survival time of 10 months. In conclusion, the MMC/CPT-11 regimen might be one treatment option for pretreated AGC in patients with good PS.

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Conflict of interest None.

Appendix

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Transcatheter Arterial Infusion Chemotherapy with a Fine-powder Formulation of Cisplatin for Advanced Hepatocellular Carcinoma Refractory to Transcatheter Arterial Chemoembolization

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Objective: The aim of this study was to assess the safety and efficacy of transcatheter arterial infusion chemotherapy using a fine-powder formulation of cisplatin for patients with advanced hepatocellular carcinoma refractory to transcatheter arterial chemoembolization.
Methods: We retrospectively examined the data of 84 consecutive patients with transcatheter arterial chemoembolization-refractory hepatocellular carcinoma who underwent transcatheter arterial infusion chemotherapy with a fine-powder formulation of cisplatin. Cisplatin was administered at the dose of 65 mg/m^2 into the feeding artery of the hepatocellular carcinoma. The treatment was repeated every 4–6 weeks, until the appearance of evidence of tumor progression or of unacceptable toxicity.
Results: Of the 84 patients, one patient (1.2%) showed complete response and two patients (2.4%) showed partial response, representing an overall response rate of 3.6% (95% confidence interval, 0.7–10.1). Of the remaining, 38 patients (45.2%) showed stable disease and 41 (48.8%) showed progressive disease. The median overall survival, 1-year survival rate and median progression-free survival in the entire subject population were 7.1 months, 27% and 1.7 months, respectively. Major Grade 3 or 4 adverse events included thrombocytopenia in 12 patients (14%) and elevation of the serum aspartate aminotransferase in 33 patients (39%). The gastrointestinal toxicities were mild and reversible.
Conclusions: Transcatheter arterial infusion chemotherapy using a fine-powder formulation of cisplatin appears to have only modest activity, although the toxicity was also only mild, in patients with transcatheter arterial chemoembolization-refractory hepatocellular carcinoma.

Key words: hepatocellular carcinoma – transcatheter arterial infusion chemotherapy – cisplatin – transcatheter arterial chemoembolization

INTRODUCTION

Hepatocellular carcinoma (HCC) is treated by one or more of a wide variety of treatment options available, depending on the tumor characteristics, including the number and size of tumors, and the presence/absence of tumor thrombosis and extrahepatic metastases (1,2). In patients with early-stage HCC, curative therapies can be applied, including resection, liver transplantation or local ablation therapy. However, the prognosis of patients with HCC is still unsatisfactory, mainly because of the high frequency of recurrence post-therapy (3–9). Transcatheter arterial chemoembolization (TACE) has been performed for unresectable advanced HCC in patients who are unsuitable candidates for local ablation therapy or surgical treatment. To date, nine randomized control trials

(RCTs) of transcatherter arterial embolization or TACE versus best supportive care have been reported (10–18). Three of these RCTs and two meta-analyses have demonstrated a survival benefit of this treatment modality in HCC patients (10,16,17,19,20). On the basis of these results, TACE has been the most commonly employed treatment modality in patients with unresectable advanced HCC, especially those with intermediate-stage disease, who are unsuitable candidates for local ablation therapy (21). However, unfortunately, the disease eventually progresses to becoming refractory to TACE.

Transcatheter arterial infusion chemotherapy (TAI) could be expected to have better antitumor efficacy and lesser toxicity than systemic chemotherapy, because it is associated with only a local increase in the concentrations of anticancer drugs, and therefore, a lower incidence of systemic adverse effects. The reported response rates to TAI with a single agent vary in the range of 9–33% (22–25), and those to TAI using combination regimens vary in the range of 44–73% (26–29). Thus, TAI has high antitumor activity and is widely used in clinical practice, especially in Japan, although no survival benefit has been established yet, because no randomized studies of TAI have been conducted until date.

Cisplatin for Intra-arterial Injection (IA-call®, Nippon Kayaku Co., Ltd) is a powder formulation and represents an improvement over the standard liquid type of cisplatin formulation for intra-arterial administration. Since the solubility of this agent is 2.86 times higher than that of standard cisplatin, the injection time can be shortened. In a clinical study of this agent for advanced HCC, a favorable tumor response rate of 33.8% was reported (25), and this agent was approved for use in the treatment of HCC by the Ministry of Health, Labour and Welfare of Japan, in July 2004. However, it has not been clarified whether this agent might also be effective for TACE-refractory HCC. Therefore, we conducted a retrospective investigation of the efficacy and safety of TAI using cisplatin in patients with HCC refractory to TACE.

PATIENTS AND METHODS

Patients and Treatment

From July 2004 to September 2008, 84 consecutive patients with TACE-refractory HCC underwent TAI using cisplatin at the National Cancer Center Hospital, Tokyo, or the National Cancer Center Hospital East, Chiba, Japan. TACE-refractory tumors were defined as those showing an increase in size or <25% reduction in size of the hypervascular lesions visualized on dynamic computed tomography (CT) and/or magnetic resonance imaging (MRI) at 1 month after TACE (30).

TAI was performed by introducing a catheter into the proper, right or left hepatic artery, or another feeding artery by the Seldinger technique, and injecting cisplatin at the dose of 65 mg/m^2 over 20–40 min. Until the appearance of evidence of tumor progression and/or of unacceptable toxicity, the treatment was repeated every 4–6 weeks for up to six cycles. Antiemetic prophylaxis with a 5-hydroxytryptamine3 antagonist (granisetron 1 mg) plus dexamethasone 8 mg was used at the physician's discretion. Patients received adequate hydration 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, and intravenous furosemide was administered if the output was judged to be inadequate. In principle, the cisplatin dose was reduced if the patient's creatinine clearance decreased to below 50 ml/min.

This retrospective study was conducted with the approval of the Institutional Review Board of the National Cancer Center and conducted in accordance with the ethical principles stated in Japanese ethics guidelines for epidemiologic studies.

Response and Toxicity Evaluations

The antitumor effect was evaluated by dynamic CT and/or MRI performed 1 month after each treatment cycle, and after the completion of six cycles, follow-up examinations were performed every 1–3 months. Responses were evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) (31). The best overall response was recorded for each patient. Progression-free survival was defined as the interval between the date of the initial TAI treatment using cisplatin and either the date of documentation of disease progression (either radiologic or symptomatic progression) or the date of death owing to any cause. Overall survival was measured from the date of the initial TAI treatment using cisplatin to the date of death or last follow-up. Survival curves were estimated using the Kaplan–Meier method. Toxicities were assessed using the Common Terminology Criteria for Adverse Events, version 3.0. Statistical analyses were performed using Dr SPSS II (SPSS Japan Inc., Tokyo, Japan).

RESULTS

Patient Characteristics

The baseline characteristics of the 84 patients enrolled in this study are shown in Table 1. The diagnosis of HCC was made either by histologic examination (44 patients, 52%), or distinctive findings on CT, MRI and/or angiography associated with elevated serum levels of α-fetoprotein or protein induced by vitamin K antagonist II (40 patients, 48%). Of the total, 42 patients each were classified as the Child–Pugh classes A and B, whereas there were no patients of the Child–Pugh class C. Twenty-six patients (31%) had tumor thrombosis in the main and/or first portal vein. Prior therapies other than TACE were hepatectomy (37 patients, 44%), local ablation therapy (33 patients, 39%), TAI (13 patients, 15%) and systemic chemotherapy (10 patients, 12%) with non-platinum-containing regimens. The median number of

Table 1. Patient characteristics ($n = 84$)

Age, median (range)	68 (37–82)
Gender, *n* (%)	
Male	69 (82)
Female	15 (18)
ECOG performance status, *n* (%)	
0	56 (67)
1	26 (31)
2	0 (0)
3	2 (2)
T factor[a]	
T1	2 (2)
T2	34 (40)
T3a	17 (20)
T3b	31 (37)
Portal vein tumor thrombosis, *n* (%)	
Present	26 (31)
Absent	58 (69)
Ascites, *n* (%)	
Present	24 (29)
Absent	60 (71)
Hepatitis virus marker status, *n* (%)	
HBsAg-positive	12 (14)
HCVAb-positive	55 (65)
Child–Pugh class, *n* (%)	
A	42 (50)
B	42 (50)
Number of previous TACE sessions	
Median (range)	4 (1–17)
Reason for TACE-refractory disease, *n* (%)	
Progressive disease	69 (82)
Stable disease (under 25% decrease)	15 (18)
AFP (ng/dl)	
Median (range)	660.2 (1.7–4 06 500)
PIVKA II (mAU/ml)	
Median (range)	600 (11–96 390)

ECOG, Eastern Cooperative Oncology Group; HBsAg, hepatitis B surface antigen; HCVAb, hepatitis C virus antibody; TACE, transcatheter arterial chemoembolization; AFP, α-fetoprotein; PIVKA, protein induced by vitamin K antagonist.
[a]T factor was evaluated according to Sobin et al. (32).

previous sessions of TACE was 4 (range 1–17), and the median period from the first TACE to the date on which the tumors were judged to be TACE-refractory was 15.8 months (range 1.0–78.0). The anticancer agents used for the previous TACE sessions were epirubicin in 79 patients, adriamycin in 17 patients and mitomycin C in 5 patients.

Treatment Delivery and Efficacy

In total, 167 cycles of TAI were administered to the 84 patients, with a median of one cycle (range 1–7) per patient. The median cisplatin dose per treatment session was 100 mg (range 50–135). A total of 83 patients received the standard dose of cisplatin in the first session, and the remaining one patient required a 50% reduction in the dose of cisplatin even from the first treatment cycle because of pre-existing renal dysfunction.

Of the study population, one patient showed complete response and two showed partial response, representing an overall response rate of 3.6% [95% confidence interval (CI), 0.7–10.1]. Stable disease was noted in 38 patients and progressive disease in 41 patients. The remaining two patients were not evaluable as they were lost to follow-up. After treatment discontinuation, 50 (60%) patients received supportive care only, 32 (38%) received additional anticancer therapy and 2 (2%) were lost to follow-up. The additional anticancer therapies were TACE with epirubicin or mitomycin in 18 patients, TAI using non-platinum drugs in 7 patients (including 5-fluorouracil with systemic interferon in 3 patients, epirubicin in 3 patients and zinostatin-stimalamer in 1 patient), systemic chemotherapy in 5 patients (including S-1, i.e. a mixture of tegafur, 5-chloro-2,4-dihydropyrimidine and potassium oxonate, in 3 patients and uracil–tegafur plus mitoxantrone in 2 patients) and immunotherapy in 2 patients. By the time of the analysis, except for eight patients who were still alive but showed disease progression, all of the patients had died. The median progression-free survival was 1.7 months (95% CI, 1.1–2.3) and the median overall survival was 7.1 months (95% CI, 4.9–9.3), with a 1-year survival rate of 27% (Fig. 1).

Adverse Events

Data of all 84 patients were analyzed for adverse events. The adverse events are summarized in Table 2. In regard to the hematologic adverse events, thrombocytopenia was the most common, with 12 (14%) patients developing Grade 3 or 4 thrombocytopenia; however, none of the patients required platelet transfusions. Grade 3 or 4 leukopenia and neutropenia occurred in only 6 and 4% of the patients, respectively. There were no events of febrile neutropenia.

The main non-hematologic adverse events were elevation of the serum aspartate aminotransferase (AST) and serum alanine aminiotransferase (ALT). Grade 3 or 4 elevation of the AST and ALT was observed in 33 (39%) and 5 (6%) patients, respectively. Gastrointestinal adverse events, such as nausea, vomiting and anorexia, were frequently observed after intra-arterial administration of cisplatin, but most were transient and manageable with appropriate medical treatment, such as antiemetic drug administration and intravenous hydration. There was no serious renal toxicity. Four patients died within 30 days of the last treatment session: two of disease progression, one of acute coronary syndrome,

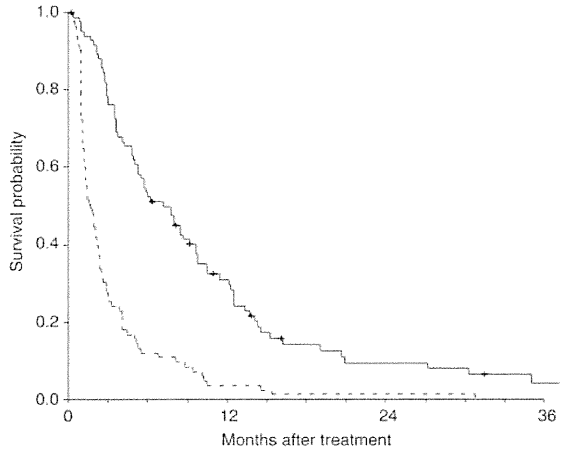

Figure 1. Overall survival (continuous line) and progression-free survival (dotted line) in the 84 patients. The marks on the curve represent censored cases.

Table 2. Adverse events

	No. of patients				Gr 3/4 (%)
	Gr 1	Gr 2	Gr 3	Gr 4	
Hematologic toxicity					
Leukocytopenia	30	29	5	0	6.0
Neutropenia	11	24	3	0	3.6
Anemia	55	18	6	1	8.3
Thrombocytopenia	36	22	12	0	14.3
Non-hematologic toxicity					
Anorexia	45	16	3	0	3.6
Nausea	40	9	3	0	3.6
Vomiting	11	6	0	0	0
Fatigue	59	11	3	0	3.6
Diarrhea	3	1	0	0	0
Constipation	20	0	0	0	0
Hypoalbuminemia	38	41	1	0	1.2
Elevated serum total bilirubin	28	33	4	1	6.0
Elevated serum aspartate aminotransferase	20	26	31	2	39.3
Elevated serum alanine aminotransferase	37	30	4	1	6.0
Elevated serum alkaline phosphatase	53	15	1	0	1.2
Elevated serum creatinine	12	1	0	0	0

Gr, grade.

showing no causal relationship with the treatment, and the remaining one due to known pulmonary artery tumor embolism.

DISCUSSION

In the current study, the response rate to TAI using cisplatin was only 3.6% in patients with TACE-refractory HCC. Moreover, the median progression-free survival of only 1.7 months was extremely disappointing. The efficacy of TAI using cisplatin for advanced HCC limited to TACE-refractory tumors was much worse than that reported from a previous Phase II study in patients with advanced HCC (response rate, 33.8%) (25). One possible explanation for this discrepancy in the response rate may be the differences in the characteristics of the enrolled patients between the two studies. Most patients in the previous Phase II trial were TACE-naïve, whereas only patients with TACE-refractory disease were included in the current study. In our previous study (30), TAI using epirubicin was reported to have unfavorable efficacy in a subset of patients with TACE-refractory HCC (response rate, 5%). When HCC is treated by TACE and/or becomes resistant to TACE, it might acquire resistance to cytotoxic agents, such as cisplatin or epirubicin. Furthermore, to select suitable candidates for this treatment, the predictive factors for disease control and survival for more than 12 months were also investigated, but could not be clarified (data not shown). Therefore, TAI using cisplatin or epirubicin cannot be recommended at present for this patient population in clinical practice.

Recently, systemic chemotherapy has become an important treatment modality for advanced HCC, because two RCTs (the SHARP trial and the Asia-pacific trial) of sorafenib versus placebo demonstrated significantly improved time-to-progression and overall survival in the drug-treated group, although sorafenib yielded a far-from-satisfactory response rate of only 2.3–3.3% (33,34). On the basis of the results of these RCTs, sorafenib is acknowledged as a standard agent for systemic chemotherapy in patients with advanced HCC. The efficacy of sorafenib for advanced HCC refractory to TACE has not yet been clarified, but in both of the aforementioned studies, the results of exploratory subgroup analyses in patients treated previously by TACE were reported. In the subset of patients with a previous history of treatment by TACE in the SHARP trial, the disease control rate (DCR) was significantly greater in the patients who were treated with sorafenib (44.2%) than in those who had received placebo (34.4%) (35). In addition, a trend towards a beneficial effect of sorafenib was also observed in relation to the median overall survival in this subpopulation of patients {11.9 vs. 9.9 months [hazard ratio (HR), 0.75; 95% CI, 0.49–1.14]}. In the Asia-pacific trial, 41% of the enrolled patients had a previous history of undergoing TACE. The DCR for sorafenib (24.6%) in these patients was higher than that for placebo (9.1%) (36). Moreover, a tendency [HR for death was 0.84 (95% CI, 0.52–1.36)] towards favorable overall survival was also noted in the HCC patients with a previous history of TACE treated with sorafenib when compared with that in the same subpopulation of patients who received placebo. Sorafenib appeared to benefit patients with

advanced HCC, regardless of whether or not they had previously been treated by TACE. Thus, molecular-targeted agents, including sorafenib, which exhibit mechanisms of action different from those of cytotoxic agents, may be superior for the treatment of HCC refractory to TACE. Therefore, patients with TACE-refractory HCC are receiving new molecular-targeted agents in clinical trials, and sorafenib is used as the standard agent for the treatment of advanced HCC in clinical practice.

In the current study, the most common Grade 3 and 4 adverse events were elevated AST, thrombocytopenia and anemia, which frequently also reflected the underlying cirrhosis. In terms of the gastrointestinal toxicities, only 4% of the patients experienced Grade 3 anorexia and nausea, and the symptoms resolved within a few days. Thus, the gastrointestinal toxicities were mild and manageable in the current study. There was no need for dose reduction or discontinuation of cisplatin on account of development of toxicities, except in one patient each with Grade 2 elevation of the serum creatinine and Grade 2 fatigue. Thus, advanced HCC patients showed good overall tolerability to TAI using cisplatin, which has also been reported to show favorable efficacy in these patients (25); in our study confined to TACE-refractory patients, however, the treatment showed only modest antitumor activity. TAI using cisplatin may therefore be easy to administer in combination with some molecular-targeted agents, such as sorafenib, since its toxicity is generally mild and its toxicologic profile is distinct from that of sorafenib.

In conclusion, TAI using cisplatin appeared to have only modest activity against TACE-refractory HCC, although this treatment was feasible and well tolerated. Further development of novel treatments is necessary to improve the prognosis of patients with TACE-refractory HCC.

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Conflict of interest statement

None declared.

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Phase I/II Study of Transjugular Transhepatic Peritoneovenous Venous Shunt, a New Procedure to Manage Refractory Ascites in Cancer Patients: Japan Interventional Radiology in Oncology Study Group 0201

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OBJECTIVE. This multicenter phase I/II study evaluated the safety and the efficacy of transjugular transhepatic peritoneovenous shunt (PVS), a new palliative treatment for malignant refractory ascites.

SUBJECTS AND METHODS. Patients with refractory malignant ascites and patent hepatic veins and vena cava were included in this study. Eligible patients underwent the placement of transjugular transhepatic PVS catheter via the jugular vein into the abdominal cavity through the hepatic vein. In phase I, a step-by-step analysis of the safety was performed. The safety and the efficacy were determined through phases I and II.

RESULTS. Thirty-three patients were entered in this study, nine in phase I and 24 in phase II. Transjugular transhepatic PVS was technically successful in all patients. No severe adverse events were observed during the placement procedure. After the placement, 22 adverse events (grade 2 or higher) occurred. Frequent adverse events were hypoalbuminemia (24%) and decrease in hemoglobin (18%), which resolved within 1 week without additional treatment. The clinical efficacy rate at 1 week after the procedure was 67%. Occlusion of the catheter due to fibrin sheath was observed in seven patients, and the revision of the system was performed.

CONCLUSION. Transjugular transhepatic PVS is a safe and feasible procedure for managing refractory ascites in patients with cancer. Sufficient efficacy was observed in our initial experience, but a larger clinical trial is warranted.

Keywords: ascites, palliative care, peritoneovenous shunt

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Malignant ascites is defined as abnormal accumulation of intraperitoneal fluid as a consequence of advanced cancer [1–3]. It is often refractory to medical therapies and is associated with a decline in patients' quality of life [1–3]. Management of malignant ascites is still a major unsolved problem in the palliative care of patients with cancer.

The causes of refractory (i.e., resistant to various medical treatments) ascites include dissemination of malignant tumor, portal hypertension, and obstruction of the inferior vena cava or portal vein. In patients with portal hypertension or mechanical venous obstruction, a transjugular intrahepatic portosystemic shunt (TIPS) or stent placement in the obstructed vein may be the treatment of choice for reducing production of ascites [4–6]. However, patients for whom these procedures are not appropriate or for whom these definitive treatments fail require palliative treatment, such as paracentesis or peritoneovenous shunt (PVS) [1, 7–9].

The Denver shunt has been widely used for PVS, and favorable clinical outcomes have been reported [1, 7, 10–12]. An implantable shunt tube with a one-way valve allows ascites to drain into the systemic circulation. The shunt tube can be implanted either surgically or percutaneously. Recent studies have shown the feasibility of the percutaneous implantation, which is less invasive than surgical implantation [7, 11–13]; however, extensive subcutaneous tunneling is very invasive compared with other interventional radiology procedures. In addition, removing or exchanging the system in cases of infectious or occlusive complications is not easy. Consequently, the development of less invasive and exchangeable PVS is desirable.

Arai et al. [14] have described a novel PVS, transjugular transhepatic PVS, in 10 patients with malignant ascites. This is a PVS through the hepatic vein with minor penetration of hepatic parenchyma using a TIPS needle. With this technique, transjugular access to the abdominal cavity is possible, and

the long subcutaneous tunneling required for the Denver shunt is not necessary. Transjugular transhepatic PVS may be less invasive and more advantageous if catheter exchange is needed; however, a prospective clinical trial is mandatory for evaluating this completely new interventional technique. Thus, we conducted a phase I/II clinical trial (Japan Interventional Radiology in Oncology Study Group [JIVROSG] 0201) that aimed to determine the safety and the efficacy of transjugular transhepatic PVS, a new palliative treatment for malignant refractory ascites.

Subjects and Methods

Study Design

This study is a prospective multiinstitutional single-arm noncomparative phase I/II study for evaluating the safety and efficacy of transjugular transhepatic PVS for the treatment of malignant refractory ascites. The study design of the phase I portion consisted of the JIVROSG 3 × 3 method, which has been described in detail elsewhere [15]. In brief, this is a step-by-step safety evaluation in the first nine patients: a cohort of three patients is treated with transjugular transhepatic PVS, and if no severe adverse events occur during the observation period of 4 weeks, the next cohort of three patients is treated followed by the next observation period, and finally the third cohort of three patients is treated. The phase II portion was designed to enroll an additional 24 patients. To determine study outcomes, all enrolled patients were included in the intention-to-treat analysis.

Patients

Patients with refractory malignant ascites interfering with their daily life were eligible for participation in this study. Additional inclusion criteria were as follows: clear and serous ascites; patent hepatic veins and vena cava on contrast-enhanced CT; Eastern Cooperative Oncology Group performance status of 0–3; adequate organ function as defined by a hemoglobin level of 8.0 g/dL or higher, WBC count of 3000/mm^3/dL or higher, platelet count of 50,000/mm^3/dL or higher, prothrombin time of 50% or more, bilirubin level of 2.0 mg/dL or lower, serum creatinine level of 2.0 mg/dL or lower, normal ECG, PaO_2 level 70 mm Hg or higher at room air; and a life expectancy of at least 4 weeks. Exclusion criteria were as follows: manageable ascites with standard anticancer treatments; planned intraperitoneal drug administration; ascites caused by liver cirrhosis, mesothelioma, pseudomyxoma, or mucin-producing tumors; hemorrhagic or chylous ascites; active infectious disease; varices or ulcers in upper gastrointestinal tract; a history of hepatectomy; implanted cardiac pacemaker; or pregnant or nursing.

The study protocol was approved by the institutional review board at each institution before patient enrollment. Written informed consent was obtained from all patients. This study is registered under Clinical Trials Registry number C000000040 (www.umin.ac.jp/ctr/index.htm).

Technique of Transjugular Transhepatic PVS

Transjugular transhepatic PVS procedures were performed using a dedicated transjugular transhepatic PVS catheter and a TIPS system (Rösch-Uchida Transjugular Liver Access Kit, Cook Medical). The transjugular transhepatic PVS catheter is a urethane catheter with a hydrophilic coating, 8.2-French in diameter and 120 cm in length, accommodating a 0.035- or 0.038-inch guidewire at the tapered tip (Fig. 1). It has a tapered 5-French pigtail-shaped tip, five side holes along the 8.2-French section 14–40 cm from the tip, and a one-way valve located 70–80 cm from the tip. We designed a tapered pigtail catheter to soften its tip so as to avoid injury to the abdominal organs. The diameter of the section containing the valve is 10-French. The pressure-activated one-way valve opens when the internal pressure is greater than 2 cm H_2O pressure, thus allowing fluid to flow one way from the abdominal cavity to the vein.

Prophylactic IV antibiotics were administered just before the procedure. Each patient underwent conscious sedation with analgesics, and sedatives were administered according to individual needs. The patient was placed in the supine position on an angiography table. After administration of local anesthesia, the internal jugular vein was punctured under ultrasound guidance and an 11-French hemostatic sheath was placed into the inferior vena cava. A 5-French selective angiographic catheter was inserted through the sheath into a peripheral branch of the hepatic vein, and digital subtraction angiography was performed to confirm the shape of the hepatic vein and the position of the catheter tip. The 11-French sheath was advanced deeper into the hepatic vein by the over-the-wire technique. The choice of hepatic venous branch depended on its shape to fit the curve of the Rösch-Uchida needle of TIPS system. An inner catheter of the TIPS system was inserted into the tip of the sheath, and a Rösch-Uchida needle with a 5-French catheter was passed through the liver parenchyma to access the abdominal cavity. A stiff 0.035-inch Amplatz guidewire (Cook Medical) was inserted into the abdominal cavity through the catheter connecting to the abdominal cavity. The 11-French hemostatic sheath without a curved guiding cannula was advanced to the abdominal cavity, and the backward flow of ascites from the sheath was confirmed.

Subsequently, a transjugular transhepatic PVS catheter was inserted into the abdominal cavity through the 11-French hemostatic sheath, and then the sheath and guidewire were removed. The position of the transjugular transhepatic PVS catheter

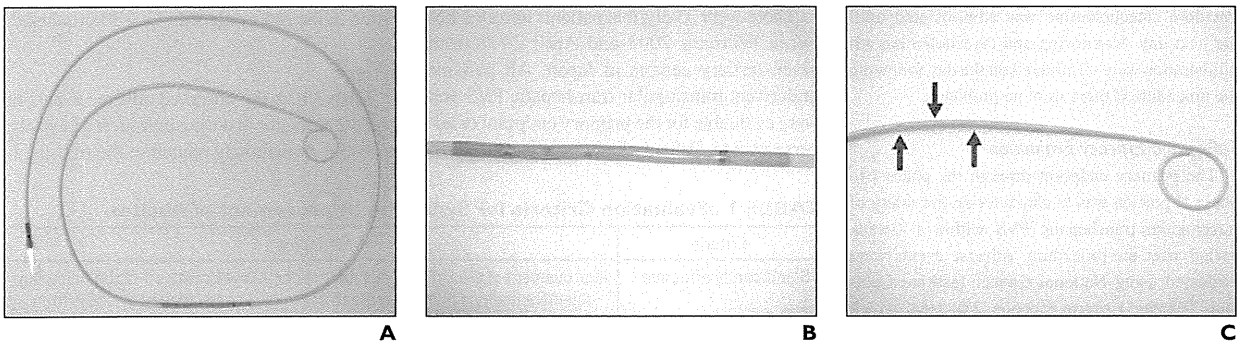

Fig. 1—Transjugular transhepatic peritoneovenous shunt (PVS) catheter.
A, Image shows tapered (5–10-French) transjugular transhepatic PVS catheter.
B, Image shows one-way valve designed to be positioned in right atrium.
C, Image shows pigtail-shaped catheter tip in abdominal portion. Side holes (*arrows*) to collect ascites are seen along 8.2-French section.

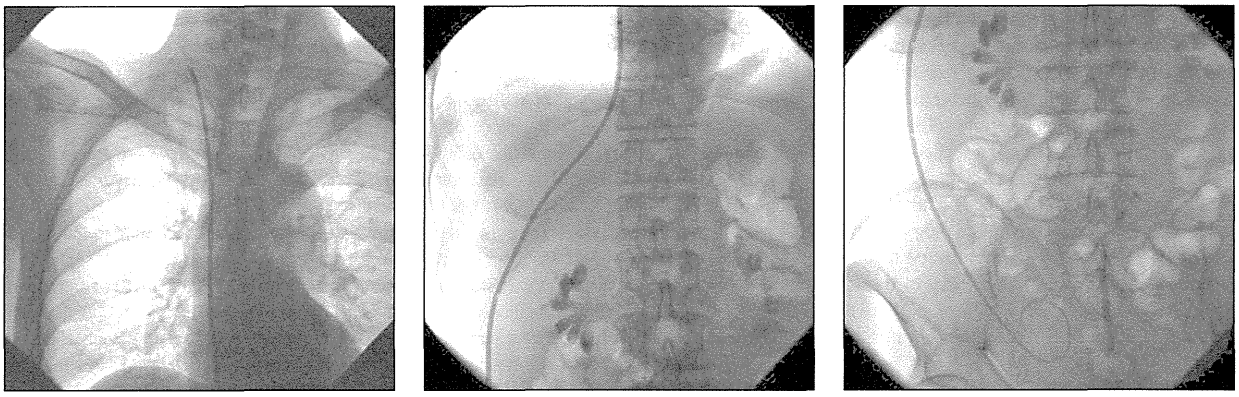

Fig. 2—Radiographs of positioning of transjugular transhepatic peritoneovenous shunt (PVS) catheter.
A, Radiograph shows chest after implantation of transjugular transhepatic PVS catheter.
B, Radiograph shows abdomen after implantation of transjugular transhepatic PVS catheter.
C, Radiograph shows pelvis after implantation of transjugular transhepatic PVS catheter.

was adjusted so that the tip and side holes were in ascites, and the one-way valve was in the superior vena cava. After the backward flow of ascites from the transjugular transhepatic PVS catheter was confirmed and the position of the transjugular transhepatic PVS catheter was verified by fluoroscopy, the catheter was sutured to the skin of the neck. The external section of the catheter was cut at 2–3 cm from the insertion site and capped with a small silicone cap. We did not totally implant the proximal tip of the catheter subcutaneously because we assumed that adverse events resulting from implanted proximal tip, such as bleeding or infection, might be considerable and confound the safety assessment of the "transhepatic" PVS, which is unique for the transjugular transhepatic PVS. The position of the catheter was recorded by radiography (Fig. 2). Abdominal and central venous pressure were measured and recorded during the procedure.

After the procedure was completed, vital signs of the patient were monitored, and continuous IV low-dose catecholamine was administered until the next day. Monitoring and catecholamine administration were terminated on the day following the procedure if there were no problems.

Safety and Efficacy Evaluation

The primary endpoint through the phase I to phase II portion was to characterize the safety of transjugular transhepatic PVS within a 4-week period after the procedure. Adverse events were evaluated using National Cancer Institute Common Toxicity Criteria (version 2.0) [16], which were the standard criteria for evaluating cancer treatments at the time of initiation of this study.

Secondary endpoints were the rate of technical success of the procedure and clinical efficacy. Clinical efficacy was evaluated at 1 week after the procedure and was followed up until death or the time of termination of the study. Because established standard criteria for symptom evaluation for ascites did not exist, we defined the efficacy criteria (Table 1).

Statistical Methods

This study was designed to detect the incidence of adverse events, which was the primary endpoint. The required number of patients was calculated to be 33, which included a dropout rate of 10%, and was based on the following variables: α, 0.05; power, 0.8; unacceptable rate of adverse events, 30%; estimated lowest rate of adverse events, 10%; and predicted rate of adverse events, 10%. Statistical analyses for patient demographics and adverse events were descriptive. The statistical significance level was set at 0.05 using a two-sided test. All statistical analyses were performed with PASW software (version 18, SPSS).

Results

Patient Characteristics and Follow-Up Period

There were 33 eligible patients enrolled between February 2003 and April 2007 from seven tertiary centers in Japan. All patients underwent transjugular transhepatic PVS and were evaluable for the primary endpoint of adverse events. Patient characteristics are summarized in Table 2. The median follow-up period was 34 days (range, 8–144 days). Eight patients died within 30 days after undergoing the transjugular transhepatic PVS procedure. In all subjects, the cause of deaths was judged to be disease progression, and the judgments were approved by the safety and efficacy evaluation committee, which is independent from this clinical trial group.

Results of Procedures

The transjugular transhepatic PVS catheter was successfully implanted in all patients. The access site was the right internal jugular vein in 28 patients (85%) and the left internal jugular vein in five patients (15%). Peritoneal access was established through the right hepatic vein in 32 patients (97%) and the middle hepatic vein in one patient (3%). The mean (± SD) pressure gradient between the abdominal cavity and central vein was 17 ± 6 cm H_2O. The duration of the procedure was 53 ± 30 minutes.

Safety

Table 3 lists the observed adverse events of grade 2 or higher that were considered possibly, probably, or definitely related to the transjugu-

TABLE 1: Evaluation Criteria for Symptom Improvement of Ascites

Criteria	Definition
Significantly effective	Improvement of the subjective symptom for > 1 week with ≥ 1 of the following objective findings of improvement: decrease in body weight to ≤ 95% from pretreatment weight, decrease in abdominal girth to ≤ 90%, and decrease in dose of diuretics
Moderately effective	Improvement of the subjective symptom for > 1 week without objective findings of improvement
Not effective	Not significantly effective and not moderately effective

TABLE 2: Patient Demographics

Characteristic	Value (*n* = 33 Patients)
Age (y), median (range)	53.2 (33–77)
Sex	
Male	11 (33)
Female	22 (67)
Performance status (Eastern Cooperative Oncology Group score)	
0	1 (3)
1	11 (33)
2	6 (18)
3	15 (45)
Primary site	
Stomach	13 (39)
Pancreas	4 (12)
Lung	3 (9)
Colon	2 (6)
Breast	2 (6)
Other	9 (27)
Use of diuretics	
Yes	26 (79)
No	7 (21)

Note—Except for age, all data are no. (%) of patients.

lar transhepatic PVS procedure. Overall, the transjugular transhepatic PVS procedure was well tolerated, with no severe adverse events encountered during the implantation. The most frequent adverse events were hypoalbuminemia (24%) and decrease in hemoglobin (18%), both of which occurred within 1–2 days after the procedure and resolved within 1 week. No grade 4 adverse events were encountered. No bleeding event related to the penetration of hepatic parenchyma was observed, and disseminated intravascular coagulation syndrome did not occur in any of the patients.

Clinical Efficacy

The efficacy of transjugular transhepatic PVS is summarized in Table 4. The clinical efficacy rate (significantly effective or moderately effective) 1 week after the procedure was 67%. In seven patients for whom the procedure was initially effective (significantly or moderately effective), an increase in ascites volume and progression of subjective symptoms was again observed 19–51 days (median, 25 days) after the transjugular transhepatic PVS procedure. The cause of the reincrease in ascites was catheter dysfunction in all seven patients. Catheter dysfunction was caused by fibrin sheath formation around the one-way valve in all patients, which was confirmed by angiography via the transjugular transhepatic PVS catheter (Fig. 3). Subsequently, additional treatments, such as catheter exchange or stripping of the fibrin sheath using a catheter and a guidewire, were undertaken. These procedures corrected the malfunctioning catheter in all patients; however, in five patients, reocclusion occurred within 10 days.

Discussion

This phase I/II study was performed as the initial step in the evaluation of transjugular transhepatic PVS. The JIVROSG 3 × 3 method, which was developed and validated in previous studies [15] by our group, was used for the phase I portion of this study. Because the concept of "dose escalation" in a phase I drug study is not applicable, the same transjugular transhepatic PVS intervention was performed throughout the study, and clinical efficacy was evaluated in all enrolled patients.

The inclusion criteria of this study were established according to the indications for the Denver shunt. In addition, patency of the vena cava, no history of cardiac pacemaker, no history of hepatic lobectomy, and no dilated intestine were included to secure a safe access route for transjugular transhepatic PVS. The exclusion criteria (i.e., cirrhosis and high risk for gastrointestinal bleeding) were added because of previous reports of severe adverse events resulting from PVS placement in cirrhotic patients [7, 11, 17, 18]. Won and coworkers [7] reported that 63% of 55 patients with refractory ascites developed variceal bleeding after Denver shunt placement. The characteristics of patients in this study, such as primary tumor, age, performance status, and the use of diuretics, may be consistent with typical patients with malignant refractory ascites.

For most of our study patients, the access site and the hepatic vein penetration site were the right internal jugular vein and the right hepatic vein, respectively, most likely because of the familiarity with right internal jugular access and the selection of the right hepatic vein resulting from experience with TIPS placement or other interventional procedures. In a few patients, however, the left internal jugular vein and middle or left hepatic vein were used, and the feasibility of these access sites was shown. Technical success was achieved in all patients from seven participating institutions, and the procedure time was approximately 1 hour. Thus, this technique is presumed to be feasible and can be generalized.

Concerning the safety of transjugular transhepatic PVS, it is significant that eight patients died within 30 days after transjugular transhepatic PVS placement, because patients considered to have 4 or more weeks

TABLE 3: Summary of Adverse Events Occurring in 33 Patients

Adverse Events	Grade 2	Grade 3	Grade 4	Total (%)
Decrease in hemoglobin	3	3	0	6 (18)
Hypoalbuminemia	8	0	0	8 (24)
Skin irritation at the access site	3	0	0	3 (9)
Pleural effusion	3	0	0	3 (9)
Congestive heart failure	0	1	0	1 (3)
Fever	1	0	0	1 (3)

TABLE 4: Clinical Efficacy of Transjugular Transhepatic Peritoneovenous Shunt for Malignant Refractory Ascites

Efficacy Parameter	No. (%) (n = 33 Patients)
Significantly effective	11 (33)
Moderately effective	11 (33)
Not effective	11 (33)

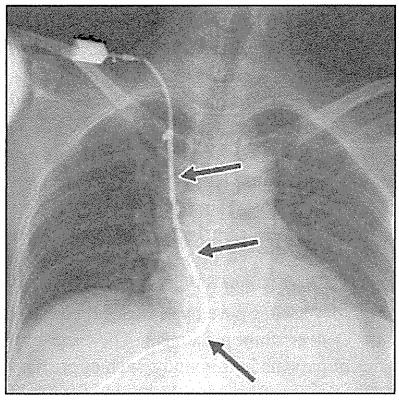

Fig. 3—Fibrin sheath formation around transjugular transhepatic peritoneovenous shunt (PVS) catheter. Angiogram shows tip of transjugular transhepatic PVS catheter at right internal jugular vein. Contrast material stagnated within and around catheter (*arrows*), which is compatible with fibrin sheath, is seen.

of life expectancy were enrolled. However, previous reports on PVS have also described early patient deaths independent from the procedure [1–3, 19, 20]. Thus, this phenomenon can be understood as a general tendency in patients with malignant refractory ascites who are candidates for PVS. Decreases in serum albumin and hemoglobin have been reported in previous studies of PVS and were explained as the results of transient dilution caused by the inflow of ascites into the blood circulation [3]. Transient pleural effusion and congestive heart failure have also been reported as adverse events after PVS and could be also explained by the increased blood volume caused by the inflow of ascites. Thus, these adverse events in our study are not thought to be specific to transjugular transhepatic PVS but to be the general results of PVS. Skin inflammation around the transjugular transhepatic PVS catheter insertion site was an adverse event unique to this procedure, although it was not a severe adverse event. Bleeding events related to the penetration of hepatic parenchyma, which was considered as an adverse event specific to transjugular transhepatic PVS, were not observed. Therefore, on the basis of these safety results, the transjugular transhepatic PVS procedure is thought to be sufficiently safe to apply future clinical usage and evaluation.

Concerning efficacy, 67% of patients achieved symptomatic improvement (significantly effective or moderately effective). The efficacy of PVS in previous studies is controversial because the evaluation criteria, including objective findings, varied and the comparability was uncertain [1, 3]. Given that the goal of this treatment is to palliate subjective symptoms, precise and consistent evaluation of the efficacy of transjugular transhepatic PVS in comparison with previous reports of PVS is impossible. However, in most of the previous reports, efficacy rates based on the improvement of symptoms were approximately 70%. Therefore, the efficacy of transjugular transhepatic PVS with regard to symptom improvement is equivalent to that in previous reports of other types of PVS.

The reason for fibrin sheath formation in seven of the 22 patients in whom the procedure was judged as significantly effective or moderately effective may be that the intravascular catheter used in transjugular transhepatic PVS is longer than the intravascular catheters used in other types of PVS or that the transjugular transhepatic PVS catheter has a one-way valve in the central vein. If these explanations are correct, they are intrinsic drawbacks of transjugular transhepatic PVS and cannot be avoided. However, no increase in ascites was seen in the other 15 patients. There have also been quite a few reports of fibrin sheath formation in previous PVS procedures [21]. The device of transjugular transhepatic PVS is developing and can be improved. Thus, the efficacy of transjugular transhepatic PVS should not be denied on the basis of this rate of fibrin sheath formation. In cases of fibrin sheath formation, exchanging the transjugular transhepatic PVS catheter is much easier compared with exchanging catheters of other implanted shunt systems, such as Denver shunts. This attribute seems to be a great advantage of transjugular transhepatic PVS. Nevertheless, improvement of the device may be the key for better clinical outcome in transjugular transhepatic PVS, particularly in the surface of the catheter where the fibrin sheath is formed. Antithrombogenic coating on the catheter would be one of the solutions. Other possibilities for refining the transjugular transhepatic PVS system include improvement of the function of the one-way valve and enlargement of the inner diameter of the catheter.

The following study limitations should be noted. The first is that the sample size was limited to 33 patients. Thus, there is a possibility that uncommon adverse events of transjugular transhepatic PVS were not detected. The second limitation is that this study was a single-arm and noncomparative study. Although the reported clinical efficacy of Denver PVS is 77.95% according to a systematic review by Becker et al. [1], which is higher than our results of 67%, we cannot determine the superiority in efficacy without direct comparison by randomized controlled trial.

With this clinical trial, we conclude that the newly developed transjugular transhepatic PVS is feasible and a safe procedure for managing refractory ascites in patients with cancer, and transjugular transhepatic PVS has sufficient efficacy to be evaluated by a larger clinical trial in the future. In addition, improvement of the transjugular transhepatic PVS catheter is needed to reduce fibrin sheath formation and to obtain better clinical outcomes.

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Clinical Studies

Phase I/II Multiinstitutional Study of Uterine Artery Embolization with Gelatin Sponge for Symptomatic Uterine Leiomyomata: Japan Interventional Radiology in Oncology Study Group Study

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PURPOSE: This multicenter prospective study was conducted to evaluate the safety and the efficacy of uterine artery embolization (UAE) with gelatin sponge for symptomatic leiomyomas.

MATERIALS AND METHODS: Patients with symptomatic uterine leiomyomas were enrolled and treated with UAE. In phase I, nine patients were evaluated for safety. In phase II, 24 patients were accrued, and an intent-to-treat analysis was performed on all 33 patients. The primary endpoint was safety. Secondary endpoints included technical success, hospital stay, change in symptoms, leiomyoma volume on magnetic resonance (MR) imaging, and incidence of treatment failure.

RESULTS: UAE procedures were performed for all 33 patients. Two patients were lost to follow-up at 3 and 12 months. The median follow-up period was 33.4 months. Minor adverse events (AEs) occurred in 10 patients (33%); major AEs of permanent amenorrhea and leiomyoma expulsion occurred in two (6%). The most common AE was transient amenorrhea. Technical success was achieved in all patients. The median hospital stay was 5 days. At 12 months after UAE, menorrhagia had improved in 90% of patients, pelvic pain in 78%, and bulk-related symptoms in 97%. The mean reduction in leiomyoma volume on MR imaging at 12 months was 61%. Treatment failure occurred in one patient, who underwent hysterectomy for recurrent menorrhagia at 21 months.

CONCLUSIONS: UAE with gelatin sponge is safe, with efficacy comparable to other embolic agents based on published data. Gelatin sponge should be an option for UAE, but a prospective comparison versus other standard UAE embolic agents may be warranted.

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Abbreviations: AE = adverse event, FSH = follicle-stimulating hormone, PVA = polyvinyl alcohol, QOL = quality of life, SIR = Society of Interventional Radiology, TAGM = tris-acryl gelatin microsphere, UAE = uterine artery embolization

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VARIOUS embolic agents have been used for uterine artery embolization (UAE); however, no definitive consensus exists regarding the choice of embolic agent. From previous reports, the choice of embolic agent seems to depend not only on its safety and efficacy, but also on its availability in each country.

Since the introduction of UAE in 1995, nonspherical polyvinyl alcohol (PVA) has been most widely used (1–4). Spherical agents such as tris-acryl gelatin microspheres (TAGMs) and

spherical PVA particles were developed in the past decade, and recently, the use of TAGMs has been expanding. In the United States, European countries, and some other countries, several types of embolic agents are available for UAE. In contrast, no embolic agent is approved for UAE in Japan, and only gelatin sponge is available.

Gelatin sponge has been used for embolization in various fields for more than 30 years. In gynecology, it has been used as part of the standard interventional procedure to control the bleeding of obstetric hemorrhage or malignant tumors (5). In the early years of UAE, gelatin sponge was used, and favorable mid- and long-term outcomes were reported in retrospective and single-institutional studies (6,7). However, no clinical trial has yet prospectively investigated gelatin sponge for UAE. Therefore, we undertook a phase I/II multiinstitutional prospective clinical trial of UAE with gelatin sponge (Japan Interventional Radiology in Oncology Study Group trial 0302). In this study, we evaluated the safety and the efficacy of UAE with gelatin sponge for patients with symptomatic uterine leiomyomata.

MATERIALS AND METHODS

Patient Eligibility

Premenopausal women with symptomatic uterine leiomyomas confirmed by imaging studies were eligible. Symptoms uncontrolled with medical therapies, adequate organ function, and an Eastern Cooperative Oncology Group performance status of 0 to 1 were required.

Exclusion criteria included pregnancy, nursing, or desire for future pregnancy; active inflammatory disease; pelvic malignancy; hormonal therapy within 12 weeks; contraindication to magnetic resonance (MR) imaging; contraindication to iodized contrast material; uncontrolled comorbid disease; and adenomyosis confirmed with MR imaging.

This study was approved by the ethics committee of the Japanese Society of Interventional Radiology and the institutional review boards of the participating institutions. All patients provided written informed consent.

Study Endpoints

The primary endpoint was safety, and the secondary endpoints were clinical outcomes and the incidence and grade of adverse events (AEs).

Study Design

This was a multiinstitutional, single-arm, open-label, noncomparative trial. In phase I, nine patients were enrolled and evaluated for safety according the three-by-three method of the Japan Interventional Radiology in Oncology Study Group. This method has been described in detail elsewhere (8), and, briefly, consists of three phases with intervals of 4 weeks between phases. With three patients entered per phase, a total of nine patients were evaluated. This method was developed to assure the safety of a new treatment with a meticulous, step-by-step approach.

In phase II, an additional 24 patients were enrolled, and the study was completed with a total of 33 patients. All enrolled patients were included in the intent-to-treat analysis for the primary and secondary endpoints. A total of 10 institutions participated in this study. Patient accrual started in May 2004 and terminated in April 2006.

Embolic Material

We used gelatin sponge in this study. Gelatin sponge is absorbable embolic material that dissolves within several days to several weeks. At present, a number of types of gelatin sponge are on the market worldwide. In Japan, three products—Spongel (Astellas, Tokyo, Japan), Gelfoam (Pfizer Japan, Tokyo, Japan), and Gelpart (Nippon Kayaku, Tokyo, Japan)—are commercially available; however, Gelpart was not available at the time of the present study. The products are supplied in various forms: Spongel in blocks of two sizes (2.5 × 5 × 1 cm and 7 × 10 × 1 cm), Gelfoam in sheets of two sizes (8 × 12.5 × 1 cm and 2 × 6 × 0.7 cm), and Gelpart in 1-mm or 2-mm particles in bottles. We used a 2.5 × 5 × 1 cm Spongel block, which weighs approximately 235 mg. A block was cut into 1-mm cubes with a scalpel and scissors according to the previously reported procedure (6) and sterilized by ethylene oxide. This preparation was performed by the principal investigator, and the particles were distributed to coinvestigators.

UAE Procedure

The UAE was performed as follows. Bilateral uterine artery catheterization was performed under local anesthesia, and a vascular sheath was inserted from the unilateral or bilateral femoral arteries. A 4-F or 5-F angiography catheter was advanced into the internal iliac arteries and a coaxial microcatheter system was used to select the uterine arteries. Embolization of both uterine arteries was performed with 1-mm^3 gelatin sponge particles. The gelatin sponge was diluted with approximately 10 mL of nonionic contrast material and aspirated in 1-mL or 2.5-mL syringes. The embolic material was injected under fluoroscopy and saline solution was injected to avoid aggregation of the gelatin sponge in a microcatheter. The embolization endpoint was stasis of blood flow in the ascending branch of the uterine artery, as confirmed by injection of contrast material under fluoroscopy. Embolization of the ovarian artery was not allowed even if the supply from this artery to the leiomyomas was observed on angiography. Evaluation of pelvic arterial anatomy was performed with aortography during UAE or MR angiography before UAE in all patients. Pain management was administered according to local practice.

The size and type of microcatheter systems, use of prophylactic antibiotics, total amount of gelatin sponge used, and pain control procedures were reported. These data were collected with dedicated case report forms.

Outcome Measures

The primary endpoint was the incidence and type of AEs. AEs and their causality and severity were evaluated based on the Society of Interventional Radiology (SIR) classification (9).

Secondary endpoints were clinical outcomes, which included technical success; linear analog pain scale score at 6, 12, 18, and 24 hours and 2 and 7 days after UAE; hospital stay; change in symptom score ranging from 0 (marked worsening) to +10 (marked improvement) on a scale on which +5

represented no change; change in volume of dominant leiomyomas on MR imaging; ovarian function measured by follicle-stimulating hormone (FSH) and presence or absence of menstruation; and treatment failure, defined as the need for subsequent intervention for symptom control, including hysterectomy and repeated embolization. According to the SIR guidelines, the UAE was considered successful when bilateral UAE was confirmed (10). Unilateral UAE was considered successful if only single-sided uterine arterial flow was present.

Baseline clinical symptoms were scored before the UAE on a scale of 0 (no interference with daily life) to 10 (marked interference with daily life). Baseline imaging was obtained by MR imaging according to the standardized protocol at each hospital with or without contrast enhancement.

Symptom change was assessed by patients with a score divided into three levels: marked improvement (score 8–10), moderate improvement (score 5–8), and none (score 5 or lower).

We assessed outcome measures at 1, 3, 6, 9, and 12 months and annually thereafter, except for the postprocedural pain score. We present 12-month results, with the exceptions of major AEs and treatment failure, which were reported through the final analysis in September 2007.

All data were collected with case report forms. Adverse events were to be reported with other items on the schedule. Severe adverse events were to be reported immediately after the events.

Statistical Analysis

In phase I, a cohort of nine patients was considered to be adequate for quick termination when the incidence of severe AEs associated with UAE with gelatin sponge exceeded one third of the population. Throughout phase I and phase II, the study was designed to detect the incidence of AEs set at 10% for the least, 10% for the predicted, and 30% for the unacceptable, with a power of 80%. Therefore, the target number of patients to be accrued was calculated to be 33, including an anticipated dropout rate of 10%.

Demographic and baseline variables were summarized by descriptive statistics. Comparisons with baseline data were performed for the FSH level with paired *t* tests. The statistical significance level was set at .05. All statistical analyses were performed with SPSS software (version 11.01; SPSS, Chicago, Illinois).

RESULTS

Patients

A total of 33 patients were enrolled. All received UAE and were assessable for study endpoints. Patient characteristics are shown in **Table 1**. Two patients were lost to follow-up at 3 and 12 months. In one patient, MR imaging was not performed at 12 months. The median follow-up period was 33.4 months (range, 13.6–41.2 months).

Table 1
Baseline Characteristics of the Patients (*N* = 33)

Variable	Value
Age (y)	
Median	43
Range	37–54
Previous treatment	
Myomectomy	5 (15)
Hormonal therapy	11 (33)
Other medication	19 (58)
Dominant leiomyoma location	
Intramural	26 (79)
Submucosal	5 (15)
Subserosal	2 (6)
No. of leiomyomas	
1	9 (27)
2–5	14 (42)
> 5	10 (30)
Dominant leiomyoma volume (mL)	
Median	321
Range	64–1,922
Presenting symptom	
Menorrhagia	32 (97)
Severity score	6.9 ± 2.6
Pelvic pain	29 (88)
Severity score	4.6 ± 3.0
Bulk-related symptoms	32 (97)
Severity score	6.7 ± 2.5

Note.—Values in parentheses are percentages. Values expressed as mean ± SD, where appropriate.

Primary Outcome

During phase I, major AEs were not encountered; therefore, the study proceeded to phase II. Among all enrolled patients, minor AEs were reported in 10 patients (33%) and major AEs were reported in two patients (6%; **Table 2**). The most common AE was transient amenorrhea. Other AEs were observed in one patient each. Permanent amenorrhea occurred in one patient who was 46 years of age whose menstruation stopped 6 months after UAE. Leiomyoma expulsion occurred at 2 months in one patient with a submucosal leiomyoma, and the leiomyoma was removed successfully without hospitalization. Complications of angiography were not encountered, and no deaths occurred. Pelvic infection, postembolization syndrome requiring prolonged admission or readmission, radiation injury, adverse drug reactions, and pulmonary embolism were not encountered.

Secondary Outcomes

UAE procedures.—Technical success was achieved in all 33 patients. Dominant ovarian arterial supply to leiomyomas was not encountered. The median procedural time was 55 minutes (range, 29–120 min), and the median fluoroscopic time was 18 minutes (range, 6–44 min). The median mass of gelatin sponge used was 168 mg (range, 80–320 mg). The sizes of the microcatheters used were 2.3 F (Microferret [Cook, Bloomington, Indiana] or Tracker-18 [Boston Scientific, Natick, Massachusetts]; *n* = 7); 2.4 F (On-the-Road [Solution, Yokohama, Japan], *n* = 2); 2.5 F (FasTracker-18 [Boston Scientific]; *n* = 3); 2.6 F (Shirabe High Flow [Piolax, Yokohama, Japan]; *n* = 3); 2.7 F (Renegade Hi-Flo [Boston Scientific]; *n* = 17); and 2.8 F (Progreat Omega [Terumo, Tokyo, Japan]; *n* = 1). Thirty-two patients underwent UAE under local anesthesia and one underwent UAE under conscious sedation. Primary pain control methods were epidural analgesic agents in 17 patients, intravenous or subcutaneous opioid agents in 14 patients, and intramuscular pentazocine in two patients. Oral or suppository nonsteroidal antiinflammatory drugs were administered in combination with primary analgesic agents. A prophylactic antibiotic was used for 1–4 days in all patients. The type of antibiotics were cephazolin (*n* = 22), piperacillin (*n* = 7), fosfomycin (*n* = 2), flomoxef (*n* = 1), and faropenem (*n* = 1).

Pain score.—The mean and SD vi-

Table 2
Summary of AEs

Event	SIR Class	At ≤ 1 Month	At 1–12 Months
Major			
Leiomyoma expulsion	C	1 (3)	0
Permanent amenorrhea	E	NE	1 (3)
Minor			
Transient amenorrhea	A	NE	6 (18)
Anemia	B	0	1 (3)
Elevated ALP	A	1 (3)	0
Elevated ALT	A	1 (3)	0
Elevated bilirubin	A	0	1 (3)

Note.—Values in parentheses are percentages. ALP = alkaline phosphatase; ALT = alanine aminotransferase; NE = not evaluable.

Table 3
Changes in Symptom Scores

Symptom/Improvement	1 Month	3 Months	6 Months	12 Months
Menorrhagia	*n* = 32	*n* = 31	*n* = 31	*n* = 30
Marked	16 (50)	21 (68)	23 (74)	23 (77)
Moderate	10 (31)	6 (19)	5 (16)	4 (13)
None	6 (19)	4 (14)	3 (10)	3 (10)
Pelvic pain	*n* = 29	*n* = 28	*n* = 28	*n* = 27
Marked	14 (48)	14 (50)	16 (57)	17 (63)
Moderate	7 (24)	7 (25)	8 (29)	4 (15)
None	8 (28)	7 (25)	4 (14)	6 (22)
Bulk-related symptoms	*n* = 32	*n* = 31	*n* = 31	*n* = 30
Marked	15 (47)	26 (84)	22 (71)	26 (87)
Moderate	13 (40)	4 (13)	8 (26)	3 (10)
None	4 (13)	1 (3)	1 (3)	1 (3)

Note.—Values in parentheses are percentages.

sual analog scale score for pain was as follows: baseline, 0.5 ± 1.8; 6 hours, 5.8 ± 3.7; 12 hours, 4.8 ± 3.7; 18 hours, 3.7 ± 2.8; 24 hours, 2.7 ± 2.6; 2 days, 2.4 ± 2.3; and 7 days, 0.2 ± 0.2.

Length of hospital stay.—The median hospital stay was 5 days (range, 2–10 d). Readmission was not observed in any case.

Clinical outcome.—Symptomatic changes are summarized in **Table 3**. At 12 months after UAE, moderate to marked improvement was observed in terms of menorrhagia in 90% of patients, in pelvic pain in 78% of patients, and in bulk-related symptoms in 97% of patients.

Imaging outcome.—Dominant leiomyoma volume on MR imaging is presented in **Table 4**. At 12 months after UAE, the volume reduction was 61.4% (95% CI, 52.9%– 69.9%).

Ovarian function.—No statistically significant increase in FSH level was demonstrated (**Table 5**). In six patients with transient amenorrhea, the median baseline FSH level was 9.2 mIU/mL. In one patient with permanent amenorrhea, the FSH level showed an increase from a baseline of 11.4 mIU/mL to 152.5 mIU/mL at 12 months.

Treatment failures.—In one patient, hormonal therapy was performed for recurrent bleeding and anemia at 12 months; however, these symptoms were not controlled. This patient underwent hysterectomy at 21 months. No patients underwent repeat UAE. Therefore, the rate of treatment failure was 3% (ie, one of 33).

DISCUSSION

Data regarding UAE with nonspherical PVA, spherical PVA, and TAGMs have been published worldwide, but there have been few studies of gelatin sponge for UAE except for single-institution experiences from Japan (6,7). Follow-up procedures or intervals vary among studies; however, there are few differences in major clinical outcomes between studies that used gelatin sponge and studies that used other embolic agents. Therefore, UAE with gelatin sponge shows safety and efficacy similar to UAE with other widely distributed embolic agents.

Several studies comparing embolic materials for UAE have been reported. Spies and colleagues (11) conducted a randomized controlled trial comparing TAGMs with nonspherical PVA by measuring the recovery after UAE and the 3-month clinical outcome. No significant difference was noted between the two embolic materials in peri- and postprocedural symptoms, tumor infarction, patient satisfaction, symptom improvement, and quality of life (QOL). A difference was observed only in the incidence of microcatheter occlusion, which was more common with PVA. Subsequently, the investigators performed a similar randomized controlled trial (12) comparing TAGMs and spherical PVA. Although no significant differences were observed in symptom control, QOL, and AEs, 500–700-μm PVA spheres were associated with a significantly higher rate of failed tumor infarction, which resulted in the early termination of the trial. In response to these results, Rasuli and coworkers (13) performed a historical comparison of spherical versus nonspherical PVA particles for UAE; UAE with spherical PVA particles resulted in less leiomyoma shrinkage and less improvement in clinical symptoms than UAE with nonspherical PVA, which supported the results of the previous trials (11,12). In terms of the degree of tumor infarction after UAE, Siskin and colleagues (25) undertook a randomized study comparing TAGM with spherical PVA. They evaluated the degree of tumor infarction using contrast-enhanced MR imaging. UAE with TAGMs showed a significantly greater degree of tumor infarction than UAE with spherical PVA, and the authors concluded that TAGMs should be the preferred embolic material for UAE. Conceptually, the spherical shape of spherical PVA particles could improve the tendency of the material to clump in the catheter; however, previous clinical trials have demonstrated the clinical and

Table 4
Changes in Dominant Leiomyoma Volume

Value	Baseline	3 Months	6 Months	12 Months
No. of Pts.	33	32	32	30
Mean volume (mL)	298 (171–426)	180 (83–277)	157 (64–251)	138 (52–224)
Mean reduction (%)	NA	43.7 (36.6–50.8)	53.6 (45.7–61.4)	61.4 (52.9–69.9)

Note.—Values in parentheses are 95% CIs. NA = not applicable.

Table 5
Changes in FSH Levels

Interval	No. of Pts.	Mean FSH (mIU/mL)	*P* Value
Baseline	33	10.3 (6.8–13.5)	NA
3 Months	32	16.7 (7.5–25.9)	.065
6 Months	32	15.3 (8.6–21.9)	.056
12 Months	31	20.7 (5.9–35.4)	.708

Note.—Values in parentheses are 95% CIs. *P* values comparing data at baseline and each month were calculated with paired *t* tests. NA = not applicable.

imaging failure of spherical PVA (12,13). To our knowledge, no study has compared gelatin sponge versus another embolic material.

The incidence of severe AEs in the present study was 6%, which was similar to those of previous reports (0%–11%; **Table 6**) (2–4,6,7,11,14–17). Minor AEs occurred at a rate of 33% in the present study, which was also similar to those of the other studies (20%–53%). Transient amenorrhea, which was seen in 18% of patients, was the most frequent AE, although no significant elevation in FSH levels was observed. Hovsepian and colleagues (18) reported that, within a 6-month follow-up period, no significant difference in FSH levels or new-onset menopausal symptoms was observed among patients undergoing UAE, hysterectomy, or myomectomy in their prospective comparison. In the present study, one case of permanent amenorrhea occurred in a patient who was 46 years of age. Of the six patients who experienced the complication of transient amenorrhea, three were 45 years of age or older. The incidence of amenorrhea after UAE is highly age-dependent, and the reported occurrence in women 45 years of age or older is 26%–58% (18,19).

The technical success rate of 100% in the present study is comparable to those of previous reports (Table 6). No periprocedural complications were observed. We did not experience any case of aggregation of gelatin sponge particles in the microcatheters. Not only nonspherical PVA particles, but also spherical PVA particles, are known to have a tendency to aggregate in microcatheters and vessels (11,20). Gelatin sponge particles are also quoted to have the same tendency; however, the use of gelatin sponge differs depending on the gelatin sponge product, institute, or country. Our procedure of preparing the gelatin sponge (Spongel) was similar to that of Katsumori and coworkers (6) and consisted of manual shaving and cutting of a block into 500–1,000-μm particles. With gelatin sponge prepared by this technique, no microcatheter occlusion or proximal arterial occlusion was experienced in the present study.

In the present study, the average maximum visual analog scale score for subjective pain after UAE was 5.8. In previous randomized and nonrandomized comparison studies (11,12, 21), the maximum score ranged from 3.0 to 5.9 after UAE, which was similar to that observed in the present study. In addition, there was no significant difference between nonspherical PVA particles and TAGMs.

Direct comparison of the cost of each embolic material in UAE practice is difficult because the availability varies greatly among countries. Dembek and colleagues (22) reported that the UAE procedure costs were significantly lower than those of myomectomy or hysterectomy in the United States, although no significant difference was noted in 12-month payer costs, mainly because of the high cost of follow-up imaging. In the present study, the UAE procedure costs were reported as a lump sum. The type and quantity of the embolic materials were not evaluated; therefore, the influence of the embolic materials on the total UAE cost was not determined. The price of embolic materials may vary depending on the country; however, the approximate price of one vial of TAGMs (Embosphere) is $240, whereas that of a block of gelatin sponge (Spongel) is $2. Given the variable use of each embolic material, the cost per procedure would be approximately $960 for TAGMs and $5 for gelatin sponge, approximately a 200-fold difference. Differences in local practices such as the length of hospital stay or the type of pain control may affect the total cost of UAE. Also, we did not perform a cost analysis in the present study; however, the low cost of gelatin sponge may have an impact on the medical cost of UAE. As long as the safety and efficacy are demonstrated in an evidence-based manner, the use of low-cost embolic materials is important to reduce the escalating health care cost of UAE.

Several weaknesses of the present trial should be acknowledged. First, this trial was not a randomized controlled trial, and therefore a direct comparison with other embolic materials was not possible. Spies (23) pointed out the importance of properly designed randomized controlled trial comparing the new embolic agents versus the established ones to answer the key question of symptom relief and tumor infarction predicting symptom recurrence. Nevertheless, our data are of value as a baseline for future randomized controlled trials of

Table 6
Comparison of Clinical Outcome of Embolic Agents in Symptomatic Leiomyomas (2–4,6,7,11,12,14–17)

Study, Year	Embolic Particle Size (μm)	Study Design	No. of Pts.	Technical Success (%)	AEs (%)	Symptom Improvement (%)	Leiomyoma Volume Reduction (%)
Nonspherical PVA							
Pelage et al (2), 2000	150–300	Prospective	76	95	Transient amenorrhea; 3; permanent amenorrhea, 5; prolonged postembolization syndrome, 9	95 (2 y)	52 (6 mo, US)
Spies et al (3), 2002	500–710	Prospective	291	99	Minor, 7; major, 4.3	NA	NA
Walker and Pelage (4), 2002	150–500	Prospective	395	99	Infection (hysterectomy), 1; leiomyoma passage, 2; permanent amenorrhea, 7; transient amenorrhea, 2	Menorrhagia, 84; pain, 79; bulk, 82	67 (6 mo)
Spies et al, (11) 2004	355–710	RCT*	46	99	17	Scores equivalent to TAGM (3 mo)	NA
Volkers (15), 2006	355–500	RCT†	88	82.7	Minor, 25.9; major, 4.9 (in-hospital); minor, 53.1; major, 11.1 (discharge 6 weeks)	Menorrhagia, 96.3 (2 y)	60.5 (2 y)
Spherical PVA							
Spies et al (12), 2005	500–900	RCT*	17	100	NA	QOL and symptom scores inferior to TAGM	NA
Siskin et al (25), 2006	500–1,200	Cohort	77	NA	26	88.3 (6 mo)	43.7 (6 mo)
TAGMs							
Spies et al (16), 2001	500–900	Prospective	30	100	Minor, 33; major, 0	Menorrhagia, 100 (6 mo)	—
Spies et al (11), 2004	500–900	RCT*	54	99	Minor, 20; major, 0	Scores equivalent to TAGM (3 mo)	NA
Spies et al (12), 2005	500–900	RCT*	19	95	NA	QOL and symptom scores superior to spherical PVA	NA
Lohle et al (17), 2006	500–1,200	Prospective	158		Permanent amenorrhea, 11; transient amenorrhea, 13; leiomyoma expulsion, 10	Menorrhagia, 91; pain, 92; bulk, 92 (12 mo)	66
Gelatin sponge							
Katsumori et al (6), 2002	500–1,000	Case series	60	98	Leiomyoma expulsion, 3; permanent amenorrhea, 2	Menorrhagia, 100; bulk, 100 (12 mo)	70
Katsumori et al (7), 2005	500–1,000	Prospective	96	NA	Minor, 23; major, 3	96 (1 y), 94.5 (2 y), 89.5 (3 y), 89.5 (4 y), 89.5 (5 y)	—
Present study, 2009	500–1,000	Prospective phase I/II	33	100	Permanent amenorrhea, 3; transient amenorrhea, 18; leiomyoma expulsion, 3	Menorrhagia, 90; bulk, 76; pain, 96 (12 mo)	61

Note.—NA = not available; RCT = randomized controlled trial.
* RCT comparing embolic agents in UAE.
† RCT comparing UAE versus other treatments.

embolic materials including gelatin sponge. Second, we did not measure QOL with preexisting QOL instruments. Although subjective symptom reports like those in the present study are essential for evaluation of the efficacy of UAE, QOL scores on instruments such as the Uterine Fibroid Symptom QOL questionnaire, Short Form–12, Short Form–36, or EuroQol have a positive meaning in the setting of the endpoints for UAE trials. Third, we did not evaluate contrast-enhanced MR imaging for follow-up imaging after UAE. Recently, this issue has been amplified with an increase in data with spherical PVA showing an unacceptably high rate of failed tumor infarction, and with data suggesting a relationship between incomplete tumor infarction and long-term clinical failure (20,24,25). As for UAE with gelatin sponge, Katsumori and coworkers (7,26) evaluated the association of tumor infarction on contrast-enhanced MR imaging with long-term clinical outcome. Of 221 cases, 100% infarction