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Phase I/II study of the pharmacokinetics, safety and efficacy of S-1 in patients with advanced hepatocellular carcinoma

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S-1, an oral fluoropyrimidine derivative, has been shown to be clinically effective against various solid tumors, and preclinical studies have demonstrated activity against hepatocellular carcinoma. We conducted a phase I/II study in patients with advanced hepatocellular carcinoma to examine the pharmacokinetics, recommended dose, safety and efficacy of S-1. In phase I, the administered dose of S-1 was approximately 64 mg/m^2 per day in three patients (level 1) and approximately 80 mg/m^2 per day in six patients (level 2). There was no dose-limiting toxicity at level 1, but two patients had dose-limiting toxicity at level 2 (grade 3 anorexia and grade 2 rash requiring eight or more consecutive days of rest). The recommended dose was finally estimated to be 80 mg/m^2 per day. There were no significant differences in the pharmacokinetics of S-1 between patients with Child-Pugh A and those with B. In phase II, five of 23 patients (21.7%) had partial responses. The median progression-free survival and overall survival were 3.7 and 16.6 months, respectively. The most common toxicities of grade 3 or 4 were elevated serum aspartate aminotransferase levels, hypochromia and thrombocytopenia. In conclusion, S-1 showed an acceptable toxicity profile and promising antitumor activity for hepatocellular carcinoma, warranting further evaluation in randomized clinical trials. (*Cancer Sci* 2010; 101: 2606–2611)

Hepatocellular carcinoma (HCC) is one of the most common cancers in the world. Outcomes remain poor because the disease is usually advanced and associated with hepatic impairment at diagnosis, and because of the high rate of recurrence resulting from either intrahepatic metastases from the primary tumor or multicentric lesions. As for therapy, surgical resection and percutaneous ethanol injection (PEI) or radiofrequency ablation (RFA) are considered the mainstays of treatment in patients with potentially curable disease. Transcatheter arterial chemoembolization (TACE) is the treatment of choice for noncurative HCC. Despite numerous clinical trials of a wide variety of cytotoxic agents, survival remains dismal in HCC.[1] Recently, sorafenib, an oral multi-kinase inhibitor that targets mainly Raf kinases and receptor tyrosine kinases associated with angiogenesis (vascular endothelial growth factor receptor [VEGFR]-2/-3 and platelet-derived growth factor receptor [PDGFR]-β), provided a significant survival benefit in patients with advanced HCC enrolled in placebo-controlled, randomized, phase III trials, including Asian as well as European subjects.[2,3] An initial phase I study in Japanese patients with HCC associated mainly with hepatitis C virus (HCV) infection showed promising antitumor activity and a favorable tolerability profile.[4] However, further improvement in the treatment of advanced HCC is essential.

S-1 is a novel, orally administered drug that combines tegafur (FT), 5-chloro-2,4-dihydroxypyridine (CDHP) and oteracil potassium (Oxo) in a molar concentration ratio of 1:0.4:1.[5] CDHP is a competitive inhibitor of dihydropyrimidine dehydrogenase (DPD), a metabolizing enzyme of 5-fluorouracil (5-FU) that is expressed in the liver. Inhibition of DPD by CDHP results in prolonged effective concentrations of 5-FU in plasma and tumor tissue.[6] Oxo, a competitive inhibitor of orotate phosphoribosyltransferase, inhibits the phosphorylation of 5-FU in the gastrointestinal tract, thereby reducing serious 5-FU-related gastrointestinal toxicity.[7] Clinically, S-1 has been shown to be effective against a variety of solid tumors, with response rates ranging 21–49% in late phase II studies conducted in Japan.[8] S-1 has yet to be evaluated in patients with HCC. However, in nude rats with human HCC xenografts, S-1 has been confirmed to have antitumor activity.[9]

Patients with HCC usually have various degrees of liver dysfunction because of associated liver disease and replacement of liver tissue by tumor, leading to pathophysiological changes that influence drug disposition. Decreased hepatic blood flow, extrahepatic and intrahepatic blood shunting and hepatocyte loss also alter drug metabolism, and decreased protein synthesis reduces drug binding to plasma proteins. In fact, the maximal tolerated dose (MTD) of 5-FU given as a 5-day continuous infusion in patients with HCC is approximately 50% of that in patients with normal organ function, and patients with cirrhosis have significantly lower clearance of 5-FU than those without cirrhosis.[10] We therefore conducted a multicenter phase I/II study to evaluate the pharmacokinetics, safety and efficacy of S-1 monotherapy in patients with advanced HCC.

Materials and Methods

Eligibility. Eligible patients had histologically or cytologically proved HCC that was not amenable to treatment by resection, liver transplantation, RFA, PEI or percutaneous microwave coagulation therapy (PMCT) and was not expected to respond to TACE. A hypervascular mass on computed tomography (CT) or magnetic resonance imaging (MRI) associated with a serum alpha-fetoprotein level or a serum protein induced by vitamin K absence or antagonist (PIVKA-II) level of more than the upper limit of normal (ULN) 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: age of at least 20 years; Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2; estimated life expectancy of at least 60 days; adequate

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hematological function (white blood cells [WBC] ≥3000/mm^3, hemoglobin ≥ 9.0 g/dL, platelets ≥ 7.0 × 10^4/mm^3); adequate hepatic function (aspartate aminotransferase [AST] and alanine aminotransferase [ALT] ≤5 times the ULN, total bilirubin ≤2.0 mg/dL, serum albumin ≥2.8 g/dL, prothrombin activity ≥40%); adequate renal function (serum creatinine ≤ULN); and a Child-Pugh class of A or B. Prior treatment for HCC, such as resection, liver transplantation, RFA, PEI, PMCT and TACE was permitted if the treatment had been performed 30 or more days before registration in the study. Patients were excluded if they had: tumor involving more than 50% of the liver; brain or bone metastasis or vascular invasion of the main trunk and first-order branch(es) of the portal vein, hepatic veins, hepatic arteries or bile duct; severe complications; other malignancies; or inability to comply with the protocol requirements. Written informed consent was obtained from each patient. The study was approved by the local institutional review boards at all participating centers.

Study design. S-1 was supplied by Taiho Pharmaceutical Co., Ltd (Tokyo, Japan) in capsules containing 20 or 25 mg of FT. Individual doses were calculated according to body surface area. The calculated dose was rounded to derive the daily dose and the number of capsules to be dispensed per patient. At each dose level, S-1 was administered orally twice daily (after breakfast and dinner) for 28 consecutive days, followed by a 14-day recovery period. Each treatment cycle was 42 days. If grade 3 or higher hematological toxicity, grade 2 or higher non-hematological toxicity, grade 3 or higher elevations of AST or ALT, or grade 2 or higher increases in the serum creatinine concentration occurred, treatment with S-1 was temporarily suspended, the dose of S-1 was reduced, or both (minimum dose, 50 mg/day). Treatment continued until there was evidence of disease progression, or if the recovery period exceeded 28 days, the patient requested treatment to be discontinued or unacceptable toxicity developed and treatment was terminated at the discretion of the investigator. Drug compliance and accountability were carefully monitored; patients were requested to record their intake of S-1 and other medications in a diary.

During phase I, the starting dose of S-1 (level 1) was approximately 64 mg/m^2 per day twice daily (80% of the standard dose), level 2 was approximately 80 mg/m^2 per day and level 0 was approximately 50 mg/m^2 per day (80% of level 1). Patients were enrolled in cohorts of three for each dose level. The dose was escalated according to the cohort and was not increased in the same patient. If none of the first three patients had dose-limiting toxicity (DLT) during the first cycle, the dose was increased to level 2. If one or two of the first three patients had DLT, three additional patients were entered at the same dose level; if only one or two of the first six patients at level 1 had DLT, the dose was increased to level 2; if all of the first three patients or three or more of the first six patients had DLT, the dose was decreased to level 0; if none of the first three patients had DLT at level 0 or level 2, three additional patients were assigned to receive the same dose level. The DLT was defined as any of the following: (i) hematological toxicity ≥grade 4; (ii) non-hematological toxicity ≥grade 3; (iii) AST, ALT ≥15 times the ULN; or (iv) a rest period of 8 or more consecutive days was required. The recommended dose (RD) determined in the phase I part of this study was used in phase II.

Pharmacokinetics. Blood samples (5 mL) were obtained from each patient assigned to receive level 2 in the phase I part of the study. The samples were taken before and 1, 2, 4, 6, 8, 10 and 12 h after administration of S-1 on days 1 and 8 of the first treatment cycle. Plasma was separated from the whole-blood samples by centrifugation and stored at −20°C until analysis. Plasma FT concentrations were measured by high-performance liquid chromatography with ultraviolet detection. Plasma concentrations of 5-FU, CDHP and Oxo were measured by gas chromatography-negative ion chemical ionization mass spectrometry, as described previously.[11]

Pharmacokinetic data, including the maximum plasma concentration (C_{max}, ng/mL), time to reach C_{max} (T_{max}, h), area under the plasma-concentration–time curve for 0–12 h (AUC_{0-12}, ng h/mL) and the elimination half-life ($T_{1/2}$, h) were calculated by noncompartment model analysis using WinNonlin software, version 4.1 (Pharsight, Cary, NC, USA).

Assessment of efficacy and toxicity. All patients who received at least one dose of the study drug were included in the evaluations of response and toxicity. During each course of treatment, tumor response was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) by computed tomography (CT) or magnetic resonance imaging (MRI), with a slice thickness of no more than 5 mM.[12] The primary efficacy end-point in the phase II part of this study was the overall response rate, assessed on the basis of changes in tumor dimensions. The other end-points were overall survival (OS) and progression-free survival (PFS). The PFS was defined as the interval between the date of initiating treatment and the date on which disease progression was first confirmed or the date of death from any cause. Overall survival was defined at the interval from the date of initiating treatment to the date of death from any cause. Median OS and median PFS were

Table 1. Patient characteristics

	Level 1 (*n* = 3)	Level 2 (*n* = 23)
	n (%)	*n* (%)
Median age (range) (years)	67.0 (63–68)	68.0 (45–78)
Gender		
Male	2 (66.7)	21 (91.3)
Female	1 (33.3)	2 (8.7)
Virus marker		
HBs (+)	1 (33.3)	3 (13.0)
HCV (+)	1 (33.3)	14 (60.9)
HBs(−), HCV(−)	1 (33.3)	6 (26.1)
Child-Pugh classification		
A	3 (100)	16 (69.6)
B	0 (0)	7 (30.4)
Stage		
Stage II	1 (33.3)	3 (13.0)
Stage III	1 (33.3)	10 (43.5)
Stage IVB	1 (33.3)	10 (43.5)
Vascular invasion	0 (0)	2 (8.7)
ECOG PS		
0	3 (100)	21 (91.3)
1	0 (0)	2 (8.7)
Pretreatment		
TA(C)E	2 (66.7)	17 (73.9)
Surgery	1 (33.3)	8 (34.8)
RFA	0 (0)	7 (30.4)
HAI	2 (66.7)	6 (26.1)
PEI	0 (0)	4 (17.4)
Radiation	0 (0)	4 (17.4)
PMCT	0 (0)	3 (13.0)
Systemic chemotherapy	0 (0)	3 (13.0)
BCLC staging		
Early	0 (0)	1 (4.3)
Intermediate	2 (66.7)	11 (47.8)
Advanced	1 (33.3)	11 (47.8)

BCLC, Barcelona Clinic Liver Cancer Group; ECOG, Eastern Cooperative Oncology Group; HAI, hepatic arterial infusion; HBs, hepatitis B surface antigen; HCV, hepatitis C virus antibody; PEI, percutaneous ethanol injection; PMCT, percutaneous microwave coagulation therapy; PS, performance status; RFA, radiofrequency ablation; TACE, transcatheter arterial chemoembolization.

Table 2. Toxic effects

Toxicity	Level 1 (n = 3)		Level 2 (n = 23)		Child Pugh A (n = 16)		Child Pugh B (n = 7)	
	All grades	≥G3	All grades	≥G3	All grades	≥G3	All grades	≥G3
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
All adverse events	3 (100.0)	0 (0.0)	23 (100.0)	10 (43.5)	16 (100.0)	8 (50.0)	7 (100.0)	2 (28.6)
Hematological								
Erythropenia	1 (33.3)	0 (0.0)	21 (91.3)	1 (4.3)	14 (87.5)	1 (6.3)	7 (100.0)	0 (0.0)
Hypochromia	1 (33.3)	0 (0.0)	19 (82.6)	4 (17.4)	12 (75.0)	4 (25.0)	7 (100.0)	0 (0.0)
Leukopenia	2 (66.7)	0 (0.0)	18 (78.3)	1 (4.3)	12 (75.0)	1 (6.3)	6 (85.7)	0 (0.0)
Lymphopenia	2 (66.7)	0 (0.0)	12 (52.2)	3 (13.0)	7 (43.8)	3 (18.8)	5 (71.4)	0 (0.0)
Neutropenia	1 (33.3)	0 (0.0)	17 (73.9)	1 (4.3)	12 (75.0)	1 (6.3)	5 (71.4)	0 (0.0)
Reduced hematocrit	1 (33.3)	0 (0.0)	19 (82.6)	1 (4.3)	12 (75.0)	1 (6.3)	7 (100.0)	0 (0.0)
Reduced prothrombin content	1 (33.3)	0 (0.0)	19 (82.6)	0 (0.0)	14 (87.5)	0 (0.0)	5 (71.4)	0 (0.0)
Thrombocytopenia	1 (33.3)	0 (0.0)	18 (78.3)	4 (17.4)	12 (75.0)	4 (25.0)	6 (85.7)	0 (0.0)
Non-hematological								
Elevated alkaline phosphatase	0 (0.0)	0 (0.0)	8 (34.8)	1 (4.3)	7 (43.8)	1 (6.3)	1 (14.3)	0 (0.0)
Elevated lactate dehydrogenase	0 (0.0)	0 (0.0)	15 (65.2)	0 (0.0)	9 (56.3)	0 (0.0)	6 (85.7)	0 (0.0)
Elevated serum AST	1 (33.3)	0 (0.0)	8 (34.8)	4 (17.4)	6 (37.5)	3 (18.8)	2 (28.6)	1 (14.3)
Elevated serum bilirubin	0 (0.0)	0 (0.0)	18 (78.3)	3 (13.0)	13 (81.3)	2 (12.5)	5 (71.4)	1 (14.3)
Hyponatremic	0 (0.0)	0 (0.0)	8 (34.8)	0 (0.0)	5 (31.3)	0 (0.0)	3 (42.9)	0 (0.0)
Reduced cholinesterase	2 (66.7)	0 (0.0)	18 (78.3)	0 (0.0)	13 (81.3)	0 (0.0)	5 (71.4)	0 (0.0)
Reduced serum albumin	0 (0.0)	0 (0.0)	18 (78.3)	2 (8.7)	12 (75.0)	1 (6.3)	6 (85.7)	1 (14.3)
Reduced total protein	0 (0.0)	0 (0.0)	11 (47.8)	0 (0.0)	8 (50.0)	0 (0.0)	3 (42.9)	0 (0.0)
Anorexia	1 (33.3)	0 (0.0)	18 (78.3)	2 (8.7)	13 (81.3)	1 (6.3)	5 (71.4)	1 (14.3)
Ascites	0 (0.0)	0 (0.0)	7 (30.4)	0 (0.0)	3 (18.8)	0 (0.0)	4 (57.1)	0 (0.0)
Diarrhea	0 (0.0)	0 (0.0)	10 (43.5)	0 (0.0)	8 (50.0)	0 (0.0)	2 (28.6)	0 (0.0)
Fatigue	0 (0.0)	0 (0.0)	19 (82.6)	2 (8.7)	13 (81.3)	2 (12.5)	6 (85.7)	0 (0.0)
Pigmentation	0 (0.0)	0 (0.0)	20 (87.0)	0 (0.0)	14 (87.5)	0 (0.0)	6 (85.7)	0 (0.0)
Rash	0 (0.0)	0 (0.0)	8 (34.8)	0 (0.0)	5 (31.3)	0 (0.0)	3 (42.9)	0 (0.0)
Stomatitis	0 (0.0)	0 (0.0)	7 (30.4)	0 (0.0)	5 (31.3)	0 (0.0)	2 (28.6)	0 (0.0)

Dosage level, level 1, 2 (n = 3, 23); AST, aspartate aminotransferase.

Table 3. Efficacy in patients who received dose level 2

	Child-Pugh A (n = 16)	Child-Pugh B (n = 7)	Total (n = 23)
Partial response†	4	1	5
Stable disease‡	5	2	7
Progressive disease	7	3	10
Not evaluable	0	1	1
Response rate (90%CI)§ (%)	–	–	23.1 (9.0–40.4)
Response rate (95%CI) (%)	25.0 (7.3–52.4)	14.3 (0.4–57.9)	23.1 (7.5–43.7)
Median PFS (95% CI) (months)	3.3 (2.3–5.1)	3.7 (2.5–7.4)	3.7 (2.5–5.1)
Median OS (95% CI) (months)	17.8 (14.0–NA)	14.5 (9.6–18.7)	16.6 (14.0–24.5)
1-year survival (95% CI) (%)	–	–	69.6 (50.8–88.4)
1.5-years survival (95% CI) (%)	–	–	43.0 (22.6–63.5)
Disease control rate¶			
6W (95% CI) (%)	–	–	47.8 (26.8–69.4)
12W (95% CI) (%)	–	–	26.1 (10.2–48.4)
24W (95% CI) (%)	–	–	21.7 (7.5–43.7)

†Partial response was re-evaluated after at least 4 weeks in patients with a partial response. ‡Stable disease was reassessed after at least 6 weeks. §Response rate (90% CI) is a primary end-point. ¶Disease control rates were respectively estimated by dividing the number of patients with no disease progression by the total number of patients. Disease control was defined as a response of complete response, partial response or stable disease. CI, confidence interval; NA, not available; OS, overall survival; PFS, progression-free survival.

estimated using the Kaplan–Meier method. Physical findings and the results of serum chemical and urine analyses were assessed at 2-week intervals; vital signs were assessed as necessary. Patients were observed until death or at least 1 year after registration to determine survival status. The severity of all adverse events was evaluated according to the Common Terminology Criteria for Adverse Events, version 3.0 (CTCAE, Ver. 3.0). The duration of all adverse events and their relation to S-1 were initially assessed by the attending physicians. Subsequently, an independent review committee reviewed data on objective response and adverse events.

Statistical considerations. With the response rate as the primary end-point, a total sample size of at least 23 patients was estimated to be required in the phase II portion to allow the

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study to have a one-sided 5% significance level of 0.05 and a power of 70%, assuming a threshold response rate of 5% and an expected response rate of 20%.

Results

Patient characteristics and treatment. Between May 2006 and April 2007, a total of 26 patients (nine in phase I and 17 in phase II) were enrolled at four centers in Japan. All patients were eligible for the evaluation of toxicity and efficacy. The first six patients who received dose level 2 (80 mg/m^2 per day) during the phase I part of this study were included in the phase II assessment, along with the 17 other patients (a total of 23 patients in the phase II assessment). The characteristics of patients are summarized in Table 1. At the study entry, 11 of 26 (42.3%) had metastatic disease. Six patients (23.1%) had single extrahepatic metastases (lung metastases, three patients; lymph node metastasis, three patients). Four patients had two sites of metastases, including the lung, lymph nodes and adrenal glands. Of the 26 patients, 23 had received some prior treatment, including three who had received systemic chemotherapy.

Dose-limiting toxicity and RD. None of the three patients who received dose level 1 (64 mg/m^2 per day) in the phase I part of the study had DLT. At dose level 2 (80 mg/m^2 per day), one patient with Child-Pugh class B had grade 3 anorexia during the first course of treatment, but the other two patients in the same cohort had no DLT. Three additional patients were enrolled to confirm safety, and one patient with Child-Pugh class B had a grade 2 rash; recovery required eight or more consecutive days of rest. Because two of the six patients who received level 2 had DLT, level 2 was defined as the RD for the phase II part of the study.

Treatment delivered. Twenty-three patients received a total of 85 cycles of treatment at dose level 2 (median, three cycles per patient; range, 1–15). The dose of S-1 was reduced in seven patients (30.4%) or a total of nine cycles (10.6%). The most common reasons for dose reductions were rash in four patients, and elevated serum bilirubin concentrations and anorexia in two patients each (some overlap among patients). Treatment was delayed because of toxicity in 12 patients (20 cycles), most often in cycles 1 or 2. The most common reasons for toxicity-related treatment delays were fatigue (five patients), rash (four patients) and elevated serum bilirubin concentrations (three patients). The reasons for terminating treatment were progressive disease in 19 patients (82.6%), adverse reactions in two patients (8.7%) and other reasons in two patients (8.7%; one required 28 or more consecutive days of rest, and one withdrew consent).

Toxicity. Drug-related adverse events occurring in all 26 patients in the phase I/II portion of the study are shown in Table 2. Treatment with S-1 was generally well tolerated throughout the study. Grade 3 or 4 toxicity occurred in 10 of the 23 patients (43.5%) who received level 2. Most toxic effects were laboratory abnormalities. There was no grade 3 or 4 toxicity at level 1. The most common grade 3 or 4 hematological toxic effects were hypochromia (17.4%), thrombocytopenia (17.4%) and lymphopenia (13.0%); the most common grade 3 or 4 nonhematological toxic effects were elevated serum AST levels (17.4%) and elevated serum bilirubin concentrations (13.0%).

Efficacy. A response could be evaluated in 26 patients in the phase I/II portion of the study. In the phase I part of the study (dose level 1), one patient had a partial response, one had progressive disease and the other was not evaluable. Of the 23 patients in the phase II part of the study, five (21.7%; 90% confidence interval [CI], 9.0–40.4%) responded to treatment Among the 23 patients in whom a response could be evaluated, five had a partial response, seven had stable disease, and 10 had progressive disease (Table 3). The remaining patient underwent imaging studies, but treatment was completed after one course, and continuation of stable disease for at least 6 weeks could not be

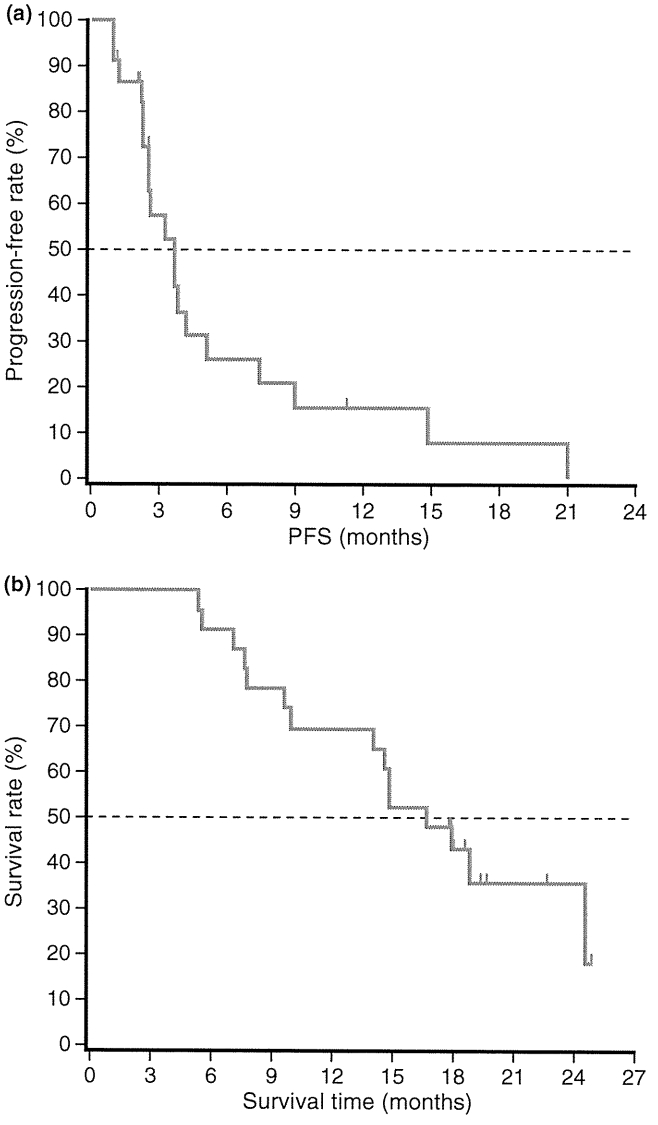

Fig. 1. Progression-free survival (PFS) (a) and overall survival (b) in patients who received dose level 2 of S-1 (n = 23). The median progression-free survival and overall survival were 3.7 and 16.6 months, respectively.

Table 4. Pharmacokinetics of FT, 5-FU, CDHP and Oxo on day 1 and day 8 in patients with HCC who received dose level 2

		C_{max} (ng/mL)	T_{max} (h)	$AUC_{0\text{-}12}$ (ng h/mL)	$T_{1/2}$ (h)
FT	Day 1	2032 ± 437	3.3 ± 1.0	17070 ± 5139	10.1 ± 2.8
	Day 8	4365 ± 1712	3.7 ± 0.8	42399 ± 18137	12.7 ± 5.0
5-FU	Day 1	114.5 ± 35.5	4.3 ± 0.8	695.3 ± 223.6	2.3 ± 1.0
	Day 8	145.8 ± 31.4	4.3 ± 0.8	936.6 ± 292.3	2.4 ± 1.0
CDHP	Day 1	267.2 ± 76.8	3.3 ± 1.0	1424.8 ± 414.2	3.3 ± 0.9
	Day 8	281.0 ± 113.8	3.3 ± 1.0	1694.4 ± 603.5	3.4 ± 0.9
Oxo	Day 1	38.5 ± 1.8	3.7 ± 0.8	231.6 ± 69.8	4.0 ± 2.1
	Day 8	33.4 ± 9.5	4.0 ± 0.0	241.5 ± 115.6	4.0 ± 2.0

Parameters are represented as mean ± SD. CDHP, 5-chloro-2,4-dihydroxypyridine; 5-FU, 5-fluorouracil; FT, tegafur; Oxo, oteracil potassium.

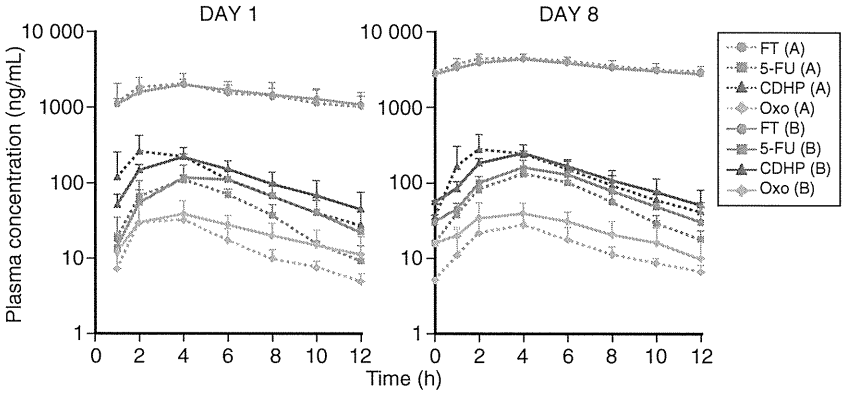

Fig. 2. Plasma-concentration–time profiles of tegafur (FT), 5-fluorouracil (5-FU), 5-chloro-2,4-dihydroxypyridine (CDHP) and oteracil potassium (Oxo) on day 1 and day 8 were similar in patients with Child-Pugh class A (n = 3) and those with Child-Pugh class B (n = 3).

confirmed. The duration of the five responses was 42, 147, 188, 238 and 371 days, respectively.

The median PFS was 3.7 months (95% CI, 2.5–5.1 months). The disease control rates at 6, 12 and 24 weeks were 47.8% (95% CI, 26.8–69.4%), 26.1% (95% CI, 10.2–48.4%) and 21.7% (95% CI, 7.5–43.7%), respectively. The PFS and OS are shown in Figure 1. The median OS was 16.6 months (95% CI, 14.0–24.5 months). Survival rates were 69.6% (95% CI, 50.8–88.4%) at 1 year and 43.0% (95% CI, 22.6–63.5%) at 1.5 years.

Pharmacokinetic analysis. Table 4 shows the pharmacokinetic data for the components of S-1 and 5-FU at level 2 on days 1 and 8. Compared with day 1, the C_{max} and $AUC_{0\text{-}12}$ of FT increased markedly on day 8; however, these increases were within the expected range given the slow elimination of FT, and repeated administration of S-1 had no effect on the T_{max} or $T_{1/2}$ of FT. There was no evidence of accumulation of 5-FU, CDHP or Oxo on day 8.

Figure 2 compares the plasma-concentration–time profiles of S-1 components and 5-FU between patients with Child-Pugh class A and those with Child-Pugh class B on days 1 and 8. The plasma-concentration–time profiles of FT, 5-FU, CDHP and Oxo were similar in patients with Child-Pugh class A and those with Child-Pugh class B on both days.

Discussion

There has been no established standard therapy for patients with advanced HCC refractory to surgery, transplantation, local ablation and TACE.[13,14] Some cytotoxic regimens have produced encouraging response rates, but survival benefits have been minimal compared with control groups, at the cost of clinically unacceptable adverse effects.[1,15]

S-1 is an anticancer drug consisting of FT, CDHP and Oxo. The conversion of FT to 5-FU is mediated mainly by hepatic cytochrome CYP2A6.[16] 5-FU is rapidly metabolized by DPD in the liver after the intravenous administration of 5-FU alone, but S-1, which includes a DPD inhibitor (i.e. CDHP), produces prolonged, effective concentrations of 5-FU in the blood. Thus, the liver plays an important role in the metabolism of FT.

The RD of S-1 in patients with HCC was estimated to be 80 mg/m^2 per day in phase I, which is similar to the dose recommended for the treatment of other solid tumors. However, in patients with HCC, Ueno *et al.*[10] reported that the DLT of 5-FU administered as a 5-day continuous infusion was stomatitis. Moreover, the MTD was equivalent to approximately 50% of that of 5-FU in patients with normal organ function,[10] suggesting that 5-FU-related gastrointestinal toxicity was reduced by Oxo in the formulation of S-1. We did not determine the MTD in this study because S-1 was approved for the treatment of other cancers. The pharmacokinetic properties of S-1 components and 5-FU in patients with HCC were similar to those in patients with pancreatic cancer or biliary tract cancer.[17,18]

Hematological toxic effects and symptomatic events such as pigmentation (87.0%), fatigue (82.6%), anorexia (78.3%) and ascites (30.4%) were more common than previously reported for S-1 in patients with other cancers. Nonetheless, severe toxic effects were comparable among patients with HCC and those with other cancers. Nonhematological toxic effects related to hepatic function were also more frequent than reported previously for S-1 in patients with other types of cancer, but such effects may have been caused by differences in underlying liver disease.

The pharmacokinetics of S-1 did not obviously differ between patients with Child-Pugh class A and those with Child-Pugh class B, suggesting that hepatic dysfunction associated with Child-Pugh class B did not affect the pharmacokinetics of S-1 components or 5-FU. The sample size of the pharmacokinetic evaluations was small because the primary end-point was to determine the RD as the evaluation of DLT in phase I. At dose level 2, DLT occurred in two patients with Child-Pugh class B (Grade 3 anorexia in one, and a Grade 2 rash requiring 8 or more consecutive days of rest in the other). There was no DLT at level 1 (given only to patients with Child-Pugh class A). However, the patient who had DLT of grade 3 anorexia had renal dysfunction at baseline, and the plasma 5-FU concentrations in this patient on day 8 were higher than those in other patients, perhaps contributing to the development of DLT (data not shown). In addition, there were no obvious differences in the incidence or grade of drug-related adverse events between patients with Child-Pugh class A and those with Child-Pugh class B, consistent with the results of pharmacokinetic analysis. These results suggested that there were no clinically meaningful differences in pharmacokinetics or safety according to Child-Pugh class or between patients with HCC and those with other cancers, and that S-1 was well tolerated in patients with HCC, similar to patients with other cancers. However, our study had several limitations: only a very small number of patients with Child-Pugh class B were included; among the patients with Child-Pugh class B, the score was heterogeneous, ranging from 7 to 9; and only patients with better scores were studied. Therefore, extra care should be taken when S-1 is given to patients with Child-Pugh class B.

As for efficacy, five of 23 patients had partial responses at dose level 2. Compared with previously reported response rates obtained with single-agent chemotherapy in patients with HCC, our results are good. In particular, the median OS appeared to be longer than that obtained with other agents in non-Japanese studies. The reason for the better OS in Japanese patients might be similar to that previously reported for sorafenib.[4] The median OS in our study was similar to that in a Japanese phase I study of sorafenib.[4] In studies of sorafenib in non-Japanese and

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Japanese patients with HCC, the median TTP and response rates were comparable, but the median OS was 15.6 months in Japanese patients compared with only 9.2 months in non-Japanese patients.[4] Differences in various treatments, including hepatic arterial infusion chemotherapy, and the palliative care of patients with progressive disease who had conditions such as hepatic decompression and variceal bleeding might be related to the longer survival time in Japanese rather than non-Japanese patients with HCC.

In conclusion, our results suggested that S-1 is effective and has an acceptable toxicity profile in patients with advanced HCC. Nonetheless, S-1 should be used with caution in the presence of liver dysfunction. Sorafenib has been established to be a standard treatment for advanced HCC. Perhaps, systemic chemotherapy with S-1 plus molecular-targeted therapies such as sorafenib will further improve survival in patients with advanced HCC or monotherapy with S-1 will be useful as a second-line regimen for chemotherapy.

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References

1 Zhu AX. Systemic therapy of advanced hepatocellular carcinoma: how hopeful should we be? *Oncologist* 2006; **11**: 790–800.
2 Cheng AL, Kang YK, Chen Z *et al.* Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol* 2009; **10**: 25–34.
3 Llovet JM, Ricci S, Mazzaferro V *et al.* Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008; **359**: 378–90.
4 Furuse J, Ishii H, Nakachi K, Suzuki E, Shimizu S, Nakajima K. Phase I study of sorafenib in Japanese patients with hepatocellular carcinoma. *Cancer Sci* 2008; **99**: 159–65.
5 Shirasaka T, Shimamato Y, Ohshimo H *et al.* Development of a novel form of an oral 5-fluorouracil derivative (S-1) directed to the potentiation of the tumor selective cytotoxicity of 5-fluorouracil by two biochemical modulators. *Anticancer Drugs* 1996; **7**: 548–57.
6 Tatsumi K, Fukushima M, Shirasaka T, Fujii S. Inhibitory effects of pyrimidine, barbituric acid and pyridine derivatives on 5-fluorouracil degradation in rat liver extracts. *Jpn J Cancer Res* 1987; **78**: 748–55.
7 Shirasaka T, Shimamoto Y, Fukushima M. Inhibition by oxonic acid of gastrointestinal toxicity of 5-fluorouracil without loss of its antitumor activity in rats. *Cancer Res* 1993; **53**: 4004–9.
8 Shirasaka T. Development history and concept of an oral anticancer agent S-1 (TS-1): its clinical usefulness and future vistas. *Jpn J Clin Oncol* 2009; **39**: 2–15.
9 Yamashita T, Kaneko S, Furuse J, *et al. Experimental and Early Clinical Studies of S-1, a Novel Oral DPD Inhibitor, Chemotherapy for Advanced Hepatocellular Carcinoma*. San Francisco: The American Association for the Study of Liver Diseases, 2008; Publication Number 1442.
10 Ueno H, Okada S, Okusaka T, Ikeda M, Kuriyama H. Phase I and pharmacokinetic study of 5-fluorouracil administered by 5-day continuous infusion in patients with hepatocellular carcinoma. *Cancer Chemother Pharmacol* 2002; **49**: 155–60.
11 Matsushima E, Yoshida K, Kitamura R, Yoshida K. Determination of S-1 (combined drug of tegafur, 5-chloro-2,4-dihydroxypyridine and potassium oxonate) and 5-fluorouracil in human plasma and urine using high-performance liquid chromatography and gas chromatography-negative ion chemical ionization mass spectrometry. *J Chromatogr B Biomed Sci* 1997; **691**: 95–104.
12 Therasse P, Arbuck SG, Eisenhauer EA *et al.* New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000; **92**: 205–16.
13 Couto OF, Dvorchik I, Carr BI. Causes of death in patients with unresectable hepatocellular carcinoma. *Dig Dis Sci* 2007; **52**: 3285–9.
14 Ng KK, Poon RT, Lo CM, Yuen J, Tso WK, Fan ST. Analysis of recurrence pattern and its influence on survival outcome after radiofrequency ablation of hepatocellular carcinoma. *J Gastrointest Surg* 2008; **12**: 183–91.
15 Thomas M. Molecular targeted therapy for hepatocellular carcinoma. *J Gastroenterol* 2009; **44**: 136–41.
16 Ikeda K, Yoshisue K, Matsushima E *et al.* Bioactivation of tegafur to 5-fluorouracil is catalyzed by cytochrome P-450 2A6 in human liver microsomes in vitro. *Clin Cancer Res* 2000; **6**: 4409–15.
17 Ueno H, Okusaka T, Ikeda M, Takezako Y, Morizane C. Phase II study of S-1 in patients with advanced biliary tract cancer. *Br J Cancer* 2004; **91**: 1769–74.
18 Ueno H, Okusaka T, Ikeda M, Takezako Y, Morizane C. An early phase II study of S-1 in patients with metastatic pancreatic cancer. *Oncology* 2005; **68**: 171–8.

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REVIEW ARTICLE

Issues and controversies of hepatocellular carcinoma-targeted therapy clinical trials in Asia: experts' opinion

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Abstract

Asia has a disproportionate share of the world's burden of hepatocellular carcinoma (HCC). However, the highly regarded clinical practice guidelines and recommendations for the design and conduct of clinical trials for HCC largely reflect Western practice. In order to design mutually beneficial international clinical trials of promising targeted therapies, it is imperative to understand how the aetiology, staging and treatment of HCC differ between Asian and Western countries. Our group, comprising experts in oncology and hepatology from countries that constitute the Eastern Asian region, convened to compare and contrast our current practices, evaluate potential compliance with the clinical trial recommendations, and offer suggestions for modifications that would enhance international collaboration. Here, we describe the results of our discussions, including recommendations for appropriate patient stratification based on potentially important differences in HCC aetiology, identification of practices that may confound interpretation of clinical trial outcomes (traditional Chinese medicine; antivirals that target hepatitis B virus; heterogeneous embolization procedures), suggestions for utilizing a common staging system in study protocols, recognition that sorafenib usage is limited by financial constraints and potentially increased toxicity in Asian patients, and expansion of patient populations that should be eligible for initial clinical trials with new agents.

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide, diagnosed in approximately 600 000 people per year (1–2). Because of its poor prognosis and high fatality rate, it ranks third among the causes of global cancer-related mortality. A vast majority of cases, and consequently deaths, occurs in the developing world (2–3). HCC is relatively common in the Asia-Pacific region and parts of Africa, but is relatively uncommon in the Americas, Europe and Australia (Table 1) (2). Indeed, more than 70% of cases are diagnosed in Asia, with China alone accounting for 55% of the global cases (3). New treatments are urgently required worldwide.

Sorafenib is the only targeted therapy currently approved for use in HCC. As in the West, sorafenib is specifically indicated in Asian countries for use in patients with unresectable disease (although availability is limited, particularly in Korea and Taiwan, by the national health insurance agencies). Clinical trials are underway or being developed for all stages of disease with this agent, as well as with a variety of other targeted therapies, including sunitinib, brivanib, foretinib, linifanib (ABT-869), pazopanib and vandetanib. In 2008, the American Association for the Study of Liver Diseases (AASLD) published guidelines intended to provide a framework for clinical trial design in HCC (4). As the majority of cases of HCC occur in Asia, it is critical to evaluate how the AASLD recommendations compare with current practice patterns throughout this region. Our group, comprising experts from China, Japan, Korea, Taiwan and Hong Kong, convened in May 2009 to compare and contrast clinical practices and evaluate potential compliance with the Western clinical trial recommendations. The goal of this review is to

Table 1. Age-standardized incidence rates for hepatocellular carcinoma by geographical region in 2002 (2)

Region	Males, rate per 100 000	Females, rate per 100 000
Asia		
China	37.9	14.2
Japan	23.1	7.6
Southeast Asia	18.2	5.7
Western Asia	4.6	2.0
South central Asia	2.6	1.4
Africa		
Middle Africa	27.8	13.4
Eastern Africa	21.1	8.6
Western Africa	15.3	5.6
Southern Africa	7.0	2.5
Northern Africa	4.2	2.2
Europe		
Southern Europe	11.6	4.0
Western Europe	6.2	1.7
Eastern Europe	5.3	2.4
Northern Europe	3.4	1.7
Americas		
North America	5.3	1.9
Central America	4.9	4.9
South America	3.7	2.8
Australia/New Zealand	3.9	1.3

summarize our findings, highlight opportunities for international collaboration, identify potential roadblocks and offer suggestions intended to better facilitate the international clinical development of promising targeted therapies for HCC. Our conclusions are summarized in Table 2 (4) and discussed in the following sections.

Aetiology and prognosis of hepatocellular carcinoma in Eastern Asia vs the West

There are notable regional differences in the aetiology and prognosis of HCC that cannot be ignored in the design and conduct of international clinical trials (5–6). These differences are likely because of both patient-related factors and practice patterns (6). Because it is not entirely clear as to why this clinico-pathological variability exists, international trials must be stratified appropriately to prevent confounding. We agree with the AALSD that stratification by region (West vs Asia) is appropriate and suggest additional stratification factors, such as viral aetiology and use of antiviral therapy for reasons described here.

There are a number of risk factors for the development of HCC, including hepatitis, cirrhosis, certain metabolic diseases and environmental carcinogens (5). Hepatitis B virus (HBV) and hepatitis C virus (HCV) are two of the most important risk factors for the development of HCC, estimated to be responsible for more than 75% of HCC cases worldwide (2). HBV-related HCC is more prevalent than HCV-related disease in most Asian countries, with the notable exception of Japan, where HCV-related disease predominates (3, 7–8). Although large-scale vaccination programmes that began in the last 10–25 years are expected to reduce the incidence of HBV and lead to a gradual decline in the incidence of HCC throughout Asia in the future, there remains a large number of people already infected with this virus who will develop HCC and require treatment in the years to come.

The predominance of HBV-related HCC in Eastern Asia compared with Japan and Western nations has implications for the design and conduct of international clinical trials. Although the AASLD cautions against 'over-stratification' for what it considers less important prognostic factors, such as aetiology, our group believes that viral aetiology may be an important stratification factor in clinical trials for several reasons. Firstly, there are important clinical differences between HBV- and HCV-related HCC. Nearly all patients with HCV-related HCC also have advanced-stage hepatic fibrosis or cirrhosis, but HBV-related HCC can occur with or without concomitant cirrhosis, an important factor affecting surgical resectability (5, 9–11). HCV-related HCC also tends to evolve more quickly than HBV-related HCC (5). It takes approximately 30 years for HCC to develop after exposure to HCV via virally contaminated blood vs 40–50 years after exposure at birth to HBV. Different mechanisms of carcinogenesis probably explain these findings. It is presently believed that HCV-related HCC occurs as a result of inflammatory processes; the HCV genome does not integrate into the host's genome. Conversely, HBV-related HCC appears to result from both virally induced activation of oncogenic processes and chronic inflammation. Although published reports of the prognostic significance of viral aetiology in advanced HCC are conflicting (6, 12, 13), it is biologically plausible that it affects the clinical course of HCC. Until we have a better understanding of these differences, it may be prudent to stratify clinical trials, particularly those conducted primarily in Asia, by viral aetiology.

A second rationale for stratification by viral aetiology is to avoid potential confounding by the use of antiviral therapy. Because HBV-related HCC predominates in Eastern Asia (with the exception of Japan), antiviral therapy is commonly used during and after HCC treatment. Cancer patients who receive the antiviral agent lamivudine as an adjunct to chemotherapy experience lower rates of HBV reactivation and hepatitis, less severe hepatitis episodes, fewer chemotherapy disruptions and reduced mortality related to HBV reactivation (14–17). In patients undergoing curative resection, radiofrequency ablation (RFA) or other local, non-chemotherapeutic treatments for HBV-related HCC, post-procedural antiviral therapy with lamivudine, adefovir dipivoxil or entecavir increases residual liver volume and/or function and may improve overall survival (OS) (18–20). Other evidence suggests that adjuvant interferon improves recurrence-free survival after potentially curative surgery for HCC (21, 22). Because the use of antiviral therapy

Table 2. Eastern Asian views on American Association for the Study of Liver Diseases recommendations for clinical trial design and endpoints

AASLD recommendations (4)	Authors' perspectives
Diagnosis: pathological confirmation OR noninvasive criteria per AASLD guidelines	Agree
Target population:	
Homogenous, based on one BCLC stage or stratified accordingly	BCLC stage is acceptable, but clinical protocols must take into account portal vein involvement and liver function
Focus on Child Pugh (CP) A because best prognosis; in CP-B/C, death from cirrhosis could mask treatment effects	There is a need for treatment options for Child–Pugh B/C; we believe that in advanced/metastatic HCC, Child Pugh B/C is an ideal population to study but limit to ECOG PS 0 (not 0–1)
Stratification:	
By BCLC stage	Stratification by viral aetiology is important in trials conducted within Eastern Asia
For BCLC stage C, stratify by ECOG PS (0 vs 1–2), tumour burden, and CP score	Stratification by use of antivirals should also be considered
By region (West vs Asia)	Protocols should standardize antiviral therapy and include appropriate monitoring parameters
Overstratification is not desirable (e.g., aetiology and age are less important)	
Control arm for RCTs:	
PEI and RFA are standards of care for early HCC	Heterogeneity in TACE/TAE practices needs to be addressed
Chemoembolization is standard for intermediate stage HCC	Placebo-controlled trials are feasible in unresectable disease, especially for those who are indicated for locoregional therapy, pending maturity of post-TACE sorafenib data
Sorafenib is considered standard of care by most investigators for advanced HCC	Recommendation for sorafenib as comparator in advanced disease is not necessarily reflective of real-world use in North East Asia at this time (e.g., high cost, intolerable side effects)
Liver function:	
Cirrhotic patients present challenge to management and interpretation of toxicities with new agents; trials should separately include and/or evaluate patients with and without cirrhosis	Agree; however, trials should separately include and/or evaluate patients based on presence of cirrhosis *or* grade of liver function
Definition of cirrhosis and method of diagnosis should be identified in the protocol	
CP is the gold standard, but future trials should also consider MELD	
Evaluate liver-related toxic effects via serum aminotransferase; bilirubin; PT	
Phase I trials:	
BCLC CP-A population to define dose, toxicity, and liver-related events	There is interest in conducting phase I trials specifically in Asia because of the potential for PK/PD differences between Asian and Western populations; however, Asian phase I trials may not be necessary for all targeted agents
	CP-A population or CP score up to 7–8 (subgroup of CP–B) would be feasible for standard phase I trials
	Patients with poorer liver reserve (CP-B with score 8–9 and CP-C) could be enrolled in phase I trials testing agents at lower doses
Phase II trials:	
Single arm trials acceptable if contemporary control arm available; otherwise, RCT	For first-line studies in advanced HCC, recommendation for sorafenib is not necessarily reflective of real-world use in North East Asia at this time (e.g., high cost, intolerable side effects)
TTP as primary endpoint; imaging surveillance every 6–8 weeks; OS as secondary endpoint	Agents demonstrated effective as second-line therapy in phase II trials (not necessarily phase III trials) can be compared with sorafenib in first-line studies
Targeted therapy RCT should collect tissue and/or serum samples for correlative studies	
Control arm for initial treatment of advanced disease should be sorafenib, while placebo/BSC is acceptable for second-line studies	
Only agents demonstrated effective for 2nd-line use in phase III trials should then be compared to sorafenib in first-line studies	
New compounds for neoadjuvant/adjuvant use should be compared with placebo or BSC	
Phase III trials:	
OS is the primary endpoint; control arm is current standard of care	OS endpoint but will soon no longer be appropriate in advanced disease with the introduction of multiple line of therapies; hence PFS may be a surrogate but will need to evaluate how well it correlates with OS (i.e., as what was done in colorectal cancer)
Trials of adjuvant or locoregional therapies should include TTR; studies that utilize TTR should conduct molecular studies to differentiate recurrence from *de novo* metachronous tumour	

Table 2. Continued

AASLD recommendations (4)	Authors' perspectives
Designs of new agent+sorafenib vs sorafenib are acceptable; direct comparison to sorafenib as initial therapy only if sufficient evidence of efficacy in phase II studies Prefer initial testing in Child–Pugh A patients	In unresectable disease, the most appropriate endpoint is unknown because of difficulty distinguishing recurrence from second primary in the liver and unreliability of RECIST; time to development of new lesion is a possible endpoint Non-inferiority trials are acceptable if new agents have potential for less toxicity

RCT, randomized controlled trial; TTP, time to progression; OS, overall survival; BSC, best supportive care; MELD, model of end-stage liver disease; PT, prothrombin time; PK/PD, pharmacokinetic/pharmacodynamic; TTR, time to recurrence.

Table 3. Summary of staging systems used in eastern Asia

Geographical region	Staging systems
China	China Criteria of Primary Liver Cancer (PLC)
Hong Kong	Chinese University Prognostic Index (CUPI)
Japan	Liver Cancer Study Group of Japan (LCSGJ) 4th ed Japan Integrated Staging (JIS) American Joint Committee on Cancer (AJCC) 6th ed
Korea	Modified International Union Against Cancer criteria (mUICC)
Taiwan	Barcelona Clinic Liver Cancer criteria (BCLC)

differs by region, it may be an important stratification factor. Ideally, efforts should be made to standardize antiviral therapy in the clinical trial protocols to prevent confounding.

Staging systems used in Eastern Asia

Hepatocellular carcinoma differs from other solid tumours because it frequently occurs in an already-diseased organ, which complicates staging as well as the interpretation of survival outcomes in clinical trials (5, 23). As in other tumour types, staging is used to plan therapy, but there is no universally accepted HCC staging system. Indeed, different staging systems are used throughout Eastern Asia (Table 3). The Barcelona Clinic Liver Cancer (BCLC) system (Table 4) (24), recommended by the AASLD as the standard for clinical trial design (4), is currently used only in Taiwan and, even there, only in some institutions. Many clinicians in Eastern Asia believe that the risks associated with invasive testing required to diagnose portal hypertension, a component of BCLC staging, are not acceptable, and such testing is, therefore, not performed routinely. Tables 5 (25–27) and 6 (28) summarize the key features of the other staging systems that are used in Eastern Asia.

In China, the Chinese Society of Liver Cancer published the revised Staging Criteria of Primary Liver Cancer in 2001. These criteria are based on tumour size, number and location; portal vein thrombosis; lymph node spread; extrahepatic metastasis; and liver function based on the Child–Pugh score (29). This system is preferred to BCLC because it includes portal vein thrombosis, which has been shown to be a robust independent predictor of mortality (30). In the Japanese staging system, liver function is the first category of evaluation. The degree of liver damage is determined based on levels of serum bilirubin, serum albumin, prothrombin activity, ICG R_{15} and ascites. This information is considered to be in concert with the Liver Cancer Study Group of Japan (LCSGJ) staging system, which assesses the primary tumour (T), regional lymph nodes (N) and the presence or absence of distant metastases (M). Hong Kong does not have a unified staging system; BCLC is considered to be a valuable tool for treatment planning, but it is less useful for prognostication in this population. The prognostic value of the CUPI system, however, has been validated in a population of advanced HCC patients with mainly HBV-related HCC at one centre in Hong Kong (31). Finally, in Korea, the modified International Union Against Cancer (mUICC) system is used.

Overall, we recognize that BCLC staging can be useful for treatment planning, and if BCLC staging is required for international trials that are designed to meet regulatory requirements in the United States or European Union, Eastern Asian countries should be able to comply. However, protocols will need to take into account the portal vein involvement and liver function to better reflect current practices in our countries. For example, it may be necessary to create subclassifications within the BCLC Stage C disease to differentiate patients identified with advanced disease because of extrahepatic metastases vs portal vein thrombosis.

Current treatment patterns in Eastern Asia – resection and transplant

One of the purported advantages of the BCLC staging system is its linkage to a treatment algorithm (Figs 1–4) (32–34). According to this algorithm, patients with early-stage HCC are candidates for a potentially curative treatment, including surgical resection, liver transplant and percutaneous ethanol injection or RFA (32). Chemoembolization is reserved for the treatment of intermediate-stage disease, whereas new agents can be considered in advanced-stage disease. In intermediate- and advanced-stage HCC, participation in randomized controlled trials is also recommended.

Table 4. Barcelona Clinic Liver Cancer staging system for hepatocellular carcinoma (24)

Descriptor	Stage	ECOG PS	Tumour	Liver function
Early stage	A1	0	Single tumour < 5 cm	No portal hypertension
	A2			Portal hypertension; normal bilirubin
	A3			Portal hypertension; abnormal bilirubin
	A4		Up to three tumours < 3 cm	Not applicable
Intermediate	B	0	Large multinodular	Child–Pugh A-B
Advanced	C	1–2	Vascular invasion or extrahepatic disease	
Terminal	D	3–4	Any	Child–Pugh C

ECOG PS, Eastern Cooperative Group Performance Status Score.

Table 5. TNM-based staging systems used in eastern Asia

	LCSGJ (25)	AJCC/UICC 6th ed. (26)	Modified UICC 6th ed. (27)
TNM descriptors			
T1	Single tumour, < 2 cm, no vascular involvement	Solitary tumour without vascular invasion	
T2	Any 2 criteria required for T1	Solitary tumour with vascular invasion or multiple tumours but none > 5 cm	
T3	Any 1 criterion required for T1	Multiple tumours > 5 cm or tumour involving a major branch of the portal or hepatic vein(s)	
T4	Meets none of the T1 criteria	Tumour(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum	
N1	Regional lymph node metastasis		
M1	Distant metastasis		
Stages			
Stage I	T1N0M0	T1N0M0	IA: single tumour ≤ 2 cm IB: single tumour > 2 cm, without vascular invasion
Stage II	T2N0M0	T2N0M0	IIA: if multiple tumours, none > 5 cm and no vascular invasion IIB: tumour with segmental macroscopic vascular invasion
Stage III	T3N0M0	IIIA: T3N0M0 IIIB: T4N0M0 IIIC: Any T, N1, M0	
Stage IV	IVA: T4N0M0 or Any T, N1, M0 IVB: Any T, Any N, M1	Any T, Any N, M1	

LCSGJ, Liver Cancer Study Group of Japan; AJCC, American Joint Committee on Cancer; UICC, International Union Against Cancer.

Table 6. CUPI Staging System for hepatocellular carcinoma (28)

Variables	Weight/score	CUPI Stage
TNM stage (5th edition)		
I/II	– 3	
IIIa/IIIb	– 1	
IVa/IVb	0	
Asymptomatic on presentation	– 4	
Ascites	3	
AFP ≥ 500 ng/ml	2	
Total bilirubin (micromol/L)		
< 34	0	
34–51	3	
≥ 52	4	
ALP ≥ 200 IU/L	3	
Total score	– 7 to 1	Low risk
	2 to 7	Intermediate risk
	8 to 12	High risk

AFP, α-fetoprotein; ALP, alkaline phosphatase.

Practice patterns in Eastern Asia generally overlap with the BCLC recommendations, but there are notable differences (Figs 1–4) (32–34). Surgical resection is the treatment of choice for non-cirrhotic patients worldwide; however, the prevalence of cirrhosis varies from approximately 95% in Western patients to about 60% in Asian patients, suggesting that a greater number of patients in Asia are potential surgical candidates (32). Unlike resection, liver transplant has the potential to cure both the cancer as well as any underlying cirrhosis, but transplant is not currently a standard of care in much of Eastern Asia. There is a shortage of cadaveric organs due in large part to social and ideological issues (35, 36). Living donor liver transplant (LDLT) is used increasingly in Asia, but selection criteria for appropriate candidates with HCC remain controversial (35). As a result of these differences, rates of use of potentially curative treatments differ between Asia and the West. Within Asia, surgery is performed most frequently in China, Taiwan and Japan, where 34–40% of patients undergo resection.

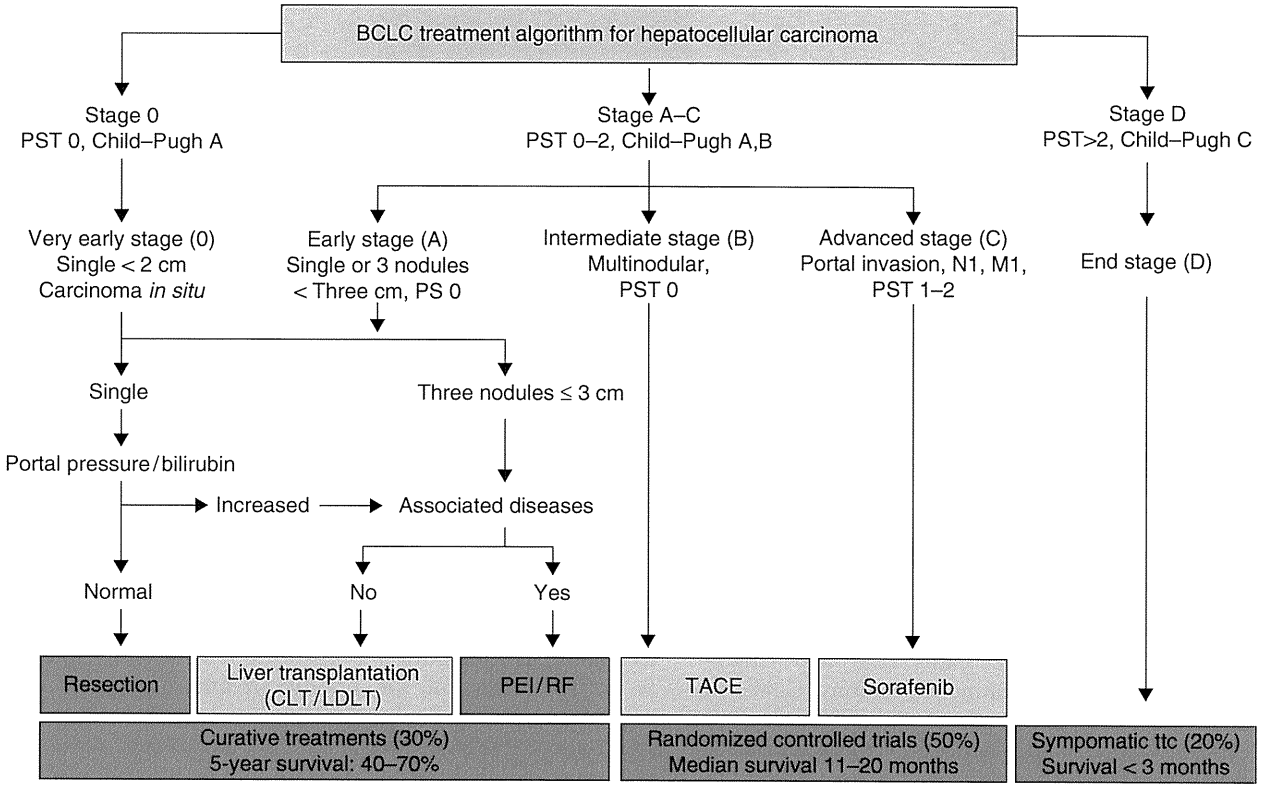

Fig. 1. Barcelona Clinic Liver Cancer (BCLC) staging classification and treatment algorithm (32).

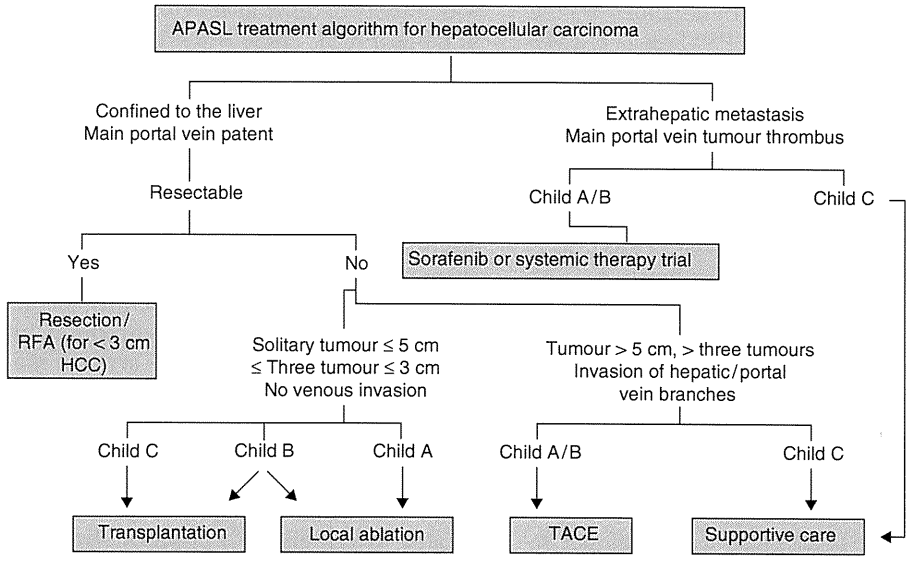

Fig. 2. Asia Pacific Association for the Study of the Liver (APASL) treatment algorithm for hepatocellular carcinoma (kindly provided by Prof. Ann-Lii Cheng, National Taiwan University Hospital). This algorithm forms the basis for treatment in some Taiwanese institutes.

Approximately 15–20% of patients in Korea and Hong Kong undergo resection. In the US, where transplant is more widely available, it is estimated that fewer than 20% of patients undergo potentially curative treatment with either resection or transplant (37).

Other variations in practice are indicated in recent guidelines from the Asian Pacific Association for the Study of Liver Disease (APASL) currently used in Taiwan (Fig. 2). The APASL recommends stratifying patients first by the extent of tumour spread and portal vein involvement

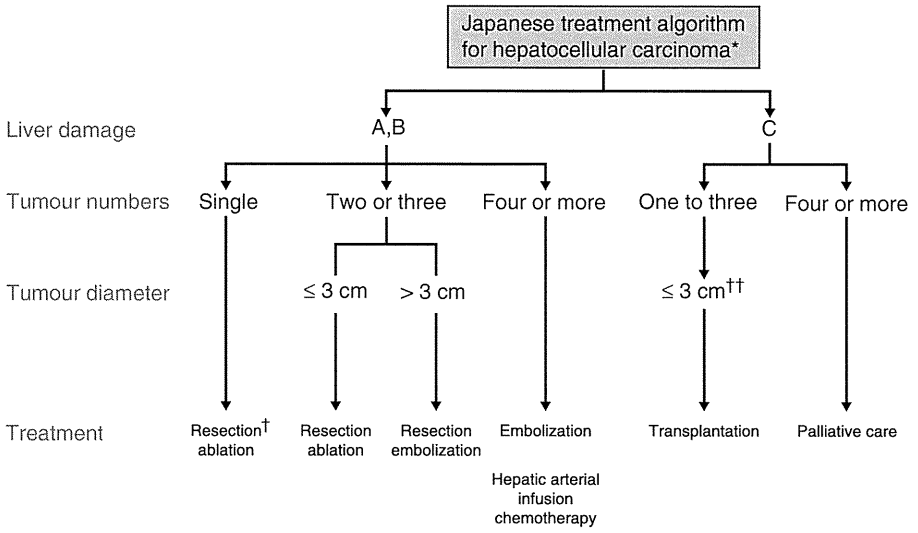

Fig. 3. Treatment algorithm for hepatocellular carcinoma utilized in Japan (33). *Presence of vascular invasion of extraheptic metastasis to be indicated separately. †Selected when the severity of liver damage is class B and tumour diameter is ≤2 cm. ††Tumour diameter is ≤5 cm when there is only one tumour.

rather than by performance status (PS) and Child–Pugh score when making treatment decisions. Unlike in the BCLC algorithm, some patients with Child–Pugh C HCC can be considered for transplant. This difference is also seen in the guidelines from the Japanese Society of Hepatology; however, transplant is an option only for patients with Child–Pugh C HCC in Japan (Figs 1–4) (33). The Korean treatment algorithm provides a general overview of treatment options, which are guided by the mUICC stage, Child–Pugh score and PS (Figs 1–4) (34). Most hepatic resections in Korea are performed in patients with Child–Pugh A liver dysfunction and ECOG PS ≤ 2; when transplant is offered, it is nearly always a LDLT (34).

Unlike other guidelines, those from the Chinese Society of Liver Cancer focus on local resection with reresection for recurrence and, importantly, recognize the role that traditional Chinese medicine (TCM) plays in managing this disease. The two main types of TCM used in the setting are prescribed (a) for general liver health and to slow the progression of cirrhosis or (b) to counter the side effects of chemotherapy. Because TCM could be a confounder in international clinical trials, this issue needs to be addressed. It is important for international trials to allow for the use of TCM administered for general liver health as patients and clinicians are unlikely to abandon this practice. However, if necessary, it would be acceptable to exclude TCM given as an adjunct to chemotherapy from future trials.

Treatment trends for unresectable hepatocellular carcinoma

Transarterial embolization and chemoembolization (TACE) are well-accepted standards of care for the treatment of early-stage, unresectable HCC. However, embolizing materials and techniques vary widely from country to country and institution to institution. Moreover, there is no consensus on the optimal frequency of these procedures, the optimal interval between procedures or most appropriate efficacy endpoints. Although TACE procedures could be standardized in international clinical trial protocols, such an approach could limit the number of institutions that are willing and able to participate, thereby prolonging the recruitment period. In addition, a wide variety of other locoregional therapies are also in use in Eastern Asia. These issues present a major obstacle to the design and conduct of rigorous international trials.

In China, TACE is used in patients with small tumours that are unresectable, in those who have confined disease but uncompensated liver disease and in those with multiple large tumours who have compensated liver disease. Embolizing materials used are lipiodol and/or gelatin sponge particles, which are administered with chemotherapy agents, including fluorouracil, cisplatin, epirubicin and mitomycin-C. Other locoregional therapies used in China are intratumoural injection, laser therapy, cryotherapy, hepatic arterial infusion (HAI), RFA and microwave coagulation therapy.

In Hong Kong, agents used for TACE include cisplatin, lipiodol and gelatin sponge particles. The protocol, in general, includes assessment of the tumour size and vascularity, as determined by the hepatic arteriogram. A cisplatin–lipiodol emulsion is then infused until a reduction of arterial blood flow occurs with the feeding arteries embolized with gelatin sponge particles. The goal is to reduce the arterial blood flow without totally occluding the vessel. For patients with good lipiodol uptake by the tumour, TACE can be repeated serially. A clinical trial evaluating TACE in Hong Kong at a university medical centre utilized a similar protocol with a longer treatment interval of 2–3 months (38).

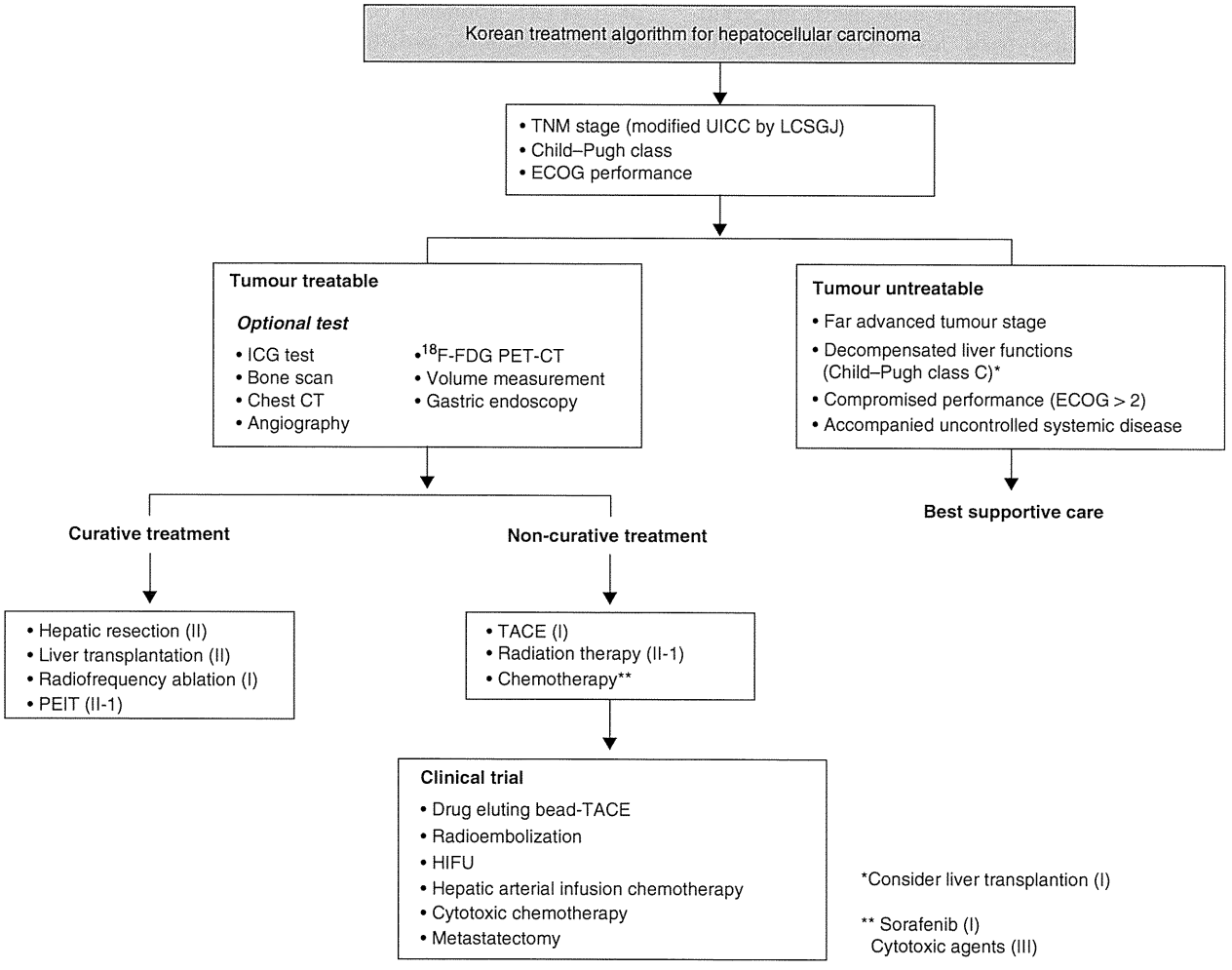

Fig. 4. Treatment algorithm for hepatocellular carcinoma utilized in Korea (34). Levels of evidence are indicated as follows: Level I, evidence obtained from at least one properly designed randomized controlled trial; level II-1, evidence obtained from well-designed controlled trials without randomization; level II-2, evidence obtained from well-designed cohort or case–control analytical studies, preferably from more than one centre or research group; level II-3, evidence obtained from multiple time series with or without the intervention or from dramatic results in uncontrolled trials; level III, opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees. HIFU, high-intensity focused ultrasound; ICG, indocyanine green 15-min retention rate.

In Japan, TACE is a standard treatment. If residual HCC lesions are observed, TACE is repeated until severe liver damage occurs. Embolizing materials used are a mixture of lipiodol with epirubicin or cisplatin followed by gelatin sponge particles. For patients with portal vein thrombosis at the first branch or portal trunk or patients with multiple and/or large tumours, HAI is used. Chemotherapy regimens that are used for HAI include cisplatin alone, 5-FU and cisplatin (FP) and 5-FU and interferon.

In Korea, TACE is the most commonly utilized treatment for HCC, especially for intermediate and advanced disease. Embolizing material for TACE includes doxorubicin, alone or in combination with 5-FU or cisplatin, and gelatin sponge particles. Other treatments used to manage unresectable disease include HAI, concurrent chemotherapy/radiotherapy and supportive care (39–40).

In Taiwan, TACE is used in patients who have unresectable tumours confined to the liver, no portal vein thrombosis, and either tumours of > 5 cm, more than three tumours or hepatic/portal vein branch invasion and a Child–Pugh classification of A/B. A combination of lipiodol and doxorubicin is commonly used.

Treatment trends in advanced hepatocellular carcinoma

Chemotherapy has not been shown to prolong OS in HCC (41). Targeted therapies are now at the forefront of clinical research, with results being available for sorafenib, sunitinib, ABT-869, brivanib, pazopanib, vandetanib and erlotinib plus bevacizumab in advanced HCC (42–55). Of the targeted therapies studied to date in HCC, only sorafenib has been approved for use in Asia and Western nations. Initially approved for the treatment

of advanced disease, sorafenib is now also being evaluated in global clinical trials for adjuvant use, after resection, ablation or TACE (56).

The initial approval of sorafenib was based on the results of two randomized, placebo-controlled trials that used similar eligibility and staging criteria and were conducted in parallel: one in the West (the SHARP study) and the other in Eastern Asia (China, South Korea, Taiwan) (4, 43). In SHARP, sorafenib significantly prolonged survival in patients with advanced HCC relative to placebo [hazard ratio (HR) = 0.69; 95% CI, 0.55–0.87; $P < 0.001$] (4). Median survival times were 10.7 months in the sorafenib arm vs 7.9 months in the placebo arm. Survival was also prolonged in the Asian study (HR = 0.68; 95% CI 0.50–0.93; $P = 0.014$) (43). Median survival times were 6.5 months in the sorafenib arm compared with 4.2 months in the placebo arm. The reasons for the lower median survival times in each arm of the Asian study relative to the corresponding arm of the SHARP study are not entirely clear, but the finding is consistent with other published data that suggest that Asian patients have poorer survival than their Western counterparts (6, 57–59). One possible explanation is that in SHARP, fewer patients (82–83%) had BCLC stage C disease relative to the Asian trial (95–96%).

Another apparent discrepancy between the results of the pivotal sorafenib studies is the rate of adverse events reported in each population. Hand–foot skin reactions (HFSR) were more frequent in the Asian population, although the difference appears to be because of an increase in the incidence of low-grade events. In the SHARP study, HFSR of any grade occurred in 21% of patients, but the incidence was 45% in the Asian trial (42, 43). Grade 3 HFSR events occurred in 8 and 11% of patients, respectively, and dose reductions for HFSR were reported in 5 and 11% respectively (42, 43). HFSR has complicated other Asian studies, and it is currently not uncommon for lower doses of sorafenib to be used in practice in Eastern Asia. In a phase I study of sorafenib in Japanese patients, eight of 14 patients (57%) who received sorafenib 400 mg twice daily developed HFSR; the rate was lower (38%) in the group that received 200 mg twice a day (60). In one Korean study of 97 patients, 56% developed the hand–foot syndrome, with 9% experiencing grade 3/4 toxicity (61). Treatment was interrupted in 34% of patients because of adverse events, most commonly HSFR, and 25% of patients required dose reduction during sorafenib therapy. Grade 3/4 hyperbilirubinaemia associated with marked elevations of ALT was seen in four patients (4%), but the researchers could not determine whether these events were because of hepatotoxicity or massive tumour necrosis or both. It has been reported recently that sorafenib-induced hyperbilirubinaemia may be because of pharmacogenetics (62). A patient with a UGT1A1 polymorphism developed isolated hyperbilirubinaemia during sorafenib treatment, which may be explained by the fact that sorafenib inhibits UGT1A1. In the setting of a low endogenous production of UGT1A1, sorafenib could theoretically cause elevations of bilirubin, and more specifically, unconjugated bilirubin, due to the inhibition of UGT1A1.

Although sorafenib has been approved for the treatment of advanced HCC, it is not widely used throughout Asia at the current time, mainly because of cost (10). In the Korean trial, it is notable that approximately 10% of patients discontinued sorafenib prematurely and against medical advice, mainly because of cost (61). We estimate that approximately 10–15% of eligible patients in Hong Kong receive sorafenib, with a much lower usage ($\leq$ 3%) in China, Korea and Japan. In some areas, patients only have access to sorafenib if they can pay for it themselves. Several cost-sharing programmes have been started to manage this issue, and they have been successful to a certain extent in that they allow expanded use in a targeted population. However, this practice is unsustainable in the long term.

Ultimately, the greatest impact that the approval of sorafenib has had on practice in Eastern Asia is to decrease the therapeutic nihilism associated previously with the systemic treatment of HCC and to increase referral rates for trials of systemic therapy vs repeat TACE. However, it should be noted that the recommendation of the AASLD that sorafenib be the comparator in randomized phase II and phase III trials does not reflect the current practice in Eastern Asia and may be difficult to achieve because of cost. The use of sorafenib as a control arm may be required in trials designed to gain the regulatory approval of other agents; ideally, the agent would be provided at no cost by the sponsor(s) of these trials. Such an arrangement could require an unusual degree of collaboration between competing pharmaceutical companies or may necessitate that academic or cooperative groups design and conduct these studies with financial support from all commercial interests. Irrespective of funding, Asian investigators will also want to see protocols that include flexible dosing strategies to allow for lower dosing based on tolerability to the greatest extent possible.

Finally, we also support the slight modifications to the recommended population for initial clinical research. The AASLD recommends conducting trials first in patients with Child–Pugh A liver impairment, initiating studies in patients with more severe liver impairment only after safety and efficacy are demonstrated in this population. However, given the great need for effective agents in patients with advanced HCC and Child–Pugh advanced B or C liver impairment, we believe that this is an ideal population in which clinical trials should be conducted. Eligibility should be restricted, however, to those with an acceptable PS, such as ECOG PS0.

Perspectives on drug development and endpoints for hepatocellular carcinoma clinical trials

There is a great need for clinical trials to be conducted in patients with resectable disease. In addition to the usual paradigm in oncology, in which agents are first evaluated in patients with metastatic disease, we believe that

promising agents can also be initially evaluated in resectable disease, given the lack of effective systemic therapies in this setting. These patients remain at risk for recurrent disease and the development of new lesions in the remaining liver.

For patients with unresectable disease, it is still feasible to conduct placebo-controlled trials, although opportunities are limited and data on the results of on-going studies with sorafenib post-TACE are pending. We would suggest that studies in this setting be limited to patients who have achieved maximal response after TACE, based on modified EASL criteria (63). Such an approach helps to create a more homogeneous study population and may make it easier to define subsequent disease progression. Nonetheless, more research is required to determine the optimal clinical endpoints in this setting. One possible endpoint to consider is time for the development of a new lesion, an endpoint that would not require distinguishing recurrent disease from a second primary cancer.

In advanced disease, there is a great interest in identifying effective agents for second-line therapy, as well as treatments for patients with Child–Pugh B and C liver impairment. In general, we agree that OS is the most important endpoint for randomized phase III trials, but it must be recognized that with the introduction of multiple lines of therapy for advanced disease, OS will soon be confounded. In the near future, we may need to use surrogate outcomes for OS in phase III trials. Progression-free survival should be evaluated as an appropriate surrogate, like the cases that have been done in colorectal cancer (64), especially post-TACE. Disease-free survival should be evaluated as an endpoint in the adjuvant setting. Finally, it should be noted that we believe that non-inferiority trial designs would be acceptable in Eastern Asia to demonstrate the efficacy of novel agents that have the potential to be better tolerated or less toxic than current treatment options.

Conclusions

Hepatocellular carcinoma is a heterogeneous disease that is managed differently throughout the world. Because of differences in aetiology, staging and treatment, clinical practice guidelines and recommendations for the design and conduct of clinical trials that have been developed primarily in the West cannot be used throughout the world without modification. Major differences between Eastern Asia and the United States and European Union include a greater burden of HBV-related HCC in Asia; use of locally developed and validated staging systems; different rates of use of potentially curative treatments such as surgery and transplant; heterogeneous TACE procedures; and lack of access to and lower tolerability of sorafenib among patients with advanced HCC. The burden of HCC falls markedly in Asian countries, and more effective treatments are urgently needed. Researchers in Eastern Asia can be effective partners in international clinical drug development when the differences in local practice are recognized and addressed in a thoughtful, collaborative process.

References

1. Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. *J Clin Oncol* 2006; **24**: 2137–50.
2. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin* 2005; **55**: 74–108.
3. Yuen MF, Hou JL, Chutaputti A. Asia pacific working party on prevention of hepatocellular carcinoma. Hepatocellular carcinoma in the Asia pacific region. *J Gastroenterol Hepatol* 2009; **24**: 346–53.
4. Llovet JM, Di Bisceglie AM, Bruix J, *et al.* Panel of experts in HCC-design clinical trials. Design and endpoints of clinical trials in hepatocellular carcinoma. *J Natl Cancer Inst* 2008; **100**: 698–711.
5. Bartlett DL, DiBisceglie AM, Dawson LA. Cancer of the liver. In: DeVita VT, Lawrence TS, Rosenberg SA, eds. *DeVita, Hellman, and Rosenberg's Cancer: Principles and Practice of Oncology*, 8th edn. Philadelphia, PA: Lippincott Williams & Wilkins, 2008; 1129–56.
6. Hsu C, Shen YC, Cheng CC, *et al.* Geographic difference in survival outcome for advanced hepatocellular carcinoma: implications on future clinical trial design. *Contemp Clin Trials* 2010; **31**: 55–61.
7. Kim SR, Kudo M, Hino O, *et al.* For the organizing commmittee of the Japan-Korea liver symposium (JKLS). Epidemiology of hepatocellular carcinoma in Japan and Korea. *Oncology* 2008; **75**: 13–6.
8. Han KH, Kim JK. Liver cancer in Korea. *Hepatol Res* 2007; **37**: S106–9.
9. Luk JM, Wang X, Liu P, *et al.* Traditional Chinese herbal medicines for treatment of liver fibrosis and cancer: from laboratory discovery to clinical evaluation. *Liver Int* 2007; **27**: 879–90.
10. Poon D, Anderson BO, Chen L-T, *et al.* Management of hepatocellular carcinoma in Asia: consensus statement from the Asian oncology summit 2009. *Lancet Oncol* 2009; **10**: 1111–8.
11. Beasley RP, Hwang LY, Lin CC, Chien CS. Hepatocellular carcinoma and hepatitis B virus. A prospective study of 22 707 men in Taiwan. *Lancet* 1981; **2**: 1129–33.
12. Chen C-H, Huanga G-T, Yanga P-M, *et al.* Hepatitis B- and C-related hepatocellular carcinomas yield different clinical features and prognosis. *Eur J Cancer* 2006; **42**: 2524–9.
13. Cantarini MC, Trevisani F, Morselli-Labate AM, *et al.* for the Italian liver cancer (ITA.LI.CA) group. Effect of the etiology of viral cirrhosis on the survival of patients with hepatocellular carcinoma. *Am J Gastroenterol* 2006; **101**: 91–8.
14. Yeo W, Chan PK, Ho WM, *et al.* Lamivudine for the prevention of hepatitis B virus reactivation in hepatitis B

s-antigen seropositive cancer patients undergoing cytotoxic chemotherapy. *J Clin Oncol* 2004; **22**: 927–34.
15. Martyak LA, Taqavi E, Saab S. Lamivudine prophylaxis is effective in reducing hepatitis B reactivation and reactivation-related mortality in chemotherapy patients: a meta-analysis. *Liver Int* 2008; **28**: 28–38.
16. Loomba R, Rowley A, Wesley R, *et al.* Systematic review: the effect of preventive lamivudine on hepatitis B reactivation during chemotherapy. *Ann Intern Med* 2008; **148**: 519–28.
17. Jang JW, Choi JY, Bae SH, *et al.* A randomized controlled study of preemptive lamivudine in patients receiving transarterial chemo-lipiodolization. *Hepatology* 2006; **43**: 233–40.
18. Li N, Lai EC, Shi J, *et al.* A comparative study of antiviral therapy after resection of hepatocellular carcinoma in the immune-active phase of hepatitis B virus infection. *Ann Surg Oncol* 2010; **17**: 179–85.
19. Kuzuya T, Katano Y, Kumada T, *et al.* Efficacy of antiviral therapy with lamivudine after initial treatment for hepatitis B virus-related hepatocellular carcinoma. *J Gastroenterol Hepatol* 2007; **22**: 1929–35.
20. Koda M, Nagahara T, Matono T, *et al.* Nucleotide analogs for patients with HBV-related hepatocellular carcinoma increase the survival rate through improved liver function. *Intern Med* 2009; **48**: 11–7.
21. Breitenstein S, Dimitroulis D, Petrowsky H, *et al.* Systematic review and meta-analysis of interferon after curative treatment of hepatocellular carcinoma in patients with viral hepatitis. *Br J Surg* 2009; **96**: 975–81.
22. Shen YC, Hsu C, Chen LT, *et al.* Adjuvant interferon therapy after curative therapy for hepatocellular carcinoma (HCC): a meta-regression approach. *J Hepatol* 2010; **52**: 889–94.
23. Weber S, Jarnagin W, Duffy A, *et al.* Liver and bile duct cancer. In: Abeloff MD, Armitage JO, Niederhuber JE, Kastan MB, McKenna WG, eds. *Abeloff's Clinical Oncology*, 4th edn. Philadelphia, PA: Elsevier, 2008; 1569–84.
24. O'Neil BH, Venook AP. Hepatocellular carcinoma: the role of the north American GI steering committee hepatobiliary task force and the advent of effective drug therapy. *Oncologist* 2007; **12**: 1425–32.
25. Ueno S, Tanabe G, Nuruki K, *et al.* Prognostic performance of the new classification of primary liver cancer of Japan (4th edition) for patients with hepatocellular carcinoma: a validation analysis. *Hepatol Res* 2002; **24**: 395–403.
26. National Comprehensive Cancer Network. *NCCN Clinical practice guidelines in oncology: hepatobiliary cancers. v.2.2009.* National Comprehensive Cancer Network Available at http://www.nccn.org (accessed 25 September 2009).
27. Kee KM, Wang JH, Lee CM, *et al.* Validation of clinical AJCC/UICC TNM staging system for hepatocellular carcinoma: analysis of 5,613 cases from a medical center in southern Taiwan. *Int J Cancer* 2007; **120**: 2650–5.
28. Leung TW, Tang AM, Zee B, *et al.* Construction of the Chinese university prognostic index for hepatocellular carcinoma and comparison with the TNM staging system, the Okuda staging system, and the cancer of the liver Italian program staging system: a study based on 926 patients. *Cancer* 2002; **94**: 1760–9.
29. Chinese Society of Liver Cancer. The criteria of clinical diagnosis and staging of primary liver cancer. *Chin J Hepatol* 2001; **12**: 324.
30. Tandon P, Garcia-Tsao G. Prognostic indicators in hepatocellular carcinoma: a systematic review of 72 studies. *Liver Int* 2009; **29**: 502–10.
31. Yeo W, Liem TG, Chan SL, *et al.* Prognostic system for hepatitis B virus (HBV)-related hepatocellular carcinoma-prospective validation of the Chinese university prognostic index. *J Clin Oncol* 2008; **26**: abstract 4591.
32. Bruix J, Sherman M. AASLD practice guideline: management of hepatocellular carcinoma. *Hepatology* 2005; **42**: 1208–36.
33. Japan Society of Hepatology. Clinical practice guidelines for hepatocellular cancer 2005. Available at http://www.jsh.or.jp/english/02-Contents.pdf (accessed 14 October 2009).
34. Korean Liver Cancer Study Group and National Cancer Center. Practice guidelines for management of hepatocellular carcinoma 2009. *Korean J Hepatol* 2009; **15**: 391–423.
35. Ng KK, Lo CM. Liver transplant in Asia: past, present and future. *Ann Acad Med Singapore* 2009; **38**: 322–31.
36. Kudo M. Review of the 4th single topic conference on HCC. *Hepatol Res* 2007; **37**: S83–7.
37. El-Serag HB. Epidemiology of hepatocellular carcinoma in USA. *Hepatol Res* 2007; **37**: S88–94.
38. Lo CM, Fan ST, Liu CL, *et al.* Ten-year experience with liver transplantation at Queen Mary Hospital: retrospective study. *Hong Kong Med J* 2002; **8**: 240–4.
39. Park JY, Ahn SH, Yoon YJ, *et al.* Repetitive short-course hepatic arterial infusion chemotherapy with high-dose 5-fluorouracil and cisplatin in patients with advanced hepatocellular carcinoma. *Cancer* 2007; **110**: 129–37.
40. Han KH, Seong J, Kim JK, *et al.* Pilot clinical trial of localized concurrent chemoradiation therapy for locally advanced hepatocellular carcinoma with portal vein thrombosis. *Cancer* 2008; **113**: 995–1003.
41. Mathurin P, Rixe O, Carbonell N, *et al.* Review article: overview of medical treatments in unresectable hepatocellular carcinoma - an impossible meta-analysis? *Aliment Pharmacol Ther* 1998; **12**: 111–26.
42. Llovet JM, Ricci S, Mazzaferro V, *et al.* For the SHARP investigators study group. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008; **359**: 378–90.
43. Cheng AL, Kang YK, Chen Z, *et al.* Efficacy and safety of sorafenib in patients in the Asia-pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol* 2009; **10**: 25–34.
44. Zhu AX, Sahani DV, di Tomaso E, *et al.* Sunitinib monotherapy in patients with advanced hepatocellular carcinoma (HCC): insights from a multidisciplinary phase II study. *J Clin Oncol* 2008; **26** (abstract 4521).
45. Faivre SJ, Raymond E, Douillard J, *et al. Journal of Clinical Oncology* 2007. 2007 ASCO Annual Meeting Proceedings Part I. Vol 25, No. 18S (June 20 Supplement), 3546.

46. Koeberle D, Montemurro M, Samaras P, *et al.* Continuous sunitinib treatment in patients with unresectable hepatocellular carcinoma (HCC): a multicenter phase II trial (SAKK 77/06 and SASL 23). *J Clin Oncol* 2009; **27**: 15s (abstract 4591).
47. Hoda D, Catherine C, Strosberg J, *et al.* Phase II study of sunitinib malate in adult pts (pts) with metastatic or surgically unresectable hepatocellular carcinoma (HCC). 2008 ASCO Gastrointestinal Cancers Symposium, abstract no. 267.
48. Raoul JL, Finn RS, Kang YK, *et al.* An open-label phase II study of first- and second-line treatment with brivanib in patients with hepatocellular carcinoma (HCC). *J Clin Oncol* 2009; **27**: 15s (abstract 4577).
49. Finn RS, Kang Y, Park J, *et al.* Phase II, open label study of brivanib alaninate in patients (pts) with hepatocellular carcinoma (HCC) who failed prior antiangiogenic therapy. 2009 ASCO Gastrointestinal Cancers Symposium, abstract no. 200.
50. Toh HC, Chen P, Knox JJ, *et al.* International phase 2 trial of ABT-869 in patients with advanced hepatocellular carcinoma (HCC). *Eur J Cancer Suppl* 2009; **7**: 366. Abstract PD-6517.
51. Hsu C, Yang TS, Huo TL, *et al.* Evaluation of vandetanib in patients with inoperable hepatocellular carcinoma (HCC): a randomized, double-blind, parallel group, multicentre, phase II study. Joint ECCO 15–34th ESMO Multidisciplinary Congress 2009, abstract no. PD-6518. Available at http://ex2.excerptamedica.com/CIW-09ecco/index.cfm?fuseaction=CIS2002&hoofdnav=Abstracts&content=abs.details&what=AUTHOR&searchtext=hsu&topicselected=*&selection=ABSTRACT&qryStartRowDetail=7 (accessed 2 November 2009).
52. Yau CC, Chen PJ, Curtis M, *et al.* A phase I study of pazopanib in patients with advanced hepatocellular carcinoma. *J Clin Oncol* 2009; **27**: 15s (abstract 3561).
53. Govindarajan R, Siegel ER, Makhoul I, Williamson SK. Phase II study of efficacy of bevacizumab and erlotinib in inoperable previously untreated hepatocellular carcinoma (HCC). 2009 ASCO Gastrointestinal Cancers Symposium, abstract no. 264.
54. Thomas MB, Morris JS, Chadha R, *et al.* Phase II trial of the combination of bevacizumab and erlotinib in patients who have advanced hepatocellular carcinoma. *J Clin Oncol* 2009; **27**: 843–50.
55. Kaseb AO, Iwasaki M, Javle M, *et al.* Biological activity of bevacizumab and erlotinib in patients with advanced hepatocellular carcinoma (HCC). *J Clin Oncol* (abstract 4522).
56. Kudo M. Hepatocellular carcinoma 2009 and beyond: from the surveillance to molecular targeted therapy. *Oncology* 2008; **75**: 1–12.
57. Llovet JM, Bustamante J, Castells A, *et al.* Natural history of untreated nonsurgical hepatocellular carcinoma: rational for the design and evaluation of therapeutic trials. *Hepatology* 1999; **29**: 62–7.
58. Llovet JM, Bruix J. Systemic review of randomized trials for unresectable hepatocellular carcinoma: chemoembolization improves survival. *Hepatology* 2003; **37**: 429–42.
59. Yeung YP, Lo CM, Liu CL, *et al.* Natural history of untreated nonsurgical hepatocellular carcinoma. *Am J Gastroenterol* 2005; **100**: 1995–2004.
60. Furuse J, Ishii H, Nakachi K, *et al.* Phase I study of sorafenib in Japanese patients with hepatocellular carcinoma. *Cancer Sci* 2008; **99**: 159–65.
61. Lee HC. Systemic chemotherapy of hepatocellular carcinoma – Korean experience. *Oncology* 2008; **75**: 114–8.
62. Meza-Junco J, Chu QS, Christensen O, *et al.* UGT1A1 polymorphism and hyperbilirubinemia in a patient who received sorafenib. *Cancer Chemother Pharmacol* 2009; **65**: 1–4.
63. Bruix J, Sherman M, Llovet JM, *et al.* Clinical management of hepatocellular carcinoma. Conclusions of the barcelona-2000 EASL conference. European association for the study of the liver. *J Hepatol* 2001; **35**: 421–30.
64. Saad ED, Katz A, Hoff PM, Buyse M. Progression-free survival as surrogate and as true end point: insights from the breast and colorectal cancer literature. *Ann Oncol* 2010; **21**: 7–12.

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A Conundrum for Randomized Controlled Trials: Experience from a Small Hepatocellular Carcinoma Trial

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Objective: The aim of this study was to explore why patients accepted or declined to participate in a randomized clinical trial, which was subsequently discontinued because of a low recruitment rate.
Methods: Forty-one patients were invited to participate in a randomized clinical trial that aimed to compare local ablation therapies and surgery to treat small asymptomatic hepatocellular carcinomas. These patients were then asked to answer a questionnaire that assessed patient perception and reasons for accepting or declining to enroll in the randomized clinical trial. When patients had a strong preference for a specific treatment, the questionnaire assessed why, how and when they had chosen it.
Results: The response rate was 6/6 (100%) and 30/35 (86%) for the participant and non-participant groups, respectively. Among the 30 non-participants, 23 had a strong preference for local ablation therapies, which was less invasive and offered shorter hospitalization. Patient preference for a specific treatment often stemmed from their consultations with a clinician who referred them to a specialist hospital. Patients without strong preference for a specific treatment participated in the randomized clinical trial because of altruistic motivations.
Conclusion: When new treatments that are innovative and less burdensome become widespread, they are difficult to compare with standard therapy utilizing a well-designed randomized clinical trial. Consequently, when an innovative treatment is developed, investigators should consider designing a randomized clinical trial as early as possible.

Key words: small asymptomatic hepatocellular carcinomas – local ablation therapies – liver resection – randomized clinical trial

INTRODUCTION

Randomized clinical trials (RCT) are the gold-standard to evaluate the safety and efficacy of proposed new treatments (1–3). When a new treatment shows benefits, it is introduced into general practice and is expected to improve the quality of care. However, an appropriate evaluation of an unproven new treatment through a RCT is difficult when it becomes integrated into general clinical practice because of its innovative and minimally burdensome nature (3). Consequently, the co-existence of a new treatment and a standard therapy often leads to diminished patient access to beneficial treatments.

Small asymptomatic hepatocellular carcinomas (HCC) are increasingly recognized as a problem in Japan since the initiation of periodic surveillance of high-risk populations (4). Surgical resection has been accepted as the first-line treatment for HCC. In addition, several local ablation therapies (LAT) have been developed to treat HCC, including percutaneous ethanol injection (PEI) (5) and radiofrequency ablation (RFA) (6). They are minimally invasive and have been recognized as an alternative to surgery in small HCC patients. Retrospective studies have reported that the prognosis of patients undergoing PEI (7–10) or RFA (6,11) for small HCC was equivalent to that of patients selecting surgery. However, the optimal therapeutic strategy for small HCC is under debate. Patient decisions regarding treatment are often guided by the expertise of their consulting clinician, which is frequently affected by sectionalism that is predominant in the Japanese medical community.

In 2002, a RCT (the parent study) was organized to settle the longstanding debate comparing the benefits of LAT relative to surgery in treating small HCC (i.e. three or fewer tumors, where each tumor is 3 cm in diameter or smaller). Table 1 shows the study outline. The trial was carried out in three cancer hospitals (Institutions A, B and C) and a university hospital (Institution D), where physicians and surgeons had the opportunity to build a framework for cooperation. We reached a consensus on what to include in the informed consent form and how to obtain it from patients. Specifically, we explained the clinical equipoise by noting: (i) the probability of 5-year disease-free survival associated with the two treatments was 25 and 10% for surgery and LAT, respectively; and (ii) the probability of 5-year survival associated with the two treatments was 62 and 59% for surgery and LAT, respectively (10). The purpose of the parent study and difference between two treatments were explained in informed consent form as follows; the purpose of this study is to compare the effectiveness, risk, burden and cost between surgery and LAT. Surgery has been usually performed for your type of cancer. LAT has been found to be effective and spread widely, but there is no solid evidence that LAT has a similar benefit to surgery. Currently, the proportion of recurrence in surgery is lower than LAT. However, there is little difference in long-term survival between surgery and LAT. LAT imposes less burden and invasiveness on patients than surgery. The comparative table of benefit, burden and cost in two treatments also was put on the form.

Table 1. Outline of the parent study

	Contents
Purpose	To compare local ablation therapies (RFA, PEI) with surgical resection
Eligibility	Hepatocellular carcinoma, three or fewer tumors each 3 cm in diameter or smaller, Child-Pugh class: A or B
	Age: ≥20, <80
Endpoints	
Primary endpoints	Overall survival and disease-free survival
Secondary endpoints	Medical costs, hospitalization period, Toxicity
Sample size	120 patients
Recruit period	2 year
Institutions	Cancer hospitals (Institution A, B, C), University hospital (Institution D)

Between October 2002 and April 2003, 41 patients were invited to participate in this study. Among these patients, six agreed and 35 refused to participate. Although a similar study was completed in China (12), the steering committee decided to discontinue the trial because of the low recruitment rate. Within this context, the aim of this study was to explore why patients accepted or declined to participate in the trial, and to use this information to provide insights for future research.

PATIENTS AND METHODS

We invited 41 patients, who were originally asked to participate in the parent study, to take part in this study. These patients were then asked by an attending clinician to respond to a questionnaire accompanied by an envelope. Patients were directed to place the completed questionnaire into the envelope and deliver it to the hospital staff. This study was approved by the National Cancer Center Hospital research ethics committee.

The questionnaire contained both multiple-choice and open-ended questions that aimed to assess the reasons behind patient decisions to participate in the study. We also examined views of non-participants towards random allocation. When non-participants had a strong preference towards a specific treatment, we assessed their perception by inquiring why, how and when they developed this preference. The questionnaire, developed by the investigators, was pilot-tested with laypersons to ensure clarity and comprehensibility of the questions. The questionnaires are shown in the Supplementary data, Appendix, available at http://www.jjco.oxfordjournals.org.

RESULTS

The survey was performed between May and July of 2003. Among the six participants and 35 non-participants, 6 (100%) and 30 (86%) patients, respectively, responded to the questionnaire. Table 2 shows the number of patients who accepted or declined participation in the parent-trial. Table 2 also shows the number of non-participants who chose surgery or LAT. Only 15% of patients participated in the parent-trial. There were no differences among institutions. Among the 30 respondents who declined trial entry, four had surgery, 25 had LAT and the remaining one was unknown.