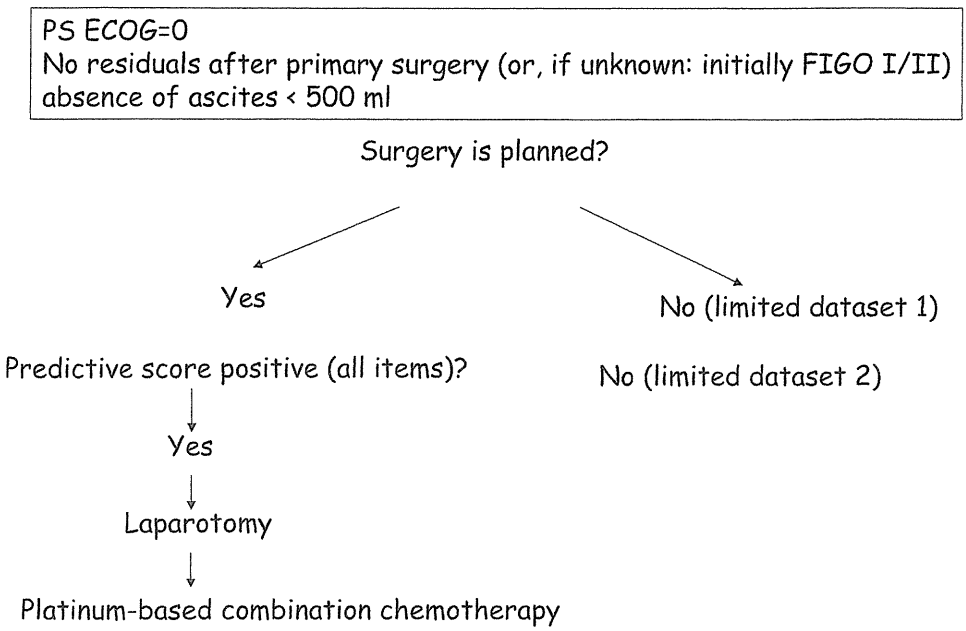

図1 AGO DESKTOP OVAR II : Prospective validation of a predictive score for resectability in platinum-sensitive ROC (PFS > 6 months)

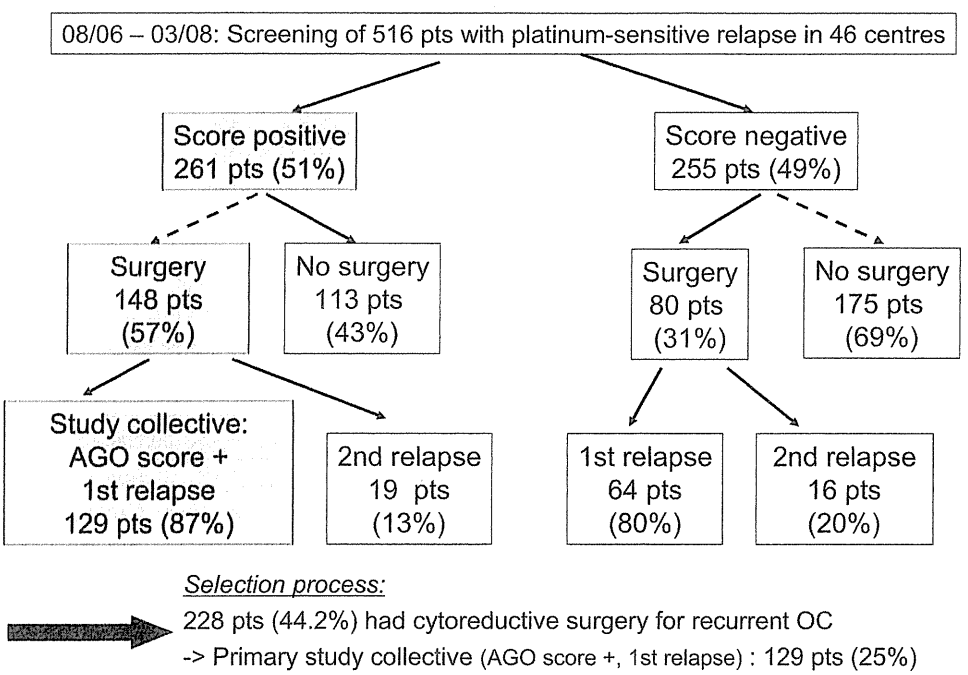

図2 AGO DESKTOP OVAR II — FLOW CHART

卵巣癌症例で，PS：0，初回手術で残存腫瘍なし，腹水がないかあっても少量である患者を対象としてSCSを行い実際に完全摘出が可能であるのかを検証している．さらにその後にSCS＋化学療法と化学療法単独のランダム化比較試験が計画されている（図4）．また，Gynecologic Oncology Group（GOG）においてもSCSの有無を割り付けるランダム化比較試験（GOG213）が実施されている（図5）．

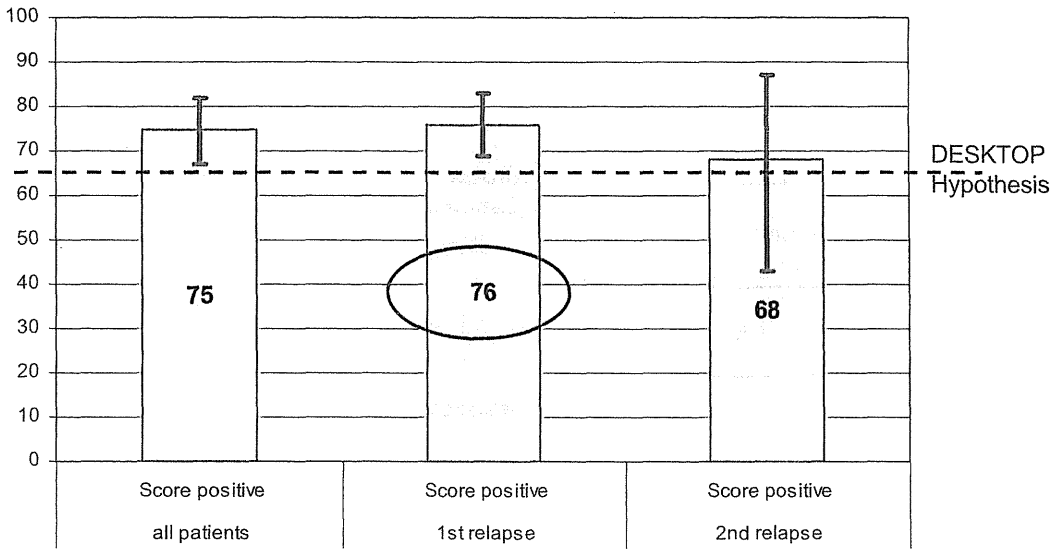

図3 AGO DESKTOP OVAR II：Surgical results
Frequency of complete resection by applying the AGO Score

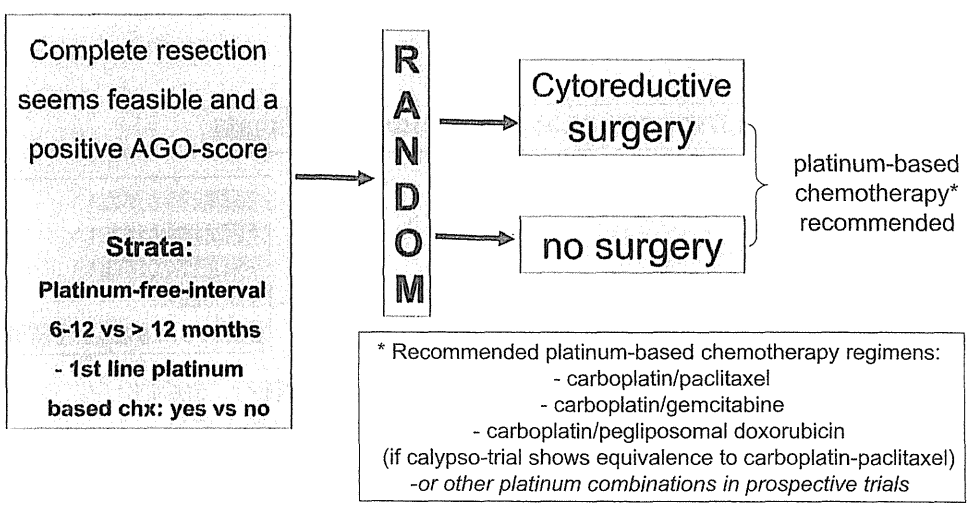

図4 AGO-OVAR DESKTOP III：A randomized trial evaluating cytoreductive surgery in patients with platinum-sensitive recurrent ovarian cancer

SCS 症例の検討—慈恵医大—

慈恵医大における再発卵巣癌に対する SCS に関して後方視的検討を行った．東京慈恵会医科大学附属病院，東京慈恵会医科大学附属青戸病院，東京慈恵会医科大学附属第三病院，東京慈恵会医科大学附属柏病院の4病院において初回手術が2000年以降に施行され，6カ月以上の TFI を有する104例の再発上皮性卵巣癌を対象とした．SCS の適応決定に際しては明確な基準がないのが現状であったが，遠隔転移がない，腹膜播種がない，多量腹水がない，PS が良いなどの条件を満たし，場合によっては臓器合併切除によって腫瘍が摘出できると考えられた症例に対して SCS を検討した（図6）．再々発例を含む25例に対して SCS が施行された．一方，多発転移，癌性腹膜炎があるものは当然ながら，その他に明確な基準はない中で SCS を施行しなかった症例は79例であった．SCS 施行例において評価可能であった19例の詳細を表6に示す．完全摘出を成し得た症例は19例中11例（58%）であった．

自験例をまとめると，1. 手術適応の決定に際

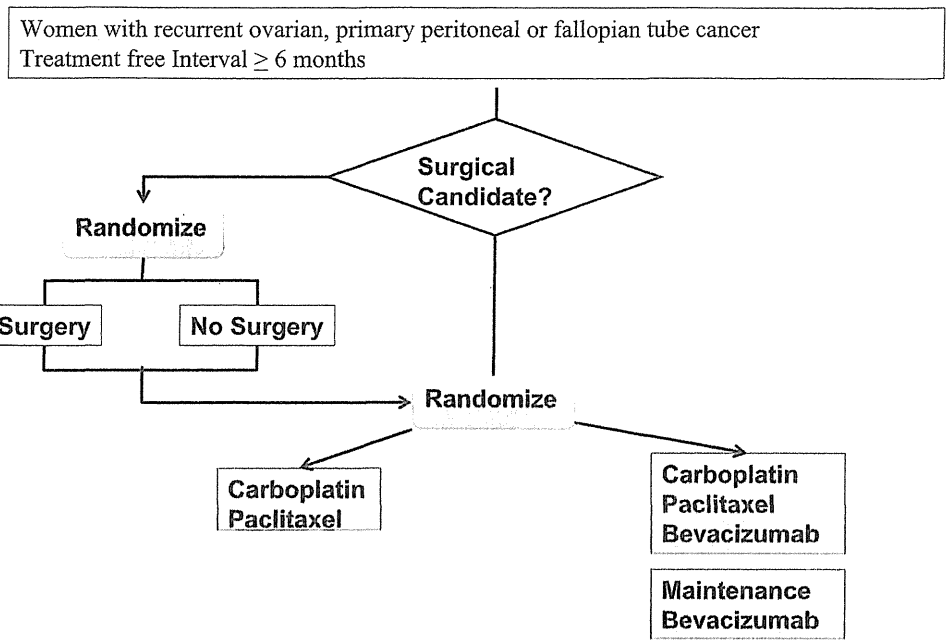

図5　GOG213

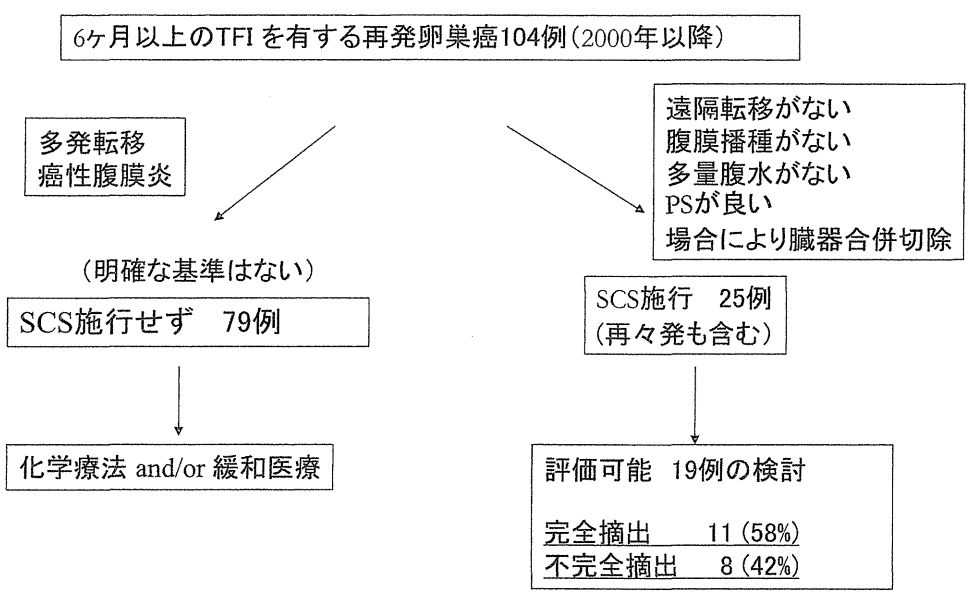

図6　慈恵医大附属4病院　SCS症例

し，PSが良い，多発転移がない，腹膜播種がない，などを考慮していたものの明確な基準はなかった．2. 完全摘出率は58%でDESKTOP OVAR II score positive例（75%）に比し良好とは言えなかった．3. 腹膜播種を伴わない腹腔内再発が少数ながら存在した．しかし，術前に播種の有無を正確に診断できたわけではなく診断法に検討の余地がある．今後の展望としてPS，残存腫瘍，腹水などの因子を検証することは必須であるが，さらに完全摘出の予測因子があるかを検討することが重要と考えられた．

おわりに

現在のところ化学療法と腫瘍減量手術のどちら

表6 腫瘍減量手術（SCS）施行例 慈恵医大（2000年～）

case	stage	histology	RT（1stOP）	PS	ascites	TFI	resection	prognosis	note
1	IIIb	endometrioid	0	0	0	20	complete	NED	低位前方切除
2	IIIb	serous	0	0	0	23	complete	NED	肝切
3	Ic	serous	0	0	0	50	complete	NED	膣断端
4	IIc	clear	0	NE	NE	31	complete	NED	横行結腸
5	IIIc	serous	0	NE	NE	19	complete	AWD	PALN
6	IIIc	undiff.	＜1cm	NE	NE	22	complete	NE	低位前方切除
7	IIIb	undiff.	＜1cm	0	0	6	complete	DOD	肝切
8	IIIc	adeno ca.	＜1cm	0	0	39	complete	DOD	PLN
9	IIIc	serous	＜1cm	1	0	18	complete	NED	肝切
10	IIIc	serous	＞2cm	0	0	18	complete	DOD	腹壁
11	IIIc	serous	＞2cm	0	NE	15	complete	NED	回腸・結腸
12	IIc	mucinous	0	0	＜500ml	17	incomplete	DOD	小腸，腹壁
13	IIIc	serous	＜1cm	0	0	24	incomplete	DOD	低位前方切除
14	IIIc	serous	NE	0	0	61	incomplete	AWD	低位前方切除
15	IIIc	serous	＜1cm	1	NE	26	incomplete	DOD	脾摘，結腸
16	IIc	clear	＜1cm	NE	NE	9	incomplete	AWD	膀胱浸潤
17	IIIb	serous	＜1cm	NE	NE	9	incomplete	AWD	脾摘，肝円索
18	IIIc	serous	＞2cm	0	0	22	incomplete	DOD	横隔膜，腸間膜
19	IIc	clear	0	0	＜500ml	26	incomplete	DOD	横隔膜

NE, not evaluated；NED, no evidence of disease；DOD, dead of disease；AWD, alive with disease

を選択すべきかエビデンスはなく手術のルーチン化は推奨されていないが，完全摘出が期待できる症例は明らかに存在する．再発卵巣癌の治療としてSCSを選択する意識が高まりつつある．しかし，再発卵巣癌に対するSCS＋化学療法が化学療法単独より予後を有意に改善することを証明したランダム化比較試験はなく，日常臨床でSCSを実施する場合は十分なインフォームド・コンセントが必要である．また，SCSの適応決定に際し，再発腫瘍が孤立性であるか否か，MRI，FDG-PET/CTなどの評価を含め，さらなる診断法の検討が必要と思われた．今後は前方視的試験によりSCSが生存率へ与える影響が明らかになるであろう．

謝辞

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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

was achieved in 142 (group A), 90%–99% in 74 (group B), and less than 90% in 5 (group C). The cumulative rates of symptom control at 5 years were 93%, 71%, and 60% in groups A, B, and C, respectively. According to these results, a high rate of tumor infarction was achieved with gelatin sponge in conjunction with a favorable long-term clinical outcome (7,26).

In conclusion, UAE with gelatin sponge is safe, with efficacy equivalent to previous data for other widely used embolic materials. Gelatin sponge should be an option for UAE, but randomized controlled trials including cost analysis will be needed to determine the impact of gelatin sponge on UAE clinical practice.

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CLINICAL INVESTIGATION

Ultrasound-Guided Radiological Placement of Central Venous Port via the Subclavian Vein: A Retrospective Analysis of 500 Cases at a Single Institute

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Abstract The purpose of this study was to assess the technical success rate and adverse events (AEs) associated with ultrasound (US)-guided radiological placement (RP) of a central venous port (CVP) via the subclavian vein (SCV). Between April 2006 and May 2007, a total of 500 US-guided RPs of a CVP via the SCV were scheduled in 486 cancer patients (mean age ± SD, 54.1 ± 18.1 years) at our institute. Referring to the interventional radiology report database and patients' records, technical success rate and AEs relevant to CVP placement were evaluated retrospectively. The technical success rate was 98.6% (493/500). AEs occurred in 26 cases (5.2%) during follow-up (range, 1–1080 days; mean ± SD, 304.0 ± 292.1 days). AEs within 24 h postprocedure occurred in five patients: pneumothorax ($n = 2$), arterial puncture ($n = 1$), hematoma formation at the pocket site ($n = 2$), and catheter tip migration into the internal mammary vein ($n = 1$). There were seven early AEs: hematoma formation at the pocket site ($n = 2$), fibrin sheath formation around the indwelling catheter ($n = 2$), and catheter-related infections ($n = 3$). There were 13 delayed AEs: catheter-related infections ($n = 7$), catheter detachments ($n = 3$), catheter occlusion ($n = 1$), symptomatic thrombus in the SCV ($n = 1$), and catheter migration ($n = 1$). No major AEs, such as procedure-related death, air embolism, or events requiring surgical intervention, were observed. In conclusion, US-guided RP of a CVP via the SCV is highly appropriate, based on its high technical success rate and the limited number of AEs.

Keywords Central venous port · Ultrasound · Subclavian vein · Venous access · Indwelling catheter

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Introduction

Central venous catheter placement is generally required for repeated continuous infusion of anticancer agents or total parenteral nutrition (TPN). To reduce problems caused by central venous catheter placement and to improve the quality of life of patients, a central venous port (CVP) is widely used [1–14]. Thus, the placement of a CVP is an indispensable procedure in the management of cancer patients, especially outpatients receiving repeated intravenous chemotherapy or TPN [15]. Since the report by Morris et al. in 1992 [1], radiological placement (RP) of a CVP has become a widely accepted interventional radiology procedure, although ultrasound (US)-guided RP via the internal jugular vein (IJV) is the most commonly used method [12, 13]. One possible reason for this preference is the higher rate of pneumothorax complications associated with RP of a CVP via the subclavian vein (SCV) [11, 12, 16].

In a randomized trial concerning the insertion of a central venous catheter via the SCV, Mansfield et al. reported that US guidance was not superior to landmark guidance [17]. Other reports have concluded that US guidance is safe and efficient [14, 16, 18–20]. Thus, the clinical efficacy of US-guided RP of a CVP remains controversial, and more data regarding this procedure are needed to enable better clinical decisions. Based on these background factors, we retrospectively assessed the technical success rate and adverse events (AEs) associated with US-guided RP of a CVP via the SCV.

Materials and Methods

Between April 2006 and May 2007, a total of 505 CVPs were implanted at our institute. After excluding 5 cases in which the central venous catheter was inserted via the femoral vein because of neuralgic pain or a bulky tumor of the chest wall, we analyzed the remaining 500 CVPs implanted in the chests of 486 patients by referring to the interventional radiology report database and the patients' records. Institutional Review Board approval was obtained for this study. Among the 486 patients, 265 were male and 221 were female, and the age range was 3–85 years (mean ± SD, 54 ± 18.1 years). Their primary diseases are listed in Table 1. CVP implantation was indicated for chemotherapy in 375 patients (75%), for TPN in 64 patients (12.8%), and for other reasons in 61 patients (12.2%).

Procedure

All procedures were performed by interventional radiologists on X-ray fluoroscopy tables equipped with a portable US device. Antibiotic prophylaxis was used in 334 procedures but was not used in 166 procedures. The reason for this difference is that some referring physicians do not agree with the use of antibiotic prophylaxis despite our recommendation, because the clinical significance of prophylaxis has not been fully established. Local anesthesia was used for all patients, but conscious sedation was not routinely employed except in 34 children (6.8%), with a pediatrician's assistance. None of the procedures was attended by an anesthesiologist.

The CVP was routinely implanted on the side opposite to the patient's dominant hand to enable them to use their dominant hand to easily remove the needle from the port after the completion of infusion. However, if the conditions were unsuitable for implantation on this side, in the case of postmastectomy or radiation therapy areas, the port was placed on the same side as the dominant hand.

The patient was placed in a supine position on the table, and the selected side of the upper anterior chest walls was widely prepared using 10% Popiyodon (Yoshida Pharmaceutical Co. Ltd., Tokyo) and draped. A US probe covered with a sterile disposable vinyl bag was placed at the infraclavicular position and a longitudinal image of the SCV was obtained (Fig. 1). The SCV was distinguished from the subclavian artery by the following characteristics: no pulsations, diameter changes with respiration, and distension with the Valsalva maneuver [20]. A 7.5-MHz linear array probe with a real-time, portable, battery-operated ultrasound device (Site Rite; Dymax Corp., Pittsburgh, PA, USA) was utilized for all cases.

Table 1 Distribution of patients (number) according to primary disease

Diagnosis	
Brain tumor	8 (1.6%)
Lung cancer	6 (1.2%)
Breast cancer	23 (4.7%)
Gastrointestinal system malignancies	310 (63.8%)
Hematological malignancies	18 (3.7%)
Urinary system malignancies	11 (2.3%)
Gynecological malignancies	13 (2.7%)
Unknown primary disease	2 (0.4%)
Other	95 (19.6%)
Total	486 (100%)

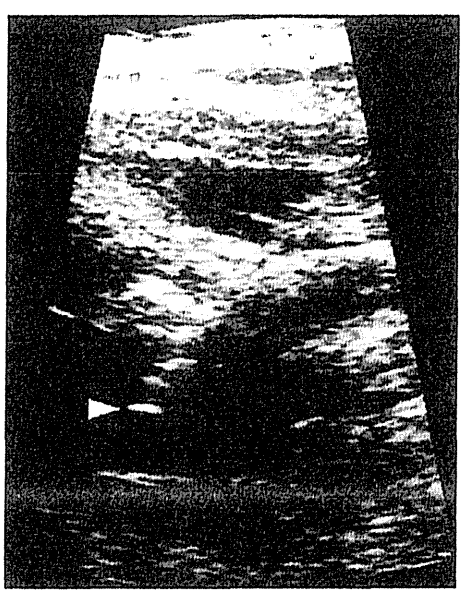

Fig. 1 US imaging of left subclavian vein access. The needle is advanced with visualization of both the needle tip (*arrowhead*) and the subclavian vein (*longitudinal view*). Note that the left side of the figure is proximal

Under US guidance, a 23-G needle was then inserted through the skin directly anterior to the vessel, and subcutaneous 1% lidocaine was injected to spread along the pathway of the catheter. The most proximal possible portion of the SCV (near the subclavian bone) was punctured using an 18-G indwelling needle under real-time US guidance, with the patient breathing quietly. No needle attachment was used, and a freehand procedure was utilized in all cases (Fig. 2). Successful puncture of the SCV was confirmed when blood was drawn back using a 0.035-in., J-shaped guidewire (GW) inserted via the needle. It is important to confirm successful puncture in this manner before inserting the GW because the outer cannula sometimes does not extend right into the vein lumen due to the difference in length between the inner metal needle and the outer cannula, regardless of the appearance on US. An indwelling catheter was then inserted coaxially using an appropriate peel-away sheath. When a Groshong catheter was used, the GW was removed and the catheter was inserted through the sheath. The tip of the indwelling catheter was placed at the level of the atriocaval junction using radiological landmarks.

A subcutaneous pocket for port placement on the anterior upper chest wall was made using a 4-cm-long skin incision in a blunt dissection manner. The proximal side of the indwelling catheter was passed through a subcutaneous tunnel to the pocket, cut to an adequate length, and connected to the port. After confirming that 10 ml of saline could be injected into the port without any problems, all systems were implanted and the skin incision was sutured. After completion of the entire procedure, a chest X-ray was obtained while the patient was lying on the table, to confirm the position of the catheter and port (Fig. 3). Twelve interventional radiologists, including seven rotating residents from other departments performed the procedures. Five of the interventional radiologists had experience with more than 200 CVP placements. The rotating residents performed RP of a CVP under the direction of an interventional radiologist, after sufficient experience with freehand US-guided venous access (more than 20 catheter insertions via the SCV). These residents were already experienced in the landmark method of CVC placement.

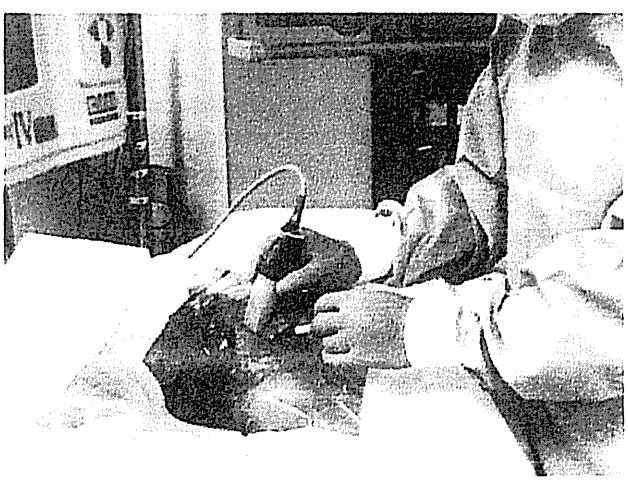

Fig. 2 Setup for the procedure. During each procedure, the interventional radiologist wears a cap, mask, and disposable sterilized gown. The venous puncture is performed freehand

Devices

The following three types of CVP kits, approved for use in Japan, were used in this study: 8-Fr Groshong catheters and MRI ports (Bard Inc., Salt Lake City, UT, USA) in 442 cases; 6-Fr Anthron PU catheters (Toray Medical Co., Tokyo) and CELSITE ports (B. Braun Medical Inc., Bethlehem, PA, USA) in 36 cases; and 5-Fr IV catheters and Septum ports from Orca CV kits (Sumitomo Bakelite Co., Tokyo) in 22 cases.

Maintenance

In most patients, the CVP was used on the day following implantation, from the viewpoint of safety in the administration of chemotherapy. A 24- or 22-G Huber point needle was used for infusion. Saline (10 ml) was injected into the port after each infusion. If the CVP was not used for a long period, 10 ml of saline was injected at least

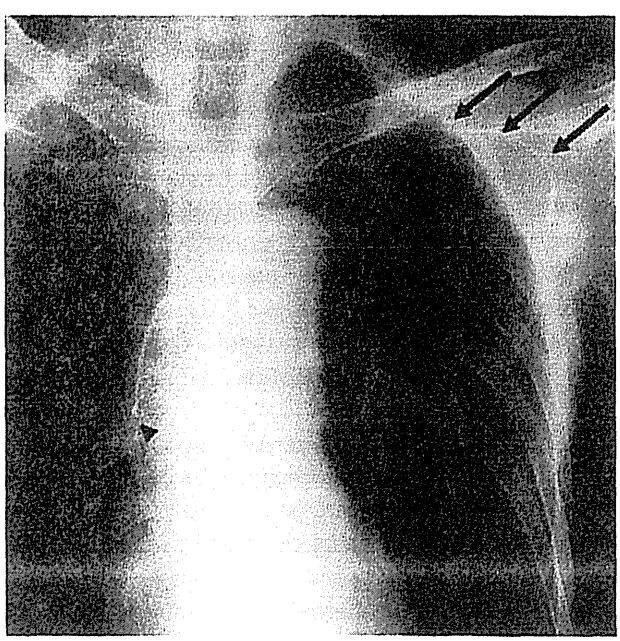

Fig. 3 Chest X-ray of an ideally placed central venous port. The curve of the catheter is gentle, and the catheter tip (*arrowhead*) is adjusted to the level of the atriocaval junction. Note the short subcutaneous tunnel (*arrows*) between the venous access site and the implanted port

every 4 weeks. Port flush was performed by the referring physician or a nurse. Anticoagulants were not used, except in patients with a history of anticoagulant therapy.

In cases of port dysfunction, contrast medium injection was performed via the port, in the interventional suite. These examinations were also reviewed and evaluated.

Evaluation

Technical success was defined as the presence of an indwelling catheter inserted into the SCV via a US-guided puncture from the primarily intended entry site, and the presence of a port connected to the indwelling catheter and implanted in the upper anterior chest wall, with adequate CVP function.

AEs were graded according to the Common Terminology Criteria of Adverse Events (CTCAE), version 3, and were divided into immediate (<24 h), early (24 h–30 days), or late (>30 days) events according to the SIR guidelines [21]. Catheter-related infections were defined according to the SIR guidelines [21]. Follow-up care was evaluated until March 2009.

Results

Technical success was achieved in 493 of the 500 cases, yielding a technical success rate of 98.6% (95% CI, 97.1–99.3%). A total of 446 CVPs were implanted on the left side, and 54 on the right. In the seven failed cases, SCV puncture under US guidance could not be performed because of collapse of the SCV ($n = 3$), thrombosis in the SCV ($n = 3$), and extreme obesity ($n = 1$). Among these failed cases, venogram-guided puncture of the SCV, US-guided puncture of the internal jugular vein, and US-guided puncture of the SCV on the opposite side were performed in three, one, and three cases, respectively. Finally, RP of the CVP was completed in all patients.

AEs were observed in 26 of the 500 cases (5.2%) during the follow-up period (range, 1–1080 days; mean ± SD, 304.0 ± 292.1 days). Six immediate AEs occurred: grade (G) 2/1 pneumothorax ($n = 2$), G1 arterial puncture ($n = 1$), G2/G1 hematoma formation at the pocket site ($n = 2$), and G1 catheter tip migration into the internal mammary vein ($n = 1$). The following early AEs occurred: G3 hematoma formation at the pocket site ($n = 2$), G3 fibrin sheath formation around the indwelling catheter ($n = 2$), and G3/G2 catheter-related infection ($n = 3$; G3 catheter-related sepsis in two patients and G2 bacteremia in one patient). The following delayed AEs occurred: G3/G2 catheter-related infection ($n = 7$; G3 catheter-related sepsis in two patients, G3 sepsis in one patient, G3 pocket infection in one patient, and G2 bacteremia in three patients), G3 catheter detachment (retrieved by percutaneous procedure; $n = 3$), G2 catheter occlusion ($n = 1$), G2 symptomatic SCV thrombosis ($n = 1$), and G1 catheter migration ($n = 1$). A summary of AEs during the entire follow-up period is provided in Table 2. In 10 patients, contrast material injection was performed via the port to evaluate the cause of very slow infusion rate or pain during infusion, which revealed 2 cases of fibrin sheath formation, 3 cases of catheter detachment, and no abnormal findings in 5 patients. No major AEs occurred, such as procedure-related death, air embolism, or events requiring surgical intervention.

Table 2 Summary of adverse events during the entire follow-up period

Complication	Grade	*n*
Immediate		
Pneumothorax	2(1)/1(1)	2 (0.4%)
Arterial puncture	1	1 (0.2%)
Hematoma formation at pocket site	2/1	2 (0.4%)
Catheter tip migration	1	1 (0.2%)
Early		
Hematoma formation at pocket site	3	2 (0.4%)
Fibrin sheath formation	3	2 (0.4%)
Catheter-related infection	3(2)/2(1)	3 (0.6%)
Delayed		
Catheter-related infection	3(4)/2(3)	7 (1.4%)
Catheter detachment	3	3 (0.6%)
Catheter occlusion	2	1 (0.2%)
Subclavian venous thrombosis	2	1 (0.2%)
Catheter migration	1	1 (0.2%)

Note: *n* number of patients

Discussion

US-guided insertion has been the main method of CVP placement, especially with access via the IJV [12, 13]. One reason for this preference is that real-time US offers the following benefits over venographic guidance: no risk of allergic medium reactions or renal impairment and lower radiation exposure [16]. Venogram-guided access via the SCV is another popular route for CVP placement [3, 4, 8, 9], because it offers several advantages: catheter placement is not influenced by neck motion of the patient, catheter length is much shorter than that required for IJV access, and development of a hematoma will not result in airway compression [8].

The RP of a CVP was first described by Morris et al. in 1992, in a series involving 101 cases [1]. Subsequently, some reports have compared US-guided SCV access with

US-guided IJV access. Randolph et al. performed a meta-analysis of eight reports (six studies examining IJV access, one examining SCV access, and one examining both access routes) and concluded that real-time US-guided insertion was better than landmark-guided insertion, for both access routes, from the viewpoints of technical success, time required for vein puncture, and complications [18]. Hind et al. reported a meta-analysis of 10 randomized trials comparing real-time US-guided insertion with landmark-guided insertion for IJV access. Their results showed that US-guided insertion was superior from the viewpoints of overall technical success, technical success of the first puncture, and complications [19]. Brooks et al. described the technical details of US-guided RP of CVP in 55 cases; however, the technical success rate for SCV access was lower than that for IJV access [10]. Biffi et al. reported a single-institutional randomized trial comparing US-guided SCV puncture, landmark-guided IJV puncture, and cephalic vein cut-down with regard to technical success and complications. They concluded that no differences in the rates of complications were seen among the arms but that real-time US-guided SCV puncture had the highest rate of technical success [14].

Concerning AEs, the risk of catheter-related infection was reportedly lower for SCV access than for jugular or femoral vein access, at least in critically ill patients [22, 23]. The rate of thrombosis was reportedly lower for SCV access than for IJV access (10 vs. 42%, respectively) [23], though the opposite conclusion has also been reported [12]. Therefore, US-guided RP of a CVP via the SCV appears to be an adequate procedure but has yet to be sufficiently evaluated in clinical trials involving a large number of cases.

Our study is the largest reported series of US-guided RP of a CVP via the SCV. Compared with the report by Biffi et al. [14], the technical success rate of 98.6% in the present study is high and favorable. Accordingly, our results indicate that US-guided RP of a CVP via the SCV has a high technical success rate if SCV puncture is performed under real-time US guidance. Nevertheless, the combination of this procedure with X-ray fluoroscopy, which would enable the position of the catheter and GW to be checked immediately, could further enhance this success rate [16].

Pneumothorax is the most serious AE associated with SCV access. However, its incidence in our series was only 0.4% of 500 cases, which is the lowest incidence to be reported to date. Only one subclavian arterial puncture occurred; this AE was managed by a few minutes of astriction, after which the patient was asymptomatic. This incidence rate of 0.2% is comparable to those reported in other series. We experienced no cases of bleeding at the puncture site that could not be controlled by astricition, although a smaller branch of the subclavian artery may not have been identified by US in all cases.

The incidence of other AEs was also similar to those reported previously, but unlike pneumothorax and asymptomatic arterial puncture, these events are not strictly related to SCV access; instead, they occur as natural events. The point of SCV puncture under US guidance is usually more peripheral than that resulting from the landmark technique [16, 20]; the risk of "pinch-off syndrome" is reported to be low with this lateral approach [16]. In fact, no case of pinch-off syndrome was noted in the present study despite the three cases of catheter disconnection, in which injury was seen at the connection site between the port and the catheter. In contrast, the incidence of subcutaneous catheter flexure or migration caused by movement of the patient appears to be higher with the lateral approach; however, catheter migration was observed in only one case in our series. This result might be associated with the fact that the most proximal possible portion of the SCV was punctured. Therefore, in terms of AEs, US-guided RP of a CVP can be considered a permissible procedure.

US-guided venous access can be performed using either the transverse (short-axis) view or a longitudinal (long-axis) view. Longitudinal view is generally associated with a longer learning curve compared with transverse view because a plastic needle guide can be used with the transverse view. The advantages of the longitudinal view are a wider range of view and better visualization of the advancing needle tip, without the need for constant adjustment to follow its path. Using the transverse view, the advancing needle tip must be followed to maintain the appropriate plane as it progresses. The longitudinal view is recommended by the American College of Emergency Physicians, and we also adopted this method. In the present study, the rotating residents could use the longitudinal (long-axis) view technique competently. In our experience, even rotating residents who were already experienced in the landmark method of CV catheter placement could make use of the technique under the direction of staff from our department [24].

The limitations of this study include its retrospective nature and single-center design. In addition, we did not record the number of puncture attempts made during each procedure, which closely correlates with AEs [25]. We experienced the clinical phenomenon of venous hematoma after multiple failed attempts compressed the vein, progressively reducing its diameter and making the next puncture more difficult. This effect could not be remedied even by using the Valsalva maneuver and was seen, in four cases of failed venous attempts, to puncture a patent target vein.

Nevertheless, our study included a large number of cases, and the procedures were performed by various experienced physicians, including rotating residents; thus, these results indicate that US-guided RP of a CVP via the SVC is an appropriate procedure because of its high technical success rate and limited number of AEs. In conclusion, US-guided RP of a CVP via the SCV can be regarded as a standard procedure by interventional radiologists.

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Conflicts of Interest The authors declare that they have no conflicts of interest.

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Phase I/II Study of Hepatic Arterial Infusion Chemotherapy With Gemcitabine in Patients With Unresectable Intrahepatic Cholangiocarcinoma (JIVROSG-0301)

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Objectives: No established therapy exists for unresectable intrahepatic cholangiocarcinoma (ICC). We conducted a phase I/II study to ascertain the recommended dose (RD) of hepatic arterial infusion using gemcitabine (GEM) for ICC and to assess the efficacy and safety.

Methods: For patients with unresectable ICC, GEM was administered through the hepatic artery via the port system as a 30-minute infusion on days 1, 8, and 15 every 4 weeks for 5 cycles. In phase I, dosage for levels 1, 2, and 3 was set at 600, 800, and 1000 mg/m^2, respectively, and was increased in 3 to 6 patients at a time. Maximum tolerated dose was defined as a dosage resulting in dose-limiting toxicity in 2 of 3 patients or 3 of 6 patients, and RD was estimated during the first cycle. In the phase II, more RD patients were added to assess tumor response and toxicity.

Results: During the phase I, 16 patients were enrolled. Maximum tolerated dose was not reached. Assuming RD at 1000 mg/m^2, the phase II enrolled a total of 13 patients. The following Grade 3 toxicities were observed: neutropenia 20%, increased gamma-glutamyl transpeptidase 8%, increased aspartate aminotransferase 4%, increased alanine aminotransferase 4%, increased bilirubin 4%, nausea 4%, and fatigue 4%. The tumor response rate was 7.7% (complete response 0, partial response 1, stable disease 8, and progressive disease 4).

Conclusion: Whereas the toxicity of hepatic arterial infusion with 1000 mg/m^2 GEM for ICC was tolerable, expected efficacy could not be obtained, thus suggesting only minimal activity.

Key Words: intrahepatic cholangiocarcinoma, hepatic arterial infusion, gemcitabine, phase I/II study, clinical trial

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Intrahepatic cholangiocarcinoma (ICC) constitutes 5% to 15% of cases of the primary hepatic cancer in Japan. It is a cancer with a relatively low incidence, but is characterized by spread from the biliary epithelium to Glisson capsule. ICC has a high incidence of lymph node metastasis and vascular invasion and also tends to invade adjacent organs, so that in a fair number of cases it is already advanced and unresectable at the time of detection.[1–3] Chemotherapy is the treatment option for unresectable ICC, but no standard therapy has been established.[4,5] Typically, drug regimens centered on 5-fluorouracil (5-FU) have been used, but recently, gemcitabine hydrochloride (GEM) has appeared promising.[6]

Hepatic arterial infusion (HAI) chemotherapy is one local therapy for unresectable malignant hepatic tumors and its anticancer effect is obtained by raising the local concentration of the anticancer agent. Local therapy also reduces systemic adverse response and can increase the effect on the hepatic lesions by infusing the active medicinal agent into a hepatic artery.[7] In Japan, HAI with percutaneous placement of a catheter-port system is highly feasible,[8–10] and HAI of GEM can be continued systematically. If a local effect for ICC supplying from the hepatic artery can be obtained with HAI of GEM, this treatment may contribute to prolonging patient survival.

With this as background, we designed a phase I and II clinical trial to evaluate HAI chemotherapy with GEM for unresectable ICC, and a multicenter study was carried out by the Japan Interventional Radiology in Oncology Study Group.

MATERIALS AND METHODS

Study Design and Patient Eligibility

A phase I and II clinical trial at multiple institutions was designed to determine the dose-limiting toxicity (DLT) and recommended dose (RD) for HAI chemotherapy with GEM to treat unresectable ICC, as well as to evaluate its safety and tumor response effect. Dose-limiting toxicity and recommended dose of hepatic arterial infusion of GEM were determined as the primary end point, and the frequency and severity of adverse events, tumor response effect in the liver only, and tumor response effect in the whole body were the secondary end points. In phase I portion, DLT was assessed and RD was estimated, and in phase II portion, cases were added at the estimated RD, and the tumor response effect was evaluated. Toxicity assessment was conducted in all patients with HAI chemotherapy.

The inclusion criteria were the following conditions for cases of unresectable ICC:

1. Cases of histologically confirmed ICC (initial tumor or recurrence after resection), which was determined to be unresectable by a hepatic surgeon at each institution, or it was judged to be the prognosis-determining factor, even when metastasis was found as extrahepatic lesions.
2. Cases that were previously untreated with GEM or that were previously treated with agents other than GEM in the past, but had received no chemotherapy for at least 4 weeks from the last session, and were not responded by the chemotherapy.
3. Cases in which measurable lesions that corresponded to the target lesions on response evaluation criteria in solid tumors were located in the liver and had maximum tumor diameters of 20 mm or more

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on computed tomography (CT) images with 10-mm slices or 10 mm or more on CT images with slices of 5 mm or less.
4. Cases in which a port-catheter system for HAI was placed percutaneously, and arterially infused contrast medium was distributed through the entire liver or at least the entire hepatic lesions and in whom it was confirmed that there was no distribution of the arterially infused contrast medium in the surrounding extrahepatic organs based on CT angiography or MR angiography from the implanted port.
5. Cases aged 20 years or more with an Eastern Cooperative Oncology Group performance status classification of 2 or less.
6. Cases in which major organ function was maintained (white blood cell count $\geq$3000/mm^3 and $\leq$12,000/mm^3, platelets $\geq$100,000/mm^3, transaminase $\leq$5 times the institution's upper limit of normal, serum total bilirubin $\leq$3.0 mg/dL, serum creatinine $\leq$1.5 mg/dL, electrocardiogram not indicating the need for treatment) and in whom hepatic function was Grade 2 or less on National Cancer Institute-Common Toxicity Criteria (NCI-CTC) (version 2.0) with consideration of the influence of the hepatic lesion.
7. Cases of life expectancy of more than 8 weeks.
8. Cases in which written informed consent was obtained.

Patients excluded from the trial were the patients who scheduled for radiation therapy for the hepatic portal region because of hepatic portal region invasion or lymph node metastasis, or who had previously undergone radiation therapy; patients with concurrent infection excluding viral hepatitis, fever of 38°C or above, or who required antibiotics; patients with serious complications (intestinal paralysis, intestinal obstruction, interstitial pneumonia, pulmonary fibrosis, intractable diabetes mellitus, cardiac failure, renal failure, hepatic failure, etc); patients with other concurrent cancer; patients who could not undergo angiography because of allergy to iodinated contrast material; patients with serious mental disabilities; patients who were pregnant or may have been pregnant, and nursing mothers; and patients whose catheters for HAI chemotherapy were placed via laparotomy.

This study protocol was approved by the ethics committee of the Japanese Society of Interventional Radiology and the institutional review boards of the participating hospitals.

Treatment Protocol and Evaluation Methods

Using a percutaneously placed HAI catheter-port system, 1 course was defined as HAI of GEM on days 1, 8, and 15; a course was performed every 4 weeks for a total of 5 courses.

In phase I portion, the GEM dosage was set at Level −1, 400 mg/m^2; Level 1, 600 mg/m^2; Level 2, 800 mg/m^2; and Level 3, 1000 mg/m^2. Because the approval dosage of GEM is 1000 mg/m^2 in Japan, we defined it as the upper limit in this study. The design called for increase at each level in 3 to 6 patients from Level 1. Three patients were enrolled at each level. The study on the next dose level was not conducted until all 3 patients had completed the first cycle without any problems regarding safety and tolerance. If a DLT of any type was detected in 1 of 3 patients during the first cycle, an additional 3 patients were enrolled. If DLT was detected in more than 2 patients, the dose was defined as the maximum tolerated dose (MTD). RD was estimated to be one level below that judged to be MTD. DLT was defined as follows and judged during the first course: Grade 4 leukopenia or neutropenia; Grade 4 thrombocytopenia; nonhematologic toxicities of Grade 3 or more (excluding that from PD, nausea/vomiting, and alopecia; for patients whose pre-enrollment level of transaminase or serum total bilirubin was Grade 2, DLT was taken to be more than twice the pre-enrollment level); not meeting the criteria to start administration (same as the enrollment criteria) for the next course on day 29 because of toxicity.

In phase II portion, up to 13 patients were added at the dose found to be RD in phase I portion and the tumor response effect was judged using response evaluation criteria in solid tumors. Because HAI was being used, the target lesion was limited to hepatic lesions. Tumor size was measured on intravenous contrast-enhanced CT within 2 weeks before enrollment, and the tumor response effect was judged after the completion of courses 1, 3, and 5, and as needed.

Toxicity assessment was done in all cases using NCI-CTC (version 2.0) and the frequency of the worst grade was obtained during all courses. Physical examination and blood tests were done immediately before the start of each treatment and recorded.

Statistical Analysis

In phase I portion, the number of enrolled patients per level from Level −1 to Level 1 was minimum 6. The maximum number of patients up to Level 3, in case that MTD was reached, was 18 patients in the dose finding stage. In phase II portion, when the threshold tumor response rate was taken to be 20% and the expected efficacy rate was set at 50%, 13 patients would be needed to judge the tumor response effect under conditions of $\alpha = 0.1$ and $\beta = 0.2$, and 7 to 10 cases would need to be added at the estimated RD. For the entire study, a maximum of 25 patients was needed.

RESULTS

Patient Backgrounds

A total of 16 patients were enrolled in the phase I portion (May 2004–November 2005), and 9 patients were added for the phase II portion (February 2006–November 2006). All patients met the eligibility requirements. A summary of all 25 patients is shown in Table 1.

Phase I Portion

In phase I portion, 6 patients were registered at Level 1, 6 at Level 2, and 4 at Level 3. DLT appeared in 2 of the 6 patients at Level 1, and 2 of the 6 patients at Level 2, but DLT did not appear at Level 3. The third and fourth patients at Level 3 were registered at almost the same time. Four patients did not meet the criteria to start administration for the second course on day 29. In these 4 patients, the administration of drugs had been delayed because of Grade 1 and 2 leukopenia (n = 3) or thrombocytopenia (n = 4) in the first course. No Grade 4 hematologic toxicity or nonhematologic toxicity of Grade 3 or more was seen in the first course (Tables 2, 3). MTD was not reached up to Level 3. Accordingly, the RD was assumed to be the Level 3 dose of 1000 mg/m^2.

Phase II Portion

Nine patients were added at GEM 1000 mg/m^2. In these patients, together with the patients at Level 3 in phase I portion (total: 13 patients), the tumor response effect was complete response 0/partial response 1/stable disease 8/progressive disease 3/not evaluated 0 in the liver only, and complete response 0/partial response 1/stable disease 8/progressive disease 4/not evaluated 0 in the whole body. The response rate was 7.7% (95% confidence interval [CI], 0.2%–36.0%). Although disease control was not one of the assessment items, the disease control rate with SD added was 69% (95% CI, 38.6%–90.9%). The tumor response effect and survival in all 25 treated patients are shown in Table 4 and Figure 1.

Toxicity

The incidence of adverse events (NCI-CTC version 2.0) of Grade 3 or more in all treated cases was 20% neutropenia, 8% elevated gamma-glutamyl transpeptidase (GGT), 4% elevated aspartate aminotransferase (AST), 4% elevated alanine aminotransferase (ALT), 4% elevated bilirubin, 4% nausea, and 4% fatigue. The only

TABLE 1. Patients' Characteristics

Phase	Phase I			Phase II	
Level of GEM Dose	Level 1	Level 2	Level 3	Estimated RD	All Patients
GEM dose	600 mg/m^2	800 mg/m^2	1000 mg/m^2	1000 mg/m^2	600, 800, 1000 mg/m^2
No. patients	6	6	4	9	25
Age (yr)					
Median (range)		64 (34–76)		56 (46–74)	58 (34–76)
Gender					
Male	3	5	3	7	18
Female	3	1	1	2	7
ECOG PS					
0	4	5	3	7	19
1	1	1	1	2	5
2	1	0	0	0	1
Previous therapy					
None	4	2	3	4	13
Resection	1	3	1	5	10
Chemotherapy	1	0	1	2	4
Embolization or ablation	0	2	0	1	3
Extrahepatic lesions					
None	3	3	2	8	16
Lymph node	3	3	2	0	8
Peritoneum	1	0	0	0	1
Lung	0	1	2	1	4
Median no. courses administered	5	4.5	4		5
Median no. administrations	15	14	12		15
Relative dose intensity	81.9%	87.3%	84.8%		84.7%

ECOG indicates Eastern Cooperative Oncology Group performance status.

TABLE 2. No. Patients With Hematologic Toxicities (Cycle 1, Phase I Portion, n = 16)

	Level 1 600 mg/m^2 6				Levele 2 800 mg/m^2 6				Level 3 1000 mg/m^2 4			
Level Dose n Grade	1	2	3	4	1	2	3	4	1	2	3	4
Leucocytes	1	2	0	0	1	3	0	0	2	1	0	0
Neutrophils	0	2	1	0	1	1	2	0	1	1	0	0
Hemoglobin	0	1	0	0	0	0	0	0	0	0	0	0
Platelets	2	2	0	0	2	1	0	0	1	1	0	0

Grade 4 event was elevated bilirubin in 1 patient in the second course, but this was accompanied by portal vein tumor thrombosis (Tables 5, 6).

Events related to the HAI procedure included difficulties with the placed catheter-port system in 5 patients (catheter obstruction in 3 patients, port damage in 2 patients), and hepatic artery occlusion in 1 patient. In 2 of the patients with catheter obstruction and the 2 patients with port damage the catheter or port was exchanged and the treatment continued. The remaining patient with catheter obstruction showed an antitumor effect of PD, so the catheter was not replaced and the treatment was stopped. In the patient with hepatic artery occlusion, a left hepatic artery occlusion occurred in the second course, which meant that the drug was not reaching the left lobe of the liver, and the treatment was discontinued.

TABLE 3. No. Patients With Adverse Events (Cycle 1, Phase I Portion, n = 16)

	Level 1 600 mg/m^2 6				Level 2 800 mg/m^2 6				Level 3 1000 mg/m^2 6			
Level Dose n Grade	1	2	3	4	1	2	3	4	1	2	3	4
Nausea	0	2	0	0	2	0	0	0	3	0	0	0
Vomiting	0	1	0	0	0	0	0	0	2	0	0	0
Fatigue	1	1	0	0	3	0	0	0	0	0	0	0
Stomatitis	0	0	0	0	1	0	0	0	0	0	0	0
Headache	0	0	0	0	1	0	0	0	0	0	0	0
Diarrhea	0	0	0	0	0	0	0	0	0	0	0	0
Fever without neutropenia	0	0	0	0	0	0	0	0	1	0	0	0
Anorexia	0	0	0	0	0	0	0	0	0	0	0	0
Alopecia	0	0	0	0	1	0	0	0	0	0	0	0
Alkaline phosphatase	2	0	0	0	1	0	0	0	1	0	0	0
Bilirubin	1	0	0	0	0	0	0	0	0	0	0	0
GGT	1	0	0	0	0	1	0	0	0	0	0	0
Hypoalbuminemia	0	0	0	0	0	0	0	0	1	0	0	0
SGOT (AST)	1	0	0	0	0	0	0	0	1	0	0	0
SGPT (ALT)	0	0	0	0	0	1	0	0	1	0	0	0
Hyperkalemia	0	0	0	0	1	0	0	0	0	0	0	0
Hyponatremia	0	0	0	0	0	0	0	0	1	0	0	0