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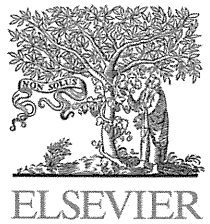

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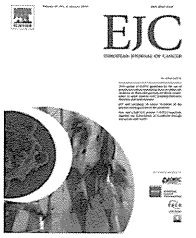

Phase III study of sorafenib after transarterial chemoembolisation in Japanese and Korean patients with unresectable hepatocellular carcinoma ☆

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ABSTRACT

Background: In Japan and South Korea, transarterial chemoembolisation (TACE) is an important locoregional treatment for patients with unresectable hepatocellular carcinoma (HCC). Sorafenib, a multikinase inhibitor, has been shown effective and safe in patients with advanced HCC. This phase III trial assessed the efficacy and safety of sorafenib in Japanese and Korean patients with unresectable HCC who responded to TACE.

Methods: Patients ($n = 458$) with unresectable HCC, Child-Pugh class A cirrhosis and $\geqslant 25\%$ tumour necrosis/shrinkage 1–3 months after 1 or 2 TACE sessions were randomised 1:1 to

☆ Results from this trial were presented at the American Society of Clinical Oncology Gastrointestinal Cancers Symposium, Orlando, Florida, USA, 22–24 January 2010.

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Randomised
Controlled trial

sorafenib 400 mg bid or placebo and treated until progression/recurrence or unacceptable toxicity. Primary end-point was time to progression/recurrence (TTP). Secondary end-point was overall survival (OS).

Findings: Baseline characteristics in the two groups were similar; >50% of patients started sorafenib >9 weeks after TACE. Median TTP in the sorafenib and placebo groups was 5.4 and 3.7 months, respectively (hazard ratio (HR), 0.87; 95% confidence interval (CI), 0.70–1.09; $P = 0.252$). HR (sorafenib/placebo) for OS was 1.06 (95% CI, 0.69–1.64; $P = 0.790$). Median daily dose of sorafenib was 386 mg, with 73% of patients having dose reductions and 91% having dose interruptions. Median administration of sorafenib and placebo was 17.1 and 20.1 weeks, respectively. No unexpected adverse events were observed.

Interpretation: This trial, conducted prior to the reporting of registrational phase III trials, found that sorafenib did not significantly prolong TTP in patients who responded to TACE. This may have been due to delays in starting sorafenib after TACE and/or low daily sorafenib doses.

1. Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide, the third most common cause of cancer deaths in men and the sixth most common in women.[1] It has been estimated that 650,000 people per year die from HCC, about three-quarters in East Asian countries.[2,3] Aetiologic factors vary by geographic region; ~70% of HCC patients in the Asia-Pacific (AP) region have chronic hepatitis B virus (HBV) infection, except in Japan, where ~75% of HCC patients have chronic hepatitis C virus (HCV) infection.[2,3]

Many patients with HCC are not diagnosed until the disease is unresectable, such that only non-curative treatment options are available.[4,5] The most frequent locoregional treatment for unresectable HCC is transarterial chemoembolisation (TACE), which concentrates chemotherapeutic agents at the tumour site while blocking the primary artery feeding the tumour.[6,7] Compared with symptomatic treatment alone, TACE has been found to enhance survival in patients with unresectable HCC.[8,9] A meta-analysis of seven randomised trials of arterial embolisation in 545 patients showed that chemoembolisation with cisplatin or doxorubicin showed a significant 2-year survival benefit compared with control, whereas embolisation alone showed no benefit.[10] A subsequent meta-analysis of randomised trials showed that TACE improves patient survival compared with untreated patients, but not when compared with patients treated with arterial embolisation alone.[11] Furthermore, no chemotherapeutic agent was found superior to any other, and there was no evidence that lipiodol had any benefit.[11]

Although TACE effectively delays HCC progression or prevents recurrence within 6 months, it is less effective over longer periods,[12] with 2-year survival rates of 24–63%.[13] Recent trials in Asian patients have found that 2-year overall survival (OS) rates following TACE with a suspension of a fine powder formulation of cisplatin in lipiodol, an emulsion of doxorubicin in lipiodol, and epirubicin-loaded superabsorbent polymer microspheres were 76%, 46% and 59%, respectively.[14,15] Although multiple courses of TACE may improve local tumour control,[11] it may also worsen liver function, both because TACE itself damages the hepatic arterial system[16] and because many patients have poor underlying liver function due to cirrhosis.[17] New and effective treatment strategies for patients with unresectable HCC are therefore needed, including the optimisation of TACE and its combination with other treatment modalities.

The high rate of HCC recurrence after TACE may be due to its enhancement of angiogenesis and upregulation of vascular endothelial growth factor (VEGF) expression, resulting in the formation of rich vascular beds in residual tumours.[18–20] Post-TACE treatment with systemic multikinase inhibitors that are both antiproliferative and antiangiogenic may therefore lengthen time to recurrence, improve survival, and target lesions distal to the TACE site.

Sorafenib is a multikinase inhibitor with antiangiogenic and antiproliferative properties, targeting multiple pathways.[21–23] Two large randomised phase III studies, the Sorafenib Health Assessment Randomised Protocol (SHARP)[24] and Sorafenib Asia-Pacific (AP)[25] trials, demonstrated that sorafenib significantly improves OS in patients with advanced HCC, leading to its approval for the treatment of HCC in more than 90 countries. To date, sorafenib remains the only available systemic therapy proven to extend survival in these patients.

In patients with unresectable HCC, sorafenib after TACE may prolong time to recurrence/progression and/or minimise loss of liver function associated with repeated courses of TACE. This double-blind, placebo-controlled, phase III trial, designed before the results of the SHARP and Sorafenib AP trials were reported, assessed the efficacy and safety of sorafenib in patients in Japan and South Korea with unresectable HCC who responded to TACE.

2. Patients and methods

We screened patients ⩾18 years of age with unresectable HCC and Child-Pugh A cirrhosis who sustained a response 1–3 months after TACE, defined using the then-prevailing criteria in Japan as ⩾25% tumour necrosis and/or shrinkage.[26,27] Additional inclusion criteria were life expectancy ⩾12 weeks; maximum target lesion size of 70 mm; ⩽10 target lesions; Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1; and adequate bone marrow (absolute

neutrophil count $\geqslant 1000/mm^3$; platelet count $\geqslant 50 \times 10^9/L$; prothrombin time [PT] – international normalised ratio $\leqslant 2.3$ or PT $\leqslant 6$ s above control), liver (total bilirubin $\leqslant 3$ mg/dL; alanine aminotransferase and aspartate aminotransferase $\leqslant 5 \times$ upper limit of normal [ULN]), and renal (serum creatinine $\leqslant 1.5 \times$ ULN; amylase and lipase $\leqslant 2 \times$ ULN) function.

Patients were excluded if they had macroscopic vascular invasion, renal failure, history of cardiac disease, active clinically serious infection, history of human immunodeficiency virus infection, symptomatic metastatic brain or meningeal tumour, extrahepatic metastasis, seizure disorder requiring medication, prior use of systemic agents for advanced HCC (although prior use of interferon, retinoid and/or vitamin K_2 as adjuvant treatment after curative local treatment was allowed), use of hematopoietic growth factors within 3 weeks before start of study drug, concomitant treatment with cytokines after the last course of TACE, history of organ allograft, documented history of substance abuse, or were pregnant or breast-feeding.

All patients provided written informed consent. The study was approved by the appropriate ethics committees and institutional review boards at each centre, and complied with Good Clinical Practice Guidelines, the Declaration of Helsinki, and local laws and regulations. Ongoing safety and efficacy were assessed independently by the Data Monitoring Committee. This study was registered at Clinicaltrials.gov as trial number NCT00494299.

2.1. Procedures

TACE was performed by injecting gelatin foam plus lipiodol in all cases. The chemotherapeutic agents used concurrently were epirubicin, cisplatin, doxorubicin and mitomycin. Eligible patients were stratified by response to TACE (complete response [CR], defined as 100% tumour necrosis or shrinkage versus non-complete response [non-CR], defined as $\geqslant 25\%$ but <100% tumour necrosis or shrinkage),[26] by ECOG PS (0 versus 1), and by number of courses of TACE (one versus two). Patients were blindly randomised 1:1 to 400 mg (two 200-mg tablets) sorafenib (Bayer Schering Pharma; Leverkusen, Germany) or matching placebo twice daily.

Treatment interruptions and dose reductions (first 400 mg qd, then 400 mg qod) were allowed for drug-related toxicity. Patients were monitored for adverse events (AEs) using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0, except that the hand-foot skin reaction (HFSR) was classified and managed by a protocol-defined scale. Treatment continued until radiologic progression or recurrence of HCC, unacceptable toxicity associated with study drug, or withdrawal of consent.

The trial was divided into 28-day cycles. Patients were evaluated for safety and compliance every 2 weeks during cycles 1–3, and every 4 weeks thereafter. Tumours were evaluated, centrally at an image registration centre, $\leqslant 28$ days before the first dose of study drug and every 8 weeks thereafter, or when evaluating recurrence or progression. Throughout treatment, lesions were evaluated by dynamic computed tomography (CT), preferably by the same investigator or radiologist as at screening.

The primary study end-point was time to progression (TTP) by central review, defined as time to recurrence in patients with CR and TTP in those with non-CR at study entry. Progression was defined as a $\geqslant 25\%$ increase in tumour size or development of a new lesion. The secondary end-point was OS, defined as time from randomisation to death from any cause. Exploratory analyses included TTP by investigator assessment and subgroup analyses of TTP by central review, based on aetiology (HBV versus HCV), response to TACE (CR versus non-CR), number of lesions ($\leqslant 3$ versus >3), number of prior courses of TACE (1 versus 2), age (<65 versus $\geqslant 65$ years), sex, treatment lag ($\leqslant 9$ versus >9 weeks), country of enrolment (Japan versus South Korea), and ECOG PS (0 versus 1).

2.2. Statistical analysis

Patient sample size was estimated based on TTP. If 30% and 70% of patients achieved CR and non-CR, respectively, in response to TACE, the median TTP for the placebo group in the mixed population would be 5.7 months. Clinically meaningful improvement was defined as median TTP 50% higher in the sorafenib than in the placebo group. Assuming one formal interim and one final analysis performed using an O'Brien-Fleming-type alpha spending function with a two-sided alpha of 0.05, 318 events would be required to achieve a statistical power of 95%. Accrual of 372 patients (186 in each group) within 18 months would be expected to result in 318 events after 30 months; if 10% of patients were lost to follow-up, 414 patients would have to be randomised to observe 318 events.

Efficacy was assessed in the intention-to-treat (ITT) population, defined as all randomised patients. The safety population included all patients who received at least one dose of study medication. TTP and OS in the two treatment arms were calculated by the Kaplan–Meier method and compared by the log-rank test, as were subgroups stratified by response to TACE (CR versus non-CR), ECOG PS (0 versus 1) and number of prior courses of TACE (1 versus 2). Hazard ratios (HRs) for sorafenib versus placebo and 95% confidence intervals (CI) were estimated by Cox proportional hazards models.

2.3. Role of the funding source

The study sponsors were involved in the design of the study; the collection, analysis and interpretation of data; the writing of the report; and the decision to submit the paper for publication.

3. Results

3.1. Patients

From 27th April 2006 to 10th July 2009, 552 patients were screened at 69 centres in Japan and seven centres in South Korea. Of these, 458 patients (387 at 67 centres in Japan and 71 at six centres in South Korea) met the eligibility criteria and were randomised, 229 each to the sorafenib and placebo groups. All were included in the ITT analysis (Fig. 1), whereas

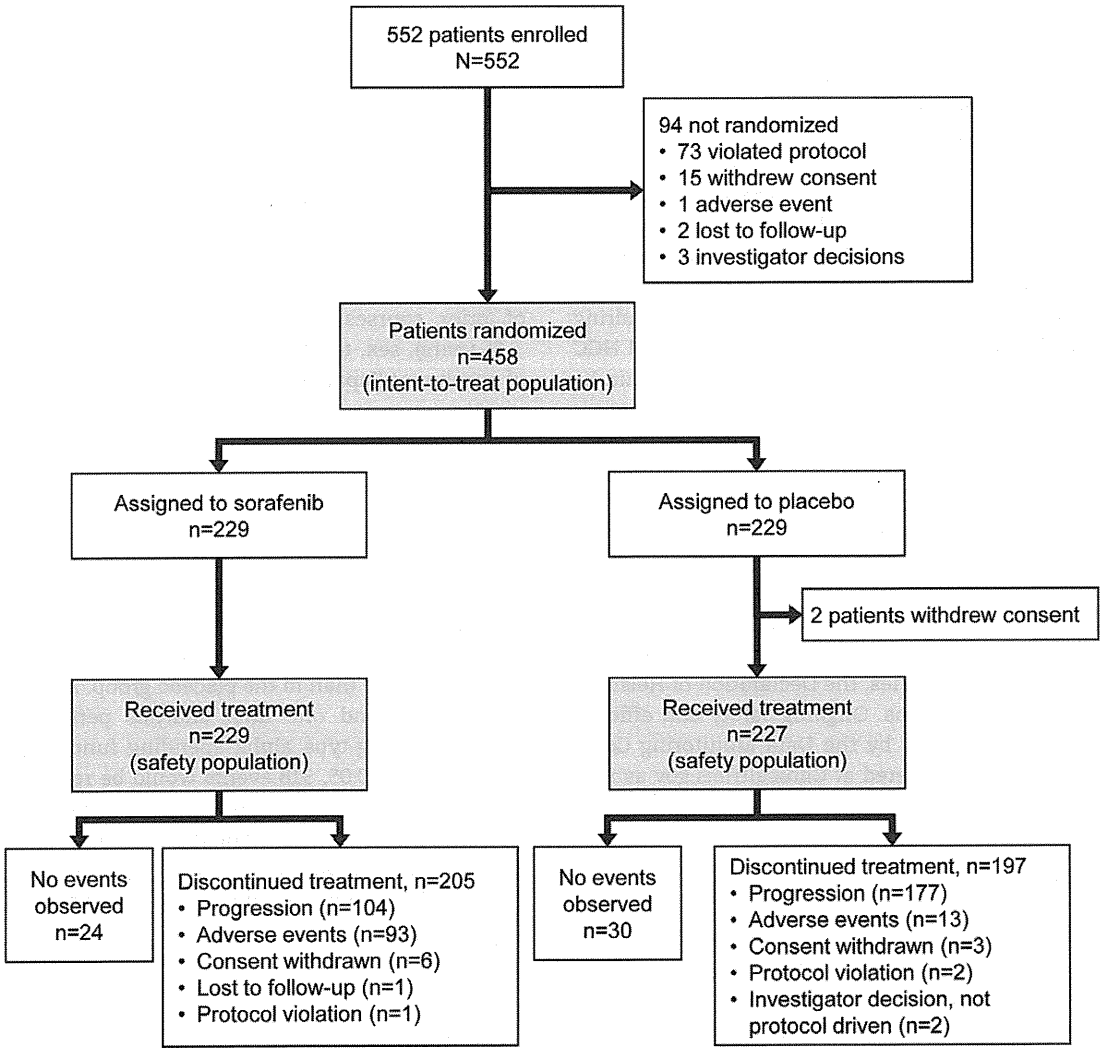

Fig. 1 – Enrolment and outcomes.

the 456 who received at least one dose of study drug were included in the safety analysis.

Demographic and baseline disease characteristics were similar in the sorafenib and placebo groups (Table 1). Of the 458 patients, 342 (74.7%) were male and 306 (66.8%) were ⩾65 years. Median age was 69 years (range, 29–86 years). At baseline, 403 patients (88.0%) had an ECOG PS of 0, 287 (62.7%) had HCV infection, and 336 (73.4%) had ⩽3 tumours. TACE consisted of gelatin foam plus lipiodol in all 458 patients, 60 for palliative intent and 398 for curative intent. Of these 458 patients, 355 received TACE monotherapy, including epirubicin ($n = 219$), cisplatin ($n = 89$), doxorubicin ($n = 49$) and mitomycin ($n = 1$); and 103 received combination treatments, including epirubicin + mitomycin ($n = 57$), cisplatin + epirubicin ($n = 16$), cisplatin + doxorubicin + mitomycin ($n = 13$), mitomycin + mitoxantrone ($n = 8$), doxorubicin + mitomycin ($n = 5$) and doxorubicin + iodixanol ($n = 4$). The median time from last TACE to randomisation was 9.3 weeks (range, 5.6–13.3 weeks), and the median time from initial diagnosis to study entry was 9.8 months (range, 1.6–144.3 months). Ten patients (2.2%) had received prior systemic anticancer therapy, consisting of prior adjuvant treatment with interferon, retinoid and/or vitamin K2 treatment after curative local treatment, and 219 (47.8%) had previously undergone some type of locoregional treatment, including radiofrequency ablation alone (10.7%), surgery alone (9.6%), percutaneous ethanol injection alone (5.9%), microwave coagulation therapy alone (0.2%) and other procedures (0.2%), with 21.2% having undergone multiple procedures (Table 1).

3.2. *Primary efficacy analysis*

By the cutoff date of 10th July 2009, 324 progression events (137 in the sorafenib and 187 in the placebo group) were confirmed by the Response Evaluation Committee. Median TTP by central review was 5.4 months (95% CI, 3.8–7.2 months) in the sorafenib group and 3.7 months (95% CI, 3.5–4.0 months) in the placebo group (HR [sorafenib/placebo], 0.87; 95% CI, 0.70–1.09; $P = 0.252$; Fig. 2). The 3-month progression-free rates in the sorafenib and placebo groups were 65.0% and 58.7%, respectively, and their 6-month progression-free rates were 45.7% and 33.5%, respectively.

Table 1 – Demographic and baseline characteristics of randomised patients (ITT population).

Variable	All patients			Japanese patients			Korean patients		
	Sorafenib + placebo (*n* = 458)	Sorafenib (*n* = 229)	Placebo (*n* = 229)	Sorafenib + placebo (*n* = 387)	Sorafenib (*n* = 196)	Placebo (*n* = 191)	Sorafenib + placebo (*n* = 71)	Sorafenib (*n* = 33)	Placebo (*n* = 38)
Median age (years)	69	69	70	71	70	71	60	61	59
Male (%)	74.7	76.0	73.4	72.9	74.0	71.7	84.5	87.9	81.6
ECOG PS[a] (%)									
0	88.0	87.8	88.2	91.5	91.3	91.6	69.0	66.7	71.1
1	12.0	12.2	11.8	8.5	8.7	8.4	31.0	33.3	28.9
Number of lesions (%)									
≤3	73.4	72.9	73.8	70.8	69.9	71.7	87.3	90.9	84.2
>3	26.6	27.1	26.2	29.2	30.1	28.3	12.7	9.1	15.8
Aetiology (%)									
Alcohol	6.8	8.3	5.2	6.5	7.7	5.2	8.5	12.1	5.3
HBV	21.1	20.5	22.7	12.7	12.2	13.1	70.4	69.7	71.1
HCV	62.7	60.7	64.6	71.3	68.4	74.3	15.5	15.2	15.8
Other	5.9	7.0	4.8	7.0	8.2	5.8	0	0	0
Liver cirrhosis[b] (%)	68.3	69.4	67.2	66.7	67.3	66.0	77.5	81.8	73.7
Number of prior TACE[a] (%)									
1	64.4	64.2	64.6	66.7	66.3	67.0	52.1	51.5	52.6
2	35.6	35.8	35.4	33.3	33.7	33.0	47.9	48.5	47.4
Response to prior TACE[a,c] (%)									
CR	62.0	62.0	62.0	58.1	58.7	57.6	83.1	81.8	84.2
Non-CR	38.0	38.0	38.0	41.9	41.3	42.4	16.9	18.2	15.8
Prior local therapy (%)									
RFA	10.7	11.8	9.6	10.3	11.7	8.9	12.7	12.1	13.2
Surgery	9.6	7.0	12.2	10.3	8.2	12.6	5.6	0	10.5
PEI	5.9	4.8	7.0	6.5	5.1	7.9	2.8	3.0	2.6
MCT	0.2	0.4	0	0.3	0.5	0	0	0	0
Others	0.2	0.4	0	0	0	0	1.4	3.0	0
Multiple	21.2	20.5	21.8	24.0	23.0	25.1	5.6	6.1	5.3
Prior systemic therapy (%)	2.2	3.1	1.3	2.6	3.6	1.6	0	0	0

ITT = intention-to-treat; ECOG PS = Eastern Cooperative Oncology Group performance status; HBV = hepatitis B virus; HCV = hepatitis C virus; TACE = transarterial chemoembolisation; CR = complete response; non-CR = non-complete response; RFA = radiofrequency ablation; PEI = percutaneous ethanol injection; MCT = microwave coagulation therapy.

[a] Protocol-defined stratification factor.

[b] Clinically and/or histologically confirmed liver cirrhosis.

[c] Complete response was defined in the study protocol as 100% tumour shrinkage or necrosis.

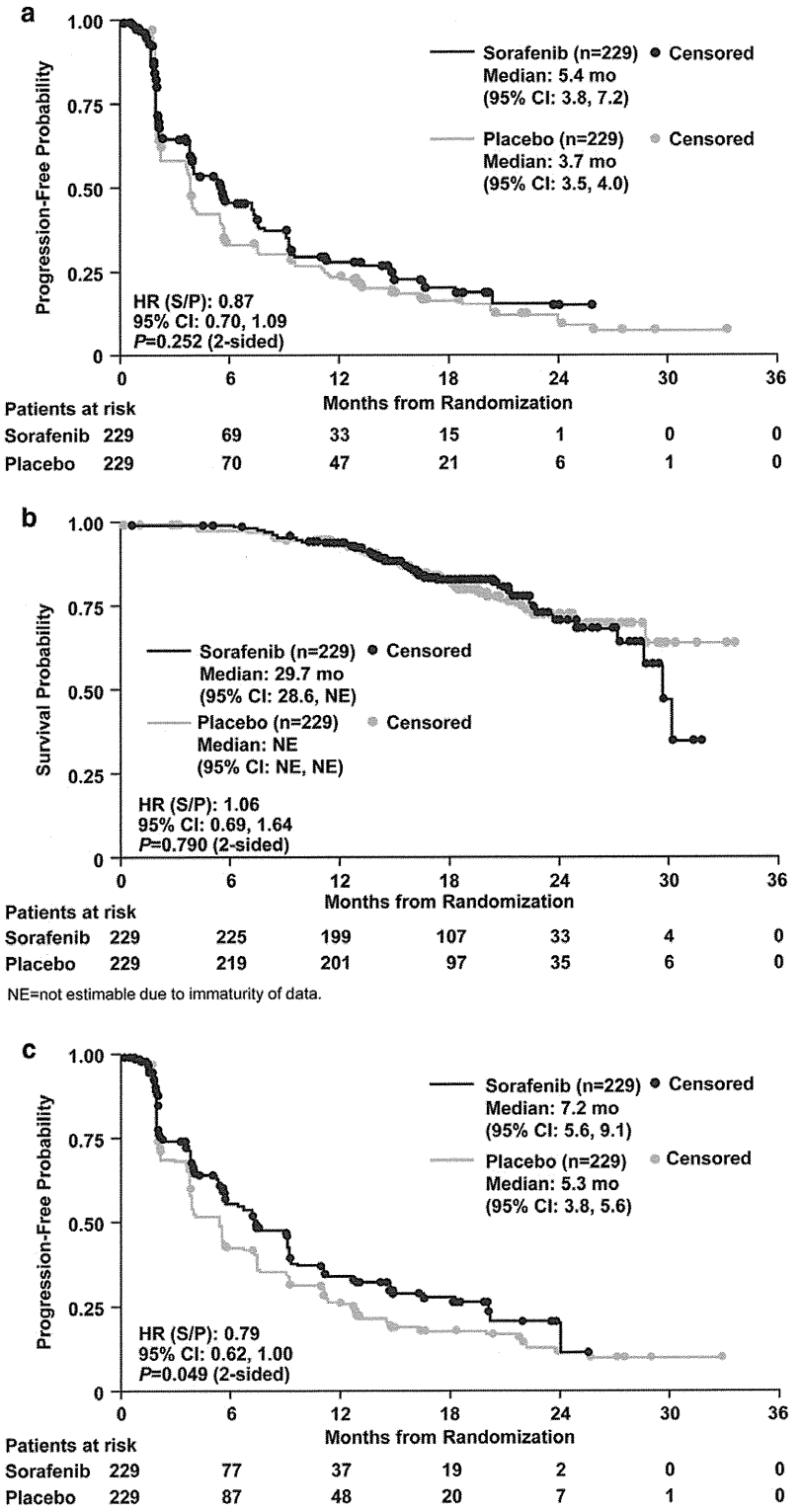

Fig. 2 – Kaplan–Meier analysis of time to progression (TTP) and overall survival (OS). (a) TTP by central review (primary intention-to-treat (ITT) analysis); (b) OS (secondary ITT analysis) and (c) TTP by investigator assessment (exploratory ITT analysis).

3.3. *Secondary efficacy analysis*

At the same cutoff date, there were 84 deaths, 43 in the sorafenib and 41 in the placebo group; the remaining patients were censored on that date. Median OS was 29.7 months in the sorafenib group (95% CI, 28.6 months – not yet reached) but had not yet been reached in the placebo group (HR [sorafenib/placebo], 1.06; 95% CI, 0.69–1.64; $P = 0.790$). The

Table 2 – Exploratory subgroup analyses of TTP by central review based on demographic, baseline and prognostic characteristics (ITT population; subgroups that included at least 10% of patients).

Variable	Subgroup	*n*	Number of events	Number of patients censored	Median TTP (95% confidence interval [CI]) (months)		Hazard ratio [HR] (95% CI) for Sorafenib/placebo
					Sorafenib	Placebo	
Aetiology	HBV	99	56	43	9.1 (5.6–20.3)	5.6 (3.7–10.9)	0.84 (0.49–1.44)
	HCV	287	217	70	5.3 (3.7–7.1)	3.6 (2.0–3.7)	0.81 (0.62–1.07)
Response to TACE	CR	284	179	105	7.4 (5.6–9.2)	5.3 (3.7–7.4)	0.84 (0.63–1.14)
	Non-CR	174	145	29	2.1 (1.8–3.9)	1.9 (1.8–3.6)	0.85 (0.61–1.18)
Number of lesions	⩽3	336	219	117	7.1 (5.3–7.8)	3.8 (3.7–5.5)	0.83 (0.64–1.09)
	>3	122	105	17	3.7 (2.0–5.3)	2.0 (1.9–3.7)	0.87 (0.59–1.29)
Number of prior TACE	1	295	212	83	5.4 (3.8–7.4)	3.7 (3.5–5.5)	0.91 (0.70–1.20)
	2	163	112	51	5.3 (3.7–7.8)	3.7 (2.1–3.8)	0.76 (0.52–1.11)
Age group	<65 years	152	90	62	9.1 (5.6–18.2)	3.7 (3.5–7.2)	0.68 (0.44–1.03)
	⩾65 years	306	234	72	3.8 (3.5–5.4)	3.7 (2.1–3.9)	0.99 (0.76–1.28)
Sex	Male	342	241	101	5.4 (3.8–7.4)	3.7 (3.5–5.3)	0.78 (0.60–1.00)
	Female	116	83	33	5.3 (3.6–7.4)	3.7 (2.1–5.3)	1.16 (0.75–1.79)
Treatment lag[a]	⩽9 weeks	205	150	55	5.5 (3.9–9.1)	3.7 (3.5–5.3)	0.74 (0.53–1.03)
	>9 weeks	253	174	79	5.1 (3.7–7.2)	3.7 (2.0–5.3)	0.95 (0.71–1.29)
Country of enrolment	Japan	387	289	98	3.9 (3.7–5.5)	3.7 (2.1–3.8)	0.94 (0.75–1.19)
	South Korea	71	35	36	NE[b] (9.0–NE)	5.5 (3.7–11.0)	0.38 (0.18–0.81)
ECOG PS	0	403	286	117	5.4 (3.8–7.2)	3.7 (3.6–5.3)	0.88 (0.69–1.11)
	1	55	38	17	5.4 (1.8–16.6)	3.5 (1.8–5.5)	0.78 (0.40–1.51)

[a] Treatment lag was defined as time from the most recent TACE to randomisation.
[b] NE = not estimable due to censored data.

1-year survival rates in the sorafenib and placebo groups were 94.6% and 94.1%, respectively, and their 2-year survival rates were 72.1% and 73.8%, respectively.

3.4. *Exploratory analyses*

At the cutoff date, investigators had reported 304 progression events, 120 in the sorafenib and 184 in the placebo group. Median TTP by investigator assessment in the sorafenib and placebo groups were 7.2 months (95% CI, 5.6–9.1 months) and 5.3 months (95% CI, 3.8–5.6 months), respectively (HR [sorafenib/placebo], 0.79; 95% CI, 0.62–1.00; P = 0.049). Their 3-month progression-free rates were 74.1% and 67.9%, respectively, and their 6-month progression-free rates were 54.9% and 41.4%, respectively.

Exploratory analyses of TTP by central review were performed in subgroups containing ⩾10% of patients, including by aetiology (HBV versus HCV), response to TACE (CR versus non-CR), number of lesions (⩽3 versus >3), number of prior courses of TACE (1 versus 2), age (<65 versus ⩾65 years), sex, treatment lag (⩽9 versus >9 weeks), ECOG PS (0 versus 1) and country of enrolment. These analyses were performed to provide descriptive information only; the study was not powered to compare subgroup response to treatment, and no adjustments were made for multiple comparisons. Median TTP and the HR for TTP (sorafenib/placebo) in each subgroup are shown in Table 2, and Forest plots of HRs for TTP are shown in Fig. 3. Most HRs favored sorafenib. Differences were observed, however, between Japanese and Korean patients. The HR for TTP was 0.94 (95% CI, 0.75–1.19) for Japanese patients and 0.38 (95% CI, 0.18–0.81) for Korean patients (Fig. 4). Median TTP in sorafenib-treated patients in the

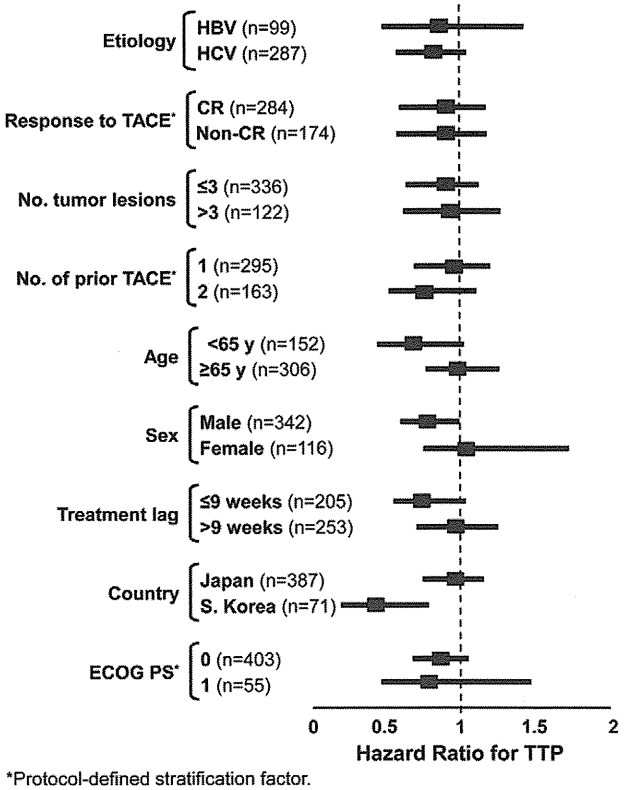

Fig. 3 – Subgroup analyses of TTP by central review (exploratory ITT analyses in subgroups that include at least 10% of patients): forest plot depicting hazard ratio (HR) for TTP (sorafenib over placebo) for each subgroup.

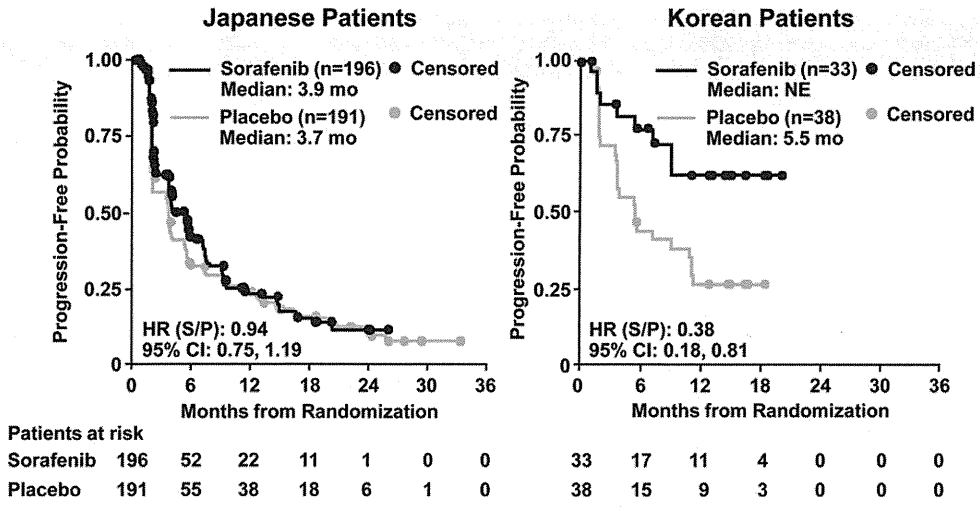

Fig. 4 – Kaplan–Meier analysis of TTP by central review, by country of enrolment (exploratory ITT analysis).

Korean subgroup could not be estimated since it was not attained by the study cutoff date.

3.5. *Safety*

The safety analysis included 229 sorafenib-treated and 227 placebo-treated patients; their incidence of drug-related AEs (DRAEs) were 100% and 61%, respectively. Most DRAEs were mild to moderate (Table 3), with the most frequent in the sorafenib and placebo groups being HFSR (82% versus 7%), elevated lipase (44% versus 8%), alopecia (41% versus 3%) and rash/desquamation (40% versus 11%). In the sorafenib group, 24% and 4% of patients experienced grades 3 and 4 elevated lipase, respectively, compared with 3% and <1%, respectively, in the placebo group. There was no radiographic or clinical evidence of pancreatitis in either group. The overall incidences of grade 3 HFSR (protocol-defined scale) in the sorafenib and placebo groups were 35% and 0%, respectively, and the overall incidence of serious DRAEs was 18% and 9%, respectively. There were no drug-related deaths.

The median durations of treatment in the sorafenib and placebo groups were 17.1 weeks (range, 1.0–112.1 weeks) and 20.1 weeks (range, 2.1–144.1 weeks), respectively (Table 4), and the median daily doses of sorafenib and placebo were 386.0 mg (range, 112.0–794.5 mg) and 785.8 mg (range, 276.1–810.3 mg), respectively. In the sorafenib group, 40 patients (17.5%) received >80% of the planned dose, compared with 206 (90.7%) in the placebo group. The most common reasons for discontinuing treatment in the sorafenib and placebo groups were disease progression (104/229 [45%] versus 177/229 [77%]) and adverse events (93/229 [41%] versus13/229 [6%]).

Doses were reduced in 166 of the 229 sorafenib-treated (72.5%) and in 33 of the 227 placebo-treated (14.5%) patients,

Table 3 – Treatment-emergent, drug-related adverse events occurring in ⩾20% of patients in either group.[a]

Adverse event	Sorafenib ($n = 229$) Grade (%)			Placebo ($n = 227$) Grade (%)		
	Any	3	4	Any	3	4
HFSR	82	35	–	7	0	–
Elevated lipase[b]	44	24	4	8	3	<1
Alopecia	41	–	–	3	–	–
Rash/desquamation	40	4	0	11	0	0
Other metabolic abnormality	32	8	1	4	2	<1
Diarrhoea	31	6	0	5	1	0
Hypertension	31	15	0	7	1	0
Hypophosphatemia	28	16	0	6	3	0
Thrombocytopenia	25	11	1	2	<1	0
Elevated AST	25	12	<1	5	3	0
Elevated ALT	21	8	<1	5	2	0
Elevated amylase	21	6	1	8	2	<1

HFSR = hand–foot skin reaction; AST = aspartate aminotransferase; ALT = alanine aminotransferase; NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

[a] Patients were monitored for adverse events using NCI-CTCAE v3.0, except for HFSR, which was classified according to a 3-grade, protocol-defined scale (grade 1, HFSR does not disrupt normal activities; grade 2, HFSR affects the activities of the patient; and grade 3, patient is unable to work or perform activities of daily living because of HFSR).

[b] There was no radiographic or clinical evidence of pancreatitis in either arm.

Table 4 – Summary of study drug administration.

Assessment	All patients		Japan		South Korea	
	Sorafenib (*n* = 229)	Placebo (*n* = 227)	Sorafenib (*n* = 196)	Placebo (*n* = 190)	Sorafenib (*n* = 33)	Placebo (*n* = 37)
Median duration of treatment (weeks)	17	20	16	20	31	33
Median daily dose (mg)	386	786	382	786	403	766
Patients with dose reduction (%)	73	14	71	11	82	32
Patients with dose interruption (%)	91	18	92	17	85	24
Patients with discontinuation (%)	90	87	93	88	70	78
Due to progression (%)	51	90	52	90	39	90
Due to adverse events (%)	45	7	44	7	57	3
HFSR	11	0	10	0	18	0
Thrombocytopenia	4	0	5	0	3	0
Hypophosphatemia	4	<1	4	1	3	0
Hypertension	4	0	5	0	0	0
Neutropenia	4	<1	4	1	0	0
Elevated AST	2	<1	2	1	3	0
Rash/desquamation	2	0	2	0	3	0
Elevated ALT	2	1	1	1	6	0
Diarrhoea	1	0	1	0	3	0
Other	11	4	19	3	18	3

HFSR = hand–foot skin reaction; AST = aspartate aminotransferase; and ALT = alanine aminotransferase.

due primarily to AEs (163 versus 27). Forest doses were interrupted temporarily in 208 of the 229 sorafenib-treated (90.8%) and 41 of the 227 placebo-treated (18.1%) patients, again due primarily to AEs (206 versus 38).

A total of 107 patients – 94 of the 229 (41.0%) in the sorafenib group and 13 of the 227 (5.7%) in the placebo group – permanently discontinued study drug due to AEs. The most common AEs leading to discontinuation of sorafenib were HFSR (11.4%), thrombocytopenia (4.4%), hypertension (3.9%), hypophosphatemia (3.9%) and neutropenia (3.5%); the most common AE leading to discontinuation of placebo was increased ALT (0.9%).

Death within 30 days of receiving study drug occurred in one patient (0.4%) in each group; neither was deemed drug-related.

4. Discussion

This phase III randomised, controlled trial, assessing the efficacy and safety of sorafenib after response to TACE in Japanese and Korean patients with unresectable HCC, employed a protocol consistent with the practice of TACE in these countries at that time.[28,29] Moreover, the protocol was designed before the combination or sequential use of TACE and sorafenib or their optimal timing had been adequately studied, and before the effect of TACE on susceptibility to sorafenib had been characterised. In this setting, sorafenib did not significantly prolong TTP or OS by central review in patients with unresectable HCC who responded to TACE. Exploratory secondary and subgroup analyses suggested, however, that post-TACE sorafenib had a positive impact on these patients. Median TTP by investigator review was approximately 2 months longer in the sorafenib than in the placebo group, and exploratory subgroup analyses suggested that TTP may have been affected by several factors, including age, number of prior TACE courses, treatment lag, treatment duration, total exposed dose and nationality.

Several factors may have contributed to these results. For example, unusually high percentages of sorafenib-treated patients required dose reductions (73%) and/or interruptions (91%), resulting in a much lower than planned median daily dose of sorafenib (386 mg). In comparison, 26% and 44% of sorafenib-treated patients in the SHARP trial, and 31% and 43% of those in the Sorafenib AP trial, required dose reductions and interruptions, respectively, due to AEs,[24,25] and median daily doses of sorafenib were higher in the SHARP (797 mg) and Sorafenib AP (795 mg) trials.

The better outcomes observed in Korean patients may have been due to their substantially longer median treatment duration (31 versus 16 weeks), resulting in a favourable HR in Koreans (0.38; 95% CI, 0.18–0.81). Moreover, the Korean and Japanese subgroups differed in baseline characteristics. Japanese patients were older and a higher percentage had ⩾3 lesions on enrolment. Moreover, Japanese patients were less likely to have received >1 TACE to achieve CR prior to sorafenib. Finally, these subgroups differed in principal aetiology of HCC, in that ~70% of Japanese patients had HCV and ~70% of Korean patients had HBV.

We found that the incidence of treatment-emergent adverse events in the sorafenib-treated patients in this trial was generally higher than that observed in previous trials of sorafenib in patients with HCC. We found that the rates of all grade HFSR, Grade 3 HFSR and discontinuation due to HFSR were higher in this trial than in the SHARP[24] and Sorafenib AP[25] trials. We also found that the rates of all grade alopecia; rash/desquamation; hypertension, including grade 3 hypertension; thrombocytopenia and elevated liver function enzymes were higher in this trial than in the two previous phase III trials of sorafenib in patients with HCC. These results were unexpected and may have been due to the combination of TACE with sorafenib treatment in this trial. These findings suggest that adjustments in sorafenib dose (e.g. starting at a lower dose after TACE) or the timing of sorafenib treatment with respect to TACE may be required for these two

modalities to be tolerated in combination and also have synergistic effects.

The timing of post-TACE sorafenib may also have contributed to the absence of a positive effect of sorafenib observed in this study. Local hypoxia resulting from TACE can induce angiogenesis[18] and enhance serum concentrations of VEGF,[19,20] suggesting that sorafenib may exert its greatest antiangiogenic effects when administered immediately after or even before TACE. Serum VEGF concentrations have also been found to correlate with impaired liver function, tumour size, tumour number, macroscopic vascular invasion,[30] and poor OS.[31] Of our sorafenib-treatment patients, 60% had a treatment lag >9 weeks prior to randomisation, due primarily to the need for central review of CT scans, and shorter lag time has been found associated with better outcomes.

Several ongoing phase II/III trials in patients with unresectable HCC may provide insight into the optimal combination treatment and the optimal timing of sorafenib relative to TACE. These include trials testing TACE with doxorubicin-eluting beads and sorafenib or placebo and alterations in timing of conventional TACE relative to sorafenib or placebo.[32–35]

5. Conclusion

Sorafenib did not significantly improve median TTP by central review in Japanese and Korean patients with unresectable HCC who responded to TACE, although exploratory analyses suggested that sorafenib may have clinical benefits in certain patient subsets, including males, patients <65 years of age, and those with a shorter treatment lag between TACE and sorafenib; and that longer treatment duration and greater total daily dose may be associated with clinical improvements. No new or unexpected AEs were observed. The results of these and other clinical investigations may help refine the use of sorafenib and TACE, and define their optimal combination, in patients with unresectable HCC.

Author contributions

Drs. Masatoshi Kudo and Kiwamu Okita were involved with the study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; statistical analysis; and study supervision.

Drs. Kazuho Imanaka, Nobuyuki Chida, Kohei Nakachi, Won-Young Tak, Tadatoshi Takayama, Jung-Hwan Yoon, Takeshi Hori, Hiromitsu Kumada, Norio Hayashi, Shuichi Kaneko, Hirohito Tsubouchi, Dong Jin Suh, Junji Furuse, Takuji Okusaka, Katsuaki Tanaka and Osamu Matsui were involved with the acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; statistical analysis; and study supervision.

Drs. Michihiko Wada, Iku Yamaguchi, Toshio Ohya and Gerold Meinhardt were involved with the study concept and design; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; statistical analysis; administrative and technical support; and study supervision.

Clinical trials

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Conflict of interest statement

Masatoshi Kudo received advisory and speaker fees and research and travel grants from Bayer. Won-Young Tak received advisory and speaker fees from Bayer, Junji Furuse received advisory fees from Bayer, Takuji Okusaka received advisory and speaker fees, research and travel grants from Bayer. Osamu Matsui received consulting and advisory fees and research grants from Bayer. Michihiko Wada, Iku Yamaguchi, Toshio Ohya and Gerold Meinhardt are employees of Bayer. Kiwamu Okita received consulting fees from Bayer. All other authors declared no conflicts of interest.

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

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

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

INTRODUCTION

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

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

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

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

PATIENTS AND METHODS

Patients and Treatment

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

TAI was performed by introducing a catheter into the proper, right or left hepatic artery, or another feeding artery by the Seldinger technique, and injecting cisplatin at the dose of 65 mg/m^2 over 20–40 min. Until the appearance of evidence of tumor progression and/or of unacceptable toxicity, the treatment was repeated every 4–6 weeks for up to six cycles. Antiemetic prophylaxis with a 5-hydroxytryptamine3 antagonist (granisetron 1 mg) plus dexamethasone 8 mg was used at the physician's discretion. Patients received adequate hydration for protection against cisplatin-induced renal dysfunction, and the urine output was carefully monitored, especially during the first 3 days after intra-arterial administration of cisplatin, and intravenous furosemide was administered if the output was judged to be inadequate. In principle, the cisplatin dose was reduced if the patient's creatinine clearance decreased to below 50 ml/min.

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

Response and Toxicity Evaluations

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

RESULTS

Patient Characteristics

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

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

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

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

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

Treatment Delivery and Efficacy

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

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

Adverse Events

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

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

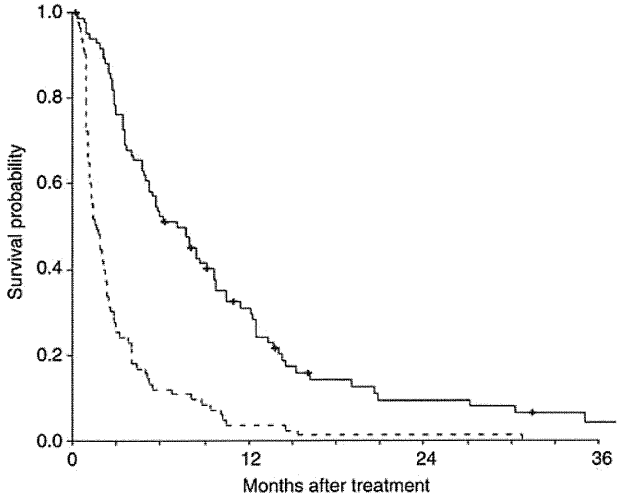

Figure 1. Overall survival (continuous line) and progression-free survival (dotted line) in the 84 patients. The marks on the curve represent censored cases.

Table 2. Adverse events

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

Gr, grade.

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

DISCUSSION

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

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

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

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

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

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Conflict of interest statement

None declared.

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A Phase I/II Study of Combined Chemotherapy with Mitoxantrone and Uracil/Tegafur for Advanced Hepatocellular Carcinoma

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Objective: The aim was to determine the recommended dose of combined chemotherapy with mitoxantrone and uracil/tegafur (Phase I part) and to clarify its efficacy and safety in patients with advanced hepatocellular carcinoma at the recommended dose (Phase II part).
Methods: Patients eligible had histologically confirmed, chemo-naive advanced hepatocellular carcinoma and were amenable to established forms of treatment. The therapy consisted of mitoxantrone administered intravenously at one of three dosages (6, 8 and 10 mg/m^2/day) on day 1 and uracil/tegafur administered orally at 300 mg/m^2 from day 1 through day 21. The treatment was repeated every 4 weeks until evidence of tumor progression or unacceptable toxicity.
Results: A total of 25 patients were enrolled. In the Phase I part, dose-limiting toxicities occurred in all three patients, given mitoxantrone at the dosage of 10 mg/m^2/day, and the recommended mitoxantrone dosage was determined to be 8 mg/m^2/day. Among 19 patients administered the drug at the recommended dosage, 1 patient (5.3%) showed partial response, 8 patients (42.1%) showed stable disease and 10 patients (52.6%) showed progressive disease. The median survival and median progression-free survival were 8.4 and 2.5 months, respectively. The most common toxicities were Grade 3–4 leukopenia (63.2%) and neutropenia (68.4%).
Conclusions: Mitoxantrone at 8 mg/m^2 combined with uracil/tegafur at 300 mg/m^2/day was determined to be the recommended regimen. Although this regimen was generally well tolerated, it appeared to have little activity against advanced hepatocellular carcinoma. These findings do not support the use of this combination regimen in practice.

Key words: hepatocellular carcinoma – chemotherapy Phase I/II – mitoxantrone – uracil/tegafur

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most commonly occurring cancers worldwide (1,2). Surgical resection, liver transplantation and local ablation therapy, including radiofrequency ablation and ethanol injection, are considered as curative treatment for HCC (3). Transcatheter arterial chemoembolization (TACE) has been applied to patients with advanced incurable HCC (4,5). However, the majority of HCC patients develop recurrence or metastasis, regardless of the treatment modalities employed. Although patients with HCC at this advanced stage are generally treated by systemic therapy, the prognosis remains poor (6,7). Sorafenib is an orally administered molecular-targeted drug that targets tumor cell proliferation and tumor angiogenesis by inhibiting the serine–threonine kinases Raf-1 and B-Raf and the receptor tyrosine kinase activity of vascular endothelial growth factor receptors 1, 2 and 3 and platelet-derived growth factor

receptor β. This drug was reported to confer an overall survival advantage, with manageable toxicity, in comparison with placebo in a Phase III trial, and it has been accepted worldwide as the first-line chemotherapy for advanced HCC (8). But the advantage is modest. There is urgent need to develop more effective regimens.

5-Fluorouracil (5-FU) has been widely used for the treatment of various gastrointestinal malignancies, including advanced HCC (9,10). A high level of efficacy can be expected when the drug is given as a continuous intravenous infusion (11). However, this would necessitate a permanent intravenous access. Uracil/tegafur (UFT) is an orally administered drug which is a mixture of uracil and tegafur at a molar ratio of 4:1. Tegafur is a prodrug of 5-FU that is hydroxylated and converted to 5-FU by hepatic microsomal enzymes, and uracil prevents the degradation of 5-FU by inhibiting the enzyme dihydropyrimidine dehydrogenase, which results in an increased level of 5-FU in the plasma and tumor tissues (12,13). UFT has been reported to be as effective as intravenous 5-FU for the treatment of malignancies (14,15) and to be effective for the treatment of advanced HCC (16,17).

The therapeutic usefulness of doxorubicin in patients with advanced HCC has also been widely explored since the 1970s. A randomized trial in which doxorubicin was compared with supportive care alone for advanced HCC showed a significant survival benefit in the doxorubicin arm. However, treatment with this drug has not been accepted as a standard chemotherapy because of the high rate of fatal complications reported (18). Mitoxantrone, another anthracycline, has shown similar antitumor activity to that of doxorubicin in both human tumor cell lines and animal models of leukemia and has fewer myelotoxic and cardiotoxic effects than doxorubicin (19). Clinical trials of mitoxantrone have also demonstrated moderate activity against HCC, with a low incidence rate of adverse effects (20,21).

Combination chemotherapeutic regimens composed of a fluoropyrimidine and an anthracycline antibiotic have been reported to show moderate efficacy against HCC with tolerable toxicity (22–24), but combined chemotherapy with UFT and mitoxantrone has not yet been examined. We conducted Phase I/II studies to determine the recommended dosage of the combination of UFT with mitoxantrone (UFM regimen) and to clarify the efficacy and safety when administered at the recommended dose in patients with advanced HCC.

PATIENTS AND METHODS

Eligibility Criteria

The eligibility criteria for study enrolment were: (i) patients with histologically confirmed HCC, who were (ii) unsuitable for surgical resection, local ablation therapy or TACE, (iii) were ≥20 years old, (iv) had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2, (v) had adequate bone marrow function (white blood cell ≥3000 cells/mm^3, absolute neutrophil count ≥1500 cells/mm^3, platelet count ≥70 000 cells/mm^3 and hemoglobin ≥8.0 g/dl), renal function [serum creatinine concentration ≤upper limit of normal (ULN)] and hepatic function [serum albumin level ≥3.0 mg/dl, total bilirubin level ≤3.0 mg/dl, serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels ≤5.0 × ULN], (vi) had a life expectancy of at least 12 weeks and (vii) provided written informed consent from each patient.

The exclusion criteria were: clinically evident congestive heart failure, serious cardiac arrhythmia, active or symptomatic coronary artery disease or ischemia, clinically serious infection, seizure disorder requiring medication, prior malignancy (any cancer treated curatively was permitted), clinically evident brain or meningeal metastasis, and pregnant/lactating women. This protocol was approved by the Institutional Review Board for clinical investigation of the National Cancer Center, in conformity with the provisions of the Declaration of Helsinki, Good Clinical Practice guidelines, and local laws and regulations.

Study Treatment

UFT was administered orally at the dose of 300 mg/m^2 per day in two divided doses for 21 consecutive days, followed by a rest period of 7 days (400 mg/body per day in patients with a body surface area of <1.50 m^2 and 500 mg/body/day in patients with a body surface area of ≥1.50 m^2). Mitoxantrone was given as a 60 min intravenous infusion on day 1. This cycle was repeated every 28 days. Patients continued to receive additional courses of this regimen until a cumulative dose of mitoxantrone of 100 mg/m^2, evidence of disease progression or the appearance of unacceptable toxicity.

Phase I Part

The objectives of the Phase I study were to investigate the frequency of dose-limiting toxicity (DLT) and to determine the recommended dose of mitoxantrone and UFT. The criteria of DLT included: Grade 4 leukopenia or neutropenia, Grade 3 neutropenia accompanied by fever (≥38°C) or infection (clinically or biologically confirmed), thrombocytopenia <25 000/mm^3 or necessity of transfusion, Grade 3 or 4 non-hematological toxicity (except nausea/vomiting, anorexia, fatigue and hyperglycemia), AST and ALT >10 times the ULN, suspension of UFT administration for over 3 successive weeks, or an over 6-week delay in the commencement of the next treatment cycle.

Three possible dosage levels of mitoxantrone (Level 1: 6 mg/m^2/day, Level 2: 8 mg/m^2/day and Level 3: 10 mg/m^2/day) were assigned for the Phase I part (Table 1). The first patient to enter the study was started at Level 1. At least three patients were treated at this level and observed for DLT. Dose escalation was continued until at least one-third

Table 1. Dose-escalation schedules of mitoxantrone and uracil/tegafur

Dose level	Mitoxantrone (mg/m^2)	UFT (mg/m^2)	Number of patients enrolled
1	6	300	3
2	8	300	6
3	10	300	3

UFT, uracil/tegafur.

of the patients in a given cohort showed DLT. If none of the first three treated patients developed DLT during the first cycle at a specific dose level, the dose escalation was continued. If one of the first three treated patients developed DLT at any dose level, three additional patients were entered at the same dose level; if only one or two of six patients at a given level experienced a DLT, the dose escalation was continued. The maximum tolerated dose (MTD) was defined as the dose level at which one-third or more of the patients experienced a DLT. The recommended dose for the Phase II study was defined as the dose level preceding the attainment of the MTD.

Phase II Part

The primary endpoint of the Phase II part was the objective response rate. The secondary endpoints were the overall survival, progression-free survival and the frequency and severity of adverse events. The Phase II part was begun after determination of the recommended dosage from the Phase I part.

Assessment of the Response and Toxicity

Physical examination including cardiac symptoms, complete blood cell counts, serum chemistries and urinalysis was performed at the baseline and at least once every 2 weeks after the start of the treatment. Dynamic computed tomography or magnetic resonance imaging was undertaken to evaluate the response at 4- to 6-week intervals after the start of treatment. Tumor response was assessed using the Response Evaluation Criteria in Solid Tumors (25). Toxicity was graded according to the National Cancer Institute common toxicity criteria, version 2.0. Progression-free survival was calculated from the first day of treatment to the appearance of evidence of tumor progression, clinical progression or last date of follow-up. The overall survival was calculated from the first day of treatment until death due to any cause or date of last follow-up. Survival data were analyzed using the Kaplan–Meier method.

Statistical Analysis

In the Phase II part, the primary endpoint was the response rate, and data from at least 19 patients were accrued. The threshold response rate was set at 5% and the expected response rate at 15%. If no responses were observed in the 19 patients and the upper limit of the 90% confidence interval (CI) did not exceed the expected rate of 15%, the UFM regimen was judged to have no activity against HCC. If response was confirmed in one or more of the 19 patients, the decision of whether or not to proceed to a further study using the UFM regimen was taken on the basis of other factors, such as the safety and rate of response, overall survival and time to progression in this study.

RESULTS

Patients

From April 2004 to April 2007, 25 patients were registered for the present study: 12 patients completed the Phase I part (Level 1: 3 patients, Level 2: 6 patients and Level 3: 3 patients). Nineteen patients who received the recommended dose (6 patients received this dose during the Phase I part) were analyzed during the Phase II part. Table 2 shows the baseline characteristics of the patients in the Phase I and Phase II parts of the study of the UFM regimen. There were 19 males and 6 females with a median age of 67 years. All the patients had a good ECOG PS score of 0–1. There were 21 (84%) and 4 (16%) patients with the Child–Pugh Stages A and B, respectively. Thirteen (68%) patients had extrahepatic metastasis, and the major sites of metastasis were lymph node [$n = 7$ (28%)] and lung [$n = 6$ (24%)].

Treatments

In the Phase I part, there was no occurrence of DLT at the Level 1 and Level 2 doses, but all of the three patients who received the Level 3 dose experienced DLT; two of these patients developed Grade 4 neutropenia and one patient developed Grade 3 creatinine elevation. The additional three patients at the Level 2 dose did not experience any DLT. Therefore, Level 3 was considered as the MTD and Level 2 (UFT 300 mg/m^2 and mitoxantrone 8 mg/m^2) as the recommended dose for the Phase II part.

At the recommended dosage level, a total of 69 courses of the UFM regimen were administered with a median of three courses to each patient (range, 1–8 courses). The dose intensity was 98.9% of the planned dosage for mitoxantrone and 97.9% for UFT.

The reasons for treatment discontinuation in the Phase I and Phase II parts were disease progression in 19 patients, liver dysfunction in 1 patient, DLT according to this protocol in 3 patients during the Phase I part and an over 6-week delay in the start of the next course because of the development of leukopenia in 2 patients. After abandoning the UFM regimen, 10 patients received the second-line treatment. Five patients received systemic chemotherapy, one patient received UFT alone and four patients received a combined chemotherapy with UFT and doxorubicin. Two