Table 2 Eastern Asian Panel's Opinions on Clinical Trial Design Aspects

Design Aspect	Panel Opinion
Patient Population	
Diagnosis	• Agree with AASLD recommendations[7] - pathological confirmation OR noninvasive criteria per AASLD guidelines
Target population	• BCLC stage is acceptable, but clinical protocols must account for portal vein involvement and liver function • Treatment options for CP B/C are needed; CP B/C (ECOG PS 0 only) is an ideal population to study in advanced/metastatic HCC
Liver function	• Agree with AASLD recommendations[7]; however, trials should separately include and/or evaluate patients based on presence of cirrhosis *or* liver function grade.
Stratification	• Stratification by viral etiology is important in trials conducted within Eastern Asia • Stratification by use of antivirals should also be considered • Protocols should standardize antiviral therapy and include appropriate monitoring parameters
Treatment	
Control arm for RCTs	• Heterogeneity in TACE/TAE practices must be addressed • Placebo-controlled trials are feasible in unresectable disease, especially for those in whom locoregional therapy is indicated, pending maturity of post-TACE sorafenib data • AASLD recommendation for sorafenib as comparator in advanced disease [7] is not necessarily reflective of real-world use in Eastern Asia at this time due to high cost and intolerable side effects
Phase-specific Clinical Trial Recommendations	
Phase I	• Consider conducting Asia-specific phase I trials due to the potential for PK/PD differences between Asian and Western populations; however, Asian phase I trials may not be necessary for all targeted agents • Population • CP-A or CP score up to 7-8 (subgroup of CP-B) would be feasible for standard phase I trials • CP-B with score 8-9 and CP-C could be enrolled in phase I trials testing agents at lower doses
Phase II	• For first-line studies in advanced HCC, AASLD recommendation for sorafenib [7] is not necessarily reflective of real-world use in Eastern Asia at this time due to high cost and intolerable side effects • Agents demonstrated effective for second-line use in phase II trials (not necessarily phase III trials) can be compared to sorafenib in first-line studies
Phase III	• OS endpoint will soon no longer be appropriate in advanced disease with the introduction of multiple lines of therapies; PFS may be a surrogate but it is necessary to evaluate correlation with OS (ie, as what was done in colorectal cancer) • In unresectable disease, the most appropriate endpoint is unknown due to 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

AASLD, American Association for the Study of Liver Diseases; BCLC, Barcelona Clinic Liver Cancer; CP, Child-Pugh; OS, overall survival; PFS, progression-free survival; PK/PD - pharmacokinetic/pharmacodynamic; RCT, randomized controlled trial; RECIST, Response Evaluation Criteria in Solid Tumors; TACE/TAE, transarterial chemoembolization/transarterial embolization

methodology and liver disease is further evaluated. Consensus in treatment must be sought to allow multinational trials and it must be recognized that first-line sorafenib is not largely feasible in Asia. Finally, Asian nations must be urged to participate in clinical trials, many of which are ongoing, to advance new treatment options in this challenging disease.

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Authors' contributions
All authors contributed equally to the writing of this review. All authors read and approved the final review.

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

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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

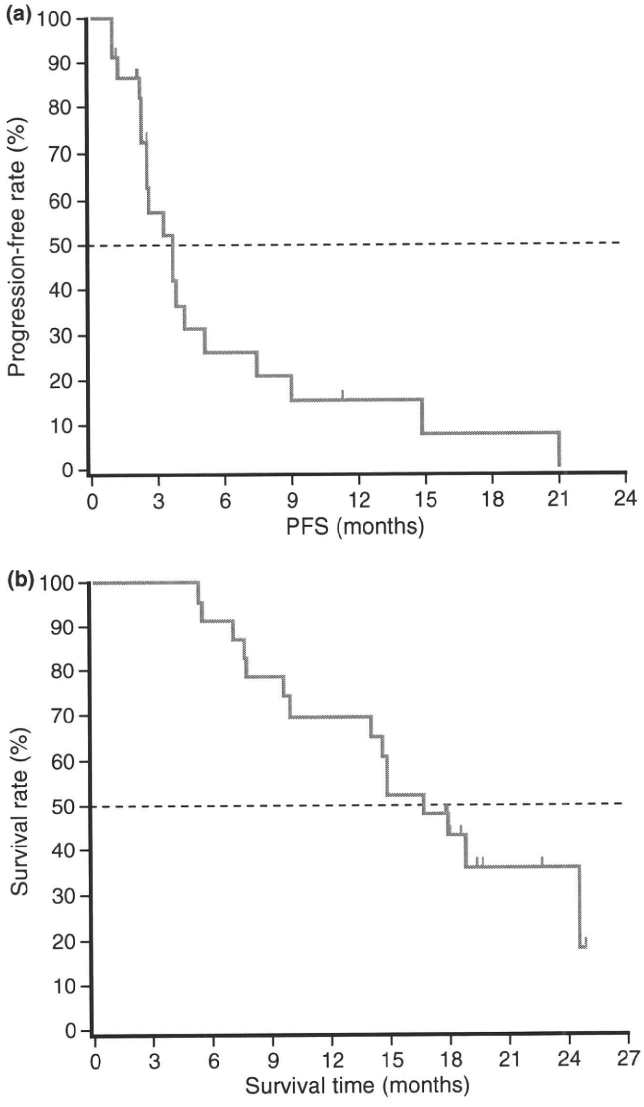

Fig. 1. Progression-free survival (PFS) (a) and overall survival (b) in patients who received dose level 2 of S-1 (n = 23). The median progression-free survival and overall survival were 3.7 and 16.6 months, respectively.

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.

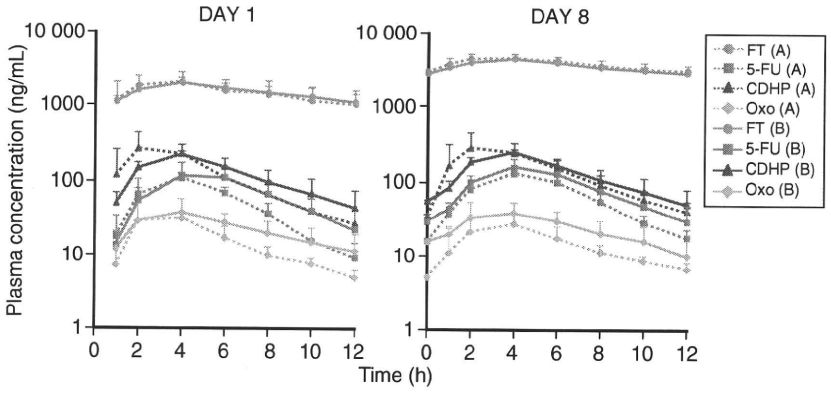

Fig. 2. Plasma-concentration–time profiles of tegafur (FT), 5-fluorouracil (5-FU), 5-chloro-2,4-dihydroxypyridine (CDHP) and oteracil potassium (Oxo) on day 1 and day 8 were similar in patients with Child-Pugh class A (n = 3) and those with Child-Pugh class B (n = 3).

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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Liver Cancer Working Group Report

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Hepatocellular carcinoma is a highly prevalent disease in many Asian countries, accounting for 75–80% of victims worldwide. The incidence of hepatocellular carcinoma varies enormously across Asia, but tends to follow the incidences of hepatitis B infection and liver cirrhosis. The incidence and etiology of hepatocellular carcinoma in Japan are different from the rest of Asia, but similar to that in Western countries because hepatitis C infection is the main etiological factor in Japan. Hepatitis B virus vaccination programs are showing great success in reducing hepatitis B virus-related hepatocellular carcinoma. Screening program improves detection of early hepatocellular carcinoma and has some positive impact on survival, but the majority of hepatocellular carcinoma patients in Asia still present with advanced hepatocellular carcinoma. Long-term outcomes following treatment of even early/intermediate or advanced disease are often unsatisfactory because of a lack of effective adjuvant and systemic therapies. Various clinical practice guidelines for hepatocellular carcinoma have been established and are in use. Clinical diagnosis of hepatocellular carcinoma by imaging diagnosis is replacing diagnosis of hepatocellular carcinoma by pathological confirmation. New imaging and treatment techniques are continuously being developed and guidelines should be updated every 3 or 4 years, incorporating new evidence. New molecularly targeted therapies hold great promise. Sorafenib is the first systemic therapy to demonstrate prolonged survival vs. the placebo in patients with advanced hepatocellular carcinoma. Various other new molecularly targeted agents are currently under investigation.

Key words: liver cancer – epidemiology – etiology – diagnosis – treatment

INTRODUCTION

The Liver Cancer Working Group report was divided into seven topics: (i) epidemiology and etiology in Asian countries; (ii) proportions of early, intermediate and advanced stages of hepatocellular carcinoma (HCC); (iii) surveillance systems and prediction of HCC development; (iv) recent developments in imaging diagnosis; (v) pathological development of early HCC, especially consensus between Asia and the West; (vi) current status of treatment strategies; (vii) future perspectives, especially in regard to sorafenib; and other molecularly targeted agents.

Epidemiology and Etiology

Liver cancer, or HCC, is endemic in Asia. It is expected that around 75–80% of HCC cases worldwide develop in Asia (Fig. 1) (1). In most Asian countries, HCC is ranked from number 1 to number 5 among the leading causes of death. In

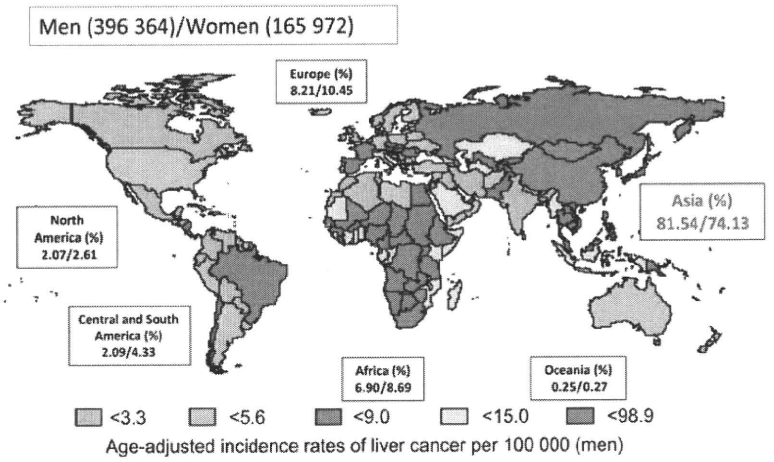

Figure 1. Liver cancer in the world (Curado et al. IARC Press, 2010).

Mainland China and Taiwan, the incidence of HCC has been increasing in the past 30 years, but in Japan, the incidence has been relatively stable during that period (2). In Korea, particularly in the male population, the incidence of HCC decreased slightly in the past 10 years. The primary etiological factor in Asia is hepatitis B. As exemplified by Korea, hepatitis B virus (HBV) accounts for 70–75% of HCC cases and hepatitis C virus (HCV) accounts for 10–15% (3). In Hong Kong, 80% of HCC cases are caused by HBV, and around 7% are caused by HCV. Japan is unique in the etiology of HCC in Asia because almost two-thirds of cases are caused by HCV and only 15% are related to HBV (2,4–6). Taiwan appears to be in between. In the early 1980s, HBV was the dominant cause of HCC in Taiwan, accounting for 88% (4), but in the past 30 years, HCV increased significantly and now accounts for more than 30%. HBV remains the predominant cause, but because of a vaccination program that was started in 1984, Taiwanese younger than 25 years old will have a carrier rate of around 1%. Thirty years from now, HBV-related HCC will decrease dramatically in Taiwan and in other countries that have adopted a nationwide HBV vaccination program (7). Regarding the age distribution of HCC, in all countries in which HBV is the dominant cause, the median age is around 55 years old. Statistics for Japan, which is characterized by HCV, show that the median age is about 10 years older.

In conclusion, HCC in the Asia-Pacific region accounts for 75–80% of victims worldwide. The incidence of HCC is on the rise in some countries, such as mainland China and Taiwan, but it is plateauing and decreasing slightly in some countries, like Japan. Except in Japan, HBV is the major etiology of HCC. The proportion of HCV has increased significantly in the past 30 years in Taiwan. Because of successful vaccination, the incidence of HBV-related HCC will decrease dramatically by 2040 (8).

Proportions of Early, Intermediate and Advanced HCC

There are various staging systems for HCC, with each system having its pros and cons and no consensus regarding which system is the best. The Barcelona Clinic of Liver Cancer, BCLC, system (9,10) is quite widely used in the West and in many clinical trials. The BCLC system stages patients into very early stage, early stage, intermediate stage, advanced stage and end stage according to the tumor size, vascular invasion, the tumor nodule number and the presence of metastasis. The BCLC system also provides a guideline for treatment according to the stage of HCC. Basically, patients with very early-stage or early-stage HCC are considered for curative treatment, either resection, liver transplantation or local ablation. Patients with intermediate-stage HCC, mainly those with multinodular disease, will be eligible for transarterial chemoembolization (TACE), and patients with advanced-stage disease showing portal invasion or distant metastasis will be considered for sorafenib or recruitment to clinical trials.

In addition to the BCLC, the Japanese TNM staging system (11) is quite widely used in Japan and Korea. This staging system takes into account three criteria for the T stage, i.e. whether the tumor is solitary or multiple, the tumor size, $\leq$2 cm or >2 cm, and the presence of any vascular or bile duct invasion. Patients are thus classified as T1, T2, T3 or T4. For N and M, it is similar to other TNM staging systems, based on the presence of lymph node or distant metastasis. By integrating Japanese TNM stage and Child–Pugh grade, Japan Integrated Staging system was developed (12) and widely used in Japan and Korea.

The current distribution of HCC based on the BCLC system is quite similar in Hong Kong and Korea, with about 30–40% of patients having early-stage disease, about 20–30% having intermediate-stage disease and about 30% having advanced-stage disease. In Japan, the proportion of early-stage HCC is very high: about 65%, whereas only 5% of

patients present with advanced-stage disease (5). Japan is thus quite different from the rest of the Asia-Pacific region, probably because of its very well-established surveillance system.

But even within a country, there can be a significant variation between regions, as exemplified by Taiwan. In northern Taiwan, about 58% of patients have early-stage HCC, whereas in the southern part, the rate is only 35.2%. This is probably related to differences in the popularity of surveillance due to cultural, social and economic differences between the populations in the north and south of Taiwan. Data generated in Japan and Korea, using the Japanese TNM staging system, are similar to the BCLC staging results and show that Japan has a higher number of patients with early-stage HCC compared with Korea.

The disease stage obviously affects the treatment modality. For early-stage cancers, curative treatments like surgery or ablation are generally implemented, whereas TACE is performed for intermediate-stage disease and systemic therapy for advanced disease. Comparison between Hong Kong and Japan shows a dominance of ablation and surgery in Japan, whereas in Hong Kong, the percentage of patients amenable to ablation is limited. Even for TACE, the proportion of patients is higher in Japan than in Hong Kong, where a large proportion of patients have advanced disease and receive systemic therapy. For early-stage disease, curative treatment is the first choice, and about 38% of patients in Hong Kong and 65% in Japan are amenable to curative treatments. For intermediate-stage HCC, the rates are 22% in Hong Kong and 30% in Japan, and for advanced-stage disease, the rates are 40% in Hong Kong and 5% in Japan.

BCLC staging has important predictive power for overall survival. Data for more than 3000 patients in Hong Kong show very good stratification of overall survival in terms of the stage. Survival data from Yonsei University (Korea) show a very similar stratification. For patients with early HCC, the 5-year survival rate is now more than 50%, whereas for patients with advanced-stage disease, the 5-year survival is $<5\%$, showing a great difference in the survival outcomes. In some countries, like Korea, evidence points to some recent improvement in the overall survival of HCC patients: comparison between 1993 and 2005 shows that the 5-year survival has improved from 10.7% to 18.9% in the most recent 5-year period.

In conclusion, there is a significant variation in the distribution of early, intermediate and advanced stages of HCC among Asia-Pacific countries, with the highest proportion of early HCC in Japan. Curative treatment for early-stage HCC is associated with the 5-year survival $>50\%$, while the prognosis of advanced-stage HCC remains dismal. These results underscore the importance of early diagnosis by means of surveillance of high-risk patients.

Surveillance Systems and Prediction of HCC

A Hong Kong study proved that a screening program can improve survival by increasing the chance of treatment in the screened group (13). Unfortunately, in Hong Kong, the percentage of patients with HCC diagnosed by screening is low, but it has increased slightly, from 29% in 1991–1997 to 33% in 1998–2004 (14). There is no government-funded surveillance program for HCC in Hong Kong or other parts of China. Korea, however, established a national surveillance program in 2003, with the target population being those over 40 years of age, with liver cirrhosis or an HBV or HCV carrier (15). Taiwan has a similar surveillance program in place, and a different testing interval is applied depending on whether the subject has cirrhosis or not: 3–6 months for cirrhosis, but 6–12 months for non-cirrhosis. There is no age limitation for surveillance of HBV carriers in Taiwan, but in Korea, the government recommends over 40 years. The surveillance program in Japan is slightly different: it selects super high-risk patients, meaning liver cirrhosis B or C, and applies a shorter interval for examination, every 3 or 4 months, and test for more tumor markers (three tumor markers, including AFP, AFP-L3 and DCP) (16,17). The surveillance programs in Korea and China prefer a 6-month interval. Japanese surveillance program also recommends CT or MRI every 6–12 months for improving sensitivity. Thus, there are some differences in HCC surveillance among Asia-Pacific countries, including the candidates for surveillance and the age limit for HBV carriers. As surveillance tools, ultrasonography and AFP are still the standards, but there is a need to know whether more tumor markers will improve the sensitivity. A study investigated whether the surveillance interval is important for improving the survival. The group with a surveillance interval of within 6 months showed better survival than that of more than 6 months.

It is important to predict the development of HCC by quantitative risk estimation. An individualized prediction model is possible by combining multiple risk factors into a comprehensive risk expression. A study identified eight independent risk factors, and a special formula was established to calculate the relative risk factors. This model enables identification of the high- and low-risk groups.

In conclusion, HCC surveillance can detect early tumors and increase the chance of a curative approach. All patients at risk of developing HCC with potentially curative treatment available are recommended for regular surveillance. At present, ultrasonography and the serum AFP test at 6-month intervals are the standard surveillance tools. To improve the detection rate of early-stage HCC, the benefit of additional tests and a shorter surveillance interval should be confirmed by a randomized clinical trial in Asia. The application of individualized prediction model to surveillance programs may improve the cost-effectiveness by focusing on the high-risk group.

Recent Developments in Imaging Diagnosis

Various clinical practice guidelines for HCC are being implemented around the world, including in Europe, Korea, America, Japan and the Asia-Pacific region. In accordance

with those guidelines, the use of dynamic imaging, such as contrast-enhanced ultrasound (US), CT and MRI, is increasing and becoming more important, whereas application of biopsy is decreasing. Angiography and fusion imaging are other imaging tools that are available for the diagnosis of HCC. These tools are based on different imaging techniques. US is the first step for imaging diagnosis of HCC in accordance with the guidelines. If a nodule is found by US examination, the next technique to be used depends on the size of the mass. For a nodule that is <1 cm in diameter, follow-up study is usually recommended. If the nodule is >2 cm in diameter, one further imaging examination, such as contrast-enhanced US, CT or MRI, is sufficient to make a diagnosis of HCC with specific findings. Specific findings consist of a hypervascular nature in the arterial phase of imaging, and a washout pattern in the equilibrium phase. Diagnosis of HCC by dynamic imaging (contrast-enhanced ultrasonography, CT or MRI) is based on the enhancement pattern according to time sequence or phase. Overt HCC shows high attenuation in the arterial phase, indicating the hypervascular nature of the tumor, iso-attenuation in the portal-venous phase and low attenuation in the equilibrium phase, indicating a rapid washout pattern. These comprise very specific findings for the diagnosis of HCC.

In the APASL Guideline 2009 for imaging diagnosis of HCC, US is a screening test, not a diagnostic test for confirmation. US can detect a nodule but cannot characterize it. However, contrast-enhanced US is as sensitive as dynamic CT or dynamic MRI for the diagnosis of HCC (18). When using a US contrast agent for the diagnosis of HCC, the arterial phase and equilibrium phase show a rapid wash-in and washout pattern, which are characteristic findings for overt HCC. Dynamic CT or dynamic MRI is recommended as a first-line diagnostic tool for HCC when a screening test is abnormal. The hallmark of HCC in a CT scan or MRI is the presence of arterial enhancement followed by washout of the tumor in the portal-venous and/or delayed phases. In the diagnostic algorithm for hypervascular masses, typical HCC can be diagnosed by imaging regardless of the size of the detected tumor if a typical vascular pattern—arterial enhancement with portal-venous washout—is obtained on dynamic CT, dynamic MRI or contrast-enhanced US. In the diagnostic algorithm for hypervascular nodules, US is the initial screening method. If a nodule is detected by US, the nodule is then characterized by dynamic CT or MRI. Further characterization is usually performed by Kupffer cell imaging, including Sonazoid-enhanced US, or gadolinium-ethoxybenzyl-diethylene triamine pentaacetic acid (Gd-EOB-DTPA) MRI (Fig. 2) (19). In the diagnostic algorithm for hypovascular masses, nodular lesions showing an atypical imaging pattern, such as iso- or hypovascularity in the arterial phase, or arterial hypervascularity alone without portal-venous washout, should undergo further examination or close follow-up (Fig. 3). Recently, new imaging techniques are being developed, including volume US using various contrast agents, US elastography (20), volume CT, dual energy CT for perfusion CT, diffusion-weighted MRI, MRI elastography, etc. The efficacy of these techniques in diagnosing HCC is being evaluated.

In conclusion, various clinical practice guidelines including diagnostic algorithm for HCC have been established and

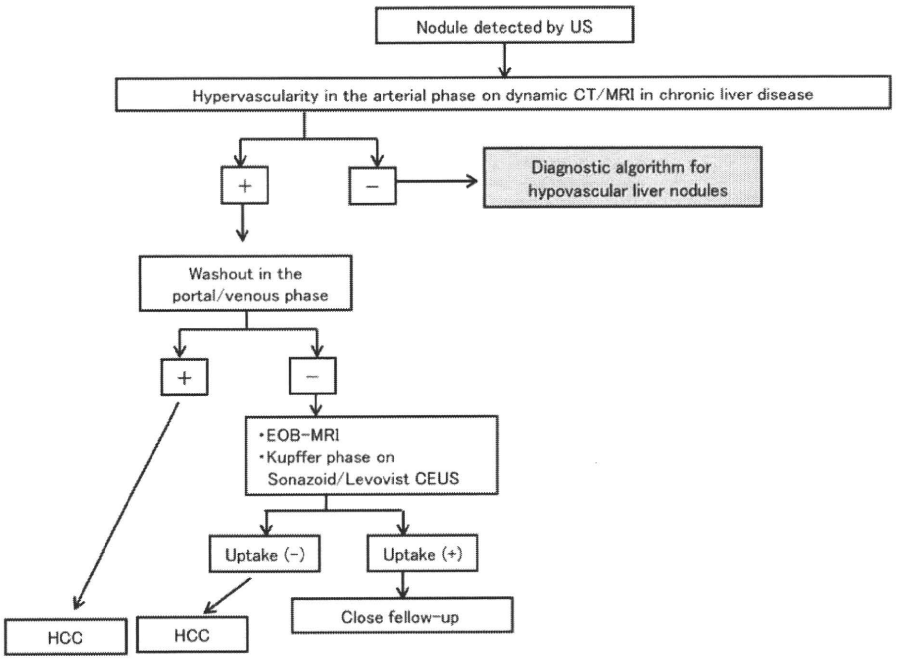

Figure 2. Diagnostic algorithm for hypervascular nodule (APASL Guideline). US, ultrasound; HCC, hepatocellular carcinoma.

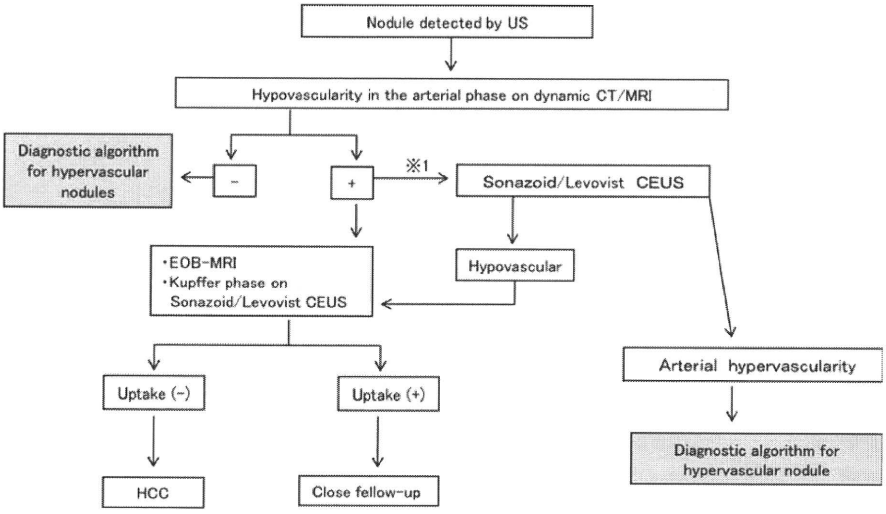

Figure 3. Diagnostic algorithm for hypovascular nodule (APASL Guideline). ※1: When the nodule is hypovascular on dynamic CT or dynamic MRI, Sonazoid-enhanced contrast US is recommended to confirm whether it is truly a hypovascular nodule.

are in use. Use of imaging diagnosis is increasing, whereas the use of biopsy is decreasing. New imaging techniques are continuously being developed. Practice guidelines should be updated to reflect the development of new imaging techniques.

Pathological Diagnosis of Early HCC

In 2009, pathologists from all over the world made great progress by reaching a consensus on the pathological diagnosis of early HCC. A consensus paper was published in the journal, *Hepatology* (21). The main topic of the consensus paper was histopathological definition of early HCC, together with premalignant lesions, dysplastic nodules and progressed HCC. Representative early HCC is a small, well-differentiated tumor, of vaguely nodular type. Microscopically, the border is unclear, and very well-differentiated cancer cells show a replacing growth pattern. They also frequently show stromal invasion, which is quite useful for making a diagnosis of cancer. However, histological atypia or histological alteration is usually very slight in early HCC, which is quite similar to the case of early cancers in other organs. Biopsy diagnosis of early HCC is especially difficult. In an example case, a slight increase in chromatin staining with substantial increase in the nuclear density is seen. Several standard techniques reveal slight changes or alterations in the tumor portion, such as a decrease in reticulin and a slight increase in proliferative activity. However, the use of some new markers, such as heat shock protein (HSP) 70, clearly highlights the tumor portion, making it more easily recognized. Greater use of tumor markers, including glypican 3 and HSP70, is likely and will increase the accuracy of diagnosis of early HCC.

Much has been learned about early HCC, but various problems remain. We know that cancer development is a multistep process, especially when there are cirrhotic changes. Early HCC grows very slowly and has a favorable outcome, whereas progressed, small HCC has a greater likelihood of showing intrahepatic spread and a worse prognosis. It is necessary to recognize that there is a gray zone between precancerous lesion and early HCC. Liver biopsy is recommended for small, equivocal lesions. Also, molecular markers are expected to raise the diagnostic accuracy, especially in the case of biopsy diagnosis of HCC. At the same time, controversy remains regarding which lesions should be examined by biopsy, and there is a risk of overdiagnosis of early cancer.

Current Treatment Strategies

Since 2001, when the Barcelona group published their consensus guideline, at least eight other guidelines have been released worldwide regarding the diagnosis and/or treatment of HCC. In 2003, the Korean guidelines were published, and in 2005, the Japanese guidelines for evidence-based clinical practice (Fig. 4) (16) were released. Clinical practice guidelines should be evidence-based, and they should represent the consensus of expert committees. Sometimes, it is very difficult to reach a consensus in the field of HCC. Guidelines must also take into consideration the socioeconomic status and current daily practice in the country or region. The socioeconomic background and daily practice regarding HCC were compared among Europe and the USA, Asia (Korea) and Japan. The major etiology of HCC is HCV in Europe, the USA and Japan, but HBV in Asia (Korea). A surveillance system has been established in Japan, is being

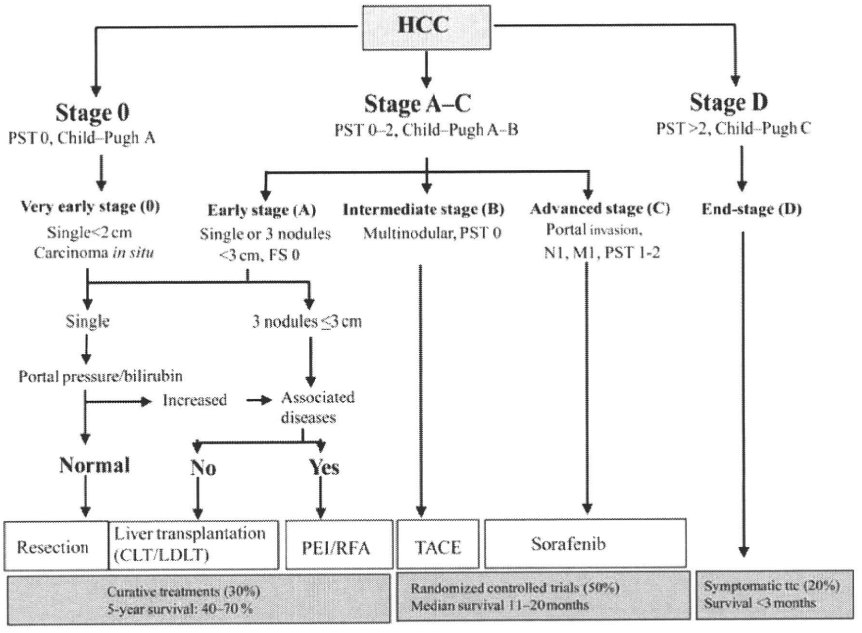

Figure 4. BCLC staging [Llovet et al. (10)]. BCLC, Barcelona Clinic of Liver Cancer; PST, performance status; CLT, cadaveric liver transplantation; LDLT, living donor liver transplantation; PEI, percutaneous ethanol injection; RFA, radiofrequency ablation; TACE, transcatheter arterial chemoembolization.

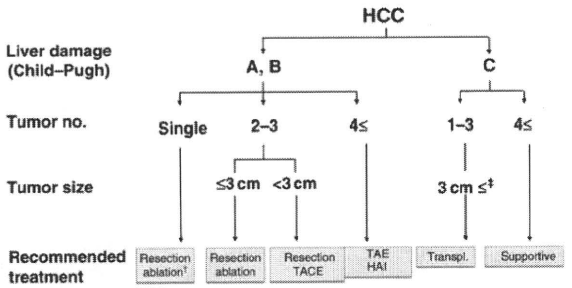

Figure 5. EBM-based algorithm for HCC treatment (J-HCC Guidelines 2009). Resection or transarterial chemoembolization (TACE) may be selected for liver damage A patients with vascular invasion. Chemotherapy may be selected for extrahepatic HCC. LT is only for ≤65 years old. †Recommended for Child B; ‡<2 cm for solitary lesion. HAI, hepatic arterial infusion.

developed in Asia (Korea), but does not exist in the Western countries. As a result, most HCC patients are diagnosed in an early stage in Japan, but at a very advanced stage in Western countries. As tumor markers, only AFP is measured in Western countries, whereas three tumor markers are measured in Japan. The risk of treatment of HCC must also be considered. The mortality of liver resection is as high as 4–5% in Western countries, but only 0.7% in Japan. Brain-dead donors for liver transplantation are very rare in Japan, but common in Western countries (22). These factors must be considered for development of treatment strategies for HCC.

The BCLC guidelines to staging and treatment of HCC are probably the most popular treatment algorithm in Western countries, but not in Asia. The Japanese guidelines were just revised in 2009, are very simple and cover a majority of early- and intermediate-stage HCC patients (Fig. 5). A Japanese consensus-based algorithm for HCC covers even very advanced-stage HCC, including patients with extrahepatic spread and vascular invasion (Fig. 6) (17,19). Sorafenib is recommended for such advanced disease with good liver function, and an ongoing trial is evaluating its use as an adjuvant therapy. The Korean guideline for management of HCC was initially published in 2003, after which they accumulated evidence, held a nationwide forum for revision of the guidelines and created a revision committee. As a result, their updated guidelines were published in 2009 (23). The algorithm for the Korean HCC treatment plan lists hepatic resection, liver transplantation, radiofrequency ablation and ethanol injection as curative treatments. There is no evidence showing which treatment is superior for cure of HCC in each patient, so the guideline recommends that the physician decide which treatment will be used. The APASL Consensus on Treatment of HCC (24) was published in 2010 and may be utilized in the Asian region.

In conclusion, several practice guidelines presenting treatment strategies for HCC in Asia have been developed. They were created based on evidence-based medicine methodology and consensus among experts in the region. They also reflect the socioeconomic status and current daily practice in the region. A number of ongoing clinical trials aim to

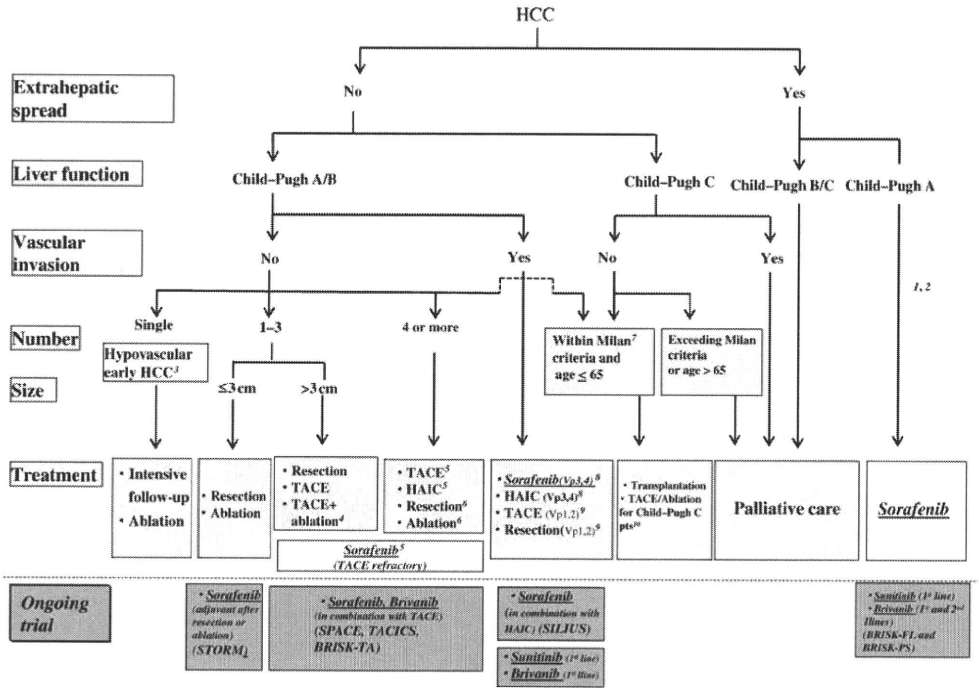

Figure 6. Consensus-based treatment algorithm for HCC proposed by Japan Society of Hepatology (JSH) 2009 revised in 2010. *1*, Treatment should be performed as if extrahepatic spread is negative, when extrahepatic spread is not regarded as a prognostic factor. *2*, Sorafenib is the first choice of treatment in this setting as a standard of care. *3*, Intensive follow-up observation is recommended for hypovascular nodules by the Japanese Evidence-Based Clinical Practice Guidelines. However, local ablation therapy is frequently performed in the following case: (i) when the nodule is diagnosed pathologically as early HCC, (ii) when the nodules show decreased uptake on gadolinium-ethoxybenzyl-diethylene triamine pentaacetic acid or (iii) when the nodules show decreased portal flow by CTAP, since these nodules are known to frequently progress to the typical advanced HCC. *4*, Even for HCC nodules exceeding 3 cm in diameter, combination therapy of TACE and ablation is frequently performed when resection is not indicated. *5*, TACE is the first choice of treatment in this setting. Hepatic arterial infusion chemotherapy (HAIC) using an implanted port is also recommended for TACE refractory patients. The regimen for this treatment is usually low-dose FP (5FU + CDDP) or intra-arterial 5FU infusion combined with systemic interferon therapy. Sorafenib is also recommended for TACE refractory patients. *6*, Resection is sometimes performed even when numbers of nodules are over 4. Furthermore, ablation is sometimes performed in combination with TACE. *7*, Milan criteria: Tumor size ≤3 cm and tumor numbers ≤3; or solitary tumor ≤5 cm. Even when liver function is good (Child–Pugh A/B), transplantation is sometimes considered for frequently recurring HCC patients. *8*, Sorafenib and HAIC are recommended for HCC patients with Vp3 (portal invasion at the first portal branch) or Vp4 (portal invasion at the main portal branch). *9*, Resection and TACE are frequently performed when portal invasion is minimum such as Vp1 (portal invasion at the third or more peripheral portal branch) or Vp2 (portal invasion at the second portal branch). *10*, Local ablation therapy or subsegmental TACE is performed even for Child–Pugh C patients when transplantation is not indicated when there is no hepatic encephalopathy, no uncontrollable ascites and a low bilirubin level (<3.0 mg/dl). However, it is regarded as an experimental treatment since there is no evidence of its survival benefit in Child–Pugh C patients. A prospective study is necessary to clarify this issue.

generate evidence for a better treatment algorithm. Guidelines should be updated every 3 or 4 years, incorporating new evidence.

Future Perspectives, Especially In Regard To Sorafenib

There was no established systemic chemotherapy for HCC. However, sorafenib has become a standard systemic treatment for advanced HCC. This section addresses the future perspectives for sorafenib and beyond sorafenib. Two randomized control studies have shown the survival benefit of sorafenib in advanced HCC patients with good liver function of Child–Pugh A. The SHARP trial (25), carried out mainly in European countries, and an Asia-Pacific trial (26) both showed that sorafenib provides a survival benefit in advanced HCC patients. Both trials yielded similar hazard ratio of 0.69 and 0.68, respectively, in favor of sorafenib over placebo. Other published reports on sorafenib for HCC include a Phase II trial conducted in Western countries (27), a Phase I Japanese study (28), a Korean study (29) and a Phase 2 Hong Kong study (30). The studies had various differences in patient background, such as involvement of HBV, HCV or others, liver function of Child–Pugh A and B, and the ECOG performance status. Those differences affected the survival outcomes in the four studies like outcomes after other treatment modalities.

Although sorafenib has become a standard systemic treatment for advanced HCC, there are still issues to be investigated with regard to this agent, including its efficacy and safety in patients with Child–Pugh B moderate liver

function, combination therapy with other treatment methods, and the need to identify predictive factors and markers for sorafenib. Various studies are currently attempting to elucidate those issues. The Phase III STORM global trial will evaluate sorafenib as an adjuvant therapy after surgery or radiofrequency ablation. A Japanese Phase II study will evaluate the efficacy and safety of sorafenib in patients with Child–Pugh A and B, with investigation of biomarkers. A global trial of combination of sorafenib with TACE is ongoing, while two Japanese Phase I studies of combination of sorafenib with hepatic arterial infusion are in progress (19). Arterial infusion chemotherapy is a very common and useful treatment in Japan (31), and one of these studies combines sorafenib with cisplatin, whereas the other combines sorafenib with 5-FU and cisplatin. It is anticipated that these trials will lead to Phase III studies.

Other Molecularly Targeted Agents

Sorafenib is the first systemic therapy approved for advanced-stage HCC, and widely used. Sorafenib prolongs time to progression and overall survival in patients with advanced HCC; however, predictive factors are unknown at the present. Good responders show a good response, but how can they be identified in advance? Researchers are currently looking for biomarkers that will identify good responders and lead to modification of the treatment algorithm. Also, a 'good response' has limitations. How can a 'complete response' be attained? Combination therapy and some adjuvant treatment, after palliative or curative treatment, will be needed. There are also many poor responders. How can a poor response be overcome? Second-line agents are necessary, as is combination therapy. Various targeted agents in addition to sorafenib are under development for HCC. They include brivanib, bevacizumab, cediranib, erlotinib, gefitinib, lapatinib, RAD001, sunitinib, thalidomide and TSU-68. These agents have similar yet slightly different mechanisms of action. The results of various clinical studies of these molecular targeted therapy agents were summarized in *Hepatology* (32). The results look good, and many Phase II and Phase III trials are ongoing. The trials can be categorized into three types: first-line or combination studies, second-line studies and adjuvant studies.

First-line or combination studies are being carried out as Phase III trials of sunitinib vs. sorafenib (terminated in 2010 because of severe adverse effect); brivanib vs. sorafenib; lilifanib vs. sorafenib; erlotinib plus sorafenib vs. sorafenib; and erlotinib plus bevacizumab vs. sorafenib. The results of these trials should be available in 2 or 3 years. There are also many first-line Phase II studies. There are two second-line Phase II studies, of brivanib vs. the placebo and RAD001 vs. the placebo, for patients who failed to respond to sorafenib. There are three Phase III adjuvant studies. The STORM study investigates sorafenib vs. placebo after resection or ablation. A second adjuvant study investigated sorafenib vs. placebo after TACE; this is already finished and the results were presented at ASCO-GI in 2010 (33). The third Phase III adjuvant study compares brivanib vs. placebo after TACE. In a first-line Phase II study of brivanib, 46% of the patients showed stable disease, and in the second-line Phase II study, 43% showed stable disease (34,35). These results were promising, and at least three trials are now ongoing for brivanib.

In conclusion, molecularly targeted therapy (MTT) has emerged as a promising approach for advanced HCC. Sorafenib impacted on MTT agents in HCC, but the benefits of sorafenib were reported to be relatively modest. Several MTT agents for first- and second-line treatments are undergoing clinical trials. The advantages of MTT agents are being explored in combination treatments as well as adjuvant therapy with resection, local ablation, radiation, hepatic arterial infusion chemotherapy and TACE.

CONCLUSION

HCC is a highly prevalent disease in many Asian countries and incidence of HCC varies enormously across Asia, but tends to follow incidences of hepatitis B infection and liver cirrhosis. Incidence and etiology of HCC in Japan is different from the rest of Asia, but similar to Western countries since hepatitis C infection is the main etiological factor. Screening program improves detection of early HCC and has some positive impact on survival, but the majority of HCC patients in Asia still present with advanced HCC. Long-term outcomes following treatment of early, intermediate or advanced disease are still unsatisfactory because of lack of effective adjuvant or systemic therapies. Sorafenib is the first systemic therapy to demonstrate prolonged survival vs. placebo in patients with advanced HCC. New molecular targeting therapies hold great promise. Many new agents are under investigation and their results are awaited.

Conflict of interest statement

The author, Joong-Won Park, participated in phase II and phase III clinical studies sponsored by Bristol-Myers Squibb, Pfizer Inc., Bayer Healthcare and Bukwang Pharmaceutical Co. He is also a member of BMS Brivanib study steering committee, Pfizer Sunitinib advisory committee, and Bukwang Pharmacetutical Co. advisory committee.

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Hepatology Research

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Special Report

Response Evaluation Criteria in Cancer of the Liver (RECICL) proposed by the Liver Cancer Study Group of Japan (2009 Revised Version)

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The World Health Organization (WHO) criteria and Response Evaluation Criteria in Solid Tumors (RECIST) are inappropriate to assess the direct effects of treatment on the hepatocellular carcinoma (HCC) by locoreginal therapies such as radiofrequency ablation (RFA) and transcatheter arterial chemoembolization (TACE). Therefore, establishment of response evaluation criteria solely devoted for HCC is needed urgently in the clinical practice as well as in the clinical trials of HCC treatment, such as molecular targeted therapies, which cause necrosis of the tumor. Response Evaluation Criteria in Cancer of the Liver (RECICL) was revised in 2009 by Liver Cancer Study Group of Japan based on the 2004 version of RECICL, which was commonly used in Japan. Major revised points of the RECICL 2009 is to provide TE4a (Complete response with enough ablative margin) and TE4b (complete response without enough ablative margin) for local ablation therapy. Second revised point is that setting the timing at which the overall treatment effects are assessed. Third point is that emergence of new lesion in the liver is regarded as progressive disease, different from 2004 version. Finally, 3 tumor markers including alpha-fetoprotein (AFP) and AFP-L3 and des-gamma-carboxy protein (DCP) were also added for the overall treatment response. We hope this new treatment response criteria, RECICL, proposed by Liver Cancer Study Group of Japan will benefit the HCC treatment response evaluation in the setting of the daily clinical practice and clinical trials as well not only in Japan, but also internationally.

Key words: Response Evaluation Criteria, hepatocellular carcinoma, WHO criteria, RECIST, Liver Cancer, Liver Cancer Study Group of Japan

INTRODUCTION

THE WORLD HEALTH Organization (WHO) criteria[1] and Response Evaluation Criteria in Solid Tumors (RECIST),[2] which are response evaluation criteria for solid tumors after chemotherapy, are commonly used for the evaluation of liver cancer treatment in Western countries. However, it is well known and obvious that both the WHO criteria and RECIST are inappropriate to assess the direct effects of treatment on the liver cancer lesions by ablative treatment and transcatheter arterial chemoembolization (TACE). Although effective treatments may exhibit a necrotizing effect on hepatocellular carcinoma (HCC) with deprivation of its blood flow, the WHO criteria and RECIST do not consider such necrotizing effects to be "effective"; instead, both criteria use only tumor size reduction as measures of effect. It has been shown that the tumor size reduction rate according to the WHO criteria and RECIST following TACE with lipiodol (Lip-TACE) is not correlated with the pathological necrosis rate.[3] When lipiodol is accumulated densely within the tumor, the early arterial staining is masked, and tumor size is not increased, the tumor is completely necrotized as confirmed by histology.[3] Even though the tumor is completely necrotized, it takes a long time to result in reduction of size. The nodule with complete necrosis after Lip-TACE can be seen for several years as a lipiodol more densely

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accumulated nodules than 2 weeks after the intervention. In case of radiofrequency ablation (RFA), the phenomenon is the same with Lip-TACE, though lipiodol accumulation is not seen.

Moreover, the WHO criteria are originally based on bi-dimensional measurement, which was changed to a uni-dimensional measurement in RECIST. Even if tumor necrosis is considered in the response evaluation criteria, uni-dimensional measurement is inappropriate for assessment of the direct treatment effect. Therefore, establishment of response evaluation criteria solely devoted for HCC is needed urgently in the clinical practice as well as in the clinical trials of HCC. The current report describes the newly established response evaluation criteria for HCC by revising the previously existing criteria established by the Liver Cancer Study Group of Japan.

CONCEPT OF THE RESPONSE EVALUATION CRITERIA IN CANCER OF THE LIVER (RECICL)

THE FIRST EDITION of Criteria for the Evaluation of Direct Treatment Effects in Hepatocellular Carcinoma was published in 1994.[4] The revised edition was published in 2004,[5] and is commonly used in Japan, but several problems remained in the revised criteria. Thus, a third revision was carried out before publishing the English edition of the General Rules for the Clinical and Pathological Study of Primary Liver Cancer edited by the Liver Cancer Study Group of Japan (third edition).

Current response evaluation criteria focuses on the following points: (i) development of simple criteria that are sufficiently applicable in routine clinical practice centering on local treatment (ethanol injection therapy, microwave coagulation therapy, RFA) and transcatheter arterial therapy, radiotherapy and systemic chemotherapy can also be included; (ii) assessment of direct treatment effects on intrahepatic target lesions and overall effects are described separately; and (iii) the criteria follow the fifth edition of the General Rules for the Clinical and Pathological Study of Primary Liver Cancer edited by the Liver Cancer Study Group of Japan.[6]

Considering the biological characteristics of HCC, high frequencies of "intrahepatic metastatic recurrence" and "multicentric carcinogenesis", it may not necessarily be appropriate for liver cancer to be indiscriminately diagnosed as "progressive disease" based on the appearance of "a new lesion" alone because such "a new lesion" has not been treated by ablation or TACE when the recurrent nodule exists outside of the treated area. Thus, evaluation of the direct effects of treatment on target lesions should focus on the direct therapeutic effect on the target lesions, and the overall evaluation should be investigated with close association with the prognosis.

Although the chemotherapeutic agent permeates through the liver in chemotherapy, the therapeutic effect of TACE and ablative treatments is limited only to the target lesion or the area fed by embolized artery with the tumor. Treatment is not done for the new lesions appearing outside the area where the ablation or TACE are performed. After the same treatment is carried out on the targeted new lesion, a similar treatment effect may be expected on the formerly treated lesion. Accordingly, when "a new lesion" appears in a region outside the treatment area, the new lesion (intrahepatic metastasis or multicentric carcinogenesis) may not directly indicate the prognosis. The basic concept of the 2004 version of the Japanese response evaluation criteria[5] was to exclude the new lesions from the evaluation of treatment effect on the formerly treated lesions. In other words, the emergence of a new lesion is regarded as out of the evaluation of the treatment effect for the former lesions, which is the most marked difference from the WHO criteria or RECIST.

Therefore, these criteria established by the Liver Cancer Study Group of Japan are exclusively specified for the Evaluation of Therapeutic Effects on Liver Cancer, and differ from other evaluation criteria for solid tumor regarding the various points described above.

The 2004 version of the Criteria for the Evaluation of Direct Treatment Effects in Hepatocellular Carcinoma are superior to the WHO criteria or RECIST because it considers the biological characteristics of HCC as follows: (i) tumor necrosis is regarded as a direct effect of treatment on the target lesion as well as tumor size reduction even though it is minimal; (ii) tumors are measured in two dimensions; (iii) the dense accumulation of lipiodol is regarded as necrosis;[3] and (iv) the emergence of a new lesion is not regarded as a "progressive disease" in evaluation of the treated nodule.

However, several problems remained in the 2004 version: (i) assessment of direct treatment effects was performed at 3 months, while the overall evaluation was performed at 6 months; and (ii) even though the direct effects on target nodules varies among treatment methods, the timing of assessment was not described. To overcome these limitations, some minor changes were made in this 2009 revised version. These criteria may be suitable mainly for local treatment and transcatheter arterial therapy, but are also applicable for radiotherapy and chemotherapy in combination with