circumstances, having the patient change the position of his or her arm or head or having him or her perform deep breathing may correct the problem, and an FCS can thus prevent redundant interventions. These findings indicate that not all patients who are suspected of having a malfunctioning CVP develop CVP system-related mechanical complications, and only half of the patients in whom an FCS produces abnormal findings require system reimplantation.

In this study, 34.8% of the patients did not have abnormal FCS findings. We suspect that non-CVP system-related malfunction including infusion pump dysfunction or human error may have caused the complaints [8,13]. Moreover, these patients may have experienced venous thrombotic complications, since such complications can occur around the catheter and are independent of CVP functioning, resulting in normal FCS findings [15,18]. In cases of arm swelling, both venography and FCS may be required to fully evaluate the existence and extent of venous occlusion, because FCS provides information only regarding the catheter tip and the downstream vein.

On the other hand, 45 (68.2%) of all the patients in whom no abnormal FCS findings were observed or in whom reimplantation of the CVP system was deemed unnecessary despite the presence of abnormal FCS findings were able to continue using the CVP without any system malfunctions during the follow-up period. These findings indicate that FCS is reliable in predicting CVP functionality.

The current study had some limitations. First, the study design was retrospective in nature, and the study had a small sample size. Furthermore, 9 of 66 patients were lost to follow up, which may have affected the results of this study. Second, the CVPs were mainly implanted via a left subclavian vein. Subclavian vein access has been used as a secondary option using US guidance by interventional radiologists, and left-sided access may increase the incidence of significant secondary shifts in the catheter course [19]. These unusual accesses for the central vein may have affected the rate of post-interventional CVP system-related complications.

Interventional radiologists have the great advantage of expertise with imaging and catheterization technology. Oncologic patients who receive chemotherapy using CVP should benefit from the skills of these experts not only for CVP implantation, but for the diagnosis and management of post-procedural CVP system-related complications.

In conclusion, FCS was effective for evaluating post-procedural CVP system-related mechanical complications and for distinguishing non-CVP system-related complications in oncologic outpatients undergoing chemotherapy. Moreover, FCS was useful for deciding whether CVP system explantation and reimplantation was required. FCS should be performed by interventional radiologists in an angiographic suite for all patients who are suspected of having a CVP system-related mechanical complication.

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ORIGINAL ARTICLE

A multi-institutional phase II trial of hepatic arterial infusion chemotherapy with cisplatin for advanced hepatocellular carcinoma with portal vein tumor thrombosis

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Abstract
Purpose The objective of this study was to evaluate the response rate, survival, and adverse effects of hepatic arterial infusion chemotherapy (HAIC) using cisplatin in patients with advanced hepatocellular carcinoma (HCC) and portal vein tumor thrombosis (PVTT).
Methods Twenty-five patients of advanced HCC with PVTT in the main or first branch, having no prior history of chemotherapy, measurable lesions, adequate liver and renal function, and adequate bone marrow reserve, were enrolled. Cisplatin was administered at the dose of 65 mg/m^2 via the proper hepatic artery. Treatment was repeated every 4–6 weeks for a maximum of six courses until the appearance of evidence of tumor progression or unacceptable toxicity.
Results The median number of treatments was 3 (range 1–6). Among the 25 enrolled patients, complete response was achieved in 1 (4 %) patient and partial response in 6 (24 %), corresponding to a response rate of 28 % (95 % CI 12–49 %). The median progression-free and overall survival times and the 1-, 2-, and 3-year survival rates in the enrolled patients were 3.6 and 7.6 months and 40.3, 36.0, 20 %, respectively. Four of the seven patients who showed complete or partial response survived for more than 3 years. The main grade 3/4 non-hematological adverse events of this treatment were elevation of the serum aspartate aminotransferase (44 %) and alanine aminotransferase (24 %).
Conclusion HAIC with cisplatin exerts moderate activity with mild toxicity in advanced HCC patients with PVTT. Especially, markedly prolonged survival can be expected in patients who respond to this treatment.

Keywords Hepatocellular carcinoma · Hepatic arterial infusion chemotherapy · Tumor thrombosis · Cisplatin · Clinical trial

Abbreviations

HCC	Hepatocellular carcinoma
PVTT	Portal vein tumor thrombosis
HAIC	Hepatic arterial infusion chemotherapy
AFP	Alpha-fetoprotein
PIVKA II	Protein induced by vitamin K absence or antagonist-II
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase

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Introduction

For advanced hepatocellular carcinoma (HCC) patients with portal vein tumor thrombosis (PVTT), chemotherapy remains one of the most important treatment modalities [1–4]. Sorafenib, an oral multikinase inhibitor targeting Raf kinase and receptor tyrosine kinases, has been acknowledged as the standard agent for advanced HCC [5, 6]. However, it has yielded rather unsatisfactory results in terms of the response and survival in patients with advanced HCC [7, 8]. Hepatic arterial infusion chemotherapy (HAIC), which can increase the local concentration of anticancer drugs with reduced systemic distribution, may be expected to exert better antitumor efficacy and lesser toxicity [9, 10]. Although promising results of HAIC have been reported for advanced HCC with PVTT [11–20], no chemotherapeutic agent or regimen has yet been shown to confer a survival benefit sufficient for adoption as standard therapy.

Cisplatin, which is a heavy metal (platinum) ion complex compound that exerts cytotoxicity by binding to double-stranded DNA, is widely used as one of the chemotherapeutic agents in transcatheter arterial embolization [21–23]. Cisplatin in the form of a fine powder suitable for hepatic artery infusion (IA-call®, Nippon Kayaku Co., Ltd.) has been developed in Japan. Since the solubility of this agent is 2.86 times higher than that of standard cisplatin, the injection time can be shortened. In a phase II trial, administration of this agent by intra-arterial injection over 20–40 min at the dose of 65 mg/m^2 in repeated doses at 4- to 6-week intervals was shown to yield favorable results (response rate 33.8 %) [24]. However, the efficacy of this regimen for advanced HCC with PVTT has not yet been fully evaluated. Therefore, we conducted a multicenter phase II trial to evaluate the efficacy and safety of HAIC with cisplatin in HCC patients with PVTT in the main and/or first branch.

Patients and methods

Eligibility

Patients eligible for study entry had advanced HCC with PVTT. The eligibility criteria were as follows: HCC confirmed by histological examination or liver tumor with a radiological hallmark of HCC and elevation of the serum α-fetoprotein (AFP) levels to ≥400 ng/mL; tumor thrombosis in the main and/or first portal vein; unsuitable candidate for surgical resection; age 20 years or over; Eastern Cooperative Oncology Group performance status of 0–2; measurable disease; interval of 4 weeks or over between the last treatment and the present therapy, and no influence of previous treatments; adequate hematological function (hemoglobin ≥9.0 g/dL, leukocytes ≥3,000/mm^3, and platelets ≥50,000/mm^3), adequate hepatic function [Child-Pugh classification of A or B, serum total bilirubin ≤2.0 mg/dL, and serum aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ≤150 U/L], adequate renal function (serum creatinine ≤1.1 mg/dL); availability of written informed consent.

The exclusion criteria were as follows: prior chemotherapy with cisplatin for HCC, prior radiotherapy, transcatheter arterial chemoembolization or intra-arterial chemotherapy for PVTT, refractory pleural effusion or ascites, no distant metastases, allergic reaction to iodine contrast medium, severe renal, heart or mental disease, active infection, excluding hepatitis B or C viral infection, active concomitant malignancy, pregnant and lactating females; females of childbearing age unless using effective contraception.

The pretreatment evaluation consisted of a complete history and physical examination and baseline assessments of organ function. In addition, dynamic computed tomography of the abdomen and chest radiography were performed for pretreatment staging to assess the local extent of the tumor and exclude the presence of distant metastasis. The number of tumors and tumor distribution were examined by computed tomography and/or angiography. This phase II study was conducted with the approval of each institutional review board and conducted in accordance with the Declaration of Helsinki.

Treatment procedure

Following conventional visceral angiography, HAIC was performed by introducing a angiographic catheter into the proper, right or left hepatic artery, or another feeding artery, and injection of cisplatin at the dose of 65 mg/m^2 over 20–40 min by Seldinger's technique, not using implanted port system for hepatic arterial infusion chemotherapy. Until the appearance of evidence of tumor progression and/or unacceptable toxicity, the treatment was repeated every 4–6 weeks for a maximum of six cycles. Neither lipiodol nor gelatin sponge was allowed in the protocol treatments. Antiemetic prophylaxis with a 5-HT3 antagonist (granisetron 1 mg) plus dexamethasone 8 mg was used at the attending physician's discretion. Patients received adequate hydration and/or diuretics for protection against cisplatin-induced renal dysfunction, and the urine output was carefully monitored, especially during the first 3 days after intra-arterial administration of cisplatin. The cisplatin dose was reduced in case of grade 4 hematological adverse events or serious events had developed during the previous cycle. Patients who were refractory to this treatment regimen were allowed to

receive other anticancer treatments at the attending physician's discretion.

Response and toxicity assessment

The antitumor effect was assessed by intravenous contrast enhanced computed tomography or magnetic resonance imaging every 4–6 weeks. Responses were evaluated according to the WHO criteria [25]. The best overall response was recorded for each patient. The duration of response was defined as the interval from the onset of partial response until the first evidence of disease progression or death. Basic laboratory tests, including a complete blood count with differential leukocyte count, and serum chemistry were performed at least once every 2 weeks during this treatment. The treatment-related adverse events were assessed using the Common Terminology Criteria for Adverse Events, v2.0. Serum levels of AFP and protein induced by vitamin K absence or antagonist-II (PIVKA II) were measured every 4–6 weeks. In patients with a pretreatment AFP level of $\geq$100 ng/mL and of PIVKAII of $\geq$100 mAU/mL, the AFP and PIVKAII responses were assessed; a positive response was defined as a >50 % reduction from the pretreatment level. Progression-free survival was defined as the time from the date of initial treatment to the first documentation of progression or death. Overall survival was measured from the date of initial treatment to the date of death or the date of the last follow-up. The progression-free survival and overall survival curves were calculated by the Kaplan–Meier method.

Statistical considerations

The primary endpoint of this trial was the response rate, and the secondary endpoints were adverse events, progression-free survival, and overall survival. The number of patients enrolled was planned using a two-step design [26] based on an expected response rate of 30 %, a response rate corresponding to no activity of 10 %, α error of 10 %, and β error of 10 %. An interim analysis was planned after 15 patients had been enrolled. If zero or one of the first 15 patients showed a partial response or complete response, the study was to be ended. If a response was detected in more than one of the first 15 patients studied, an additional 10 patients were to be enrolled in a second stage of accrual for more precise estimation of the actual response rate. If a response was detected in more than five of the 25 patients studied, this treatment was considered to be effective. This population was defined as including any patients who received at least one course of study medication. The trial was registered at UMIN-CTR (http://www.umin.ac.jp/ctr/index-j.htm), identification number (UMIN000000488).

Results

Patient characteristics

Twenty-five patients were enrolled in this trial between January 2005 and April 2007 at 3 institutions in Japan, because four patients showed partial response among the first 15 patients in the interim analysis. The characteristics of all the 25 patients are shown in Table 1. There were 20 males and five females, with a median age of 67 (range 47–79) years. Hepatitis B surface antigen and hepatitis C virus antibody were positive in 4 patients (16 %) and 15 patients (60 %), respectively. There were 17 (68 %) patients and 8 (32 %) patients with Child-Pugh class A and B, respectively. Portal vein invasion was noted in the main vein and the first branch in 19 patients (76 %) and 6 (24 %) patients, respectively.

A total of 83 courses were given, with a median of three courses (range 1–6) per patient. The median dose of cisplatin per treatment was 100 mg (range 85–130 mg). The reasons for treatment discontinuation were completion of treatment (6 courses) in 5 patients (20 %), disease progression in 16 patients (64 %), rupture of esophageal varices in 1 patient (4 %), hepatic failure in 1 patient (4 %), and accidental perforation of the colon in 1 patient (4 %). As subsequent treatments, 15 patients did not receive any treatments and the remaining 10 patients received further treatment: HAIC with epirubicin (4 patients), HAIC with interferon plus 5-fluorouracil (5-FU) (1 patient), HAIC with cisplatin (2 patients who had shown disease progression after the termination of 6 cycles of HAIC with cisplatin), and transcatheter arterial chemoembolization with epirubicin (2 patients).

Treatment efficacy

Of the 25 patients, 24 were evaluable for response; the remaining one patient (4 %) could not be evaluated because of early discontinuation of this protocol treatment. One patient (4 %) showed complete response, and 6 (24 %) showed partial response, corresponding to an overall response rate of 28 % (95 % CI 12–49 %); the mean duration of the response was 7.9 months (range 1.4–19.5 months). Eleven patients (44 %) showed stable disease and 5 patients (20 %) showed progressive disease. During the treatment, the serum AFP level decreased by more than 50 % in 7 (44 %) of the 16 patients with a pretreatment level of $\geq$100 U/mL, and the serum PIVKA II level decreased by more than 50 % in 15 (68 %) of the 22 patients with a pretreatment level of $\geq$100 mAU/mL.

At the time of the analysis, 21 patients developed tumor progression; among the remaining 4 patients, the tumor progression status could not be confirmed in 3 patients (on

Table 1 Patient characteristics ($n = 25$)

Characteristics	Number of patients	%
Age (years)		
Median	67	
Range	47–79	
Sex		
Male	20	80
Female	5	20
Eastern Cooperative Oncology Group performance status		
0	21	84
1	4	16
Hepatitis B surface antigen		
Positive	4	16
Hepatitis C antibody		
Positive	15	60
Child-Pugh classification		
A	17	68
B	8	32
Prior treatments		
Present	13	52
Resection	4	16
Local ablation	5	20
TACE	10	40
Portal vein invasion		
Main	19	76
First branch	6	24
Tumor distribution		
Unilateral	8	32
Bilateral	17	68
Ascites		
Present	6	24
Alpha-fetoprotein (ng/mL)		
Median	1,075	
Range	11.3–386,300	
PIVKAII (mAU/mL)		
Median	1,600	
Range	18–423,350	

TACE transcatheter arterial chemoembolization, *PIVKAII* protein induced by vitamin K absence or antagonist-II

account of death due to hepatic failure (1 patient), variceal rupture (1 patient), or accidental perforation of the colon (1 patient)), and one patient remains alive without tumor progression. The median progression-free survival was 3.6 months. All patients were included in the survival assessment. Of the 25 patients, 21 died. The causes of death were tumor progression (18 patients), hepatic failure (1 patient), rupture of esophageal varices (1 patient), and accidental perforation of the colon (1 patient). The median survival time and 1-, 2-, and 3-year survival rates of the patients were 7.1 months and 36, 20, and 20 %, respectively (Fig. 1). The median survival time was 45.4 months in the patients who showed complete or partial response, and four of these patients survived for more than 3 years; on the other hand, the median survival time in the patients who showed stable or progressive disease was 5.8 months.

Adverse events

The adverse events occurring in the patients enrolled in this study are summarized in Table 2. The adverse events represent the maximum grade occurring in the patients during the entire course of therapy. Grade 3–4 leukocytopenia, neutropenia, and thrombocytopenia occurred in 5 (20 %), 2 (8 %), and 4 (16 %) of the patients, respectively; however, they were all transient and recovered fully without treatment. The major non-hematological adverse events were elevations of the serum AST and ALT levels. Grade 3–4 AST and ALT elevations were observed in 11 (44 %) and 6 (24 %) of the patients, respectively. However, the levels returned to the initial levels within one month without any additional treatment. No cumulative adverse events were seen in this patient series. One patient developed perforation of the colon on day 37 after the commencement of the first cycle; however, this was judged as an accidental event not causally related to the treatment. There were no other serious non-hematological adverse events.

Discussion

HAIC is widely undertaken in Japan for patients with advanced HCC who are not suitable candidates for

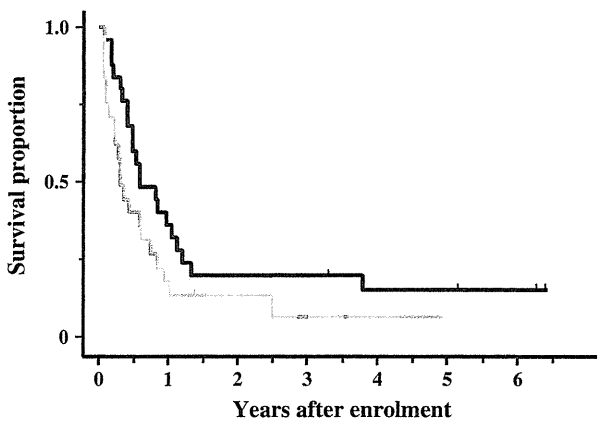

Fig. 1 Overall survival (*black line*) and progression-free survival (*gray line*) curves of the 25 patients of advanced hepatocellular carcinoma with tumor thrombosis in the main and/or first branch of the portal vein treated by hepatic arterial infusion chemotherapy using cisplatin. *Tick marks* indicate censored cases

Table 2 Adverse events

	Grade				
	1	2	3	4	3–4 (%)
Hemoglobin	6	7	0	0	0
Leukocytes	7	9	5	0	20
Neutrophils	6	7	2	0	8
Platelets	6	6	4	0	16
Nausea	10	5	0	0	0
Vomiting	9	1	0	0	0
Anorexia	13	6	0	0	0
Fatigue	8	3	0	0	0
Fever	3	0	0	0	0
Diarrhea	0	0	0	0	0
Abdominal pain	2	0	0	0	0
Weight loss	2	1	0	0	0
Total bilirubin	10	5	0	0	0
Hypoalbuminemia	6	7	0	0	0
AST	1	3	10	1	44
ALT	3	5	5	1	24
Alkaline phosphatase	3	0	0	0	0
Creatinine	3	2	0	0	0

AST, aspartate aminotransferase; ALT, alanine aminotransferase

resection, local ablative therapies, or transcatheter arterial chemoembolization, such as those with complicating PVTT [3, 4]. HAIC is usually administered using one of the following three well-reported regimens: cisplatin alone [11, 24], 5-FU plus cisplatin [12–15], and 5-FU plus interferon [16–20]. The efficacies of these regimens for HCC patients with PVTT are shown in Table 3 [11–20]. The reported response rates and disease control rates are approximately 20–40 % and 50–80 %, respectively, and the reported median survival is in the range of 7–12 months. However, optimum regimen for patients of advanced HCC with PVTT still remains controversial. Recently, a randomized phase II trial comparing 5-FU and interferon with best salvage therapy (BST), such as 5-FU plus cisplatin or cisplatin alone, has been reported [27]. Although the response rate was quite similar in both groups, the patients treated with 5-FU and interferon seemed to show inferior disease control and overall survival rates as compared to those treated by BST. Thus, the optimal regimen for HAIC has not yet been clarified. Transarterial radioembolization with yttrium-90 microspheres is one of the good options for HCC with PVTT, and the treatment efficacy has been reported to be favorable (Table 3) [28, 29]. However, this treatment has not been established as standard therapy, because the survival benefit has not been clarified by randomized trials.

In this study, cisplatin was selected as the trial chemotherapeutic agent for HAIC, because it is widely used in Japan, it can be administered by short infusion, and it requires no indwelling reservoir system for hepatic arterial infusion, unlike 5-FU plus cisplatin or 5-FU plus interferon. The response and disease control rates to HAIC with cisplatin in this study were 28 and 76 %, respectively, and the median overall survival time was 7.1 months. These results are comparable to previous reports (Table 3). Besides, in the patients who achieved complete or partial response, the median survival time was 45.4 months and four of them survived for more than 3 years. In previous reports also, the prognoses in the responders to HAIC were extremely favorable [11–13, 15–17, 19]. Thus, HAIC sometimes causes favorable tumor shrinkage, and a markedly prolonged survival time can be expected in such patients. If the tumor response to HAIC can be predicted prior to the start of the treatment, more appropriate selection of suitable candidates for HAIC may be possible. Therefore, identification of reliable markers to predict a favorable response to HAIC is warranted.

In comparison with systemic administration of anticancer agents, HAIC allows high local concentrations of anticancer drugs to be achieved, with reduced systemic distribution, thereby increasing the activity of the anticancer drug and reducing the likelihood of systemic adverse effects. With regard to the toxicity, the toxicity of HAIC with cisplatin was very mild. The main grade 3–4 adverse events were leukocytopenia (27 %), neutropenia (47 %), increased AST (40 %), and increased ALT (20 %). These adverse events were transient and reversed without any specific treatments. Furthermore, no cumulative or serious adverse events were seen in this study. Therefore, this treatment was considered to be well tolerated and even patients with Child-Pugh B could be included as candidates for this treatment.

HAIC is considered as one of the valid treatment options for advanced HCC, because it has been shown to exert a favorable effect with mild toxicities in advanced HCC patients with PVTT. However, it has not been acknowledged as a standard therapy for advanced HCC, because no chemotherapeutic agent or regimen has yet been shown to confer a survival benefit sufficient for adoption as a standard therapy [1–4]. On the other hand, sorafenib has been acknowledged as a standard agent for the treatment of patients with advanced HCC, including HCC with vascular invasion and extrahepatic metastases, because two pivotal phase III trials comparing sorafenib versus placebo have shown the survival benefit afforded by sorafenib [7, 8]. Sorafenib has a limited tumor shrinkage effect, but is capable of prolonging the time-to-progression and the overall survival. In the comparison of the efficacy between HAIC with cisplatin and sorafenib (Table 3), the efficacy of cisplatin seemed to be equivalent to that of sorafenib [7, 30]; therefore, cisplatin may be one of the promising

Table 3 Treatment efficacy of hepatic arterial infusion chemotherapy for hepatocellular carcinoma with portal vein tumor thrombosis

Regimen	*n*	RR (%)	DCR (%)	Median TTP/PFS (months)	Median OS (months)	1-year OS (%)	2-year OS (%)	3-year OS (%)	Median OS for responder (months)	References
Yttrium 90 (Child-Pugh A)	35	50	NA	5.6	10.4	NA	NA	NA	NA	Salem et al. [28]
Yttrium 90 (Child-Pugh B)	57	28	NA	5.9	5.6	NA	NA	NA	NA	Salem et al. [28]
Yttrium 90	76	NA	NA	NA	10.0	NA	NA	NA	NA	Sangro et al. [29]
Sorafenib[a]	108	NA	38.9	4.1	8.1	NA	NA	NA	NA	Bruix et al. [7]
Sorafenib[a]	44	NA	24	NA	4.4	NA	NA	NA	NA	Kang et al. [30]
5-FU/Cisplatin	48	48	77	NA	10.2	45.0	31.0	25.0	31.6	Ando et al. [12]
5-FU/Cisplatin	38	8	66	NA	6.0	21.0	NA	NA	NA	Cheong et al. [14]
5-FU/Cisplatin	18	33	72	NA	NA	28.0	NA	NA	15.0	Lai et al. [13]
5-FU/Cisplatin	52	39	65	4.1	15.9	53.3	34.8	26.1	40.7	Ueshima et al. [15]
5-FU/IFNα	55	44	51	5.2	11.8	48.9	28.6	16.4	24.4	Ota et al. [16]
5-FU/IFNα	116	52	54	NA	NA	34.0	18.0	NA	59 % (2 years)	Obi et al. [17]
5-FU/IFNα	31	29	55	5.8	7.5	29.0	5.6	NA	NA	Uka et al. [18]
5-FU/IFNα	102	39	47	2.0	9.0	36.8	21.2	10.8	25.0	Nagano et al. [19]
5-FU/IFNα	57	25	58	3.3	10.5	NA	NA	NA	NA	Yamashita et al. [20]
Cisplatin	24	21	25	NA	7.0	38.0	16.0	NA	37.3	Kondo et al. [11]
Current study (Cisplatin)	25	27	72	3.6	7.1	36	20	20	45.4	Ikeda

RR response rate, *DCR* disease control rate, *TTP* time to progression, *PFS* progression-free survival, *OS* overall survival, *5FU* 5-fluorouracil, *IFN* interferon, *NA* not available

[a] The study included the patients with macrovascular invasion

regimens for advanced HCC with PVTT. In addition, sorafenib and cisplatin have different toxicity profiles, except for causing liver dysfunction. Sorafenib and cisplatin have been reported to exert a synergistic effect against liver cancer in preclinical research [31, 32], and some clinical trials of combined regimens of sorafenib and cisplatin have been performed in patients with gastric cancer [33], nasopharyngeal carcinoma [34], and lung cancer [35]. Therefore, combined use of the two drugs may yield superior results. Furthermore, a randomized controlled trial comparing sorafenib plus HAIC with sorafenib could clarify the additional effect of HAIC and establish HAIC as a standard treatment for advanced HCC. Therefore, a phase I trial of sorafenib plus HAIC with cisplatin has already been conducted, and a randomized phase II trial of sorafenib plus HAIC with cisplatin versus sorafenib alone (UMIN000005703) is ongoing.

This study involved some limitations. First, the number of enrolled patients was not so high, and the results should be interpreted with some caution. Secondly, 10 patients received chemoembolization as prior therapy. This might lead to resistance to HAIC with cisplatin. Finally, as this was a single-arm phase II trial, the survival benefit of HAIC with cisplatin could not be clarified. All of these limitations argue for the conduct of a randomized trial to further compare this treatment with standard therapy in advanced HCC patients with PVTT.

In conclusion, HAIC with cisplatin exerts moderate activity with mild toxicity in HCC patients with PVTT. Especially, markedly prolonged survival can be expected in patients who respond to this treatment. At present, a randomized controlled trial of HAIC using a combination of cisplatin and sorafenib is under way.

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Conflict of interest None.

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CLINICAL STUDY

Phase II Study of Percutaneous Transesophageal Gastrotubing for Patients with Malignant Gastrointestinal Obstruction; JIVROSG-0205

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ABSTRACT

Purpose: This multicenter, prospective study was conducted to evaluate the efficacy of percutaneous transesophageal gastrotubing (PTEG) as an esophagostomy procedure for bowel decompression in patients with malignant bowel obstruction.

Materials and Methods: The study subjects were patients with malignant bowel obstruction treated with a nasogastric tube (NGT). After receiving PTEG, efficacy evaluations were conducted, with NGT designated as the control state. The procedure was considered effective only when discomfort in the nasopharynx was improved for at least 2 weeks. Safety was evaluated by using National Cancer Institute Common Toxicity Criteria, version 2.0. PTEG was performed by using a PTEG kit.

Results: From February 2003 to December 2005, 33 patients were enrolled. The technical success rate was 100%, and the procedure was considered effective in 30 of 33 cases. The three cases in which the procedure was ineffective could not be evaluated as a result of deterioration of general status or early death. The one recorded complication was a tracheoesophageal fistula that caused grade 2 aspiration pneumonia.

Conclusions: PTEG is an effective technique to relieve discomfort in the nasopharynx caused by NGT in patients with terminal malignant tumors. PTEG should be considered an efficacious method for bowel decompression in patients who are ineligible for surgical procedures, percutaneous gastrostomy, or percutaneous enterostomy.

ABBREVIATIONS

NGT = nasogastric tube, QOL = quality of life, PTEG = percutaneous transesophageal gastrotubing, RFB = rupture-free balloon

Gastrointestinal obstruction caused by constriction of the upper gastrointestinal tract by malignant tumor or carcinomatous peritonitis is a common symptom in terminal cancer, reportedly occurring in 5%–42% of patients. Vomiting caused by a malignant gastrointestinal tract obstruction is typically treated with a nasogastric tube (NGT) or small-bowel intubation. However, this condition has a bad prognosis, and transnasal decompression can add to the patient's distress and reduce quality of life (QOL) (1).

Gastric bypass or colostomy procedures may be performed as surgical treatment; however, these procedures are not possible for all patients because of the invasiveness of laparotomy or the general condition or prognosis of the patient (1,2). Pharmacotherapy may be given as supportive care, and a somatostatin analogue (ie, octreotide) has recently been often reported as useful (1–3). Unfortunately, because the half-life of octreotide is only 1.5 hours, continuous subcutaneous injection is needed.

As another method, percutaneous gastrostomy or percutaneous enterostomy can be performed for decompression (1,2,4,5), and metallic stents are sometimes inserted as a substitute for a gastric bypass or colostomy procedure (1,2). However, patients may sometimes show accumulation of ascitic fluid, carcinomatous peritonitis, or other pathologic conditions following gastrectomy

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that may lead to peritonitis as a result of leakage from the puncture site or tumor infiltration from the puncture route.

The current reality is that, for patients with a gastrointestinal constriction caused by a malignant tumor, no standard treatment exists that does not severely reduce QOL. The establishment of minimally invasive treatment methods for such patients to achieve bowel decompression without reducing QOL is therefore an essential challenge in palliative medicine for patients with cancer.

In 1994, Oishi et al (6) developed a method called percutaneous transesophageal gastrotubing (PTEG) that involves percutaneous insertion of a tube through the cervical esophagus so the patient feels little discomfort after tube placement. PTEG is receiving attention as a promising treatment for patients with malignant bowel obstruction accompanying constriction of the upper gastrointestinal tract or for patients with carcinomatous peritonitis caused by a malignant tumor with a poor prognosis (6). To our knowledge, no prospective clinical studies have been performed on PTEG to date, and clinical assessments have yet to be established. The present multicenter, prospective study was therefore conducted to evaluate the safety and clinical efficacy of PTEG for patients with terminal cancer with malignant bowel obstruction, such as constriction of the upper gastrointestinal tract or carcinomatous peritonitis caused by a malignant tumor.

MATERIALS AND METHODS

Study Design and Endpoints

The study design used was a nonrandomized, multicenter, phase II trial. This study was approved by the Japanese Society of Interventional Radiology and the ethics committees of each of the participating institutions, and was registered at the University Hospital Medical Information Network Clinical Trials Registry (study ID C000000249). The primary endpoint was clinical efficacy, and the secondary endpoints were the frequency of adverse events and the feasibility of the procedure.

Patient Eligibility

Inclusion criteria consisted of the following: (i) placement of an NGT or ileus tube as a result of malignant bowel obstruction, such as constriction of the upper gastrointestinal tract or carcinomatous peritonitis, with no improvement of symptoms expected; (ii) no obvious pathologic conditions in or around the cervical esophagus; (iii) adequate bone marrow, liver, renal, and cardiac function (ie, platelet count $\geq$ 50,000/mm^3, prothrombin time $\geq$ 50%, total serum bilirubin level $\leq$ 3.0 mg/dL, serum creatinine level $\leq$ 2.0 mg/dL, no obvious heart failure); (iv) Eastern Cooperative Oncology Group performance status of 0–3; (v) expected survival of more than 4 weeks; and (vi) written informed consent from the patient.

Exclusion criteria consisted of the following: (i) presence of a tracheal fistula from a tracheotomy, (ii) malignant bowel obstruction in which the lesion located most orally was no higher than the transverse colon, (iii) pregnancy or possible pregnancy, and (iv) previous or scheduled local therapy for the neck region (surgical treatment on the region from the mandible to the clavicle, radiation therapy to soft tissue in the region from the mandible to the clavicle, radiation therapy to the neck, or intravenous hyperalimentation in the jugular vein or via a supraclavicular approach).

Technique for PTEG

The PTEG was created as Ohishi et al (6) and Mackey et al (8) described (6–8) with the use of a PTEG kit (Sumitomo Bakelite, Tokyo, Japan; **Figs 1–6**) and the following procedures. (i) A rupture-free balloon (RFB) was inserted through the nose and positioned in the cervical esophagus. (ii) The RFB was inflated with approximately 10–15 mL of 4× diluted water-soluble contrast medium (Urografin; Bayer Yakuhin, Osaka, Japan), and then the thyroid gland, carotid artery, and trachea were separated, and the RFB was detected just under the skin (**Figs 2, 3**). (iii) The RFB was punctured percutaneously under ultrasound (US) guidance, and a guide wire was inserted into the RFB through the needle (**Fig 4a**). (iv) The puncture site was dilated by using a dilator with a sheath (**Fig 4b**), and then an indwelling tube was appropriately inserted into the esophagus (**Fig 5**).

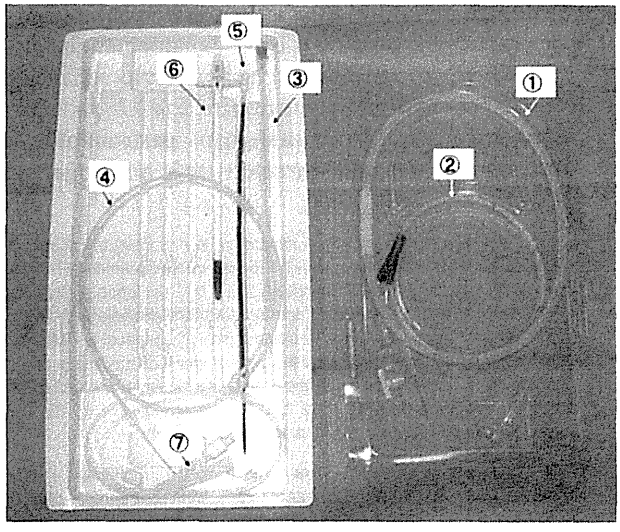
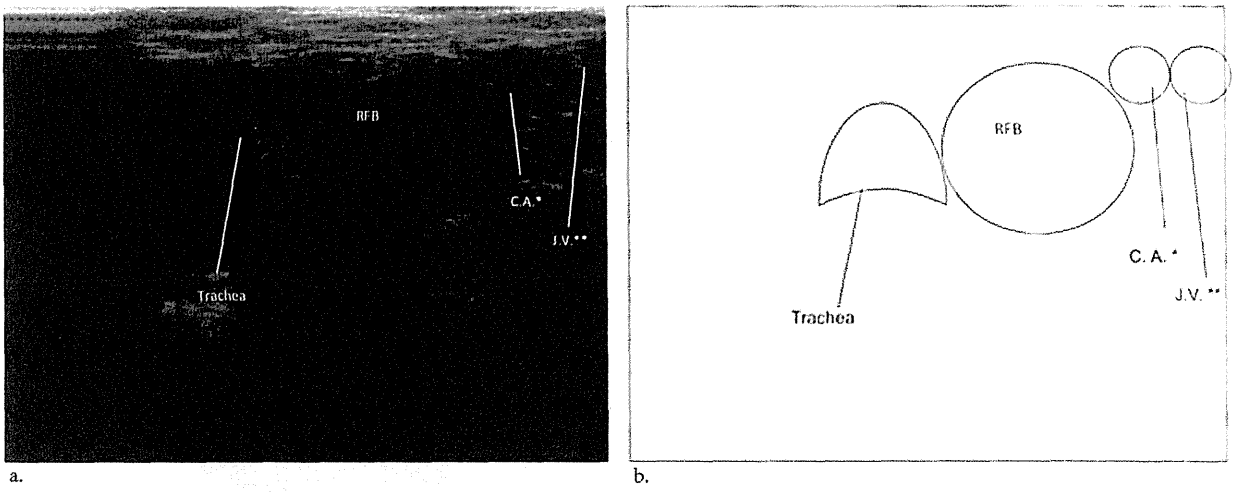


Figure 1. PTEG kit including straight-type guide wire (*1*), RFB (*2*), 18-gauge puncture needle with sheath (*3*), J-type guide wire (*4*), 8-F dilator (*5*), 16-F peel-away sheath (*6*), and indwelling tube with balloon (*7*). (Available in color online at *www.jvir.org.*)



a. b.

Figure 2. US depiction **(a)** and schema **(b)** of RFB placed at cervical esophagus and inflated with diluted contrast medium. CA = carotid artery, JV = jugular vein.

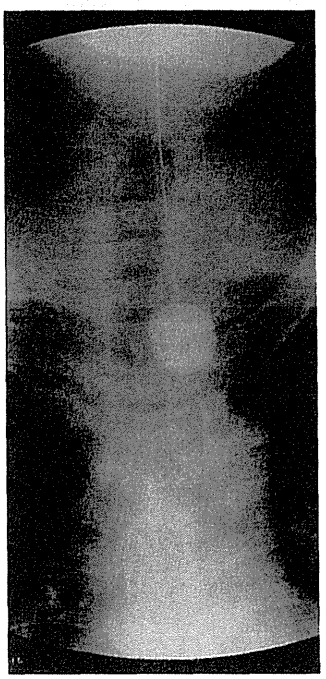


Figure 3. Radiograph of RFB placed at cervical esophagus.

Outcome Evaluation

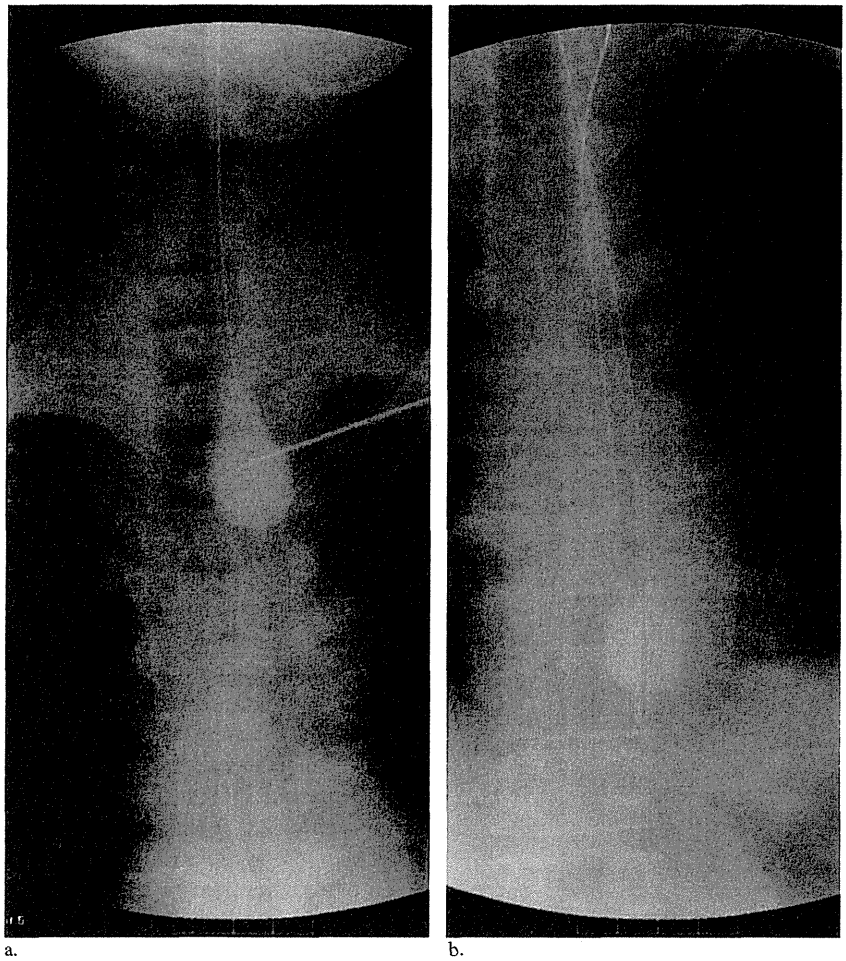
Because the median survival time for patients with terminal malignant bowel obstruction was reported to be 17 days (4), the evaluation observation period was set to 4 weeks. Subjective symptoms were monitored after 1, 2, 3, and 4 weeks and classified into the following five levels: (i) "much more comfortable than NGT"; (ii) "slightly more comfortable than NGT"; (iii) "same level of discomfort as NGT"; (iv) "slightly more uncomfortable than NGT"; and (v) "much more uncomfortable than NGT." When subjective symptoms remained at level 1 for two consecutive weeks or longer, the procedure was considered markedly effective, and when subjective symptoms remained at level 1 or 2 for two consecutive weeks or longer, the procedure was simply considered effective. The procedure was considered ineffective in all other cases. The efficacy rate was calculated as the ratio of markedly effective cases and effective cases to all those enrolled.

The safety of PTEG was evaluated by using the National Cancer Institute Common Toxicity Criteria, version 2.0. Because this study was not conducted with the aim of evaluating the functions of the indwelling tube, complications were not evaluated if the symptoms were improved by exchanging the indwelling tube.

Procedure time was calculated as the length of time from the start of nasal cavity and pharynx anesthesia to fixation of the tube to the skin. Procedure completion was defined as completed insertion of the tube from the cervical esophagus to the lower esophagus or more distal portion (anal side). The technical success rate was calculated as the ratio of cases in which the procedure was completed among all those enrolled.

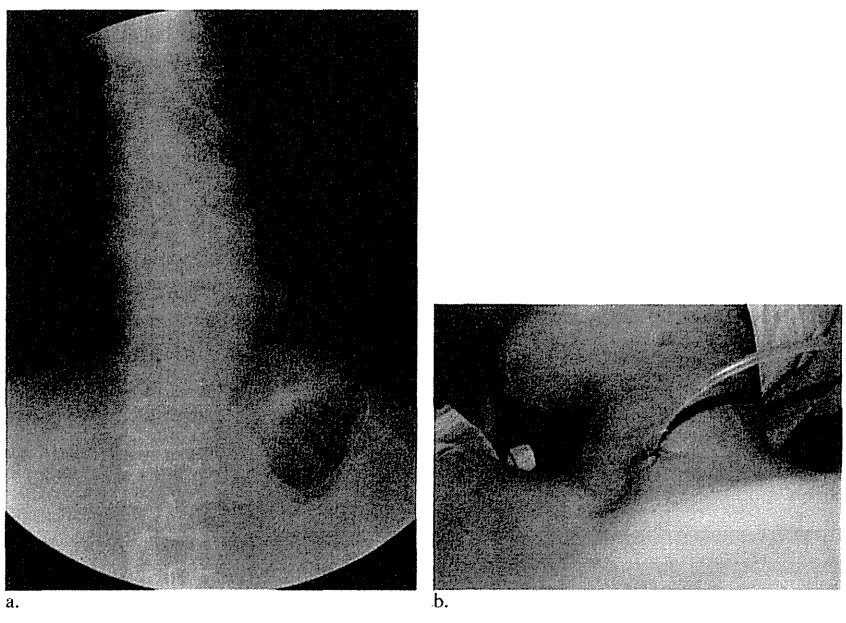
Statistical Analysis

To identify the number of cases required to evaluate serious adverse events and the efficacy rate, one-sample binomial t tests were performed (null hypothesis H0, $P = \pi 0$; alternative hypothesis H1, $P = \pi$). For adverse events with $\pi 0 = 0.10$ and $\pi = 0.30$ (where the predicted value for complications was 10%, and $\geq$ 30% was considered unacceptable), values of $\alpha = 0.05$ and $\beta = 0.20$ yielded a sample size of 30. For the efficacy rate with $\pi 0 = 0.50$ and $\pi = 0.80$, values of $\alpha = 0.05$ and $\beta = 0.20$ yielded a sample size of 19. As the required sample size for the present study, it was considered necessary to enroll 30 cases to evaluate serious adverse events, and this number was increased by 10% in anticipation of protocol deviations. Therefore, enrollment of 33 cases was planned.



a. b.

Figure 4. J-type guide wire is inserted into the balloon through the outer tube of the puncture needle **(a)** and guided to the lower esophagus along with the RFB catheter **(b)**.



a. b.

Figure 5. **(a, b)** The indwelling tube is inserted through the sheath and fixed to the skin surface. (Available in color online at *www.jvir.org.*)

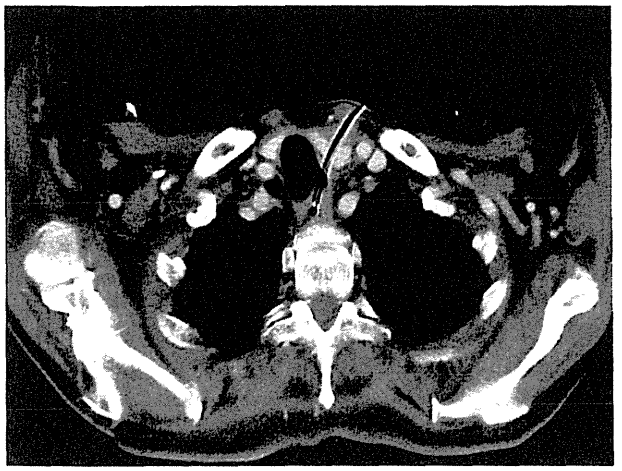


Figure 6. In the case of tracheoesophageal fistula, the tube is inserted into the esophagus through the trachea.

RESULTS

Patient Characteristics

From February 2003 to December 2005, 33 patients from five institutions (21 women, 12 men; median age, 61 y; range, 31–74 y; **Table**) were enrolled in the study. All cases fulfilled the inclusion criteria, and none met any exclusion criteria. The primary cancer sites consisted of the stomach in 18 cases, the colon and rectum in five cases, the pancreas in three cases, the ovaries in two cases, and others in five cases. Peritoneal dissemination was present in 26 cases. The median duration of NGT insertion until study registration was 13 days. The median survival time was 73 days (range, 6–340 d).

Treatment and Safety

The procedure was a success in all 33 cases. Median procedure time was 28.5 minutes (range, 6–60 min). The indwelling tube was a gastric tube in 30 cases (kit accessory, n = 4; 12-F gastric tube, n = 15; 14-F gastric tube, n = 10; 15-F gastric tube, n = 1) and an ileus tube in three cases. Nasal bleeding occurred in one case during the placement procedure and improved after conservative management. No other severe complications were observed during the procedure.

A tracheoesophageal fistula resulting in grade 2 aspiration pneumonia was observed in one case 29 days after the procedure. When changing the tube in this case, exchange of respiratory air and synchronizing air was observed from a fistula. Contrast enhancement of the fistula identified a tracheoesophageal fistula. Confirmatory computed tomography revealed that the indwelling tube passed through the trachea at one point (**Fig 6**). Low-grade fever was observed in this case before the procedure. Because the symptoms did not change during the period after completion of the PTEG procedure until the appearance of the tracheoesophageal fistula, and the patient was not feeding orally, the patient was treated conservatively with antibiotics and other treatment without removing the tube. No other serious hematologic or nonhematologic complications were observed.

Within 30 days of the PTEG procedure, death occurred in a total of seven cases; however, these deaths were confirmed by the safety and efficacy committee to have resulted from deterioration of the preexisting medical condition.

Table. Characteristics of the 33 Patients Included in the Study

Characteristic	Value
Sex	
Male	12
Female	21
Age (y)	
Median	61
Range	31–74
ECOG PS	
0	0
1	10
2	13
3	10
4	0
Primary cancer site	
Stomach	18
Colon	5
Pancreas	3
Ovary	2
Other	5
Carcinomatous peritonitis	
Yes	26
No	7
Previous tube placement	
Yes	100
No	0
Previous NGT placement time (d)	
Median	13
Range	2–18
Follow-up duration (d)	
Median	73
Range	6–340

ECOG = Eastern Cooperative Oncology Group, NGT = nasogastric tube, PS = performance status.

Efficacy

Evaluation of efficacy during the 4 weeks specified as the evaluation observation period identified 20 markedly effective cases, 10 effective cases, and three ineffective cases, for an efficacy rate of 91% (30 of 33 cases). Of the three ineffective cases, two cases could not be properly evaluated (ie, results collected for 2 wk) as a result of early death from aggravation of primary disease, and one patient could not be asked about subjective symptoms because of deterioration of general status. Each of these patients had given an evaluation of "more comfortable than NGT" in their first evaluation. None of the

33 patients gave an evaluation of "more uncomfortable than an NGT."

As of October 2011, 31 patients had died, all with their PTEG intact. Two patients were lost to follow-up; their catheters had not been removed, and they had not experienced known complications during their recorded follow-up.

DISCUSSION

The first method for placing a tube into the cervical esophagus was reported by Chen et al in 1983 (7), and Nakano et al (8) performed the first percutaneous cervical esophagus puncture and tube insertion in 1993. The method was later established as PTEG by Oishi et al (6) in 1994. This was developed to be one treatment option for the patient who needs enteral tube insertion or bowel decompression. Therefore, the main indication for PTEG is similar to that for percutaneous gastrostomy, but it is easy to create for patients with prior gastrectomy and/or malignant ascites (6,9,10) because the PTEG is then a "percutaneous esophagostomy." Since PTEG was developed, there has been no prospective evaluation performed to our knowledge. Therefore, the present study was conducted to evaluate PTEG prospectively (9).

In the present study, switching from NGT to PTEG improved subjective symptoms in 30 of 33 cases (91%). The remaining three patients who could not be evaluated also responded that PTEG was more comfortable than NGT during the period in which they could be asked about subjective symptoms, suggesting that PTEG was not necessarily ineffective in these cases. Of the 31 cases evaluated as effective, 20 were evaluated as markedly effective, demonstrating that PTEG contributes strongly to patient satisfaction (11).

Oishi et al (9) described the results of PTEG creation as 100% technical success without any major complications (minor complications, such as tube obstructions, stomal leakage, wound infection, unrecovered tube migration, and minor bleeding, occurred in 23.5% of their cases), and the time for PTEG creation was approximately 15 minutes (from RFB insertion to tube placement) (9). The present study generally used PTEG kits for the procedure, which resulted in the achievement of a 100% technical success rate. Despite the multicenter nature of the study and the short history of the procedure, no failures were encountered, and the median procedure duration was slightly less than 30 minutes, indicating the ease of the procedure. Moreover, PTEG can be used for a wide variety of cases. Because it is a gastric tube that accesses the bowels via the cervical esophagus, the procedure can also be performed for patients who have undergone gastrectomy or for patients with massive ascites or carcinomatous peritonitis, without worrying about tumor infiltration from the puncture hole or puncture route into the abdominal cavity (6,9,10,12,13). In the present study, 26 cases had peritoneal dissemination, and PTEG may be particularly well suited to such patients.

In terms of serious complications, one patient was observed to have aspiration pneumonia as a result of a tracheoesophageal fistula. No previous studies have reported tracheoesophageal fistula (6,9,10,12,13). In the PTEG procedure, the esophagus that is usually positioned behind the trachea is forced by RFB expansion to float upward to sit next to the trachea, enabling puncture only into the esophagus. In patients with a fragile trachea, it remains possible that the membranous part of the trachea may become transformed with RFB expansion as the esophagus floats upward. Alternatively, insufficient RFB expansion could result in mistaken puncture of surrounding structures.

One possibility for the case with tracheoesophageal fistula is that the membranous part of the trachea rose upward together with the esophagus so that the trachea became inserted into the puncture route, resulting in a transtracheal puncture that caused the fistula. Another possibility is that insufficient expansion resulted in inadequate displacement of the trachea, so that the puncture was made through the trachea. Transformation of the membranous part of the trachea from the RFB and the resulting erroneous puncture would not be easily visible using US alone. US can be used to make the puncture after confirming that the puncture site is a sufficient distance from the trachea to preclude erroneous puncturing of cervical veins or arteries. This could then be followed by x-ray fluoroscopy to confirm the path of the guide wire and dilator sheath or introducer sheath to avoid damage to the trachea. Alternatively, a linear probe or similar device could be used to make a vertical puncture to avoid damaging surrounding organs. The case in the present study that presented with a tracheoesophageal fistula was only treated conservatively with antibiotics and did not develop serious aspiration pneumonia. The tube should possibly have been removed as soon as the transtracheal puncture was detected.

Seven cases in the present study (21%) had an early death within 30 days; however, this was likely unavoidable, as all cases involved patients with terminal malignant tumors. The median survival time for patients with terminal malignant bowel obstruction has been reported to be 17 days (4). Moreover, Udomsawaengsup et al (12) reported that seven patients with terminal malignant bowel obstruction (41%) had an early death within 30 days (12). No other complications were observed as a result of the procedure in the present study, and no fistula infections or other serious adverse events that required PTEG removal were encountered. Even though one tracheoesophageal fistula was observed, the procedure still appears very safe to perform.

Some limitations of the present study include the single-arm, non-randomized nature of the trial and the small sample size. As the subjects were patients with NGTs, they

likely chose to participate in the study because they were feeling distress from the tube. Some degree of selection bias therefore appears likely. In addition, we did not use the approach of QOL evaluation that is widely used for this type of experiment. Finally, the small sample size may have hampered the identification of adverse events. Therefore, we have planned and are presently conducting a randomized phase III trial with a larger sample size that uses QOL evaluation as the primary endpoint.

In conclusion, PTEG appears useful for relieving pain and discomfort from NGT insertion for bowel decompression in patients with a terminal malignant tumor. PTEG should be considered an efficacious method for bowel decompression in patients who are ineligible for surgical procedures, percutaneous gastrostomy, or percutaneous enterostomy.

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CLINICAL STUDY

Prospective Study of Transcatheter Arterial Chemoembolization for Unresectable Hepatocellular Carcinoma: An Asian Cooperative Study between Japan and Korea

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ABSTRACT

Purpose: To evaluate the safety and efficacy of transcatheter arterial chemoembolization used for the treatment of unresectable hepatocellular carcinoma (HCC) with an Asian cooperative prospective study between Japan and Korea.

Materials and Methods: Patients with unresectable HCC unsuitable for curative treatment or with no prior therapy for HCC were enrolled. The patients underwent transcatheter arterial chemoembolization with emulsion of Lipiodol and anthracycline agent, followed by embolization with gelatin sponge particles, which was repeated on an as-needed basis. The primary endpoint was 2-year survival rate, and the secondary endpoints were adverse events and response rate.

Results: The 2-year survival rate of 99 patients was 75.0% (95% confidence interval, 65.2%–82.8%). The median time-to-progression was 7.8 months, and the median overall survival period was 3.1 years. Of 99 patients, 42 (42%) achieved a complete response, and 31 (31%) had a partial response. The response rate was 73% using modified Response Evaluation Criteria in Solid Tumors. The grade 3–4 toxicities included increased alanine aminotransferase level in 36%, increased aspartate aminotransferase level in 35%, thrombocytopenia in 12%, and abdominal pain in 4% of patients. All other toxicities were generally transient.

Conclusions: Asian transcatheter arterial chemoembolization demonstrated sufficient safety and reasonable efficacy as a standard treatment for unresectable HCC. These results could be useful as reference data for future trials of transcatheter arterial chemoembolization.

ABBREVIATIONS

AFP = alpha fetoprotein, ALT = alanine aminotransferase, AST = aspartate aminotransferase, CI = confidence interval, FAS = full analysis set, HCC = hepatocellular carcinoma, PIVKA II = protein induced by vitamin K absence or antagonist-II, RECIST = Response Evaluation Criteria in Solid Tumors

Primary liver cancer accounted for > 38,000 and 15,000 deaths per year in Japan and Korea, respectively; it is the fourth most common cause of death after lung, stomach, and colorectal cancers in Japan, and it is the third most

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common cause of death after lung and stomach cancers in Korea (1). Of all primary liver cancers, approximately 95% in Japan and 85% in Korea are hepatocellular carcinomas (HCCs), which are mostly attributable to chronic hepatitis or liver cirrhosis caused by persistent infection with hepatitis C or B viruses. Hepatitis B infection is more prevalent in Korea, whereas hepatitis C infection is more common in Japan (2). Despite these differences in etiology, the treatment strategy for HCC is the same in Japan and Korea. Curative therapies, such as hepatic resection or liver transplantation, are applicable in only a small proportion of patients because of excessive tumor invasion or poor hepatic function or both. Although local ablative therapy, such as radiofrequency ablation, has an effectiveness equivalent to that of hepatic resection for HCCs $\leq$ 3 cm in size and with three or fewer nodules, it is unsuitable for tumors > 3 cm or for multiple tumors. For this stage of HCC, transcatheter arterial chemoembolization is the main therapeutic option (3–5). Transcatheter arterial chemoembolization has been shown to prolong survival significantly in several randomized controlled trials compared with chemotherapy alone (6) or conservative treatment (7–13). Meta-analyses (14,15) have also demonstrated a clear survival benefit of transcatheter arterial chemoembolization for unresectable HCC (**Table 1**).

Transcatheter arterial chemoembolization with Lipiodol (Guerbet; Roissy CdG, France) and anthracycline agents followed by embolization with gelatin sponge particles has been widely used as a practical standard treatment in Asian countries for > 30 years (16). Transcatheter arterial chemoembolization was used in Asian countries long before the confirmation of its survival benefit in randomized controlled trials (6–13) because these techniques were originally developed in Japan (17–19) and spread among Asian countries. However, no prospective clinical study has been fully conducted to provide convincing data that can support this treatment. Additionally, there are many technique differences between Asian transcatheter arterial chemoembolization and transcatheter arterial chemoembolization performed in Western countries. The so-called conventional transcatheter arterial chemoembolization reported in Western studies differs from Asian transcatheter arterial chemoembolization in the details of the treatment. A prospective clinical study was conducted to evaluate Asian transcatheter arterial chemoembolization for unresectable HCC. The aim of this study was to evaluate the safety and efficacy of Asian transcatheter arterial chemoembolization with a single-arm, Japan-Korea cooperative prospective study.

MATERIALS AND METHODS

Patient Eligibility

Eligible patients for study entry had unresectable HCC that was unsuitable for curative treatments. Patient inclusion criteria were as follows: histologically or clinically diagnosed HCC excluding mixed type; no previous treatment for HCC; not a candidate for hepatic resection, liver transplantation, or local ablative therapy; hypervascular lesion showing enhancement in the early phase on computed tomography (CT) or magnetic resonance (MR) imaging with bolus contrast injection; no tumor thrombosis in the first branch or main portal vein; Eastern Cooperative Oncology Group performance status of 0–2; Child-Pugh classification of A or B; adequate hematologic, hepatic, renal, and cardiac function (leukocytes $\geq$ 3,000/mm^3, platelets $\geq$ 50,000/mm^3, serum bilirubin $\leq$ 3.0 mg/dL); age $\geq$ 20 years old; and written informed consent.

The exclusion criteria were as follows: extrahepatic metastasis; hepatic vein invasion or biliary invasion; ruptured tumor; prior biliary enteric bypass or endoscopic transampullary stent placement or percutaneous biliary drainage; clinically significant refractory ascites or pleural effusion; severe arterioportal or arteriovenous shunts in the liver; allergy to contrast medium precluding angiography; severe and active comorbidity such as heart disease or renal disease; hepatic encephalopathy or severe mental disorder; active gastrointestinal bleeding; active concomitant malignancy; pregnancy, lactation, or childbearing potential in women; and men who are sexually active and not willing or able to use medically acceptable forms of contraception. The inclusion and exclusion criteria were almost same as those in the clinical trial conducted by Llovet et al (12).

The pretreatment evaluation required a complete history and physical examination and baseline assessments of organ function. In addition, contrast-enhanced CT or MR imaging of the abdomen and x-ray or CT of the chest were performed before treatment for staging to assess the local extension of the tumor and to exclude the presence of distant metastasis.

Transcatheter Arterial Chemoembolization Procedure

Patients with unresectable HCC underwent transcatheter arterial chemoembolization using an emulsion of epirubicin or doxorubicin and Lipiodol followed by gelatin sponge injection. The dose of anticancer agents and Lipiodol used in transcatheter arterial chemoembolization was determined according to tumor size; only the maximum doses were defined in this study: 100 mg/body for epirubicin, 70 mg/body for doxorubicin, and 20 mL for Lipiodol. Epirubicin or doxorubicin dissolved in aqueous nonionic contrast medium was mixed with Lipiodol to form an emulsion using the pumping technique. The resulting emulsion had to be injected immediately. Transcatheter arterial chemoembolization was performed as follows: (i) tumor enhancement and the feeding artery were confirmed using abdominal angiography; (ii) a catheter was inserted into the feeding artery of the HCC, and the emulsion containing epirubicin or doxorubicin with Lipiodol was injected; (iii) embolization of the feeding artery was achieved using small pieces of gelatin sponge until the disappearance of tumor stain; (iv) the therapeutic effect

Table 1. Randomized Controlled Trials of Transcatheter Arterial Embolization with Conservative Therapy

Author, Year	Treatment	No. Patients	Response Rate (%)	1-y Survival (%)	2-y Survival (%)	*P* Value	Treatment Duration	Embolic Material	Anticancer Agent	Lipiodol
Lin et al, 1988 (6)	Transcatheter arterial embolization	21	62	42	25		Monthly	Gelatin sponge	None	Absent
	Transcatheter arterial embolization + 5-FU	21	48	20	20		Monthly		5-FU	Absent
	5-FU	21	9.5	13	13	< .005	Monthly		5-FU	
Pelletier et al, 1990 (7)	Transcatheter arterial chemoembolization	21	33	24	NA		2nd, 6th, 12th mo	Gelatin sponge	Doxorubicin	Absent
	Best supportive care	21	0	33	NA	NS				
GRETCH, 1995 (8)	Transcatheter arterial chemoembolization	50	16	62	38		Every 2 mo	Gelatin sponge	Cisplatin	Present
	Best supportive care	46	5	43	26	.13				
Pelletier et al, 1998 (9)	Transcatheter arterial chemoembolization + TMX	37	24	51	24		Every 3–4 mo	Gelatin sponge	Cisplatin	Present
	TMX	36	5.5	55	26	.77				
Bruix et al, 1998 (10)	Transcatheter arterial embolization	40	55	70	49		On demand	Gelatin sponge + coil	None	Absent
	Best supportive care	40	0	72	50	.72				
Lo et al, 2002 (11)	Transcatheter arterial chemoembolization	40	27	57	31		Every 2–3 mo	Gelatin sponge	Cisplatin	Present
	Best supportive care	39	2.6	31	11	.002				
Llovet et al, 2002 (12)	Transcatheter arterial chemoembolization	40	35	82	63		Every 2–6 mo	Gelatin sponge	Doxorubicin	Present
	Transcatheter arterial embolization	37	43	75	50		Every 2–6 mo	Gelatin sponge		
	Best supportive care	35	0	63	27	.009				
Doffoël et al, 2008 (13)	Transcatheter arterial chemoembolization	62	NA	51	25		Every 2–6 mo	Gelatin sponge	Epirubicin	Present
	TMX	61	NA	46	22	.68				

5-FU = 5-fluorouracil; NA = not available; TMX = tamoxifen.

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**.