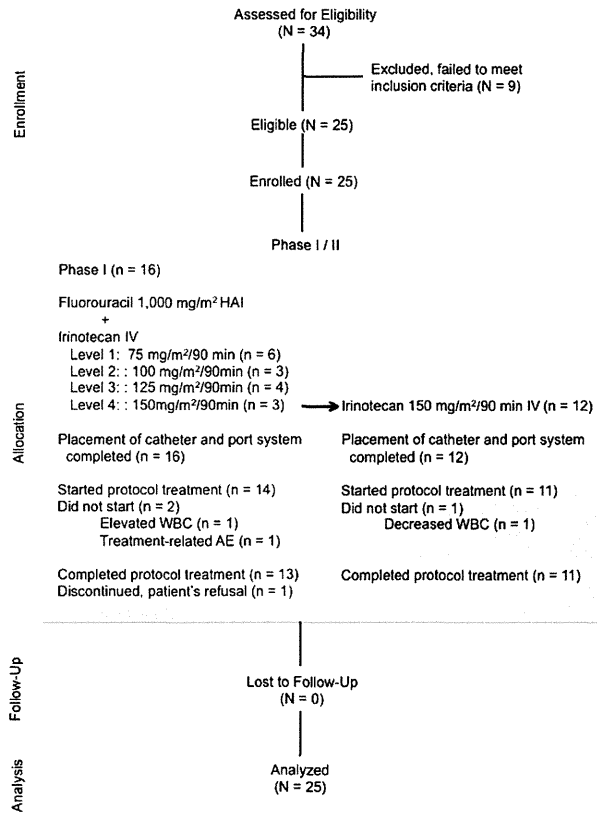

Figure 1. Consolidated Standards of Reporting Trials diagram. HAI = hepatic arterial infusion. (Available in color online at *www.jvir.org.*)

and 15 by continuous 5-hour infusion via a disposable balloon pump system. This dose was determined based on a previous phase I/II study of HAIC with fluorouracil (23). On days 1 and 15, following HAIC, irinotecan diluted in 5% glucose was administered via a 90-minute intravenous drip. The irinotecan doses planned for phase I of the trial were 75, 100, 125, and 150 mg/m^2. After the maximum tolerated dose (MTD) was determined, the study was advanced to phase II.

Patient and Tumor Evaluations

Pretreatment evaluations included medical history, physical examination, and laboratory examinations. Laboratory examinations included evaluation of complete blood counts, total bilirubin, alkaline phosphatase, lactate dehydrogenase, aspartate aminotransferase, alanine aminotransferase, and carcinoembryonic antigen. Baseline evaluation of tumors was performed by contrast-enhanced CT scans of the chest and abdomen. During the course of treatment, each patient was assessed weekly for toxicity, including laboratory determination of complete blood counts, and blood chemistry. CT examination was planned before treatment and after one, three, and five cycles of treatment. Patient responses to treatment were evaluated by three radiologists based on Response Evaluation Criteria In Solid Tumors, version 1.0. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria, version 2.0.

Study Design and Statistical Analysis

This trial was designed as a phase I/II study. The primary endpoints of phase I were to identify dose-limiting toxicities (DLTs), MTD, and the recommended dose (RD) of systemic irinotecan when combined with HAIC that uses a fixed dose of fluorouracil. DLTs in phase I were defined as any grade 4 neutropenia or thrombocytopenia or any nonhematologic toxicity of grade 3 or more severe. We treated patients in cohorts of three to six. The first cohort received the lowest dose (ie, dose level 1) of irinotecan, and doses were escalated in a stepwise fashion. If DLTs were observed in less than one third of the cohort members, subsequent patients were treated at the next dose level. If more than one third of cohort members developed DLTs, the preceding dose level was identified as the MTD.

Based on the results of previous studies, 12 patients were needed in this study with a null proportion of 30%–45% and an alternative proportion of 74% to achieve 80% power, given that the one-sided significance level was 10% (24).

Secondary endpoints of the study included HAIC initiation rate, overall response rate, response rate in the liver, and toxicity. Survival analysis was performed by using the Kaplan–Meier method. Demographics and baseline variables were summarized by using descriptive statistics. Statistical significance was set at 0.05, and differences between groups were examined by using two-tailed *t* tests. We used SPSS software (version 17; SPSS, Chicago, Illinois) to perform all statistical analyses.

RESULTS

Patient Demographics

Twenty-five patients from five participating institutions were enrolled between November 2003 and March 2008. Patient characteristics are listed in Table 2. Synchronous liver metastases were seen in 84% of the patients, and 92% of the patients had not received previous adjuvant chemotherapy.

Initiation of HAIC and Systemic Chemotherapy

A catheter and port system was successfully placed in all 25 patients. Catheters were inserted via the left subclavian artery in all patients. Treatment consisting of HAIC and systemic chemotherapy was initiated according to the study protocol in 22 patients (88%; Fig 1). Treatment was not started in three patients as a result of elevated WBC count (n = 1), decreased WBC count (n = 1), and cerebral infarction that was presumably caused by catheter placement (n = 1). The elevated WBC count observed in one patient at dose level 1 and the decreased WBC count

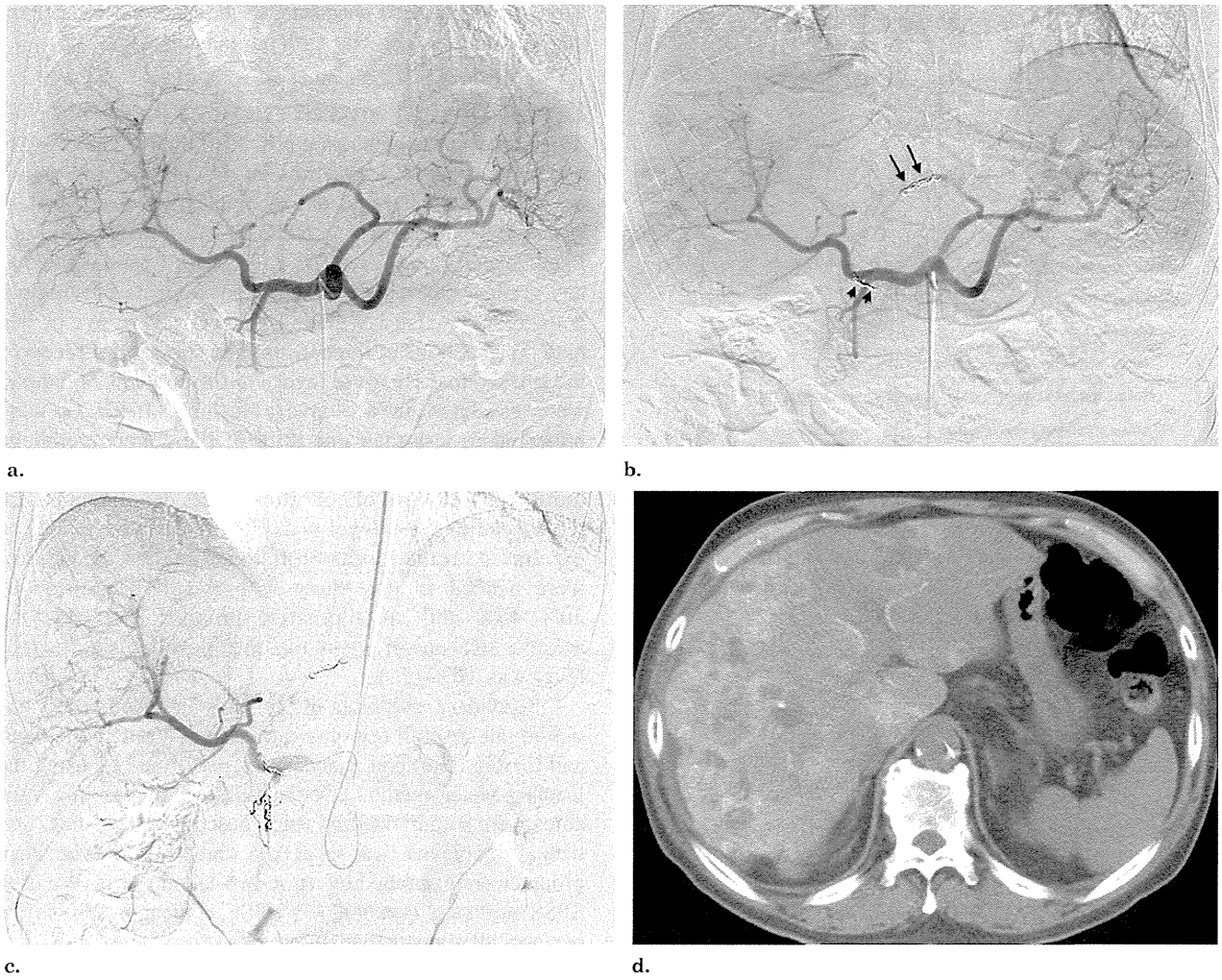

Figure 2. Image-guided insertion of catheter and port system for HAIC. **(a)** DSA of the celiac artery. The left hepatic artery is arising from left gastric artery (ie, replaced left hepatic artery). **(b)** DSA after embolization of the replaced left hepatic artery (long arrows) and right gastric artery (short arrows). The left hepatic artery is visualized from the collateral vessels. **(c)** DSA via the implanted port. The indwelling catheter is implanted via the left subclavian artery. **(d)** CT angiography via the implanted port. Adequate drug distribution is confirmed with enhancement of hepatic metastases by contrast material injected through the implanted port.

observed in one patient at dose level 4 were likely related to the primary disease process, because no clinical findings of infection were found. These two patients were removed from the study and treated by HAIC alone. Details of the patient who developed cerebral infarction are described in the Safety section. The HAIC initiation rate was 96%, including the two patients who were later removed from the study.

Dose-escalation Findings

In phase I, one of six patients developed DLT at dose level 1 (Fig 1). Of the 14 patients who started the treatment protocol, 13 patients completed five cycles. Because no DLT was encountered at dose levels 2–4, we were unable to determine the MTD of irinotecan. Dose level 4 (150 mg/m^2) was selected as the RD for phase II of the study.

Safety

There were no treatment-related deaths in this study. The incidence of grade 2 or higher adverse events (AEs) occurring during chemotherapy is shown in Table 3. In 106 cycles of protocol treatment, the following grade 3 or higher AEs occurred: leukopenia (2%), neutropenia (9%), elevated γ-glutamyl transpeptidase level (15%), hyperglycemia (15%), and hypokalemia (1%). The only grade 4 AE was neutropenia (2%).

Before the initiation of chemotherapy, one patient (4%) developed central nervous system ischemia. One day after placement of the catheter and port system, the patient developed hemiparesis, and magnetic resonance imaging confirmed multiple cerebral infarctions. The patient subsequently had moderate hemiparesis, but no other neurologic deficits. The indwelling catheter was thought to have caused the cerebral infarctions.

Table 2. Patient Characteristics (N = 25)

Characteristic	Value
Age (y)	
Median	63
Range	45–70
Sex	
Male	21 (84)
Female	4 (16)
ECOG performance status	
0	24 (96)
1	1 (4)
Location of primary tumor	
Colon	13 (52)
Rectum	12 (48)
Differentiation	
Well	7 (28)
Moderate	15 (60)
Poor	3 (12)
Synchronous	
Yes	21 (84)
No	4 (16)
Liver involvement	
< 30%	22 (88)
30%–60%	3 (12)
> 60%	0
Previous adjuvant chemotherapy	
Yes	2 (8)
No	23 (92)

Values in parentheses are percentages. ECOG = Eastern Cooperative Oncology Group.

Table 3. Per-patient Incidence of Grade 2 or Higher Adverse Events in All Cycles of Chemotherapy (N = 106)

Adverse Event	Grade 2	Grade 3	Grade 4
Nausea	3 (3)	0	0
Diarrhea	8 (8)	0	0
Stomatitis	1 (1)	0	0
Fatigue	3 (3)	0	0
Alopecia	12 (11)	0	0
Vertigo	0	1 (1)	0
Glycosuria	2 (2)	0	0
Cystitis	2 (2)	0	0
Leukopenia	21 (20)	2 (2)	0
Neutropenia	15 (14)	7 (7)	2 (2)
Anemia	10 (9)	0	0
Thrombocytopenia	2 (2)	0	0
Hyperbilirubinemia	1 (1)	0	0
GGT	11 (10)	16 (15)	0
ALP	3 (3)	0	0
Hyperglycemia	26 (25)	16 (15)	0
Hypokalemia	0	1 (1)	0

Values in parentheses are percentages. ALP = alkaline phosphatase, GGT = γ-glutamyl transpeptidase.

Response

A total of 25 patients were included in the response analyses. The overall response in the liver was 72%, and included four complete responses (16%) and 14 partial responses (56%). Four patients (16%) exhibited stable disease in the liver, and the responses of three patients (12%) could not be evaluated because the treatment protocol was not initiated. During the course of treatment, no patients developed any observable extrahepatic metastases. Therefore, the overall response rate was 72%.

Survival

Survival analysis was conducted based on all 25 patients (Fig 3). With a median follow-up period of 55.0 months (range, 22.8–87.7 mo), the median overall survival (OS) time was 49.8 months (95% CI, 27.5–78.1 mo).

DISCUSSION

The present study is a prospective trial to evaluate image-guided HAIC combined with systemic chemotherapy for patients with unresectable hepatic metastases from CRC. Our results demonstrate that this treatment may be effective and safe as an initial therapy, as 23 of the 25 patients in the study had not undergone previous chemotherapy. Twenty-one of these 23 patients were enrolled in the study after surgery to remove the primary tumor. Other noteworthy characteristics of the patients in this trial include good performance status (24 patients with a performance status of 0) and moderate tumor involvement in the liver (22 patients with < 30% involvement). To summarize, the characteristics of this patient cohort were resectable primary tumor, synchronous and unresectable liver metastases of moderate intrahepatic extent, good performance status, and limited previous chemotherapy.

We determined the feasibility and the safety of image-guided HAIC combined with systemic irinotecan. Generally, AEs caused by fluorouracil are well tolerated, and bone marrow suppression is not significant. Given that systemic irinotecan has a different toxicity profile than fluorouracil, and the intraarterial effects of fluorouracil were minimal in the present study, it could be surmised that the RD of irinotecan in this study should be the same as the standard RD of 150 mg/m^2 used in Japanese patients. However, modification of the usual treatment schedule of weekly fluorouracil HAIC to a schedule that included a 1-week treatment-free interval in the fourth week of each treatment cycle may account for the minimal hematologic toxicity we observed and the undetermined MTD (23). During phase II of this trial, grade 3 AEs were observed in 21 of 60 treatment cycles (35%), and no grade 4 AEs occurred. Furthermore, all patients, except one who did not meet the criteria for the initiation of chemotherapy, completed the planned five cycles of treatment. Therefore, this

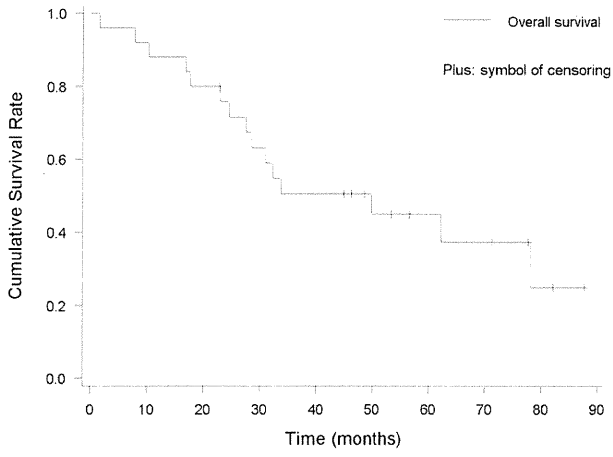

Figure 3. Graph of OS. The median OS time is 49.8 months (95% CI, 27.5–78.1 mo).

study demonstrated that image-guided HAIC with fluorouracil combined with systemic irinotecan (150 mg/m^2) is feasible and safe.

Hyperglycemia was a notable AE in this study. Hyperglycemia occurred in 56% of the 106 treatment cycles. The incidence of hyperglycemia in phase I was almost the same as in phase II. As there have been no reports of hyperglycemia as a result of irinotecan therapy, and intraarterial hydrocortisone (100 mg) was administered with fluorouracil on days 1, 8, and 15 to reduce vascular endothelial injury, this intraarterial hydrocortisone may have influenced the occurrence of hyperglycemia. There is some possibility that intraarterial direct administration of fluorouracil to the liver leads to deterioration of the glucose tolerance of the liver. Hyperglycemia does not directly alter the short-term patient prognosis, but it may become more important if longer survival is achieved with this treatment.

The HAIC initiation rate in the present study is comparable to rates seen in previous studies of image-guided HAIC. Tanaka et al (26) reported a technical success rate of 99.8% among 426 patients undergoing image-guided HAIC. Deschamps et al (27) reported a technical success rate of 94% among 93 patients. Moreover, Ganeshan et al (25) mentioned in their review of HAIC that interventional radiology played a vital role in establishing vascular access and assessing outcomes. On the contrary, the technical success rates of surgical HAIC, a technique widely employed in published randomized controlled trials, are not included in the reports of these trials or result in lower HAIC initiation rates than seen with image-guided HAIC. Kerr et al (10) reported an HAIC initiation rate of 68% following the surgical procedure used in their randomized study comparing HAIC with systemic chemotherapy. In the present small, prospective study, the HAIC initiation rate was 96%. This suggests that image-guided catheter placement is suitable for the initiation of HAIC.

In the present study, one patient developed cerebral infarction after catheter implantation. There have been several reports of cerebral ischemia as a complication of catheter implantation via the subclavian artery, and the incidence of this complication is approximately 5% (28,29). This complication should therefore be recognized as a severe AE caused by radiologic catheter placement via the subclavian artery, and other access routes such as the femoral or hypoepigastric artery should be considered.

The liver response rate of 72% we observed is similar to those of other studies of image-guided deliver of fluorouracil with the same infusion protocol through HAIC (17,21,22). This indicates that the addition of systemic irinotecan might not affect tumor response in the liver. However, previous studies have demonstrated an incidence of extrahepatic metastases of approximately 70% when patients were treated with HAIC alone. In the present study, no extrahepatic metastases were observed during the study. Therefore, systemic irinotecan may have reduced the occurrence of extrahepatic metastases. Because more than 90% of the fluorouracil administered via the hepatic artery is reported to pass through the liver and enter systemic circulation (30), irinotecan combined with fluorouracil may have prevented extrahepatic metastases in the present study.

It is notable that the median OS of the present study exceeded 4 years. The large proportion of patients with good PS may be a prominent factor in this result. Standard first- and second-line systemic chemotherapies have demonstrated a median survival of 18–24 months (31–34). Concerning the combination of HAIC with systemic chemotherapy, Kemeny et al (35) reported an OS of 36 months with fluorodeoxyuridine HAIC plus systemic oxaliplatin and irinotecan, and an OS of 22 months with fluorodeoxyuridine HAIC plus systemic oxaliplatin, fluorouracil, and leucovorin. Ducreux et al (36) reported an OS of 27 months with HAIC of oxaliplatin plus systemic irinotecan and fluorouracil. Therefore, HAIC combined with systemic chemotherapy may prolong the survival of patients with unresectable liver metastases from CRC.

The present study has several limitations. First, it was a phase I/II study involving a small number of patients. Second, we did not record postprotocol treatment. Therefore, OS may have been influenced by modern systemic chemotherapy with fluorouracil, leucovorin, oxaliplatin, irinotecan, and molecular-targeting agents. However, the OS observed in the present study is still a promising result. Thus, accurate HAIC that uses CT angiography for appropriate drug distribution in combination with systemic chemotherapy may lead to improved patient outcomes.

The present study demonstrates the feasibility of HAIC as an interventional procedure and that HAIC of fluorouracil combined with systemic irinotecan at 150 mg/m^2 is well tolerated. Also, the OS exceeding 4 years was a promising result, although it may have been affected by the treatments after the protocol. In conclusion, this combination chemotherapy should be evaluated in a larger study.

ACKNOWLEDGMENTS

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REVIEW ARTICLE

Clinical trials of interventional oncology

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Abstract Interventional oncology has great potential to be a good treatment modality in the field of oncology, because its procedures are minimally invasive and fairly quick. However, except for a few procedures such as percutaneous radiofrequency ablation and trans-catheter arterial chemo-embolization that have been recognized as standard treatments for hepatocellular carcinoma, most procedures have not been established as the standard treatment modality due to the limited number of clinical trials with compelling evidence. There are several common problems when performing clinical trials of interventional oncology. The first is that the outcomes of clinical trials are greatly influenced by the level of technical skill of the physicians. The second is that equipment and devices vary widely in countries and regions, and they also influence the outcomes. The third is that the methodology of clinical trials for techniques such as interventional oncology has not yet been established. The fourth is the difficulty of setting appropriate endpoints; quality of life is suitable for evaluating interventional oncology in palliative care, but it is not easy to set as the endpoint. The fifth is the difficulty of employing a blinded design, because the procedure cannot be performed without the physician's awareness. Despite such difficult situations, many multi-institutional clinical trials of interventional oncology have been carried out in Japan, with some challenging results. Establishing evidence is critical to making interventional oncology the standard treatment. Interventional radiologists should know the importance of clinical trials, and should move ahead in this direction in a step-by-step manner.

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Keywords Interventional oncology · Interventional radiology · Clinical trial · Evidence

Introduction

Interventional radiology is a subspecialty of diagnostic radiology, in which percutaneous treatments are conducted under an image-guidance system without any open surgery. The term interventional radiology was proposed by Malgulis as "interventional diagnostic radiology" in 1967 [1], and the concept of "interventional radiology" was established by Wallace in 1976 [2]. This procedure is minimally invasive and fairly quick. Since 2000, as the term "interventional radiology" became acknowledged in the field of oncology, a new one, "interventional oncology" has been used. Although the term is well-known, there are only a few procedures recognized as standard treatment modalities in oncology due to the limited number of clinical trials with compelling evidence.

In this review article, the current situation, issues, and challenges of clinical trials in interventional oncology are introduced.

Current situation of clinical trials in interventional oncology

Percutaneous radiofrequency ablation (RFA) is one of the typical procedures in interventional oncology. A RFA needle is inserted percutaneously into tumors under image guidance, and kills the tumor cells by a thermal ablative mechanism. RFA has been established as the standard treatment modality for multi-nodular ($n \leq 3$) hepatocellular carcinoma less than 3 cm in diameter [3]. The main