was confirmed using contrast-enhanced CT or MR imaging (bolus injection) after 6 weeks ± 2.

The treatment was repeated if tumor progression was observed. The treatment could also be repeated even without tumor progression for disease control on an as-needed basis. If no residual tumor was found, transcatheter arterial chemoembolization was not performed periodically, and a follow-up contrast-enhanced CT or MR imaging examination was repeated every 3 months ± 2. When tumor recurrences were observed on a follow-up CT or MR imaging examination, the transcatheter arterial chemoembolization procedure was repeated. The protocol treatment was discontinued if any of the following criteria for the discontinuation of the protocol therapy occurred: obvious tumor progression at the site of treatment at an evaluation performed 6 weeks ± 2 after transcatheter arterial chemoembolization, tumor thrombosis in the first branch or main portal vein, intended use of another appropriate therapy for persistent or recurrent tumors, grade 4 nonhematologic toxicities other than aspartate aminotransferase (AST) or alanine aminotransferase (ALT), an accumulated dose of epirubicin > 750 mg/m^2 body surface area or an accumulated dose of doxorubicin > 500 mg/m^2 body surface area, or technical difficulties associated with the performance of transcatheter arterial chemoembolization. If the protocol therapy was discontinued, another anticancer treatment was allowed without restriction. Also, if transcatheter arterial chemoembolization was effective in reducing the tumor and the patient was eligible for other curative therapies, hepatic resection or local ablative therapy was allowed.

Response and Toxicity Assessment

Contrast-enhanced CT or MR imaging was performed at 6 weeks ± 2 after transcatheter arterial chemoembolization and every 3 months ± 2 thereafter. The tumor response was evaluated according to the modified Response Evaluation Criteria in Solid Tumors (RECIST) (19). Serum alpha fetoprotein (AFP) and protein induced by vitamin K absence or antagonist-II (PIVKA II) levels were measured at 6 weeks ± 2 after the first transcatheter arterial chemoembolization procedure. The AFP or PIVKA II response was assessed for patients who had a level before treatment of 100 ng/mL or ≥ 100 mAU/mL; a positive response was defined as a reduction by > 50% compared with the level before treatment. Regarding the adverse events that were observed, the incidence per grade based on the worst grade of the adverse events in an individual case was calculated. The severity of all adverse events was evaluated according to the National Cancer Institute Common Terminology Criteria for adverse events, version 3.0. Overall survival was measured from the date of initial treatment to the date of death or the date of the last follow-up examination. Time-to-progression was defined as the time from the date of the initial treatment to the first documentation of progression. The period until the discontinuation of transcatheter arterial chemoembolization was defined as the time from the date of the initial treatment to the discontinuation of the protocol therapy. The overall survival time and time-to-progression were calculated using the Kaplan-Meier method.

Statistical Considerations

The aim of this clinical study was to evaluate the safety and efficacy of Asian transcatheter arterial chemoembolization and to confirm the reproducibility of the therapeutic effect compared with that observed in a randomized controlled trial conducted by Llovet et al (12). The primary endpoint of this trial was the 2-year survival rate, and the secondary endpoints were overall survival, the response rate, and the frequency of adverse events. The number of enrolled patients was determined using the confidence interval (CI) method based on the assumption that the 2-year survival rate in the transcatheter arterial chemoembolization group studied by Llovet et al (12) was 63%. Because the enrollment of 100 patients in this study would ensure a 10% two-sided CI, we planned to enroll 100 patients. This clinical study was a multicenter cooperative study conducted in Japan and Korea, and the annual registration of 100 patients was feasible. The total study period was set as 3 years, estimating that case accrual would occur during the first year and that the remaining 2 years would serve as the follow-up period to determine the 2-year survival rate. This population was defined as the full analysis set (FAS), including any patients who received at least one course of the study treatment and excluding any patients who withdrew their informed consent to participate in this study. This open-label, multiinstitutional, single-arm prospective study was approved by the review board of each institution and was conducted in accordance with the Declaration of Helsinki. This trial was registered in UMIN Clinical Trials Registry (http://www.umin.ac.jp/ctr/index-j.htm), identification number (UMIN000000975). Patient registration and data collection were managed by the clinical research data center of the clinical trial office at the National Cancer Center in Japan. The quality of data was ensured through careful review by the data center staff and the coordinating investigator of this study. All the data were frozen on January 31, 2011, and all the analyses were performed by a statistician (S.Y.).

RESULTS

Patient Characteristics

Between January 2008 and January 2009, 102 patients were enrolled in this trial at 19 institutions in Japan and 8 institutions in Korea (**Table 2**). Three patients were excluded from the analysis because they withdrew their informed consent, and all their data were extracted from the study. The characteristics of the remaining 99 FAS patients are listed in **Table 3**.

Table 2. Enrolled Institutions and Numbers of Patients

Institution	No. Enrolled Patients
National Cancer Center Hospital East	12
National Cancer Center Hospital	12
Nara Medical University	10
Chonnam University Hospital	7
Aichi Cancer Center Hospital	6
Shizuoka Cancer Center	6
Kyung Hee University Medical Center	6
Ishikawa Prefectural Central Hospital	4
Kobe University	4
The Catholic University of Korea Uijeongbu St Mary's Hospital	4
The Cancer Institute Hospital of JFCR	3
Shinshu University	3
Fukuoka University	3
Keijinkai Teine Hospital	2
Niigata Cancer Center	2
Okinawa Prefectural Nanbu Medical Center & Children's Medical Center	2
Catholic University St Paul's Hospital	2
Cheju National University Hospital	2
Korea University Anam Hospital	2
Samsung Medical Center	2
Seoul National University Hospital	2
Tochigi Cancer Center	1
Ryugasaki Saiseikai Hospital	1
The Jikei University School of Medicine	1
Aichi Medical University	1
Shitennoji Hospital	1
Hyogo College of Medicine	1

Table 3. Patient Characteristics (n = 99)

Characteristics	No. Patients (%)
Korea	24 (24%)
Japan	75 (76%)
Age (y)	
Median	70
Range	45–84
Sex	
Male	67 (68%)
Female	32 (32%)
ECOG performance status	
0	86 (87%)
1	12 (12%)
2	1 (1%)
Hepatitis B surface antigen positive	19 (19%)
Hepatitis C virus antibody positive	52 (53%)
Child-Pugh classification	
A	80 (81%)
B	19 (19%)
Ascites present	5 (5%)
Maximum tumor size (mm)	
Median	39
Range	11–110
No. tumors	
Single	34 (34%)
Multiple	65 (66%)
Tumor distribution	
Unilobar	64 (65%)
Bilobar	35 (35%)
AFP (ng/dL)	
Median	35.4
Range	1.8–102,700
Protein induced by vitamin K absence or antagonist-II (mAU/mL)	
Median	154
Range	0.02–66,400

AFP = alpha fetoprotein; ECOG = Eastern Cooperative Oncology Group.

Transcatheter Arterial Chemoembolization Procedure

A median of two transcatheter arterial chemoembolization procedures (range, one to nine procedures) were performed during the follow-up period. Transcatheter arterial chemoembolization using epirubicin was performed in 76 patients (77%), and transcatheter arterial chemoembolization using doxorubicin was performed in 25 patients (25%). Mainly epirubicin was used in Japan, whereas mainly doxorubicin was used in Korea. However, doxorubicin was administered together with mitomycin and cisplatin in two patients, which was judged as a serious deviation from the study's protocol. The median doses of epirubicin, doxorubicin, and Lipiodol were 45 mg/body (range, 10–70 mg/body), 40 mg/body (range, 10–60 mg/body), and 5 mL (range, 1.5–20 mL). The artery used for the administration of the anticancer agent in the initial transcatheter arterial chemoembolization was the subsegmental branch in 51 patients (37%), the segmental branch in 42 patients (30%), the left or right hepatic artery in 35 patients (25%), and other arteries such as the inferior phrenic artery in 10 patients (7%). There were 62 patients (63%) who discontinued the protocol treatment. The median period until transcatheter arterial chemoembolization discontinuation was 17.8 months. After the discontinuation of this protocol treatment, 59 patients (60%) received subsequent therapy including hepatic arterial infusion chemotherapy (14 patients), transcatheter arterial chemoembolization with other anticancer agents (13 patients), local ablation (13 patients), systemic chemotherapy (10 patients), radiotherapy (6 patients), and hepatic resection (3 patients).

Adverse Events

The adverse events associated with the first transcatheter arterial chemoembolization procedure observed in the 99 FAS patients are listed in **Table 4**. Grade 3 or higher anemia, neutropenia, and thrombocytopenia occurred in 1 (1%), 1 (1%) and 12 (12%) patients. In patients undergoing

Table 4. Adverse Events of First Transcatheter Arterial Chemoembolization (n = 99)

	No. Patients (%)			
	Grade 1*	Grade 2*	Grade 3*	Grade 4*
Hematologic toxicity				
Leukocytes	30 (30)	12 (12)	0 (0)	0 (0)
Neutrophils	11 (11)	14 (14)	1 (1)	0 (0)
Hemoglobin	53 (54)	14 (14)	1 (1)	0 (0)
Platelets	45 (45)	25 (25)	11 (11)	1 (1)
Nonhematologic toxicity				
Malaise	42 (42)	10 (10)	0 (0)	0 (0)
Anorexia	37 (37)	4 (4)	0 (0)	0 (0)
Nausea	22 (22)	4 (4)	0 (0)	0 (0)
Vomiting	10 (10)	1 (1)	0 (0)	0 (0)
Fever	55 (56)	9 (9)	0 (0)	0 (0)
Abdominal pain	24 (24)	12 (12)	4 (4)	0 (0)
Alopecia	1 (1)	0 (0)	–	–
Gastrointestinal hemorrhage	0 (0)	0 (0)	1 (1)	0 (0)
Liver abscess	0 (0)	0 (0)	1 (1)	0 (0)
Bilirubin	28 (28)	36 (36)	2 (2)	0 (0)
AST	28 (28)	32 (32)	30 (30)	5 (5)
ALT	26 (26)	31 (31)	31 (31)	5 (5)
Alkaline phosphatase	57 (58)	4 (4)	1 (1)	0 (0)
Hypoalbuminemia	49 (49)	35 (35)	0 (0)	–
Creatinine	12 (12)	3 (3)	0 (0)	0 (0)

ALT = alanine aminotransferase; AST = aspartate aminotransferase.
* Grading according to Common Terminology Criteria for Adverse Events, version 3.0.

transcatheter arterial chemoembolization for unresectable HCC, the most common nonhematologic toxicities were hepatic dysfunction, as indicated by increased AST, ALT, and bilirubin levels. Grade 3 or higher AST, ALT, abdominal pain, and bilirubin nonhematologic toxicities were observed in 35 (35%), 36 (36%), 4 (4%), and 2 (2%) patients; these toxicities were transient so the patients recovered within 1 month. No treatment-related deaths occurred in this series. During this protocol treatment, serious adverse events were observed in two patients (2%). One patient developed a grade 5 spontaneous perforation of the small intestine because of paralytic ileus occurring 32 days after transcatheter arterial chemoembolization. This patient had a past history of multiple surgeries of the ileus, and the incident was judged as being unrelated to the transcatheter arterial chemoembolization treatment by an independent data monitoring committee. The other patient developed a grade 3 gastrointestinal hemorrhage on day 2 after the transcatheter arterial chemoembolization procedure. This hemorrhage was caused by Mallory-Weiss syndrome as a result of frequent vomiting after transcatheter arterial chemoembolization; the patient recovered without any specific treatment. No cumulative toxicities, including cardiac toxicity, were reported in this study.

Tumor Response

All 99 treated patients were included in the response evaluation, and the tumor response at 6 weeks ± 2 after the first transcatheter arterial chemoembolization procedure was evaluated using modified RECIST. A complete response was shown in 42 patients (42%), and 31 patients (31%) had a partial response, producing an overall response rate of 73% (95% CI, 64%–82%). Stable disease was present in 18 patients (18%), and 7 patients (7%) had progressive disease. Serum AFP and PIVKA II levels were reduced by > 50% in 76% and 90% of the patients who had a level before treatment of ≥ 100 ng/mL and ≥ 100 mAU/mL, respectively.

Overall Survival and Time-to-Progression

Of the 99 patients, 86 had developed disease progression at the time of the analysis. The median time-to-progression was 7.8 months. The pattern of disease progression was locoregional recurrence in 66 patients (67%), a new lesion in the liver in 53 patients (54%), vascular invasion in 8 patients (8%), and distant metastases in 8 patients (8%). At the time of the analysis, 33 patients had died, and the median survival time, 1-year survival rate, and 2-year survival rate for all 99 patients were 3.1 years, 89.9% (95% CI, 81.7%–94.3%), and 75.0% (95% CI, 65.2%–82.8%) (**Fig 1**). In addition, the median survival time, 1-year survival rate, and 2-year survival rate of 97 patients, calculated after excluding the two patients treated with doxorubicin together with mitomycin and cisplatin, were also almost the same (data not shown). The 2-year survival rates were 77.4% in Japan and 67.0% in Korea ($P = .57$) (**Fig 2**).

Figure 1. Overall survival and progression-free survival curves for 99 patients who underwent transcatheter arterial chemoembolization (TACE) for unresectable HCC. The tick marks indicate censored cases. (Available in color online at *www.jvir.org.*)

DISCUSSION

The survival benefit of transcatheter arterial chemoembolization for unresectable HCC has been confirmed by several randomized controlled trials (6,11,12) and meta-analyses (14,15). However, there is no consensus on the standard method of transcatheter arterial chemoembolization regarding the use of anticancer agents, embolic material, technical details, and the treatment schedule. The term "conventional transcatheter arterial chemoembolization" or "classic transcatheter arterial chemoembolization" has been widely used in the literature more recently. Common understanding is that conventional transcatheter arterial chemoembolization refers to Lipiodol chemoembolization, no matter what drug or embolic agent is used. However, there is no definition or consensus in terms of technical aspects of conventional transcatheter arterial chemoembolization. Conventional transcatheter arterial chemoembolization lacks consistency and includes a wide variety of anticancer drugs and dosages and techniques, which precludes the comparison of the previous studies of transcatheter arterial chemoembolization. For example, transcatheter arterial chemoembolization procedures with Lipiodol using a single drug or combination of two or three drugs and procedures with or without particulate embolic agents including gelatin sponge, polyvinyl alcohol, and spherical beads all have been referred to as "conventional transcatheter arterial chemoembolization." The schedule of conventional transcatheter arterial chemoembolization treatments has also been inconsistent among previous studies; transcatheter arterial chemoembolization was performed regularly in some studies and on an as-needed basis in others. Conventional transcatheter arterial chemoembolization cannot be justified as being the standard transcatheter arterial chemoembolization when conducting a randomized trial evaluating new treatments such as drug-eluting beads.

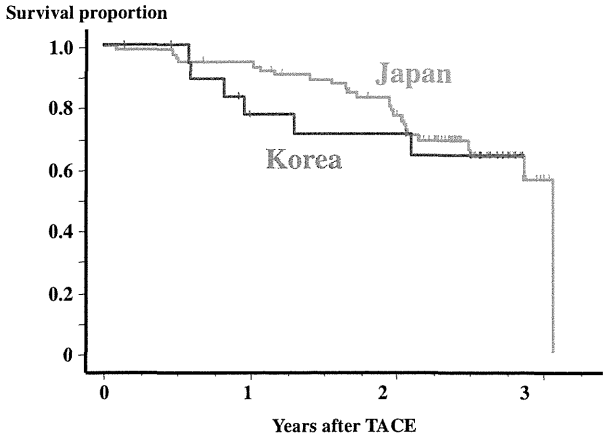

Figure 2. Comparison of overall survival curves between Japan (red line) and Korea (blue line). The tick marks indicate censored cases. TACE = transcatheter arterial chemoembolization. (Available in color online at *www.jvir.org.*)

Asian transcatheter arterial chemoembolization is characterized by using anthracycline agents with Lipiodol and gelatin sponge in an on-demand basis. It may be categorized as conventional transcatheter arterial chemoembolization; however, the technique is different from other conventional transcatheter arterial chemoembolization procedures. Elucidation of Asian transcatheter arterial chemoembolization by a prospective clinical study is warranted to develop better and new treatments for HCC. Because a randomized controlled trial comparing transcatheter arterial chemoembolization with a conservative therapy as a control is not feasible in countries such as Korea and Japan, where Asian transcatheter arterial chemoembolization has been performed as a practical standard therapy for a long time, we decided to conduct a single-arm prospective study to clarify the treatment efficacy and safety of Asian transcatheter arterial chemoembolization.

For comparison with the results of Llovet et al (12), which was the most notable study and had the most favorable antitumor effect among eight randomized controlled trials (**Table 1**) (6–13), the eligibility criteria except age and cardiac ejection fraction (**Table 5**) and study endpoints were set to be same. However, regarding transcatheter arterial chemoembolization procedures, we maintained the Asian transcatheter arterial chemoembolization in this study. With regard to the comparison of the patient characteristics between our study and the Llovet et al (12) study (**Table 5**), the median age before transcatheter arterial chemoembolization was slightly younger and the proportions of men and patients infected with hepatitis C virus were slightly higher in Llovet's study than in the present study. The hepatic reserves, as indicated by the Child-Pugh classification and the presence of ascites, were favorable in our study. The tumor-related factors were similar between our study and their study. The numbers of transcatheter arterial chemoembolization treatment sessions were also similar. Statistically, no significant differences in the patient characteristics were observed between our study and their study.

Table 5. Differences between Current Study and Llovet's Study

		Current Study (n = 99)		Llovet's Study (n = 40)		*P* Value
Eligibility criteria						
Age		Not limited		≤ 75 y		
Cardiac ejection fraction		Not limited		< 50%		
Treatment						
Anticancer agent		Doxorubicin or epirubicin		Doxorubicin		
Maximum dose of anticancer agents		Doxorubicin, 70 mg/body; epirubicin, 100 mg/body		75 mg/m^2		
Maximum dose of Lipiodol		20 mL		10 mL		
Periods of transcatheter arterial chemoembolization		On demand		Periodically		
Patient characteristics*						
Age (y)	Mean [95% CI]	69	[65–75]	63	[61–66]	
Sex	Male	67	(68)	32	(80)	
	Female	32	(32)	8	(20)	.21
ECOG performance status	0	86	(87)	35	(88)	
	1	12	(12)	4	(10)	
	2	1	(1)	1	(3)	.77
Hepatitis B surface antigen	Positive	19	(19)	4	(10)	.28
Hepatitis C virus antibody	Positive	52	(53)	33	(82)	.002
Child-Pugh classification	A	80	(81)	31	(78)	
	B	19	(19)	9	(23)	.83
Ascites	Present	5	(5)	6	(15)	.10
Maximum tumor size (mm)	Mean [95% CI]	42	[30–48]	49	[40–58]	
No. tumors	Single	34	(34)	13	(32)	
	Multiple	65	(66)	26	(65)	.99
Tumor distribution	Bilobar	35	(35)	19	(47)	.55
Antitumor effects						
Response evaluation		Modified RECIST		WHO criteria		
Response rate		73.7%		35%		< .0001
Overall survival						
1 y		89.9%		82		
2 y		75.0%		63		
Median (y)		3.1		2.1		

CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; RECIST = Response Evaluation Criteria in Solid Tumors; WHO = World Health Organization.
* Unless otherwise indicated, values are number (%).

Patients with advanced HCC treated with transcatheter arterial chemoembolization tend to experience severe myelosuppression and hepatotoxicity because most of them have liver cirrhosis, which is usually associated with compromised hepatic function, leukocytopenia, and thrombocytopenia. However, in this study, the hematologic toxicities were very mild because small amounts of epirubicin (median, 45 mg/body) and doxorubicin (median, 40 mg/body) were used as combined anticancer agents. Hepatotoxicity, as indicated by increases in AST and ALT levels, was frequently observed (grade 3–4 increased AST, 35%; grade 3–4 increased ALT, 36%), but these toxicities were transient. There were no treatment-related deaths, and transcatheter arterial chemoembolization was generally tolerated in patients with advanced HCC.

In 2006, when this study was initially planned, we planned to evaluate the tumor response according to our original modified RECIST version 1.0. The concept of our modified RECIST, which evaluate tumor response based on the change in the viable part of the HCC, had been adapted into the study protocol. Unexpectedly, this concept was similar to that of modified RECIST advocated by Lencioni and Llovet in 2010 (20), which are now often used to evaluate tumor response in patients with advanced HCC. Therefore, we evaluated the response rate according to modified RECIST. The response rate in this study was very high (73%), possibly because approximately two-thirds of the transcatheter arterial chemoembolization procedures were performed subsegmentally (37%) or segmentally (30%). In Japan and Korea, transcatheter arterial chemoembolization might be performed more selectively and carefully (21,22).

The median survival time, 1-year survival rate, and 2-year survival rate for all 99 FAS patients were 3.1 years, 89.9%, and 75.0%, and no significant differences were observed between the Japanese and Korean patients. A favorable overall survival was obtained in our study, and the result was superior to the result reported by Llovet et al (12) (2-y survival, 63%). In addition, the 2-year survival rate for all subgroups in this study except for the Child-Pugh B subgroup and the subgroup with ascites seemed to be superior to Llovet's study (**Table 6**). Our results could

Table 6. Subgroup Analysis of Patients Treated with Transcatheter Arterial Chemoembolization

		n	2-y Survival (%)	*P* Value
Host-related variables				
Age (y)	≥ 70	49	72.7	
	< 70	50	76.9	.86
Sex	Male	67	77.6	
	Female	32	69.0	.36
Hepatitis B surface antigen	Positive	19	66.2	
	Negative	80	77.1	.87
Hepatitis C virus antibody	Positive	52	75.5	
	Negative	47	74.5	.14
Ascites	Present	5	40.0	
	Absent	94	77.1	.03
Performance status	0	86	77.8	
	1–2	13	52.7	.18
Child-Pugh classification	B	19	39.1	
	A	80	83.7	< .0001
Country	Korea	24	67.0	
	Japan	75	77.4	.57
Tumor-related variables				
No. tumors	Single	34	87.3	
	Multiple	65	68.7	.007
Maximum tumor size (cm)	> 3.0	64	66.1	
	≤ 3.0	35	90.6	.02
Tumor stage (UICC 6th edition)	III	57	66.7	
	I or II	42	89.6	.0008
AFP (ng/mL)	< 100	62	82.6	
	≥ 100	35	63.7	.14
PIVKA II (mAU/mL)	≥ 100	49	64.6	
	< 100	37	84.5	.12
Treatment-related variables				
Epirubicin		73	76.7	
Doxorubicin		23	65.4	.50

AFP = alpha fetoprotein; PIVKA II = protein induced by vitamin K absence or antagonist-II; UICC = Union Internationale Contre le Cancer (International Union Against Cancer).

be regarded as reference data for the usefulness of Asian transcatheter arterial chemoembolization for HCC, and the results of Asian transcatheter arterial chemoembolization in this study might be used as a reference arm for the development of new therapies for unresectable HCC in the future. Several reasons for the superior survival of our study compared with Llovet's study (12) may be pointed out. The first is the treatment interval between repeated sessions. In our study, treatment was repeated on demand, whereas in Llovet's study treatment was repeated regularly with a scheduled interval (see earlier). The second reason is the transcatheter arterial chemoembolization techniques. Experience with transcatheter arterial chemoembolization is much greater in Japan and Korea than it is in Western countries, and various microcatheter systems and CT angiography systems were used in our study. The third reason is the selection bias of the enrolled patients. No significant differences in patient characteristics were observed between our study and Llovet's study; however, the patients of our study might have had better backgrounds in hepatic function or tumor condition. It has been speculated that host genetic factors and environmental factors may affect the tumor behavior, which may account for the differences between our study and the Llovet et al (12) study.

This study has several limitations. It is a single-arm, non–randomized controlled study, and it is impossible to clarify the difference of results compared with other studies, although no statistically significant differences were observed in patient characteristics. Also, in this cooperative study of two countries, there might be some differences in the details of transcatheter arterial chemoembolization techniques and medical care to the patients. However, these limitations do not have a major influence on the interpretation of our results because this study was carried out as a prospective clinical study.

Drug-eluting beads have been introduced more recently as a new embolic material for transcatheter arterial chemoembolization (23,24). Combination therapy using transcatheter arterial chemoembolization and molecularly targeted agents, such as sorafenib, has also been reported (25,26). The survival benefit of transcatheter arterial chemoembolization for unresectable HCC has been confirmed by the results of several randomized controlled trials (6,11,12) and meta-analyses (14,15), and transcatheter arterial chemoembolization has been recognized as an effective palliative treatment option for advanced HCC. However, the optimal transcatheter arterial chemoembolization procedures, including combination with anticancer agents and embolic material; optimal timing of the transcatheter arterial chemoembolization procedures; proper patient selection for transcatheter arterial chemoembolization; and survival benefit of the combination of molecularly targeted agents with transcatheter arterial chemoembolization have not yet been fully clarified. To improve the survival of patients with advanced HCC treated with transcatheter arterial chemoembolization, these problems should be resolved by prospective trials.

In conclusion, Asian transcatheter arterial chemoembolization, which has been widely used for many years in Asian countries, showed a favorable efficacy for unresectable HCC in patients without curative treatment options, with reasonable survival data and tolerable adverse events. Our data suggest Asian transcatheter arterial chemoembolization can be regarded as one of the standard treatments in this field, and these study results could be useful as reference data for future trials of transcatheter arterial chemoembolization.

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● 特別寄稿 ●

医師主導の多施設共同臨床試験におけるUMINインターネット症例登録センター（UMIN-INDICE）の活用: 日本腫瘍IVR研究グループ（Japan Interventional Radiology in Oncology Study Group: JIVROSG）での評価

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Shared Web-Based Data Center for Multi-Institutional Clinical Trials: Evaluation of UMIN-INDICE (University Hospital Medical Information Network-Internet Data and Information Center for Medical Research) in Clinical Trials of JIVROSG (Japan Interventional Radiology in Oncology Study Group): Miyuki Sone[*1], Yasuaki Arai[*2], Takahiro Kiuchi[*3], Hirono Ishikawa[*3], Noriaki Aoki[*3], Yoshitaka Inaba[*4], Tetsuya Yoshioka[*5], Takeshi Aramaki[*6], Takeshi Kobayashi[*7], Toshiyuki Matsuoka[*8], Hiroshi Anai[*9], Noboru Tanigawa[*10], Keigo Osuga[*11], Yoshito Takeuchi[*2], Takushi Okusaka[*2], Susumu Kanazawa[13], Osamu Matsui[*14] and Keigo Endo[*15] ([*1]*Iwate Medical University*, [*2]*National Cancer Center*, [*3]*The University of Tokyo*, [*4]*Aichi Cancer Center*, [*5]*Narumi Hospital*, [*6]*Shizuoka Cancer Center*, [*7]*Ishikawa Prefectural Central Hospital*, [*8]*Osaka City University*, [*9]*Nara Medical University*, [*10]*Kansai Medical University*, [*11]*Osaka University*, [*12]*Okayama University*, [*13]*Kanazawa University*, [*14]*Gunma University*)

Summary

A patient registration system is mandatory for establishing the scientific credibility of the multi-center clinical trials. The Japan Interventional Radiology in Oncology Study Group (JIVROSG) was organized in 2002 to establish evidence supporting the procedures used in interventional radiology. The Internet Data and Information Center for Medical Research (INDICE), provided by the University Hospital Medical Information Network (UMIN), has been utilized for patient registration in the clinical trials of JIVROSG. In this study, the safety and efficacy of UMIN-INDICE were evaluated. From 2002 to 2010, 18 clinical trials, including one international trial, were conducted. A total of 736 patients were enrolled from 51 institutions. No significant trouble was encountered during this period. A questionnaire survey demonstrated that 90% of participating researchers could use this system without difficulties. UMIN-INDICE may contribute to promoting clinical trials as an infrastructure of multicenter studies. **Key words**: Clinical trials, Internet, Data center, Infrastructure (*Recevied May 31, 2011/Accepted Aug. 3, 2011*)

要旨 前向き研究として行われる臨床試験においては，研究の科学的信頼性を担保するために症例の事前登録が必須である。日本腫瘍IVR研究グループ（Japan Interventional Radiology in Oncology Study Group: JIVROSG）は，画像ガイド下に経皮的治療を行うinterventional radiology（IVR）のがん治療におけるエビデンスを確立することを目的に2002年に発足した多施設共同臨床試験組織であり，開始当初より大学病院医療情報ネットワーク（University hospital Medical Information Net

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work: UMIN）が提供する共同利用型のインターネット・データセンター（Internet Data and Information Center for Medical Research: INDICE）を用いて症例登録を行ってきた。本研究では，UMIN-INDICEの安全性と有用性をJIVROSGにおける運用実績に基づき検証した。2002～2010年の間に行われた27本の臨床試験において，85施設から736症例が登録され，研究遂行に支障を来す運用トラブルやセキュリティに関連するトラブルはみられなかった。また，研究者を対象に行ったアンケート調査では，90%という高い頻度で「UMIN-INDICEを用いた症例登録は容易ないしは比較的容易」との回答であった。UMIN-INDICEは多施設共同臨床試験における症例登録システムとして安全性が高く，かつ研究者にとって有用であり，臨床研究のインフラストラクチャーとしてエビデンス生成に寄与すると考えられた。

はじめに

臨床試験におけるインフラストラクチャーは，多施設共同臨床研究を遂行する上で最も重要な要件の一つである。しかし，研究者主導の場合，データセンターなどのインフラストラクチャー構築は容易ではなく，臨床研究推進の障壁の一つとなっている。

日本腫瘍IVR研究グループ（Japan Interventional Radiology in Oncology Study Group: JIVROSG）は，画像ガイド下に経皮的治療を行うinterventional radiology（IVR）のがん治療におけるエビデンスを確立することを目的として，2002年に発足した[1]。JIVROSGでは活動開始当初より，研究遂行のためには昼夜を問わず症例登録が可能なシステムを用いることが必要と考え，大学病院医療情報ネットワーク（University Hospital Medical Information Network: UMIN）が提供するインターネット・データセンターINDICE（Internet Data and Information Center for Medical Research）を利用してきた。

インターネットを利用した症例登録システムやデータセンターの有用性，利便性は過去にも報告されているが，一つのプロジェクトのために独自に構築したものが多い[2-4]。一方，UMIN-INDICEは共同利用型のデータセンターであり，多数の研究に実績をもつ信頼性の高いシステムを安価に利用することが可能である[5]。本研究の目的は，複数の研究を随時施行する多施設共同研究組織において，共同利用型のインターネット・データセンターを利用することの安全性ならびに有用性を評価することである。

I．対象・方法

1．JIVROSGの概要

JIVROSGは公的競争的研究費を経済的基盤として，研究者主導による臨床試験を行っている多施設共同研究組織である。2011年1月の時点で85施設が参加し，これまでに27試験を実施し，海外施設との共同試験も行った。主要構成メンバーはIVRを専門とする放射線科医であるが，これに若干名の内科，外科，整形外科，産婦人科医なども含まれている。

2．UMIN-INDICEの概要

UMIN-INDICEは研究者主導の臨床試験におけるインフラストラクチャーを提供している。症例登録と割り付け，データ収集，ホームページ・サービス，メーリングシステムからなり，2000年に運用が開始された。症例登録システムは，UMINの基本システムを基に研究プロトコールごとにカスタマイズする形で開発されるため，研究グループがサーバなどのハードやソフトウエアを購入する必要はない。システムはパスワードで保護されたウェブサイト上に構築され，サーバの保守作業の時以外は24時間365日，登録が可能である。IDはUMINの他のコンテンツと共通のものが使用され，パスワードは共通のものに加えて研究グループ固有のものが発行される[6]。ソフトウエアの開発にはおおよそ2～6か月を要し，費用は当該研究依頼者がUMINに支払う形となっている。

UMIN-INDICEのサーバの管理・保守は専門の技術者により無休で運営されており，物理的侵入対策としてセンター入室者の指紋による個人認証，カメラによる入退室監視を施行している。また，ネットワーク侵入対策として，ファイアウォールの二重設置，侵入検知システム，通信の暗号化を行い，さらにデータは毎日バックアップされ遠隔保存も行われている。

3．JIVROSGでの臨床試験運用の実際

研究に参加する担当医は，インターネットを介してJIVROSGの研究者のみがアクセスできる研究者限定ページ[6]にログインし，該当する試験の症例登録ページを選択する（図1）。必要項目を記入すると症例選択規準がシステムにより確認され，登録番号およびランダム化比較試験の割り付けが決定される（図2，3）。割り付け・登録が完了すると研究グループ担当者へ登録番号と施設のみを記載したE-mailが送付される。インターネットを介して行うのは症例登録のみであり，これ以降のデータ収集はcase report form（CRF）をJIVROSGのデータセンターにFAXで送信して行う。症例登録に関する質問やトラブルの相談がある場合には，JIVROSGのUMIN担当医師に連絡し，必要に応じてUMINにも連絡をとり対処する。

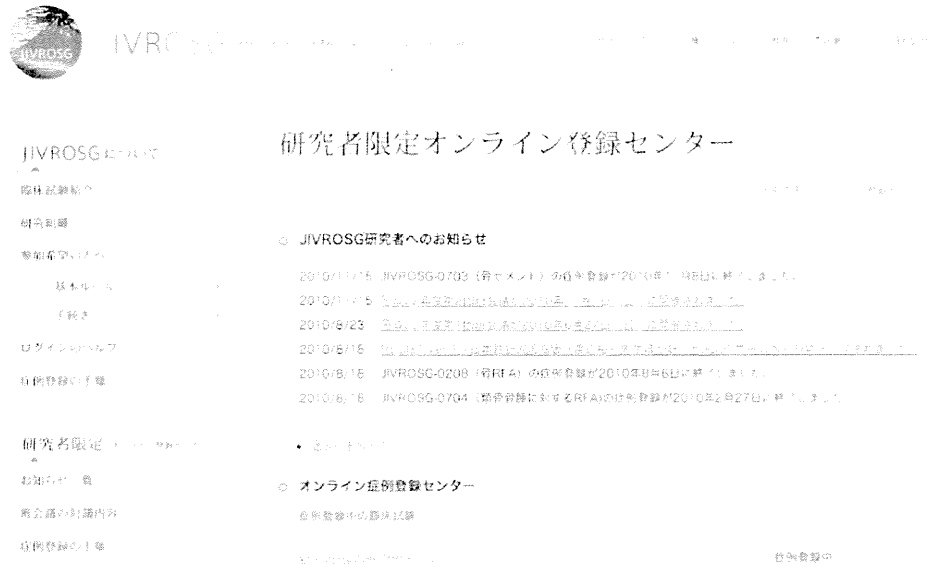

図 1　JIVROSG の研究者限定ページ（http://jivrosg.umin.jp/）

◇適格条件チェックリスト

1	総胆管を主座とする根治術不能悪性胆道閉塞を有す症例	● Yes ○ No
2	チューブによる内外瘻化が完了している症例	● Yes ○ No
3	P.S.（ECOG）：0，1，2	● Yes ○ No
4	血清ビリルビン値 5．0mg/dl 以下	● Yes ○ No
5	主要臓器（骨髄、心、肝、肺、腎など）機能が保持されている症例 1) 白血球数 ＞＝ 3，000 2) 血小板数 ＞＝ 50，000 3) プロトロンビン時間 ＞＝ 50％ 4) 血清 Cr ＜＝ 2．0mg/dl 5) Normal EKG（ただし、臨床的に問題とならない不整脈、虚血性変化は適格）	1) ● Yes ○ No 2) ● Yes ○ No 3) ● Yes ○ No 4) ● Yes ○ No 5) ● Yes ○ No
6	4週間以上の生存が見込める	● Yes ○ No
7	患者本人から文書による同意が得られている	● Yes ○ No

◇除外条件チェックリスト

1	胆管空腸吻合術後再発、肝転移癌、十二指腸癌、癌性腹膜炎、粘液産生腫瘍症例ではない	● Yes ○ No
2	ファーター乳頭部より肛門側の腸管に通過障害がない	● Yes ○ No

図 2　UMIN-INDICE の症例登録画面

4．運用実績の検討

UMIN-INDICE を用いた JIVROSG 臨床試験における登録の症例数と，登録に伴うトラブルの有無および種類について検討した。

5．システムの安全性と安定性の検討

症例登録システムのトラブルや個人情報漏洩の有無について検討した。

6．ユーザの利便性の検討

研究者に対して，システムの利便性および満足度についてのアンケート調査を行った。対象は，JIVROSG 開始当初より参加し，症例登録経験をもつ研究者 41 名である。質問票を郵送し，回答を FAX にて回収した。質問票は，回答者の特徴，JIVROSG における症例登録の経験，利便性（5 段階評価），他の研究への参加経験がある場合はそれとの比較（5 段階評価）で構成した。

Ⅱ．結　果

1．運用実績

2003 年 2 月～2010 年 7 月までに 27 の臨床研究が JIVROSG にて施行され，このうち 18 試験で UMIN-INDICE を用いた症例登録が行われた。UMIN-INDICE を用いなかったのは，後ろ向き研究と別の症例登録シス

登録完了

ベア・ステント（A群）

へ割り付けされました

割り付け結果	
症例登録番号	BS-047
割付番号	A-025
割付群	ベア・ステント (対照群)
カルテ番号	000-0000
生年月日	昭和30年03月03日
登録時点の年齢	55
登録日時	2010/08/15 17:07:52

図 3 UMIN-INDICE の登録・割り付け終了画面（テスト登録用）

表 2 UMIN-INDICE における登録の難易度（n=30）

	人数（%）
登録回数	
1	3 (10)
2～10	21 (70)
11～20	3 (10)
20<	3 (10)
症例登録システムへのログオン	
容易	11 (36)
比較的容易	15 (50)
どちらでもない	2 (7)
比較的困難	2 (7)
困難	0 (0)
症例登録	
容易	13 (43)
比較的容易	14 (47)
どちらでもない	2 (7)
比較的困難	1 (3)
困難	0 (0)

テムが使用された前向き研究である。51 施設（うち海外 9 施設）から総数 736 症例の登録が行われた。

登録に伴うトラブルとして，研究者のパスワード紛失または未取得による事務局での代理登録が 5 回，第 I 相試験での登録一時停止の際の周知不備が 1 回みられた。これらのトラブルは電話または電子メールで 2 日以内に対処され，治療の遅延や症例登録の中止はみられなかった。

2．システムの安全性と安定性

UMIN-INDICE のシステムに起因する登録不能やデータ消失などのトラブルはみられなかった。ランダム化比較試験において，センターでのランダム化に関連するトラブルはみられなかった。また，個人情報漏洩が危惧されるトラブルはみられなかった。

表 1 アンケート回答者の背景（n=30）

特徴	人数（%）
性別	
男性	28 (93)
女性	2 (7)
年齢（歳）	
20～29	0 (0)
30～39	14 (47)
40～49	13 (43)
50～59	3 (10)
パソコン使用年数	
<1	0 (0)
−5	2 (7)
−10	5 (16)
10<	23 (77)
インターネット使用年数	
<1	0 (0)
−5	4 (13)
−10	14 (47)
10<	12 (40)

表 3 UMIN-INDICE の利便性についての満足度（n=30）

満足度	人数（%）
満足	15 (50)
やや満足	12 (40)
どちらでもない	3 (10)
やや不満足	0 (0)
不満足	0 (0)

3．ユーザの利便性に関するアンケート結果

該当する 41 名のうち，30 名（73%）から回答が得られた。93%が男性であり，30 歳台，40 歳台が 90%を占めた。パソコン使用歴は 10 年以上が 93%，インターネット使用歴は 10 年以上が 87%であった（表 1）。

登録サイトへのログオンについては，「容易」または「比較的容易」の回答が 86%，症例登録については，「容易」または「比較的容易」の回答が 90%であった（表 2）。UMIN-INDICE の利便性については，「満足」ないし「やや満足」が 90%であった（表 3）。他の共同研究に参加経験のある 17 名によると，他の研究での症例登録方法で最も多いのは FAX（82%）であった。17 名中 15 名（88%）が，「他の方法よりも UMIN-INDICE のほうがよい」と回答した。

Ⅲ．考　察

エビデンスを創るために前向き研究として行われる臨床試験において，症例の事前登録は研究の科学的信頼性を担保するために必須である[5-7]。複数の試験を行う多施設共同研究グループにおいては，グループ内に設置した

データセンターの業務の一つとして患者登録システムを運営することが多く，かつてはFAXや電話がその手段であった。近年，インターネットの普及に伴い，インターネットを用いた症例登録が増加している[2-4]。症例登録にインターネットを用いることの利点として，症例適格性のチェックと症例番号の発行が即時完了できること，24時間いつでも症例登録が行えることがあげられる。特に時間帯の制限がないことは，多忙な日常診療と並行して行われる臨床研究において大きな利点である。われわれの検討では，700例を超える症例すべてで症例登録が問題なく完遂されており，UMIN-INDICEの実行可能性ならびに有効性は極めて高いと考えられた。

研究者主導でインターネットを用いた研究基盤を構築するには，自前のサーバを立ち上げてデータセンターを構築する方法と，企業に依頼して構築する方法，公的データセンターを利用する方法がある。自前のシステム構築には，ソフトウエアの開発とシステム維持に手間やコストがかかり，研究資金や人的資源が限定される研究者主導のグループでは実現困難なことが多い。企業に依頼する場合は，研究グループの手間は節減されるが，ソフトウエアの開発に要する時間は大幅に減少するとは限らず，また，一般に開発および維持のコストは高額であり，研究資金が恒常的に確保されないと使用は難しい。国内には国営の公的データセンターは存在しないが，UMIN-INDICEはこれに近い位置付けであり，データセンター用の情報システムおよびその運用管理を種々の研究グループが共同利用する形態をとっている[5]。この結果，研究グループが自前でサーバを用意する必要はなく，運用コストは大幅に削減される。UMIN-INDICEは2000～2010年に159のプロジェクトで利用され，登録された症例の合計は107万例を超えており[8]，このような運用管理の集中化が結果として信頼性とセキュリティならびにユーザの利便性の向上につながっている[5]。われわれの経験においても，UMIN-INDICEの利便性と信頼性が再確認された。一方，UMIN-INDICEは，データセンター機能のすべてを提供しているわけではない。データセンターに必要な人材のうち情報処理専門家，システムエンジニア，プログラマー，オペレーターを擁しているが，研究計画の作成やデータの品質管理にかかわる生物統計学者やデータマネージャーは含まれていない。このため，生物統計学者およびデータマネージャーは，研究グループごとに依頼する必要がある。

UMIN-INDICEの利便性については，われわれの検討においては高いと考えられた。理由として，同じシステムを用いることにより操作法の習得が1回で済むことと，パスワードが共通で管理が容易であることがあげられる。したがって，複数の臨床試験を行うJIVROSGのような研究グループにおいては，特に有用性が高いと考えられる。ユーザの利便性を考えるに当たっては，インターネット環境が近年急速に整備されたことも重要な要素である。マイナーなトラブルとしてパスワードの紛失があったが，研究グループ内での連絡先および対処法を明確にしておくことで迅速に対応でき，登録不能のトラブルはみられなかった。

本研究の限界として，他の症例登録法との直接比較を行っていない点があげられる。しかし，JIVROSGでは他の多施設共同研究への参加経験がない研究者が多数を占めており，そのような初心者にとっても使用しやすいシステムであることが示された点は意味があると考えられる。

結論として，複数の臨床研究を行う多施設共同研究組織であるJIVROSGにおいて，共同利用型のUMIN-INDICEは症例登録システムとして有用かつ安全性が高く，臨床研究のインフラストラクチャーとしてエビデンス生成に寄与すると考えられた。

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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

Event	Grade				Total	3/4
	1	2	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.

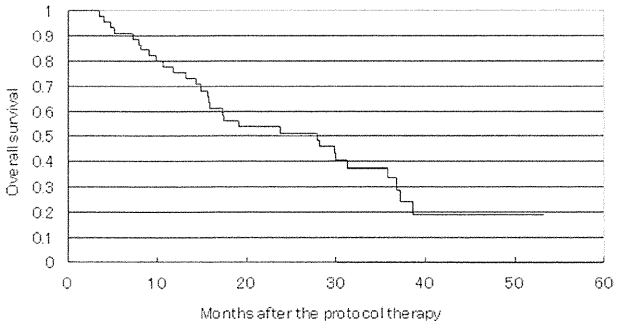

Figure. Kaplan–Meier curve shows the overall survival after protocol therapy. The 1- and 2-year survival rates were 75.3% and 51.3%, respectively. The median survival time was 27.8 months.

(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.