permissible with the approval of the independent data monitoring committee. If DLTs occur in three or more patients, transition to the phase II study will be terminated.

In the phase II study, 100 patients will be allocated to either of the two arms to evaluate the safety and efficacy of GC plus WT1 peptide vaccine, in comparison with GC alone. The sample size was determined based on the feasibility of the study after considering the research period, the number of participating institutions, and the available financial resources. A total of 66 patients in the GC plus WT1 peptide vaccine arm would enable the 1-year overall survival rate to be estimated with an accuracy of ±10%.

Interim analysis and monitoring

We do not plan to perform an interim analysis in this study. In-house monitoring will be performed every 6 months by the Data Center to evaluate the study progress and to improve the quality of the study.

Discussion

So far, no consensus exists regarding the "best criteria" for evaluating the effectiveness of cancer immunotherapy. Evidence of therapeutic activity may be difficult to obtain in early-phase trials using standard endpoints such as the antitumor response according to the Response Evaluation Criteria in Solid Tumors (RECIST), because most cancer immunotherapies are not expected to result in notable tumor shrinkage. Recently published FDA guidance suggests that the development of a cancer vaccine may present different considerations for clinical trial design than the development of a traditional cytotoxic drug or biological product for the treatment of cancer (http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm).

We retrieved clinical trials using immunotherapy for biliary tract cancer through PubMed (http://www.ncbi.nlm.nih.gov/pubmed) and ClinicalTrial.gov (http://clinicaltrials.gov/), although no reports or ongoing studies were found in this category, except for two trials: our previous phase I study examining GEM plus the WT1 peptide vaccine [8], and another study (phase II) examining chemoradioimmunotherapy, with interleukin 2 and 13-cis-retinoic acid being used for the immunotherapy [11]. Both studies conducted for pancreatic or biliary tract cancer showed some promise for a survival advantage, although the reported evidence was immature. We initiated the current phase I and randomized phase II studies to evaluate the efficacy and safety of adding the WT1 peptide vaccine to GC for the treatment of advanced biliary tract cancer. These studies are only the initial step in the development of immunotherapy for this disease, although we hope that the trial may provide useful data for assessing the true activities of this treatment.

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Conflict of interest None.

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Phase I study of TAC-101, an oral synthetic retinoid, in Japanese patients with advanced hepatocellular carcinoma

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Preclinical models have shown that TAC-101 (4-[3,5-bis(trimethylsilyl) benzamide] benzoic acid), an oral synthetic retinoid, has antitumor activity in hepatocellular carcinoma (HCC). We conducted a phase I study in Japanese patients with advanced HCC to examine the pharmacokinetics, recommended dose, safety, and efficacy of TAC-101. The administered dose of TAC-101 was 10 mg/day in four patients (level 1), 20 mg/day in six (level 2), and 30 mg/day in three (level 3). There was no dose-limiting toxicity at level 1. Only one patient each had dose-limiting toxicity at level 2 (grade 2 fatigue, recovery requiring eight or more consecutive days of rest) and at level 3 (grade 3 splenic vein thrombosis). Level 3 (30 mg/day) was considered the maximum tolerated dose and 20 mg/day the recommended dose by a panel of medical experts, placing maximum emphasis on safety. The most frequent adverse events were fatigue, headache, and dermal symptoms such as rash. Pharmacokinetic parameters in Japanese patients with HCC were similar to those in patients in the United States, most of whom were Caucasian. Although no patient had a complete or partial response, the disease control rate was 38.5%. In conclusion, the recommended dose of TAC-101 for patients with HCC is 20 mg/day. TAC-101 had an acceptable toxicity profile, warranting further evaluation in clinical trials. (*Cancer Sci* 2012; 103: 1524–1530)

Hepatocellular carcinoma (HCC) is one of the most common cancers in the world. Outcomes remain poor because disease is usually advanced at diagnosis and associated with hepatic impairment and a high rate of recurrence, resulting from either intrahepatic metastases from the primary tumor or multicentric lesions. Surgical resection, liver transplantation, radiofrequency ablation (RFA) or percutaneous ethanol injection (PEI) are the mainstays of treatment in patients with potentially curable disease. Transcatheter arterial chemoembolization (TACE) is the procedure of choice for noncurative HCC. Currently marketed systemic chemotherapeutic agents, with the exception of sorafenib, provide only marginal benefits.[1–3] Despite the survival benefit demonstrated for sorafenib, more effective systemic therapy for HCC is required.

TAC-101 (4-[3,5-bis(trimethylsilyl) benzamido] benzoic acid) is an orally absorbed synthetic retinoid. This analogue of vitamin A (retinol) binds to nuclear retinoic acid receptor-α (RAR-α), activates RAR-α transcriptional activity, and has shown antitumor activity in primary and metastatic preclinical models of liver cancer.[4,5] TAC-101 inhibits tumor growth in the liver with low toxicity and markedly improves survival in both primary HCC and metastatic colon cancer models.[6]

In the United States, an initial dose-escalation study was performed in patients with advanced cancer. TAC-101 was orally administered daily, without a rest period. The most frequent toxicities were skin and mucosal membrane disorders, myalgia/arthralgia, fatigue, and triglyceridemia. Dose-limiting toxicities (DLT) occurring during the first 28 days of treatment (cycle 1) were fatigue, arthralgia/joint pain, myalgia, and venous thromboembolism (VTE). VTE developed in nine of 29 patients as a characteristic adverse reaction of TAC-101; the dose ranged from 12 to 34 mg/m^2.[7] In a phase I/II study, TAC-101 was administered orally in 21-day cycles (14 days on/7 days off) to patients with advanced HCC. In the phase I portion of the study, the initial dose was 40 mg/day. Two patients had DLT, and the dose was reduced to 20 mg/day. Since only 1 of 6 assessable patients had DLT during the first two cycles of therapy, 20 mg/day was designated as the maximum tolerated dose (MTD) for the 21-day treatment cycle. At this dose level, TAC-101 was generally well tolerated, and the most common drug-related adverse events were increased blood triglyceride levels, fatigue, dermatitis, pruritus, nausea, dry skin, myalgias, dry mouth, arthralgias, anorexia, diarrhea, and headache. Among 21 evaluable patients, no patient had a complete response (CR) or partial response (PR), but 12 (57%) had stable disease (SD). Median progression free survival (PFS) and overall survival (OS) were 3.4 months and 19.2 months, respectively.[8]

We report the results of the first phase I study of TAC-101 in Japanese patients with HCC. Our major goals were to evaluate safe dose levels, tolerability, pharmacokinetics, and efficacy.

Materials and Methods

Eligibility. Eligible patients had pathologically or clinically proved advanced HCC that was not amenable to standard treatments. A hypervascular mass on diagnostic imaging was considered a sufficient non-invasive diagnostic criterion for HCC. At least one measurable lesion on CT or MRI (not including necrotic lesions caused by prior treatment) was required. Other eligibility criteria included an age of 20 to 75 years; an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2; an estimated life expectancy of at least 60 days; adequate hematologic function (white blood cell [WBC] $\geq 3000/mm^3$, hemoglobin ≥ 8.0 g/dL, platelets $\geq 5.0 \times 10^4/mm^3$); adequate hepatic function (aspartate aminotransferase [AST] and alanine aminotransferase [ALT] ≤ 5 times the upper limit of normal [ULN], total bilirubin ≤ 2.0 mg/dL, serum albumin ≥ 2.8 g/dL, and prothrombin activity $\geq 40\%$); adequate renal function (serum creatinine

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Clinical trial registration: This trial was not registered in the clinical trial database because it was an early phase trial and not a controlled study.

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Table 1. Summary of patient background characteristics

Background characteristics		10 mg/day	20 mg/day	30 mg/day	Total (%)
No. eligible patients		*n* = 4	*n* = 6	*n* = 3	*n* = 13
Gender	Male	3	5	3	11 (84.6)
	Female	1	1	0	2 (15.4)
Age (years)	<65	2	0	2	4 (30.8)
	≥65	2	6	1	9 (69.2)
	Median	64	72	60	70
	Min., Max.	59, 70	66, 74	45, 70	45, 74
ECOG, PS	0	4	5	3	12 (92.3)
	1	0	1	0	1 (7.7)
Stage*	Stage I	0	0	0	0 (0.0)
	Stage II	1	1	0	2 (15.4)
	Stage III	2	4	2	8 (61.5)
	Stage IVA	0	0	0	0 (0.0)
	Stage IVB	1	1	1	3 (23.1)
Child–Pugh classification	A	3	2	3	8 (61.5)
	B	1	4	0	5 (38.5)
	C	0	0	0	0 (0.0)
Grade of histological differentiation	Well differentiated	2	1	0	3 (23.1)
	Moderately differentiated	0	3	1	4 (30.8)
	Poorly differentiated	0	0	1	1 (7.7)
	Unknown	2	2	1	5 (38.5)
Extrahepatic metastasis	No	3	5	2	10 (76.9)
	Yes	1	1	1	3 (23.1)
History of hepatectomy	No	1	3	2	6 (46.2)
	Yes	3	3	1	7 (53.8)
History of nonsurgical therapy	No	0	0	0	0 (0.0)
	Yes	4	6	3	13 (100.0)

*According to the staging system of the Liver Cancer Study Group of Japan (4th edition). ECOG, PS Eastern Cooperative Oncology Group performance status.

≤1.5 times the ULN); and a Child–Pugh class of A or B. Resection was permitted if the procedure had been performed at least 180 days before registration in the study. Other prior treatments for HCC were permitted if such treatment had been performed at least 30 days before registration. Patients were excluded if they had tumors involving more than 50% of the liver; brain or bone metastases or vascular invasion of the main trunk and first branch(es) of the portal vein, the main trunk of the left/middle/right hepatic veins, the inferior right hepatic vein, the short hepatic veins, or the inferior vena cava; severe complications; other malignancies; or inability to comply with the protocol requirements. Patients were also excluded if they had a history of VTE. Patients who were receiving anticoagulants or hormone replacement therapy were excluded. Written informed consent was obtained from each patient. The study was approved by the local institutional review boards of the National Cancer Center Hospital, Japan.

Study design and treatment plan. TAC-101 was supplied by Taiho Pharmaceutical Co., Ltd. (Tokyo, Japan). This study evaluated the pharmacokinetics of TAC-101 and established the MTD for two courses of treatment. Patients received the assigned dose of TAC-101 once daily (after breakfast) for 14 consecutive days, followed by a 7-day rest (a 21-day treatment course). If grade 3 or higher hematologic toxicity or grade 2 or higher nonhematologic toxicity occurred, the dose of TAC-101 could be reduced (minimum dose, 10 mg/day). If DLT occurred, treatment with TAC-101 could be temporarily suspended. Treatment was continued until evidence of disease progression. Treatment was terminated if recovery from an adverse event required more than 21 days, if the patient requested treatment to be discontinued, or if unacceptable toxicity developed in the opinion of the investigator.

The starting dose of TAC-101 (level 1) was 10 mg/day, level 2 was 20 mg/day, level 3 was 30 mg/day, level 4 was 40 mg/day, level 5 was 50 mg/day, and level 6 was 60 mg/day. Patients were enrolled in cohorts of three for each dose level. The dose was escalated according to cohort and was not increased in the same patient. If none of the first three patients had DLT during the first two cycles of therapy, the dose was increased to the next dose level. If one or two of the first three patients had DLT, three additional patients were assigned to the same dose level; if only one or two of the first six patients had DLT, the dose was increased to the next dose level; if all of the first three patients or three or more of the first six patients had DLT, the dose was defined as the MTD; the recommended dose (RD) was defined as the level one step below the MTD. A total of six patients received the RD to confirm the safety profile. DLT was defined as any of the following: (i) hematologic toxicity ≥Grade 4; (ii) nonhematologic toxicity ≥Grade 3; (iii) AST, ALT ≥10 times the ULN; or (iv) a rest period of eight or more consecutive days was required.

Pharmacokinetics. Blood samples for pharmacokinetic analysis were collected before and 2, 4, 6, 8, 10 to 12, and 24 h after administration of TAC-101 on day 1 and after repeated treatment (days 8–13) during the first cycle (approximately 4 mL for each time point). The blood samples were centrifuged, and the resulting plasma samples were stored at −20°C until analysis. Spontaneously voided urine was collected before treatment on day 1 (baseline urine), from 0 to 8 h after treatment (0–8 h pooled urine), and from 8 to 24 h after treatment (8–24 h pooled urine). The urine samples were stored at −20°C until analysis.

Plasma concentrations of TAC-101 were measured using a validated method. The analyte was extracted with *tert*-butyl methyl ether and analyzed by liquid chromatography/tandem mass spectrometry (LC/MS/MS; Waters 2690/Finnigan MAT TSQ7000) with negative ion-electrospray ionization mode, using deuterium-labeled TAC-101 as an internal standard.

Pharmacokinetic parameters were calculated from the plasma concentrations of TAC-101 by non-compartmental analysis using WinNonlin software, version 4.1 (Pharsight, Cary, NC, USA).

For both plasma and urine samples, the metabolites of TAC-101 were preliminarily analyzed using an ultraviolet detector-equipped, high-performance liquid chromatograph and LC/MS/MS (Agilent 1100 series/Applied Biosystems API 4000, Carlsbad, CA, USA). The metabolites TAC-101-M-1, TAC-101-M-2, and TAC-101-M-3 were identified by comparison with authentic samples synthesized by Taiho Pharmaceuticals (Tokyo, Japan). The structures of conjugates were estimated by analyzing the mass fragmentation spectra. Concentrations of TAC-101-M-1 and TAC-101-M-2 were determined using an LC/MS/MS method similar to that used for the assay of TAC-101.

Assessment of efficacy and toxicity. All eligible patients who received at least one dose of the study drug were included in the evaluations of response and toxicity. The criteria of the Japan Society of Clinical Oncology, which closely resemble the World Health Organization criteria, were used to evaluate unblended radiographic tumor responses at the study site. Computed tomography or MRI was used to evaluate measurable disease; the same imaging modality was used at baseline and follow-up. The efficacy endpoints were the overall response rate, the duration of antitumor effect, OS, time to progression (TTP), and time to treatment failure (TTF). Vital signs, physical findings, and the results of hematological and biochemical testing, including thrombosis panel and urine analyses, were assessed at 2-week intervals during treatment and after the 7-day recovery period. The severities of all adverse events were evaluated according to the National Cancer Institute Common Toxicity Criteria, version 2.0 (NCI-CTC Ver. 2.0). The durations of all adverse events and their relations to TAC-101 were initially assessed by the attending physicians. Subsequently, an independent review committee reassessed data on adverse events and evaluated the radiologic tumor responses in a blinded manner using Response Evaluation Criteria in Solid Tumors (RECIST).[9]

Statistical considerations. All data were summarized using descriptive statistics for continuous variables and frequencies and percentages for discrete variables. Median times to events were estimated using the Kaplan–Meier method.

Results

Patient characteristics and treatment. Between October 2003 and May 2005, a total of 13 patients were enrolled at a single site in Japan. All patients were eligible for the evaluation of toxicity and efficacy. The first four patients received dose level 1 (10 mg/day), the next six patients received dose level 2 (20 mg/day), and the last three patients received dose level 3 (30 mg/day). The characteristics of the patients are summarized in Table 1. At study entry, three (23.1%) of the 13 patients had metastatic disease. All 13 patients had received some prior treatment, including one previously given systemic chemotherapy with the oral fluoropyrimidine tegafur-uracil (UFT).

Dose-limiting toxicity and recommended dose. One of the first three patients assigned to level 1 (10 mg/day) discontinued the study medication before completing two courses of treatment because of non-drug-related serious adverse events mentioned in the section of adverse events. Therefore, another patient was assigned to this level, and safety was evaluated in a total of four patients. Because no DLT occurred at this level, the dose was increased to level 2 (20 mg/day). One of the first three patients given level 2 had DLT, and three patients were additionally assigned to this dose level; safety was thus

Table 2. Drug-related adverse events with incidence ≥20% or grade 3–4

Drug-related adverse event	10 mg/day (*n* = 4)		20 mg/day (*n* = 6)		30 mg/day (*n* = 3)		Child–Pugh A (*n* = 8)		Child–Pugh B (*n* = 5)		Total (*n* = 13)	
	All grade (%)	Grade ≥ 3 (%)	All grade (%)	Grade ≥ 3 (%)	All grade (%)	Grade ≥ 3 (%)	All grade (%)	Grade ≥ 3 (%)	All grade (%)	Grade ≥ 3 (%)	All grade (%)	Grade ≥ 3 (%)
Splenic vein thrombosis	0 (0)	0 (0)	0 (0)	0 (0)	1 (33)	1 (33)	1 (13)	1 (13)	0 (0)	0 (0)	1 (8)	1 (8)
Headache	4 (100)	0 (0)	2 (33)	0 (0)	1 (33)	0 (0)	5 (63)	0 (0)	2 (40)	0 (0)	7 (54)	0 (0)
Cough	1 (25)	0 (0)	5 (83)	0 (0)	0 (0)	0 (0)	2 (25)	0 (0)	4 (80)	0 (0)	6 (46)	0 (0)
Rhinorrhea	1 (25)	0 (0)	3 (50)	0 (0)	0 (0)	0 (0)	1 (13)	0 (0)	3 (60)	0 (0)	4 (31)	0 (0)
Alopecia	1 (25)	0 (0)	2 (33)	0 (0)	1 (33)	0 (0)	2 (25)	0 (0)	2 (40)	0 (0)	4 (31)	0 (0)
Eczema	1 (25)	0 (0)	3 (50)	0 (0)	0 (0)	0 (0)	2 (25)	0 (0)	2 (40)	0 (0)	4 (31)	0 (0)
Rash	3 (75)	0 (0)	1 (17)	0 (0)	3 (100)	0 (0)	6 (75)	0 (0)	1 (20)	0 (0)	7 (54)	0 (0)
Arthralgia	1 (25)	0 (0)	3 (50)	0 (0)	1 (33)	0 (0)	3 (38)	0 (0)	2 (40)	0 (0)	5 (39)	0 (0)
Myalgia	2 (50)	0 (0)	0 (0)	0 (0)	1 (33)	0 (0)	3 (38)	0 (0)	0 (0)	0 (0)	3 (23)	0 (0)
Fatigue	1 (25)	0 (0)	4 (67)	0 (0)	1 (33)	0 (0)	3 (38)	0 (0)	3 (60)	0 (0)	6 (46)	0 (0)
Blood cholesterol increased	1 (25)	0 (0)	0 (0)	0 (0)	3 (100)	0 (0)	4 (50)	0 (0)	0 (0)	0 (0)	4 (31)	0 (0)
Blood lactate dehydrogenase increased	1 (25)	0 (0)	1 (17)	0 (0)	3 (100)	0 (0)	4 (50)	0 (0)	1 (20)	0 (0)	5 (39)	0 (0)
Blood triglycerides increased	3 (75)	0 (0)	4 (67)	0 (0)	3 (100)	0 (0)	7 (88)	0 (0)	3 (60)	0 (0)	10 (77)	0 (0)
Fibrin D dimer increased	2 (50)	0 (0)	6 (100)	0 (0)	3 (100)	0 (0)	6 (75)	0 (0)	5 (100)	0 (0)	11 (85)	0 (0)
Thrombin-antithrombin III complex increased	1 (25)	0 (0)	5 (83)	0 (0)	3 (100)	0 (0)	6 (75)	0 (0)	3 (60)	0 (0)	9 (69)	0 (0)
Blood alkaline phosphatase increased	2 (50)	0 (0)	1 (17)	0 (0)	1 (33)	0 (0)	3 (38)	0 (0)	1 (20)	0 (0)	4 (31)	0 (0)

The worst grade was used to calculate the incidence according to grade.

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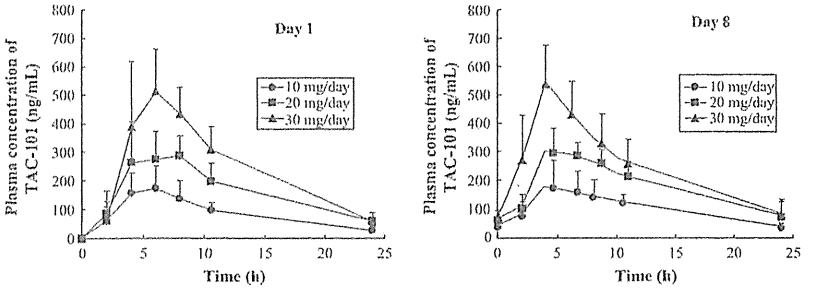

Fig. 1. Plasma concentration-time profile of TAC-101 (4-[3,5-bis(trimethylsilyl) benzamide] benzoic acid) in patients with hepatocellular carcinoma.

Table 3. Pharmacokinetic values of TAC-101 in patients with hepatocellular carcinoma

Blood sampling day	PK parameter	10 mg/day			20 mg/day			30 mg/day		
		No. patients	Mean	SD	No. patients	Mean	SD	No. patients	Mean	SD
Day 1	C_{max} (ng/mL)	4	189.2	85.5	6	333.0	88.6	3	512.1	149.5
	t_{max} (h)	4	5.5	1.0	6	5.7	2.0	3	6.0	0.0
	AUC_{0-24} (ng h/mL)	4	2084	640	6	3900	1140	3	5780	1489
	AUC_{inf} (ng h/mL)	3	2526	497	4	4680	1657	3	6261	1596
	$t_{1/2}$ (h)	3	5.54	0.75	4	6.92	1.67	3	5.57	0.57
	Vd/F (L)	3	32.2	5.6	4	45.5	12.7	3	39.9	9.6
	CL/F (L/h)	3	4.08	0.89	4	4.83	2.15	3	4.98	1.11
Day 8	C_{max} (ng/mL)	4	207.7	71.0	6	326.0	66.9	3	543.9	138.9
	t_{max} (h)	4	6.0	2.9	6	5.7	2.0	3	4.0	0.0
	AUC_{0-24} (ng h/mL)	4	2401	630	6	4191	1063	3	6099	1772
	AUC_{inf} (ng h/mL)	3	2906	755	4	4674	820	3	7257	2410
	$t_{1/2}$ (h)	3	6.47	0.92	4	7.50	0.97	3	8.16	3.59
	Vd/F (L)	3	32.9	5.1	4	46.9	6.4	3	49.3	13.9
	CL/F (L/h)	3	3.62	1.05	4	4.39	0.81	3	4.55	1.87

AUC_{inf}, area under the plasma concentration-time curve up to infinity; AUC_{0-24}, area under the plasma concentration-time curve up to 24 h post-dose; CL/F, oral clearance; C_{max}, maximum plasma concentration; SD, standard deviation; t_{max}, time of maximum concentration; $t_{1/2}$, elimination half-life; Vd/F, apparent volume of distribution.

assessed in a total of six patients. The DLT was grade 2 fatigue requiring eight or more consecutive days of rest for recovery. Because no other patient had DLT, the dose level was increased to level 3 (30 mg/day). Splenic vein thrombosis, a grade 3 drug-related adverse event, occurred in one patient at this level. Although only one patient given 30 mg/day of the study drug had DLT, this dose level was designated as the MTD and 20 mg/day as the RD by a panel of medical experts on an independent monitoring committee, who considered the thromboembolic event to be of great importance on the basis of the results of studies conducted in the United States, in which the event developed in nine of 29 patients and was potentially fatal.

Treatment delivered. Four patients received a total of 14 cycles of treatment at 10 mg/day (median, three cycles per patient; range, 1–7). Six patients received a total of 21 cycles of treatment at 20 mg/day (median, three cycles per patient; range, 2–8). Three patients received a total of seven cycles of treatment at 30 mg/day (median, three cycles per patient; range, 2–3). The dose of TAC-101 was not reduced in any patient. The reasons for terminating treatment were progressive disease in nine patients (69.2%), adverse events in two (15.4%), and other reasons in two (15.4%; one required 21 or more consecutive days of rest, and one withdrew consent).

Adverse events. Drug-related adverse events occurring in the 13 patients are shown in Table 2. Treatment with TAC-101 was generally well tolerated throughout the study. Grade 3 or 4 toxicity (splenic vein thrombosis) occurred in only one patient, who received 30 mg/day of TAC-101. The patient was a 70-year-old, HCV-positive man with Child–Pugh A liver cirrhosis, hypersplenism, and hypertension. He had multiple tumors smaller than 3 cm in diameter in the liver, without vascular invasion or extrahepatic metastasis. Splenic vein thrombosis was noted during a routine restaging CT scan of the target lesion at the end of the third course of therapy. The patient received aspirin, and the thrombosis was considered resolved 85 days after the initiation of treatment with aspirin. The most common toxic effects were fibrin D dimer increased (84.6%), blood triglycerides increased (76.9%), thrombin-antithrombin III complex increased (69.2%), headache and rash (53.8%). Serious adverse events were anorexia, hepatic encephalopathy, renal disorder, aspiration pneumonia, and sepsis in one patient who received 10 mg/day. These events were considered unrelated to the study medication. As for differences in drug-related adverse events between the Child–Pugh A and B groups, the incidences of some events were at least 20 percentage points higher in the Child–Pugh B group than in the Child–Pugh A group, such as cough (25% *vs* 80%), rhinorrhea (13% *vs* 60%), fatigue (38% *vs* 60%), and fibrin D dimer increased (75% *vs* 100%). However, the incidences and severities of most other events were similar in the two groups.

Efficacy. Response could be evaluated in all 13 patients. No patient had a CR or PR. A total of nine patients (69.2%, 9/13) had no change (NC): two of four patients at 10 mg/day, five of six at 20 mg/day, and two of three at 30 mg/day. Four

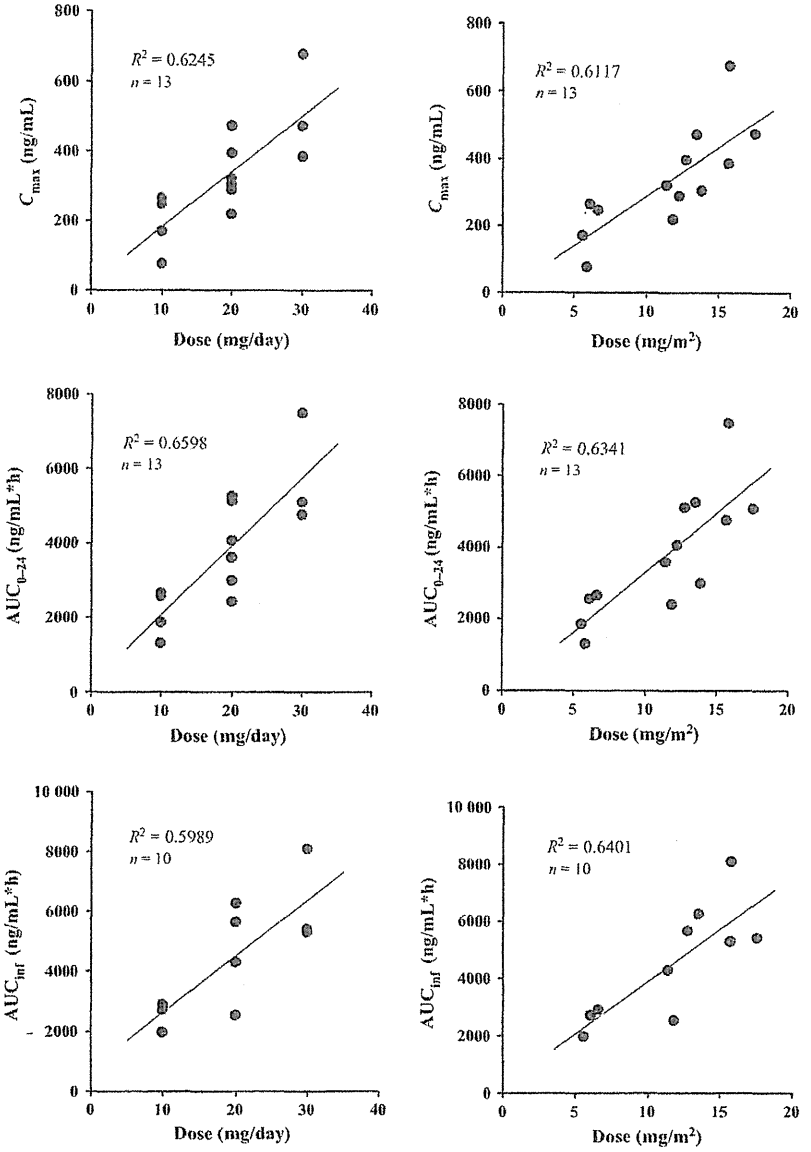

Fig. 2. Relation between TAC-101 (4-[3,5-bis(trimethylsilyl) benzamide] benzoic acid) dose and C_{max} or AUC in patients with hepatocellular carcinoma on day 1 (single dose). The x axes of the left- and right-hand figures represent the dose per day and dose per m^2, respectively.

patients (30.8%, 4/13) had progressive disease (PD): two of four at 10 mg/day, one of six at 20 mg/day, and one of three at 30 mg/day. No change was maintained for 8 weeks (56 days) or longer (long-term NC) in five patients, and the disease control rate (CR + PR + long-term NC) was thus 38.5% (5/13 patients). Median TTF was 60.0 days (95% CI, 46.0-65.0). Median TTP and OS were 86.0 days (95% CI, 58.0 –146.0) and 427.0 days (95% CI, 369.0-unknown), respectively. When response was evaluated according to RECIST, none of the 13 patients had a PR or CR, 7 (53.8%) had SD, and five (38.5%) had PD.

Pharmacokinetic analysis. Mean plasma concentration-time profiles after administration of TAC-101 on day 1 and on day 8 are shown in Figure 1. The calculated pharmacokinetic parameters of TAC-101 are summarized in Table 3. TAC-101 concentrations in plasma reached peak values approximately 6 h after administration and declined with a half-life ($t_{1/2}$) of 5 –8 h. Consistent with the relatively short $t_{1/2}$, increased plasma concentrations after multiple doses of TAC-101 once daily were not apparent. The relations between the dose of TAC-101 and the maximum plasma concentration (C_{max}), area under the plasma concentration-time curve up to 24 h post-dose (AUC_{0-24}), and area under the plasma concentration-time curve up to infinity (AUC_{inf}) after a single dose (day 1) are shown in Figure 2. These variables generally increased proportionally to the dose of TAC-101 (10–30 mg/day). The relation between the dose of TAC-101 and pharmacokinetic parameters was generally unchanged after adjusting the dose according to individual body surface area. The $t_{1/2}$ of 5.54 to 6.92 h, the apparent volume of distribution (Vd/F) of 32.2 to 45.5 L, and the oral clearance (CL/F) of 4.08 to 4.98 L/h after a single dose of TAC-101 did not differ among the dose levels. All pharmacokinetic parameters were generally similar after a single dose and after repeated doses of TAC-101, suggesting that repeated treatment was not

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associated with changes in TAC-101 metabolism or with drug accumulation.

In this clinical study, a total five patients with Child–Pugh class B disease were enrolled, but the oral clearance of TAC-101 was available for only three of the five patients at the dose level of 20 mg/day. The calculated oral clearance of TAC-101 ranged from 3.44 to 5.67 L/h in patients with Child–Pugh class A disease (n = 7, 10–30 mg/day) and from 3.19 to 7.92 L/h in those with Child–Pugh class B disease (n = 3, 20 mg/day). Although there was no apparent difference in oral clearance between the two groups, firm conclusions were precluded by the limited number of patients in this study.

The pooled plasma and urine samples were analyzed to characterize the metabolites of TAC-101. After a single dose of TAC-101, the hydroxylated metabolites TAC-101-M-1 and TAC-101-M-2 were simultaneously detected in plasma samples along with parent TAC-101. The concentrations of TAC-101-M-1 and TAC-101-M-2 in plasma as determined by LC/MS/MS were approximately 16% and 11% of the concentration of unchanged TAC-101 6 h after treatment and approximately 23% and 16% of the concentration of unchanged TAC-101 10.6 h after treatment (mean sampling time; range, 10–12 h), respectively. The respective percentages on day 8 were comparable to those after the initial dose. These results indicate that the majority of absorbed TAC-101 circulates in the body as a parent drug, with minor proportions of metabolites. In urine samples, the hydroxylated metabolite TAC-101-M-3 and the glucuronide conjugates of TAC-101-M-1 and TAC-101-M-2 were detected. The parent drug TAC-101 was not detected in urine, suggesting that hepatic metabolism is the major elimination pathway of TAC-101, which underwent hydroxylation or glucuronide conjugation, followed by partial excretion of metabolites into urine. Based on these exploratory analyses of human plasma and urine, the metabolic pathways of TAC-101 were determined as shown in Figure 3.

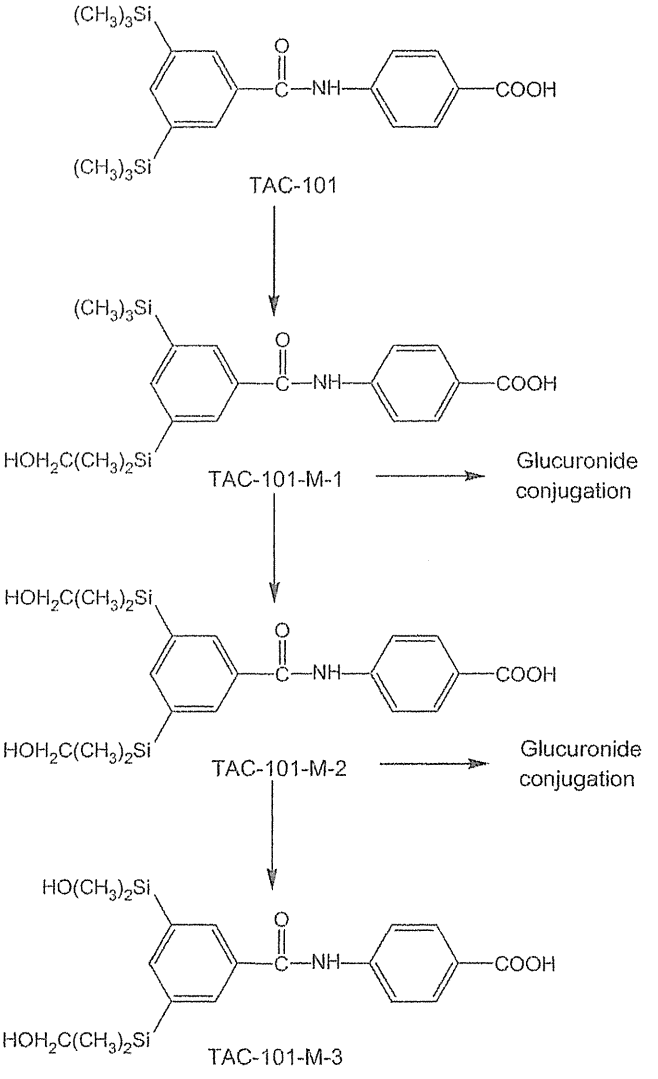

Fig. 3. Metabolic pathways of TAC-101 (4-[3,5-bis(trimethylsilyl) benzamide] benzoic acid) and its metabolites.

Discussion

In one patient given 30 mg/day, CT revealed splenic vein thrombosis, which was considered DLT. Although DLT developed in only one patient receiving 30 mg/day of TAC-101, this dose level was judged to be the MTD by a panel of medical experts who placed maximum emphasis on safety. Mechanisms that potentially trigger thromboembolic events have been studied, but the role of TAC-101 in such events remains unclear.

The most common treatment-related adverse events were fatigue, headache, and dermal symptoms such as rash. However, most adverse events were mild (grade 1 or 2), confirming that TAC-101 is well tolerated at the recommended dose of 20 mg/day. DLT comprised grade 2 fatigue in one patient given 20 mg/day and grade 3 splenic vein thrombosis in one patient given 30 mg/day. The latter was the only grade 3 drug-related adverse event. There were no treatment-related adverse events of grade 3 or higher in patients given 10 or 20 mg/day. In general, the toxic effects of TAC-101 were consistent with those of previous studies.[7,8]

Higginbotham *et al.* reported the results of pharmacokinetic studies of TAC-101 in patients with advanced hepatocellular carcinoma treated in the United States.[8] The mean pharmacokinetic parameters (t_{max}, 4.3 h; C_{max}, 242 ng/mL; AUC_{0-24}, 3067.6 ng h/mL; AUC_{inf}, 4241.1 ng h/mL) obtained for a dose of 20 mg were generally consistent with our data in Japanese patients. The slightly lower C_{max} and AUCs values in the American study might be attributed to general differences in body size between Caucasians and Japanese.

Both maximum (C_{max}) and overall exposures (AUCs) to TAC-101 were generally dose-related within the range of 10 to 30 mg/day. The parent compound TAC-101 was not excreted into urine, suggesting that hepatic metabolism is the major elimination pathway of TAC-101. The primary metabolism of TAC-101 was characterized by hydroxylation of the trimethylsilyl group, producing some primary metabolites, which then underwent glucuronide conjugation. However, the concentrations of the metabolites in plasma were low, suggesting that the biologic activity of TAC-101 is generally attributed to systemic exposure to unchanged TAC-101.

On the basis of the pharmacokinetic and safety profiles of TAC-101 in this study, 20 mg/day, the dose one level below the MTD, was determined to be RD. This dose is the same as the RD in the United States.

As for antitumor effect, no patient had a CR or PR, but nine had NC (69.2%, 9/13 subjects). The median TTF was 60.0 days, the median TTP was 86.0 days, and the MST was 427.0 days. The results for efficacy in this study were also similar to those in the study performed in the United States.[8] Unfortunately, tumor shrinkage was not evident, and the median TTP seemed to be unfavorable on the basis of MST. However, we believe that further evaluations are warranted,

because the mechanisms of action of TAC-101 and other retinoids are considered cytostatic as opposed to cytotoxic, and the TTP in this study may be comparable to those in studies of sorafenib (2.8–5.5 months).[2,3]

In conclusion, our results suggest that TAC-101 is well tolerated at an oral dose of 20 mg/day (dose level 2). This dose, given once daily after breakfast for 14 consecutive days followed by a 7-day rest period, was determined to be the RD for HCC. Additional studies of TAC-101 as a single agent as well as in combination with molecular-targeted agents such as sorafenib are warranted to further delineate potential clinical benefits and risks.

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Disclosure Statement

The authors have no conflict of interest.

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PHASE II STUDIES

A randomized phase II trial of intra-arterial chemotherapy using SM-11355 (Miriplatin) for hepatocellular carcinoma

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Abstract *Background* SM-11355 is a platinum complex developed to treat hepatocellular carcinoma (HCC) via administration into the hepatic artery as a sustained-release suspension in iodized oil. We conducted a multicenter phase II trial in patients with HCC to evaluate the efficacy and safety of SM-11355, using a Zinostatin stimalamer suspension in iodized oil as a reference. *Methods* Patients with unresectable HCC were randomized 2:1 to receive administration of the SM-11355 or Zinostatin stimalamer suspension into the hepatic artery. A second injection was given 4–12 weeks later. Efficacy was evaluated by CT 3 months after treatment and categorized as therapeutic

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effect (TE) V to I, where TE V was defined as disappearance or 100% necrosis of all treated tumors. *Results* A total of 122 patients were evaluated for efficacy and toxicity (SM-11355, n=83; Zinostatin stimalamer, n=39). Baseline characteristics were similar in the two groups. The TE V rates were 26.5% (22/83) and 17.9% (7/39) in the SM-11355 and Zinostatin stimalamer groups, respectively. In the SM-11355 group,the most frequent drug-related adverse events (AEs) of≥grade 3 were elevated AST, elevated ALT, thrombocytopenia, and hyperbilirubinemia. The AEs with the largest difference between the two groups (SM-11355 vs. Zinostatin stimalamer) were hepatic vascular injury (0 vs. 48.4%) and cosinophilia (84.3 vs. 41.0%). The 2-year and 3-year survival rates were 75.9% vs. 70.3% and 58.4% vs. 48.7%, respectively. *Conclusions* The results suggest that SM-11355 in iodized oil has similar efficacy to Zinostatin stimalamer and that repeated dosing of SM-11355 is possible without hepatic vascular injury in cases of relapse.

Keywords Iodized oil · MIRIPLA · Liver cancer · Suspension · Parallel study

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Introduction

International cancer statistics from 2002 indicate that hepatocellular carcinoma (HCC) ranks third behind lung and gastric cancer in the number of deaths [1]. The impact of current standard treatments for advanced HCC, including conventional transcatheter arterial chemoembolization (TACE) using doxorubicin or cisplatin is limited and the prognosis is unsatisfactory [2]. Therefore, there is a clear need for new treatments in management of this disease.

SM-11355, (SP-4-2)-[(1*R*,2*R*)-cyclohexane-1,2-diamine-*N*,*N*']bis (tetradecanoato-*O*) platinum monohydrate (Fig. 1) is a highly lipophilic platinum derivative that can be delivered suspended in iodized oil, an oily lymphographic agent, via injection into the hepatic artery [3]. Following injection into an HCC-feeding artery, iodized oil selectively accumulates in the tumor. Similarly, an iodized oil suspension of SM-11355 accumulates selectively within HCC nodules, allowing continuous release of active platinum compounds into tumor tissues. A phase I dose-finding study using different injection levels indicated a recommended dose of 20 mg/mL and an upper limit of the injection volume of 6 mL [4]. In an early phase II trial , SM-11355 showed a promising anticancer effect with a mild toxicity profile in patients with advanced HCC. Responses were evaluated by computed tomography (CT) three months after treatment, with complete response (CR) defined as disappearance or 100% necrosis of all tumors. Iodized oil accumulation in tumors was taken to indicate necrosis. Of 16 eligible patients, 9 (56%) showed CR [5]. This CR rate was superior to our expectation, because the CR rate in conventional TACE is 15–20% based on the same evaluation criteria [6, 7]. Therefore, the results of the early phase II study

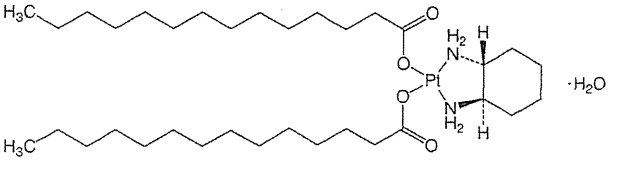

Fig. 1 Structural formula of SM-11355

indicated that SM-11355 has potential as an alternative to TACE in treatment of advanced HCC.

Based on these findings, we conducted a late phase II open-label trial of SM-11355. The aims of the study were to re-evaluate the efficacy, safety and pharmacokinetics of SM-11355 in a larger population, since only 16 eligible patients were included in the previous phase II study, and to confirm the candidacy of SM-11355 as an experimental treatment in a forthcoming clinical study in comparison with conventional TACE. To achieve regulatory approval of SM-11355 in Japan, it was necessary to undertake a parallel study. Therefore, we conducted a randomized phase II trial using Zinostatin stimalamer as a reference, because this agent is the only commercially available lipophilic drug for HCC in Japan and chemolipiodolization of Zinostatin stimalamer has been approved for treatment of advanced HCC in Japan [8, 9]. However, statistical comparisons between the two treatment groups were not planned since the goal of the study was re-evaluation of outcomes for SM-11355, and because the sample size required to conduct a statistical analysis was larger than expected.

Patients and methods

Inclusion criteria

Consecutive patients with HCC were eligible for the study if they had no indication for resection or local ablation therapy. The diagnosis was confirmed histologically and/or clinically using angiography and enhanced CT. Each patient was required to meet the following criteria: at least one measurable intrahepatic lesion that showed tumor staining by CT; tumor stage II or III in the staging system of the Liver Cancer Study Group of Japan [6, 7]; Child-Pugh classification A or B; adequate hematological function (WBC≥3000 /μL, blood platelets≥50000 /μL, hemoglobin≥9.5 g/dL), adequate hepatic function (AST and ALT≤ 5-fold the upper limit of normal, serum bilirubin <3 mg/dL, serum albumin≥3 g/dL), adequate renal function (serum creatinine≤the upper limit of normal); an Eastern Cooperative Oncology Group performance status of 0–2; age 20 to 74 years old; minimum life expectancy≥3 months, and provision of written informed consent. Patients who had undergone hepatic resection, local ablation therapy, and/or TACE were eligible if they showed no evidence of local tumor recurrence in the treated lesions. Patients who had undergone chemolipiodolization with anti-cancer agents other than Zinostatin stimalamer or a platinum-containing agent were also eligible if the treated lesions were resected. The previous anticancer treatment had to have been discontinued for at least 4 weeks before enrollment in this study.

Exclusion criteria

Patients were excluded if they met any of the following criteria: history of allergy to iodine-containing agents and/or contrast material; history of systemic chemotherapy; serious complication such as a cardiac disease or a thyroid disease ; concomitant malignancy; bile duct invasion; pregnant or lactating women and fertile patients who were not using effective contraception; and participation in another trial within 6 months before giving informed consent.

Study treatment

Patients who met the entry criteria were provisionally registered and randomly assigned to the SM-11355 or Zinostatin stimalamer group before undergoing angiography. Each investigator then confirmed registration after establishing that the patient met the following additional requirements based on angiographic findings: intrahepatic lesions that showed tumor staining and were fed by an artery with an appropriate structure for catheter insertion; no evidence of tumor thrombus in the portal or hepatic vein; no evidence of intrahepatic arteriovenous shunting; and no evidence of local tumor recurrence in previously treated lesions. The central random assignment by dynamic allocation to either a SM-11355 group or Zinostatin stimalamer group was stratified according to center and maximun tumor diameter.

A suspension of SM-11355 (MIRIPLA; Dainippon Sumitomo Pharma Co., Japan) or Zinostatin stimalamer (SMANCS; Astellas Pharma Inc., Japan) in iodized oil was injected into the hepatic artery using Seldinger's technique. Patients in the SM-11355 group received SM-11355 suspended in iodized oil (20 mg/mL) in a volume of up to 6 mL according to tumor size. Patients in the Zinostatin stimalamer group received Zinostatin stimalamer suspended in iodized oil (1 mg titer/mL) in a volume of up to 6 mL. When iodized oil accumulation in the treated tumor was insufficient and tumor staining was found in diagnostic imaging 5 weeks (±10 days) after the first injection, a second injection was given within 12 weeks after the first injection.

Efficacy and safety assessment

The antitumor effect was evaluated by CT or MRI 3 months after the last injection according to the response criteria proposed by the Liver Cancer Study Group of Japan [10], which are similar to the criteria proposed by the European Association for the Study of the Liver (EASL) Panel of Experts on HCC [11]. Tumor size was measured using the sum of the products of the perpendicular longest diameters of all measurable lesions. In the response evaluation criteria, iodized oil accumulation in a tumor is regarded as an indication of necrosis because significant positive correlations

have been reported between iodized oil accumulation observed on CT images and necrotic regions in resected tumors examined pathologically after TACE and after intra-arterial chemotherapy with iodized oil [5, 8, 12, 13]. Therapeutic effect (TE) was defined as follows: TE V, disappearance or 100% necrosis of all treated tumors; TE IV, more than 50% reduction in tumor size and/or more than 50% necrosis; TE III, more than 25% reduction in tumor size and/or more than 25% necrosis; and TE I, more than 25% increase in tumor size regardless of the necrotic effect. TE II was defined as a response not qualifying for classification as TE V, IV, III, or I. When a patient assigned to the SM-11355 group and judged to be TE V developed a tumor in a different region and requested SM-11355, the drug was given continuously after the study, provided that this was felt to be necessary by the investigator. The primary endpoint was the TE V rate. The secondary endpoints were the response rate based on the Response Evaluation Criteria in Solid Tumors (RECIST) and on the Japan Society for Cancer Therapy Criteria [14], which are similar to the World Health Organization (WHO) Criteria. The serum α-fetoprotein (AFP) level of each patient was measured before and 5 weeks after each treatment. Survival was evaluated using the Kaplan-Meier method. Toxicity was assessed according to the criteria of the Japan Society for Cancer Therapy [15], which are also fundamentally similar to WHO criteria.

Pharmacokinetics

Pharmacokinetic data were determined in patients in the SM-11355 group who gave written informed consent and were treated at institutions where a pharmacokinetic study could be conducted. Peripheral blood samples (5 ml) were collected 3 weeks after each treatment for determination of the total plasma platinum concentration and the platinum concentration in methanol extracts (SM-11355 metabolite concentration). The total platinum concentration in resected tissue was also determined in a patient who underwent surgery after evaluation of efficacy.

Statistical analysis

We anticipated enrollment of 120 patients at 17 participating hospitals over the study period of 3 years. A 2:1 ratio for SM-11355 to Zinostatin stimalamer randomization was chosen as a balance between the goals of the study, which were to re-evaluate the efficacy, safety and pharmacokinetics of SM-11355 in a larger population than that in the previous phase II study, and the current limited use of Zinostatin stimalamer. The number of subjects was determined based on the feasibility of the study because the sample size required to conduct a statistical analysis was larger than expected. Assuming a baseline 15% TE V rate for conventional TACE [6], the SM-11355 arm would be considered 'favorable' if there was a 10% improvement in this endpoint (to 25%) with an acceptable toxicity profile. A total of 80 patients in the SM-11355 arm is needed to estimate the TE-V rate with an accuracy of ±10%.

This study was not powered to permit formal statistical comparison between the two treatment arms. However, it does allow an initial assessment of SM-11355 in terms of TE-V, response rate, overall survival and toxicity with a view to performance of a follow-on phase III study.

Results

Patient

From April 2002 to October 2004, 131 patients were enrolled in the study, and 126 were assigned randomly at a 2:1 ratio to receive SM-11355 (85 patients) or Zinostatin stimalamer (41 patients) (Fig. 2). Five patients were excluded from the randomization because tumor staining was not observed in angiography and/or an appropriate hepatic artery for selective catheter insertion was not found (n=3), multiple tumors were observed in angiography that required reconsideration of the treatment strategy (n=1), and withdrawal of consent (n=1). After administration, 4 patients were identified as ineligible due to a platelet count <50,000/μL (n=1), esophageal cancer (n=1) in the SM-11355 group, and deviation from correct use of the investigational products (n=2) in the Zinostatin stimalamer group. Therefore, 122 patients (SM-11355 group, n=83; Zinostatin stimalamer group, n=39) were analyzed for efficacy and safety. The baseline demographic and disease characteristics of the patients are listed in Table 1.

Of the 85 original patients in the SM-11355 group, 18 were withdrawn from the study before the planned evaluation of efficacy 3 months after the first injection because of marked progression of the primary disease (n=5), serious adverse events (n=4), use of prohibited concomitant therapeutic agents or a requirement for combination therapy (n=3), and other reasons (duplicated count). Treatment was terminated in 11 patients after evaluation of the the first injection because complete necrosis of tumors (TE V) was obtained. The remaining 56 patients received a second injection.

Of the 41 patients in the Zinostatin stimalamer group, 9 were withdrawn before the planned evaluation of efficacy 3 months after the first injection, due to marked progression of the primary disease (n=2), serious adverse events (n=1), contravention of the protocol (n=1), appearance of hepatic injury (n=1), and other reasons (duplicated count). Treatment was terminated in 7 patients after evaluation of the first injection because complete necrosis of tumors (TE V) was obtained. The remaining 25 patients received a second injection.

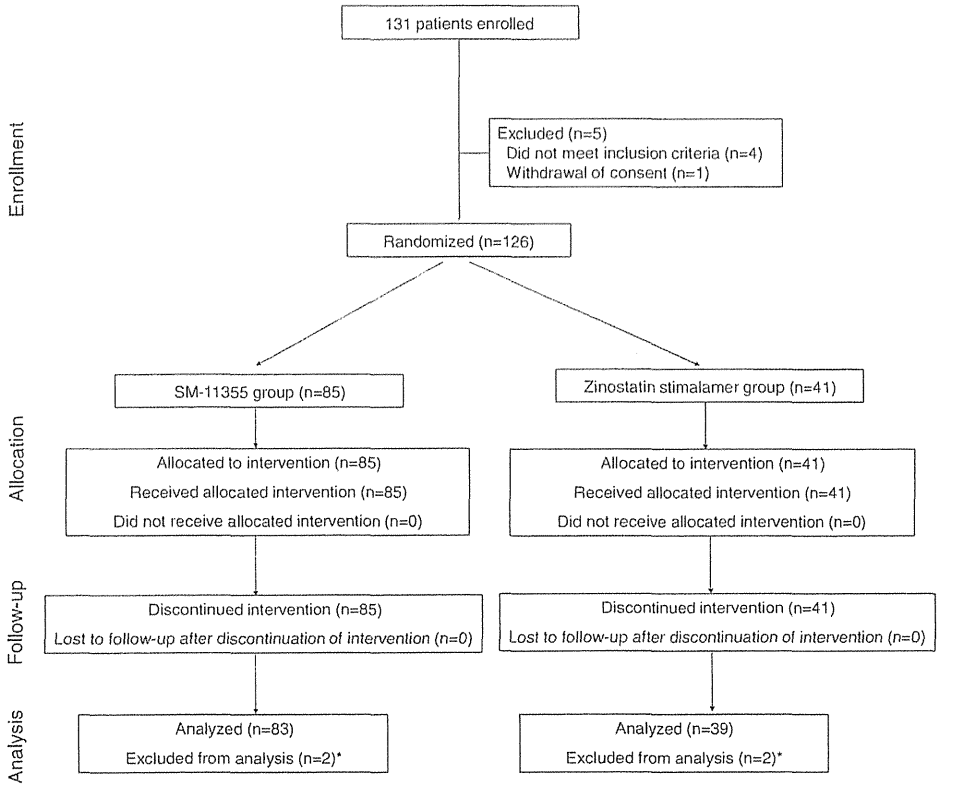

Fig. 2 Study flow diagram

Table 1 Patient background

	SM-11355	Zinostatin stimalamer
Number of patients	83	39
Sex (male:female)	70:13 (84.3%:15.7%)	30:9 (76.9%:23.1%)
Age (median)	67.0 (48–74)	68.0 (52–74)
PS (0:1:2:3:4)	80:3:0:0:0	35:4:0:0:0
HBs antigen positive	9 (13.6%)	1 (3.2%)
HCV antibody positive	55 (83.3%)	30 (96.8%)
HBs antigen · HCV antibody positive	2 (3.0%)	0 (0%)
Tumor stage (I:II:III:IV-A:IV-B)	0:43:40:0:0	0:19:20:0:0
Child-Pugh Classification (A:B:C)	61:22:0	32:7:0
Previously treated	25 (30.1%)	13 (33.3%)
Number of tumors 1	24 (28.9%)	9 (23.1%)
2	19 (22.9%)	11 (28.2%)
3	16 (19.3%)	7 (17.9%)
≥4	24 (28.9%)	12 (30.8%)
Maximum tumor diameter (mm) (Min-Max)	29.0 (10.0–80.0)	29.0 (10.0–94.0)

Table 2 Antitumor efficacy

Group	N	Antitumor efficacy						
"Criteria for Evaluation of Direct Effects on Hepatocellular Carcinoma" of the Liver Cancer Study Group of Japan								
		V	IV	III	II	I	NE	Percentage of TE V (%) [95% CI]
SM-11355	83	22	21	12	7	17	4	26.5 [17.4–37.3]
Zinostatin stimalamer	39	7	14	4	10	1	3	17.9 [7.5–33.5]
Response Evaluation Criteria in Solid Tumors (RECIST)								
		CR	PR	SD		PD	NE	Percentage of CR + PR
SM-11355	83	0	20	52		10	1	24.1 [15.4–34.7]
Zinostatin stimalamer	39	0	10	23		6	0	25.6 [13.0–42.1]
"Clinical Response Evaluation Criteria for Solid Tumor Chemotherapy" of the Japan Society for Cancer Therapy								
		CR	PR	MR	NC	PD	NE	Percentage of CR + PR
SM-11355	83	0	17	10	36	19	1	20.5 [12.4-30.8]
Zinostatin stimalamer	39	0	9	5	19	6	0	23.1 [11.1–39.3]

Efficacy

The antitumor efficacy is shown in Table 2. The percentages of TE V patients were 26.5% (22/83) [95% confidence interval (CI): 17.4–37.3%] in the SM-11355 group and 17.9% (7/39) [95% CI: 7.5–33.5%] in the Zinostatin stimalamer group. In a RECIST assessment, response rates were 24.1% (20/83) [95% CI: 15.4–34.7%] and 25.6% (10/39) [95% CI: 13.0–42.1%] in the respective groups. Based on the Japan Society for Cancer Therapy Criteria, the tumor responses were 20.5% (17/83) [95% CI: 12.4–30.8%] and 23.1% (9/39) [95% CI: 11.1–39.3%] in the respective groups (Table 2).

Of 61 patients with a pre-treatment AFP level above the upper limit of normal in the SM-11355 group, 6 / 60 (10%) had an AFP level within the normal range 5 weeks after the first injection. No data for the AFP level were available for 1 patient in the SM-11355 group at 5 weeks after the first injection. Among the 61 patients, 37 received a second injection and 6 (16%) had a normal AFP level 5 weeks after the second injection. Of the 26 patients in the Zinostatin stimalamer group with a pre-treatment AFP level above the upper limit of normal, none had an AFP level within the normal range 5 weeks after the first injection. Among the 26 patients, 18 received a second injection, but none had a normal AFP level 5 weeks after the second injection.

Cumulative survival rates are shown in Fig. 3. The follow-up period was approximately 3 years after the treatment period. The longest follow-up periods in the SM-11355 and Zinostatin stimalamer groups were both 5.6 years, and the median periods were 3.0 years and 2.8 years, respectively. The one-year survival rates in the SM-11355 and

Fig. 3 Cumulative survival rate

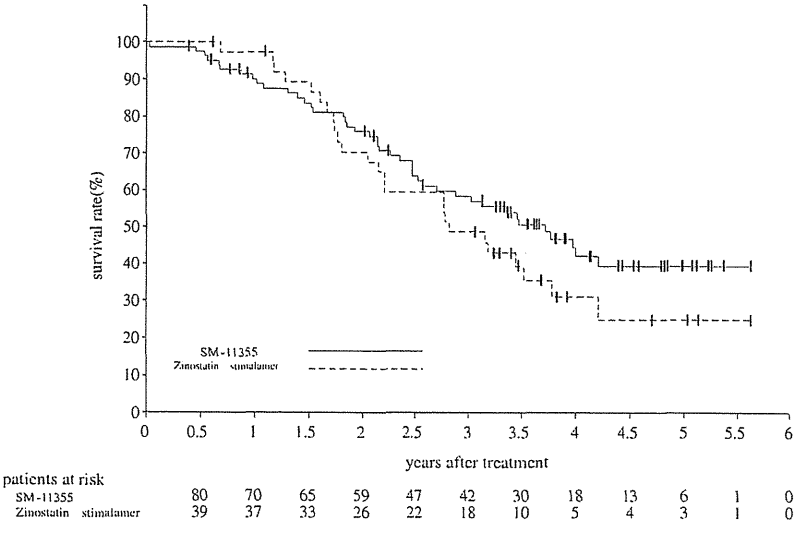

Table 3 Hematological and non-hematological adverse events

	SM-11355			Zinostatin stimalamer		
	No. of patients	All (%)	≥ Grade 3 (%)	No. of patients	All (%)	≥ Grade 3 (%)
Decrease in leukocytes	83	41.0	1.2	39	66.7	0
Decrease in lymphocytes	83	79.5	0	39	79.5	0
Decrease in neutrophils	83	53.0	8.4	39	43.6	2.6
Decrease in platelets	83	50.6	12.0	39	74.4	10.3
Decrease in hemoglobin	83	15.7	0	39	10.3	0
Increase in eosinophils	83	84.3	0	39	41.0	0
Increase in monocytes	83	57.8	0	39	76.9	0
Fatigue	83	39.8	0	39	46.2	0
Fever	83	96.4	3.6	39	97.4	0
Chills	83	39.8	0	39	51.3	0
Vomiting	83	55.4	1.2	39	51.3	0
Pain at injection site	83	43.4	0	39	41.0	2.6
Decrease in albumin	83	50.6	0	39	28.2	0
Increase in ALP	83	30.1	1.2	39	51.3	0
Increase in ALT	83	59.0	24.1	39	66.7	20.5
Increase in AST	83	62.7	26.5	39	79.5	38.5
Increase in bilirubin	83	57.8	12.0	39	71.8	5.1
Decrease in calcium	83	38.6	0	39	51.3	0
Increase in γ-GTP	83	49.4	0	39	61.5	0
Increase in glycemia	83	56.6	12.0	39	56.4	5.1
Increase in LDH	83	60.2	0	39	69.2	0
Increase in CRP	83	95.2	0	39	79.5	0
Prolonged PT time	83	42.2	1.2	39	28.2	0
Decrease in urinary creatinine	83	54.2	0	39	56.4	0
Increase in urinary creatinine	83	49.4	0	39	38.5	0
Increase in urinary NAG	83	89.2	0	39	87.2	0

Adverse events that occurred at a rate of >40% are shown

Zinostatin stimalamer groups were 90.1% and 97.4%, the 2-year survival rates were 75.9% and 70.3%, respectively, and the 3-year survival rates were 58.4% and 48.7%, respectively. The median survival time (MST) was 3.7 years in the SM-11355 group and 2.8 years in the Zinostatin stimalamer group.

Safety

Hematological adverse events were relatively mild and transient in both groups (Table 3). The incidences of neutropenia and decreased hemoglobin were similar in the two groups, but the incidence of eosinophilia was higher in the SM-11355 group, and the incidences of leukopenia and thrombocytopenia were higher in the Zinostatin stimalamer group. Most non-hematological adverse events (Table 3) were also mild and transient in both groups. Major events of grade 3 or higher involved liver dysfunction (including elevations in AST, ALT and hyperbilirubinemia) and hyperglycemia, but these had similar incidences in both groups and most were reversible.

One patient in the SM-11355 group died of esophageal variceal rupture, which occurred 12 days after the first injection, and one patient in the Zinostatin stimalamer group died of hepatic failure 168 days after the second injection. Esophageal variceal rupture was considered not to be related to the treatment because the condition was recognized before initiation of treatment and the event was not classified as a toxicity. Other serious adverse events occurred in 8 patients in the SM-11355 group (increase in AST in 2 patients; and increase in ALT, sepsis, systemic inflammatory response syndrome (SIRS: a syndrome characterized by systemic inflammation and extensive tissue damage associated with serious infection), decrease in neutrophils, acute myocardial infarction (AMI), and hypotension in 1 case each) and in 2 patients in the Zinostatin stimalamer group (respiratory distress and arrhythmia, and abdominal pain in 1 case each). All the patients recovered with appropriate treatment. Most of these events

were considered to be probable or possible drug-related toxicities, except for the cases of SIRS and AMI in the SM-11355 group. SIRS was judged to have no association with the investigational drug based on the results of blood culture and changes in test values. This patient was treated using a urinary catheter, and urinary tract infection is a cause of SIRS. A similar judgment was made for the case of AMI based on the chronological relationship between drug administration and the onset of disease.

In the subsequent angiographic examination before the second administration of SM-11355 or Zinostatin stimalamer or in postprotocol treatment, hepatic artery damage that was probably due to intra-arterial drug administration was observed in 15/31 (48.4%) patients, shunt occurred in 5/31 (16.1%), and disorders of the hepatobiliary system were observed in 3/39 (7.7%) in the Zinostatin stimalamer group. None of these events were observed in patients in the SM-11355 group. Grade 3 hepatic artery damage and a grade 4 disorder of the hepatobiliary system were observed in 1 case each in the Zinostatin stimalamer group. Hepatobiliary damage that may have been caused by arterial damage was found in 3 patients in the Zinostatin stimalamer group (1 case each of liver atrophy and bile duct dilatation, bile duct necrosis, and liver failure and bile duct stricture), whereas there were no such findings in the SM-11355 group.

In the SM-11355 group, the percentages of patients with an increase in Child-Pugh score of one or more points compared to the pre-administration score were 27.7% (23/83) and 17.9% (10/56) in the 5 weeks after the 1st administration and the 5 weeks after the 2nd administration, respectively. In the Zinostatin stimalamer group, these percentages were 35.9% (14/39) and 50.0% (12/24), respectively (Fig. 4).

Pharmacokinetics

Total plasma platinum concentrations and platinum concentrations in methanol extracts (Table 4) were determined in 30 and 24 patients in the SM-11355 group who were given one and two injections, respectively, and received median doses of 85 (Min-max: 24–120) and 120 (10–120) mg, respectively. The mean total platinum concentrations after the first and second injections were 9.6 and 12.9 ng/mL, respectively, and the mean percentages of the concentration in methanol extracts relative to the total plasma platinum concentration were 12.2% and 9.8% after the first and second injections, respectively. In one patient who underwent surgery 172 days after the second injection, the total platinum concentration was determined in the resected liver tissue. The total dose was 200 mg (first injection: 100 mg; second injection: 100 mg) and the concentration in the tumor region of sample S6, which had a 10% necrotic effect, was 62,000 ng/g tissue and that in the non-tumor region was 22,000 ng/g tissue. In contrast, the concentration in the tumor region of sample S8, which showed 50% necrosis, was 260,000 ng/g tissue and that in the non-tumor region was 67,000 ng/g tissue.

Discussion

Most anticancer agents used in TACE are water-soluble and inappropriate for suspension in iodized oil, and are usually administered as a water-in-oil emulsion. Consequently, these agents have reduced sustained release due to poorer retention in the tumor, leading to a limited antitumor effect and adverse effects caused by diffusion of the agents into the blood [16]. In contrast, lipophilic anticancer agents have a high affinity for iodized oil and those injected into the hepatic artery with iodized oil are retained selectively in tumors and exert continuous antitumor effects. SM-11355 is a structurally modified platinum complex with improved affinity for iodized oil due to increased lipophilicity [3]. In an AH109A-transplanted rat liver tumor model, the platinum concentration in the tumor was sustained for longer following administration of a iodized oil suspension of SM-11355 compared to a suspension of cisplatin, with SM-11355 distributed in tumor tissues more selectively than cisplatin [17]. Phase I and early phase II trials

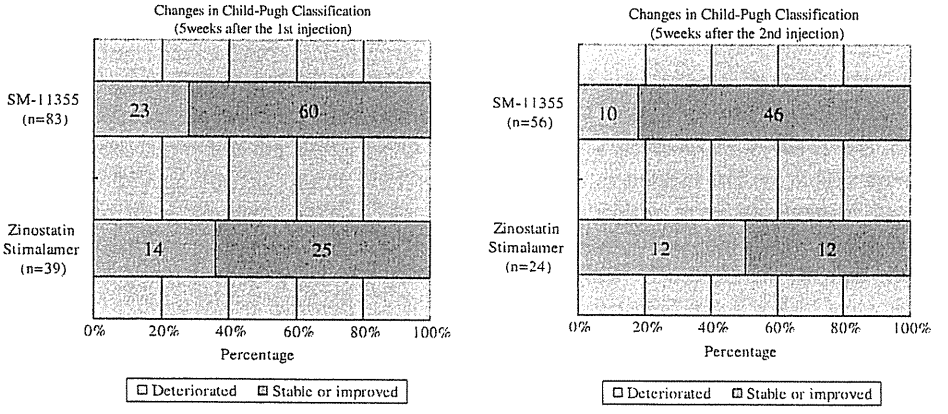

Fig. 4 Changes in Child-Pugh Classification

Table 4 Blood drug concentrations

Administration frequency		Once	Twice
Dose (mg)	Number of patients	30*	24*
	Median (Min-Max)	85.0 (24–120)	120.0 (10–120)
Total plasma platinum concentration (ng/mL)	Number of patients	30	24
	Mean	9.6	12.9
SM-11355 metabolite concentration in methanol extracts (ng/mL)	Number of patients	32	24
	Mean	1.17	1.19
[SM-11355 in methanol-extracted fraction*] / [total plasma platinum concentration] × 100 (%)	Number of patients	30	24
	Mean	12.2	9.8

Number of subjects in whom both the total plasma platinum concentration and SM-11355 metabolite concentration in methanol extracts were measured

* Methanol-extracted fraction: The fraction of SM-11355-derived substances includes components that may exert therapeutic activity as an anticancer agent and excludes components that are irreversibly bound to plasma protein

of SM-11355 have also shown that the total plasma platinum concentration is much lower than that with cisplatin [4, 5, 18]. Our pharmacokinetic data verify these results and suggest that SM-11355 is retained in liver tumors selectively and exerts a continuous effect on the tumor.

In patients in whom the total plasma platinum concentration and the platinum concentration in methanol extracts were determined after the first and second injections, the platinum concentration in methanol extracts 3 weeks after injection (estimated to be the peak of the total plasma platinum concentration) was approximately 10% of the total plasma platinum concentration. Of the platinum components released from the SM-11355 suspension and transferred into the systemic circulation, some are irreversibly bound to plasma proteins and are no longer bioactive. After exclusion of these components, the amount remaining in the plasma is estimated to be up to about 10% of the dose. The total platinum concentrations in several regions of the liver were also determined in one patient. The concentrations in tumors regions were significantly higher than those in non-tumor regions and several thousand-fold higher than the mean total plasma platinum concentration at 3 weeks ±3 days after the second injection (12.9 ng/mL). The total platinum concentration was also higher in tissues in which a higher antitumor effect was observed.

The results of the efficacy re-evaluation suggested that SM-11355 has a similar effect to that of Zinostatin stimalamer following injection of an iodized oil suspension of each drug into the hepatic artery. The primary endpoint (TE V rate based on the Criteria for Evaluation of Direct Effects on Hepatocellular Carcinoma) and the secondary endpoint (response rate based on the Japan Society for Cancer Therapy Criteria and RECIST) in the SM-11355 group were almost the same as those in the Zinostatin stimalamer group. However, the percentage of TE V cases in the SM-11355 group (26.5% [17.4–37.3%]) in this trial was lower than the value of 56% [30–80%] found in the early phase II trial. The discrepancy in the percentage of TE V cases may be due to differences in the tumor burden in the two trials. Eleven (68.8%) of 16 patients in the early phase II study had 3 or less tumors and a longest tumor diameter of 3 cm or less, whereas only 38 (45.8%) of 83 patients in the late phase II study had these characteristics.

The major toxicities of grade 3 or higher involved liver dysfunction, including increases in AST, ALT and bilirubin, and a decrease in platelets in both groups. The incidences were similar in each group and most of the effects were reversible. An increase in eosinophils was found in 84.3% of patients in the SM-11355 group, and was considered to be a SM-11355-specific adverse event. The precise mechanism is unknown, but the finding was not thought to indicate anaphylaxis because the increase in eosinophils showed no marked correlation with an increase in IgE and/or allegic symptoms like wheezing. Renal disorder was transient in patients of the SM-11355 group, except for a patient with sepsis. The incidences and severity of increased blood creatinine and positive urine protein in the SM-11355 group were higher than the respective levels in the Zinostatin stimalamer group (9/83, 10.8% vs. 2/39, 5.1%; and 22/83, 26.5% vs. 2/39, 5.1%, respectively). Based on these data, we consider that the patients were thoroughly followed up.

Injection of SM-11355 did not lead to local vascular damage and had fewer irreversible effects on the hepatobiliary system compared with Zinostatin stimalamer. Zinostatin stimalamer has been reported to have major safety problems, including hepatic arterial damage and effects on the hepatobiliary system that are irreversible and prevent repeated treatment [5, 19, 20] Therefore, SM-11355 may be advantageous for frequent repeated treatment and maintenance of liver function. The changes in Child-Pugh Class indicated a low incidence of treatment-induced hepatic dysfunction in the SM-11355 group.

Based on the results of this trial, we conclude that SM-11355 in iodized oil has similar efficacy to that of Zinostatin stimalamer, which is the only drug currently approved for chemolipiodolization for HCC in Japan. The TE V rate of 26.5% in the SM-11355 group was considered 'favorable'

based on our assumption of a TE V rate of 15% for conventional TACE before the initiation of this study, and was equivalent or superior to the rate of about 20% found in patients receiving current standard TACE treatment in a recent report [7]. Our results also suggest that repeated dosing of SM-11355 in iodized oil is possible without development of hepatic vascular injury in a case of relapse. We are currently conducting a phase III study of intra-arterial treatment with SM-11355 in comparison with conventional TACE with epirubicin, which is designed to detect the superiority of intra-arterial treatment with SM-11355 in overall survival of TACE-naïve patients with advanced HCC (Appendix).

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ORIGINAL ARTICLE

Phase I/II study of gemcitabine as a fixed dose rate infusion and S-1 combination therapy (FGS) in gemcitabine-refractory pancreatic cancer patients

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Abstract
Purpose There is no standard regimen for gemcitabine (Gem)-refractory pancreatic cancer (PC) patients. In a previous phase II trial, S-1 was found to exhibit marginal efficacy. Gem administration by fixed dose rate infusion of 10 mg/m^2/min (FDR-Gem) should maximize the rate of intracellular accumulation of gemcitabine triphosphate and might improve clinical efficacy. We conducted the phase I/II of FDR-Gem and S-1 (FGS) in patients with Gem-refractory PC.
Methods The patients received FDR-Gem on day 1 and S-1 orally twice daily on days 1–7. Cycles were repeated every 14 days. Patients were scheduled to receive Gem (mg/m^2/week) and S-1 (mg/m^2/day) at four dose levels in the phase I: 800/80 (level 1), 1,000/80 (level 2), 1,200/80 (level 3) and 1,200/100 (level 4). Forty patients were enrolled in the phase II study at recommended dose.
Results The recommended dose was the level 3. In the phase II, a partial response has been confirmed in seven patients (18%). The median overall survival time and median progression-free survival time are 7.0 and 2.8 months, respectively. The common adverse reactions were anorexia, leukocytopenia and neutropenia.
Conclusion This combination regimen of FGS is active and well tolerated in patients with Gem-refractory PC.

Keywords Chemotherapy · Pancreatic carcinoma · Second-line · Gemcitabine · S-1 · Salvage · Fixed dose rate infusion

Introduction

Gemcitabine monotherapy or gemcitabine-containing combination chemotherapy is the standard first-line therapy for advanced pancreatic cancer. In the recent phase III study, the first-line FOLFIRINOX regimen (5-fluorouracil, leucovorin, irinotecan and oxaliplatin) led to a median survival of 11.1 months compared with 6.8 months in the gemcitabine group [4]. However, the FOLFIRINOX regimen was quite toxic (e.g., 5.4% of patients had grade 3 or 4 febrile neutropenia), and a survival benefit was shown only among a highly select population with a good performance status, an age of 75 years or younger, and normal or nearly normal bilirubin levels [13]. Therefore, this combination therapy was considered to be one of the treatment options for patients in good general condition, and gemcitabine remains the mainstay of care for patients with advanced pancreatic cancer. However, after disease progression during first-line gemcitabine-containing chemotherapy, the

The registration number of this clinical trial is UMIN ID, C000000450.

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