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Eastern asian expert panel opinion: designing clinical trials of molecular targeted therapy for hepatocellular carcinoma

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Abstract

The largest burden of hepatocellular carcinoma (HCC) lies in Asia, secondary to hepatitis B virus (HBV) infection. Improved survival with sorafenib has fostered new research but many challenges remain in designing clinical trials. The disease, its management, and populations affected by it are heterogeneous worldwide and within Asia. An expert conference of Eastern Asian oncologists and hepatologists was convened to foster consensus in clinical trial design. The panel identified key areas that need to be addressed to facilitate clinical trials in Asia. Stratification by viral etiology is desirable within Asia and by region in global trials. Antiviral therapy should also be considered as a stratification factor and incorporated into HCC management in trials. The panel agreed that histological diagnosis is not required for trial entry and that Barcelona-Clinic Liver Cancer (BCLC) staging is acceptable for trials as long as portal hypertension can be better defined with standardized methodology. Consensus in treatment must be sought to allow multi-national 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.

Background

Over 600,000 cases of hepatocellular carcinoma (HCC) are diagnosed annually worldwide and the mortality-to-incidence rate ratio is second only to pancreatic cancer [1,2]. The incidence of HCC varies widely by geographical region. Asia carries the largest burden with 55% of all cases occurring in China [1]. Age-standardized incidence rates per 100,000 persons for men are 45.0 in Korea (1999-2001) [3], 37.9 in China (2002) [1], and 23.1 in Japan (2002) [1]. Corresponding rates for women are 12.0, 14.2, and 7.6. Globally, the predominant cause of HCC is viral infection with hepatitis B virus (HBV) or hepatitis C virus (HCV) [4].

Hepatocellular carcinoma is refractory to cytotoxic chemotherapy [5] and the failure of cytotoxic regimens has led to a bleak outlook. However, the recent development of molecular targeted therapies is changing the landscape and offering hope. Researchers have found new optimism for initiating clinical trials after sorafenib showed efficacy in advanced disease [6]. Currently, trials are planned or ongoing in all stages of HCC; however, many issues remain [7]. Most salient is the variability in management practices both between Asia and the West and within Asia. Key differences are apparent in the etiology, diagnosis, staging, and treatment of HCC among countries. These differences complicate the conduct of international clinical trials that will foster approval and availability of new therapeutic entities.

In order to forge a better understanding of how HCC clinical practices in the Eastern Asian region compare to current global clinical trial requirements, an expert conference was held. Participants of the panel (the authors) are oncologists and hepatologists representing China, Hong Kong, Japan, Korea, and Taiwan who have an expertise in treating HCC. Each panelist offered insight, reviewed herein, about how HCC is managed across Eastern Asia and how management practices and clinical trial requirements can be unified to advance new treatments, particularly targeted agents, for HCC.

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Etiology

Viral etiology varies by region with HBV predominating in non-Japanese Asians and accounting for approximately 70-80% of cases. In Japan, most of Europe, and in the United States, HCV is more common than HBV among viral etiologies [3,8-11]. However, in the United States, 67% of HCC cases are seronegative for both viruses [10].

The increased incidence of HBV-HCC in Eastern Asia compared to Japan and Western nations leads to different management issues and prognosis that affect clinical trial design. Hepatitis C virus-HCC is more likely to develop in the background of cirrhosis than HBV-HCC [12]. Therefore, the underlying liver disease may differ in HCC patients by region, a factor that weighs heavily in treatment decisions.

Survival differences have been observed according to geographic region and viral etiology, though the reasons for these observations remain unclear. In clinical trials of systemic therapy for advanced HCC, trials done in Asian countries reported inferior survival compared with trials done in non-Asian countries [13]. Possible reasons include variation in genetic and/or epigenetic aberrations between different viral etiologies and the propensity for Asian physicians to use local therapy more aggressively and in later stages, resulting in enrollment of a more advanced patient population to trials of systemic therapy. Survival between HBV-HCC and HCV-HCC appears similar in early-stage, resectable HCC, if staging and other clinical parameters are considered [14]. However, two retrospective studies have found poorer survival in HBV-HCC among patients with unresectable, advanced disease [15,16]. Attributing the survival difference to viral etiology alone is difficult but demonstrates the need for considering the potential differences in clinical trials.

Additionally, in contrast to HCV, HBV reactivates with immune suppression, complicating treatment with immunosuppressive regimens [17,18]. The predominance of HBV-HCC in Asia is associated with increased use of antiviral agents to prevent viral reactivation during HCC treatment. Antiviral therapy with lamivudine has reduced the incidences of HBV reactivation and hepatitis, reduced the severity of hepatitis episodes, led to fewer disruptions in chemotherapy, and reduced mortality related to HBV reactivation in clinical trials of patients with HCC or other cancers who are receiving chemotherapy [19-22]. Anti-viral therapy following curative resection, radiofrequency ablation, or other local, non-chemotherapeutic treatments for HBV-HCC, has been shown to increase residual liver volume and/or function and may prolong survival [23-25]. Furthermore, interferon, given after curative therapy, may increase recurrence-free survival rates [26,27]. These benefits indicate that use of antiviral therapy is an important confounding factor in HCC clinical trials.

A separate international expert panel has recommended stratification according to region for global trials but discouraged further stratification according to etiology [7]. However, in light of the confounding factors described herein, the current panel agreed that trials within Eastern Asia should include stratification by HBV or HCV etiology. Further, antiviral therapy should be both considered as a stratification factor and incorporated into the overall management of patients in international HCC clinical trials.

Screening

Stage at diagnosis differs both within Eastern Asia and between Eastern Asia and Western nations. Using TNM-based staging systems, China and Japan have relatively high proportion of patients diagnosed at Stage I or II compared to Hong Kong and Korea. In the United States, a higher percentage of patients are diagnosed with distant metastasis compared to Asian countries [28,29].

The differences may reflect variable screening practices. The proportion of patients who receive screening in the United States appears to vary according to the individual's healthcare. Only 25% of family practice physicians report routinely screening appropriate patients for HCC compared to 84% of physicians who are members of the Association for the Study of Liver Diseases (AASLD) [30,31]. In a study of 157 patients diagnosed with HCC at three US Veteran Affairs (VA) medical centers, 39% of patients with a known risk factor for HCC received screening [32]. With the exception of Hong Kong, where screening has been conducted in the context of study, screening high-risk populations is the standard of care in Asia. With diagnosis occurring at earlier stages, Eastern Asian countries are better able to utilize curative therapies, significantly affecting treatment paradigms and clinical trial populations.

Diagnosis

Both pathological and clinical diagnostic procedures vary according to country. The majority of pathological diagnoses are made by core biopsy in Korea, China, and Hong Kong, with fine needle aspiration (FNA) used infrequently. In contrast, 30% or fewer of pathological diagnoses are made by core biopsy in Japan, and Taiwan. Taiwan employs FNA in approximately 10% of cases but utilizes surgery for pathologic diagnosis in approximately 38% of cases. Protocols designating biopsy-proven HCC as an enrollment requirement would conflict with current practices in Japan and

Taiwan. The panel agreed that for trials conducted in the advanced/metastatic setting, histological confirmation of HCC is not necessary. Further, pre-treatment biopsy may result in tumor seeding which would complicate neoadjuvant trials.

Staging

A variety of staging systems are employed worldwide [33-36]. Several of these systems are based on the tumor-node-metastasis (TNM) paradigm or incorporate TNM groupings as a variable [33-35,37]. Other systems, such as the Barcelona-Clinic Liver Cancer (BCLC) staging system, incorporate measures of liver function and underlying disease. Complicating international clinical trial design is the variable use of these systems both within Asia and globally. Each region of Asia represented by the panel currently utilizes a different system. In China, the revised Staging Criteria of Primary Liver Cancer is used. This system was developed by the Chinese Society of Liver Cancer. The system uses criteria based on size, number and location of tumors, lymph node spread, extrahepatic metastasis, portal vein thrombosis, and liver function (Child-Pugh scores) [38]. In Japan, both the staging system and treatment algorithm apply liver function as the first category of evaluation rather than tumor size. Hong Kong does not have a unified staging system. Although BCLC is considered a valuable tool for a treatment algorithm in Hong Kong, the system is considered less useful for prognostication. The Chinese University Prognostic Index (CUPI) [37] has been found useful for prognostication at one center due to the more advanced population [39]. Korea employs a modified International Union Against Cancer (UICC) system and Taiwan uses BCLC.

The TNM-based staging systems have an important drawback: these systems do not account for underlying liver disease [40]. In HCC, the presence of liver disease is a common and important prognostic factor that is integral in determining treatment [40,41]. For these reasons, TNM-based systems have limited value in the comprehensive management of HCC. The Child-Pugh (CP) score is a widely-accepted system to evaluate liver function. Despite empirical selection of variables, this tool represents a simple, bedside tool that predicts mortality in cirrhotic patients with a degree of accuracy not substantially less than the more statistically sound model for end-stage liver disease (MELD) [42]. The BCLC staging system incorporates measures of liver function (portal hypertension, bilirubin, and CP scores at higher stages) and has emerged as the standard for clinical trial design [6,43]. However, this system is not generally used in Eastern Asia with the exception of Taiwan. China, specifically, has failed to adopt this system due to the omission of portal vein thrombosis as a factor, which has been shown to independently predict mortality [41]. Additionally, BCLC includes portal venous hypertension which requires an invasive procedure to measure that is not standard practice in Asia. However, the panel indicated that, if required for clinical trials seeking United States Food and Drug Administration approval, BCLC would be acceptable if the protocols also incorporated portal vein hypertension - measured and defined with non-invasive standardized methodology - and further evaluation of liver function.

Treatment Practices

Treatment practices vary somewhat throughout Eastern Asia and no unified treatment algorithm exists. Japan, China, Hong Kong, Korea, and Taiwan each use separate treatment algorithms, all of which differ from the BCLC treatment algorithm [7,44,45]. Such variations in treatment practices cause challenges in defining treatment protocols for international clinical trials.

Potentially Curative Treatment Options

Resection is utilized more often in Eastern Asia versus Western nations, which may reflect diagnosis at earlier stages and less cirrhosis in Asia [46]. In some centres in China, Taiwan, and Japan, between 34-40% of patients undergo resection, while the proportion is approximately 10-20% in others. In parts of East Asia [47,48], patients with recurrence undergo re-resection. Local ablation is performed in approximately 15% of patients in China, Hong Kong, and Taiwan and approximately 30% of patients in Japan. Liver transplant is the only treatment modality that offers a cure both for HCC and the underlying liver disease, but its application is limited both in Eastern Asia and the West.

Nonsurgical Local Treatments

Although TACE and transarterial embolization (TAE) are standards of care, significant heterogeneity exists among countries and institutions with respect to the types of embolizing materials and techniques utilized. Embolizing materials used typically include a mixture of iodized oil (lipiodol) and an anthracycline (epirubicin or doxorubicin) or cisplatin followed by gelatin sponge particles (Japan, Taiwan, Hong Kong). Nonetheless, other agents are used, particularly in China where 5-fluorouracil (5-FU) and mitomycin-C may be employed. Japan uses HAI with cisplatin alone, 5-FU and cisplatin (FP), or 5-FU and interferon. Currently, no consensus has been reached regarding the interval between procedures or endpoints. Other local therapies are variably utilized and include intratumoral injection, laser therapy, cryotherapy, microwave coagulation therapy, hepatic arterial infusion (HAI), intraarterial radiotherapy with yttrium-90 and conformal external radiotherapy.

Systemic Therapy With Sorafenib

Targeted therapy has been employed only for advanced disease [7,44,45]. A multitude of targeted therapies have been investigated for use in HCC; however, only sorafenib is approved for use in Asian and Western countries. These approvals were based on improved survival in the SHARP trial and the parallel Asian phase III trial [6,49]. Although sorafenib has been approved in Asia, the agent is not widely used largely due to cost [50]. Cost-sharing programs have been started in some countries to manage this issue. Such programs have been successful in that they expand usage; however, lack of long-term coverage renders the practice unsustainable.

In addition to cost, emerging evidence suggests that sorafenib may be less well tolerated by Asian patients compared to Western patients. Hand-foot skin reaction (HFSR) appears to be more frequent in Asians, particularly lower-grade reactions. Hand-foot skin reaction (all grades) occurred in 21% of patients in the US SHARP study; the rate was 45% in the Asian phase III sorafenib trial [6,46]. Grade 3 event rates were 8% in SHARP compared with 11% in the Asian trial. Korean and Japanese studies have reported rates of 56%-57% (all grades) [51,52]. In the Korean population, HFSR was the most common reason for treatment interruption. Indeed, dose reductions for HFSR were more frequent in the Asian phase III trial (11%) than in SHARP (5%) [6,46] The panelists noted that in practice, dose reduction or use of a reduced starting dose of sorafenib is common in Asia. Lower dosing is being investigated in small Asian trials. In a Japanese phase I study, sorafenib 200 mg twice daily led to a 38% incidence of HFSR [52].

Though HFSR is most common, some differences between Westerners and Asians may be present with respect to the drug's effect on the liver. The Korean population experienced a 4% rate of grade 3 or 4 hyperbilirubinemia associated with marked ALT elevations [51]. Individual differences in drug metabolism may be present. Increased bilirubin was reported separately in a patient with UGT1A1 polymorphism; the authors proposed that sorafenib inhibition of UGT1A1 in this patient may have contributed to the hyperbilirubinemia [53].

Other Systemic Therapies

Systemic cytotoxic chemotherapy has failed to prolong survival in advanced HCC [5]. Small studies of cytotoxic chemotherapy plus biochemical modulation may achieve tumor control in patients with good performance status and liver function reserves and no hypersplenism [54-56]. In Korea, chemotherapy is used as part of concurrent chemoradiotherapy protocols at some centers. In Hong Kong, systemic cytotoxic chemotherapy is considered when a patient fails or is ineligible for anti-VEGF therapy. Chemotherapy was not recommended in Japanese treatment guidelines.

In China, use of traditional Chinese medicine (TCM) is common and unique compared to Western nations. These medicines can be categorized according to two main purposes: 1) promoting liver health and delaying cirrhosis and 2) countering the side effects of chemotherapy. Panelists indicated that the first type of TCM must be allowed in clinical trials; excluding these treatments would severely restrict enrollment. However, the second type of TCM could potentially be excluded if required.

Investigational Targeted Therapy

Targeted agents are at the forefront of HCC clinical research. Promoting clinical trial participation in Asia is important to foster development of new drugs appropriate for this population. Recently completed phase II trials of new treatments are described below and ongoing phase II and III trials of targeted therapies in HCC are reviewed in Table 1.

The combination of sorafenib and chemotherapy has been investigated in phase II trials. A randomized phase II trial found superior outcomes with the combination of sorafenib plus doxorubicin compared to placebo plus doxorubicin [57]. Median progression-free and overall survival times were 6.9 months and 13.8 months in the sorafenib arm compared to 2.8 months and 6.5 months in the placebo arm, respectively. The combination was associated with a 21% incidence of left ventricular dysfunction, though mostly of grade 1 or 2 severity. The SECOX trial evaluated sorafenib plus capecitabine and oxaliplatin [58]. Response was observed in 14% with stable disease in 61%. Median time to progression (TTP) was 7.1 months and median survival was 10.2 months. Toxicities included HFSR, diarrhea, and neutropenia. When sorafenib was paired with metronomic tegafur/uracil (UFT; 125 mg/m^2 twice daily), the combination led to overall response and stable disease rates of 6% and 51%, respectively [59]. Median progression-free survival was 3.7 months and median survival was 7.4 months. The most common grade 3 or 4 adverse events were fatigue (15%), HFSR (9%), and bleeding (8%).

Sunitinib has been evaluated at various doses and schedules. The SAKK 77/06 trial utilized sunitinib 37.5 mg/day continuously in 45 Swiss patients [60]. Median progression-free survival (PFS) was 2.8 months and median survival was 9.3 months. The most frequent grade 3/4 toxicities were fatigue in 24% and thrombocytopenia in 18%. Two US studies evaluated sunitinib 37.5 mg daily for 4 weeks every 6 weeks [61,62]. Response rates were 3%-6% and stable disease rates were 35%-47%. One study reported PFS and survival; median PFS was 4.0 months and median survival was 9.9 months.

Table 1 Ongoing Phase II/III Trials in Advanced HCC

Study Name Clinicaltrials.gov Identifier	Phase	Intervention	Setting	Location
Advanced Disease				
Targeted Agents With Cytotoxic Therapy				
NCT00832637	II	Erlotinib + gemcitabine + oxaliplatin	Prior systemic therapy allowed	US
HOG GI06-101 NCT00532441	II	Erlotinib + docetaxel	Third-line or less	US
NCT00384800	II	Thalidomide + tegafur/uracil	No prior chemotherapy	Taiwan
NCT00519688	II	Thalidomide + tegafur/uracil	No prior chemotherapy	Taiwan
NCT00862082	I/II	Sorafenib + PR104 Sorafenib	First-line	US, Asia
Anti-VEGF Agents as Monotherapy				
BRISK NCT00858871	III	Brivanib + placebo Sorafenib + placebo	First-line	International
NCT00825955	III	Brivanib + placebo BSC + placebo	Sorafenib failure	International
NCT00699374	III	Sunitinib Sorafenib	First-line	International
NCT00247676	II	Sunitinib	First-line	France, Korea, Taiwan
Other Targeted Agents as Monotherapy				
NCT00225290	III	Thalidomide Placebo	Any line Poor liver reserve	Taiwan
NCT00033462	II	Erlotinib	First- or second-line	US
NCT00077441	II	Bortezomib	First-line	US, Australia, Korea, HK
NCT00390195	I/II	Everolimus (weekly or daily)	Any line	Taiwan
NCT00920192	I/II	Foretinib	Any line	Taiwan, HK
Combination Targeted Therapy				
SEARCH NCT00901901	III	Sorafenib + erlotinib Sorafenib	First-line	International
NCT00881751	II	Erlotinib + bevacizumab Sorafenib	First-line	US
NCT00365391	II	Erlotinib + bevacizumab	First- or second-line	US
TCOGP-1209 NCT00971126	I/II	Thalidomide + sorafenib	First-line	Taiwan
NCT00828594	I/II	Everolimus + sorafenib Placebo + sorafenib	First-line	International
NCT00791544	I/II	AVE1642* +/- sorafenib or erlotinib	Any line	France
Earlier-stage Disease				
STORM NCT00692770	III	Sorafenib Placebo	Adjuvant (post-resection or -local ablation)	International
BRISK-TA NCT00908752	III	Brivanib + TACE Placebo + TACE	BCLC B	International
NCT00921531	III	Thalidomide + TACE TACE	BCLC A-B	China
NCT00728078	II/III	Thalidomide, low dose	Adjuvant (post-RFA)	China
START NCT00990860	II	Sorafenib + TACE	BCLC B	Taiwan
NCT00855218	II	Sorafenib + TACE Placebo + TACE	BCLC B	International
COTSUN NCT00919009	II	Sorafenib + TACE	TNM III/IVa	Korea
NCT00576199	II	Bevacizumab	Pre- and Post-TACE	HK

Table 1 Ongoing Phase II/III Trials in Advanced HCC *(Continued)*

JLOG 0901 NCT00933816	I/II	Sorafenib + fluorouracil/platinum HAI	Not suitable for resection, ablation, TACE	Japan
NCT00293436	I/II	Erlotinib + celecoxib	Adjuvant (post-resection, -TACE, or -RFA), high-risk	US

BSC, best supportive care; ECOG, Eastern Cooperative Oncology Group; HAI, hepatic arterial infusion; HK, Hong Kong; HOG, Hoosier Oncology Group; JLOG, Japan Liver Oncology Group; RFA, radiofrequency ablation; TACE, transarterial chemoembolization; US, United States; VEGF, vascular endothelial growth factor
*Anti-insulin-like growth factor receptor-1 monoclonal antibody

The most common grade 3/4 toxicities were fatigue and elevated liver function tests. A study in Europe and Asia that evaluated high-dose sunitinib (50 mg daily for 4 weeks every 6 weeks) found similar response and stable disease rates but higher toxicity with four grade 5 events [63].

Other multiple receptor tyrosine kinase inhibitors that target VEGF under investigation include brivanib, linifanib (formerly ABT-869), vandetanib, and pazopanib. Brivanib inhibits VEGF and fibroblast growth factor; a phase II trial showed median survival of 10 months in treatment-naive patients [64] and a 58% stable disease rate in patients who failed one prior antiangiogenic therapy [65]. The most frequent grade 3/4 toxicities were hyponatremia (41%), fatigue (16%), and AST elevation (19%) [64]. Linifanib inhibits VEGF and PDGF receptor tyrosine kinases. A phase II study (n = 44; 84% treatment-naïve) showed a response rate of 7%, median PFS of 3.7 months and median survival of 9.3 months [66]. Toxicities are consistent with anti-VEGF agents. A phase II, placebo-controlled study of vandetanib, which targets VEGFR, EGFR, and RET signaling, showed activity in HCC but failed to meet its primary endpoint of tumor stabilization in a Taiwanese trial [67]. A phase I dose-ranging study of pazopanib, which inhibits VEGF, PDGF, and c-kit, showed evidence of activity [68].

Phase II trials of erlotinib plus bevacizumab are promising. In 16 previously untreated patients, the combination led to a median TTP of 2.3 months and median survival of 13.7 months [69]. In 40 patients, 73% of whom were previously untreated, the response rate was 25%, median PFS was 9.0 months, and median survival was 15.7 months [70]. In 58 patients, 76% of whom were previously untreated, median PFS times were 8.8 months in patients with no prior therapy, 7.9 months in patients previously treated with sorafenib, and 6.6 months in those previously treated with therapy other than sorafenib [71]. Corresponding median survival times were 15.6 months, 13.3 months, and 14.4 months. In all studies, adverse events were consistent with the individual drug profiles.

Asian Panel Opinions on Clinical Trial Design

In 2008, the American Association for the Study of Liver Diseases (AASLD) published a framework for clinical trial design in HCC [7]. During the current expert panel meeting, participants provided their views about clinical trial design from an Asian perspective. These views are outlined in Table 2.

The Asian panel also provided additional insights into clinical trial issues specific to disease stage. The panel noted a great need for trials in resectable disease. The panel felt that testing compounds in the adjuvant setting before establishing efficacy in the metastatic setting is possible, citing positive phase II adjuvant results with muparfostat (formerly PI-88) [72] and noting the need for effective therapies in this setting. The panel also expressed interest in chemoprevention with sorafenib and other agents after resection or local ablation. In unresectable disease, especially where locoregional therapy is indicated, placebo-controlled trials remain feasible, though the panel acknowledged opportunities are limited. In this setting, it may be beneficial to limit enrollment to patients who experience a maximal response after TACE based on modified EASL criteria [73]. Such a requirement would facilitate identification of subsequent disease progression across patients. However, additional research is necessary to identify the best clinical endpoints in this setting. Because it remains difficult to differentiate recurrent disease from a second primary cancer, time to development of a new lesion may be an appropriate outcome in this setting. Finally, in the advanced/metastatic setting, the panel felt that developing new agents in the second-line setting is warranted.

Summary

Hepatocellular carcinoma is a disease of variable incidence and etiology that is managed differently worldwide. This expert panel has identified key areas that need to be addressed to facilitate clinical trials in Asia. Stratification by viral etiology is desirable within Asia and by region in global trials. Antiviral therapy should also be considered as a stratification factor and incorporated into HCC management in trials. The panel agreed with AASLD that histological diagnosis is not required for trial entry. Staging and treatment plans vary significantly. The panel felt BCLC staging is acceptable for trials as long as portal vein hypertension can be measured and defined with non-invasive standardized

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
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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.

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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

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

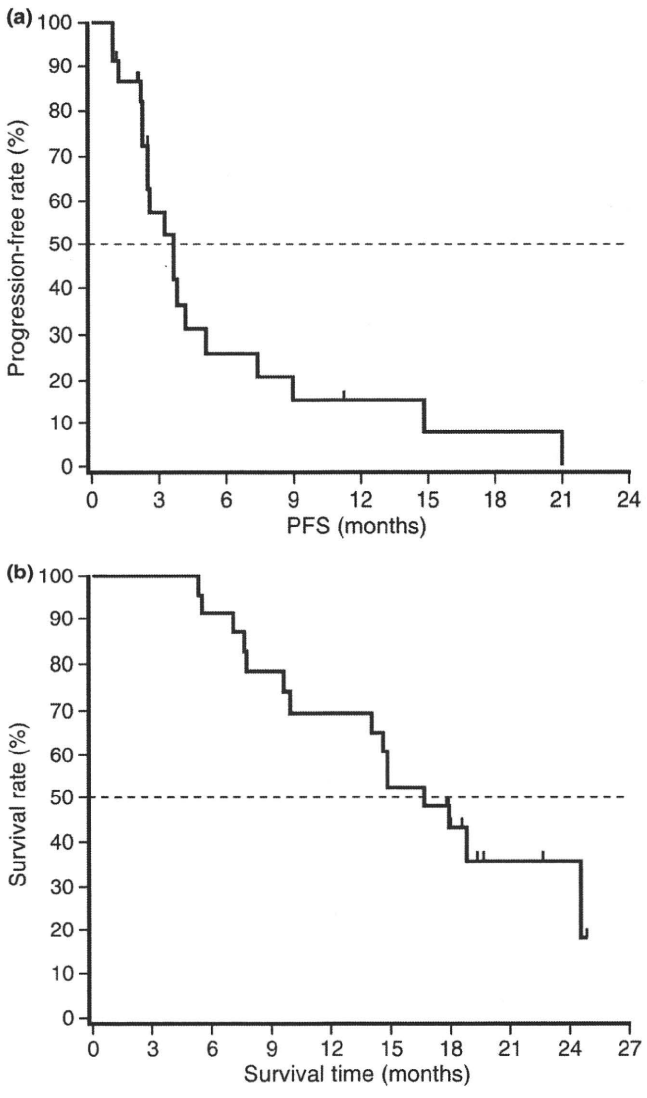

Fig. 1. Progression-free survival (PFS) (a) and overall survival (b) in patients who received dose level 2 of S-1 (n = 23). The median progression-free survival and overall survival were 3.7 and 16.6 months, respectively.

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.

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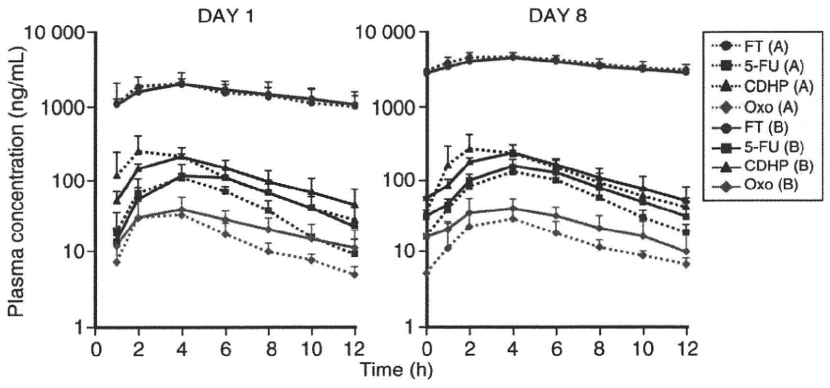

Fig. 2. Plasma-concentration–time profiles of tegafur (FT), 5-fluorouracil (5-FU), 5-chloro-2,4-dihydroxypyridine (CDHP) and oteracil potassium (Oxo) on day 1 and day 8 were similar in patients with Child-Pugh class A (n = 3) and those with Child-Pugh class B (n = 3).

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

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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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 2^{nd}-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.