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Development of systemic therapy for hepatocellular carcinoma at 2013: Updates and insights

Stephen L Chan, Winnie Yeo

Stephen L Chan, Winnie Yeo, Department of Clinical Oncology, The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong, China

Stephen L Chan, Winnie Yeo, State Key Laboratory in Oncology in South China, Hong Kong, China

Author contributions: Chan SL and Yeo W wrote the paper.

Correspondence to: Winnie Yeo, MD, FRCP, Department of Clinical Oncology, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong, China. winnieyeo@cuhk.edu.hk

Telephone: +86-852-26322118 Fax: +86-852-26487097

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combinational approaches. Future directions for testing innovative systemic agents for HCC will also be discussed.

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Core tip: This review article aims to provide an update and vision on the development of novel targeted agents for liver cancers. Recently released phase III clinical trial results as well as important future focus will be discussed.

Abstract

A growing number of multi-targeted tyrosine kinase inhibitor (TKI) has undergone testing for hepatocellular carcinoma (HCC). Unfortunately, this enthusiasm has recently been discouraged by a number of negative phase III studies on several anti-angiogenic TKIs in HCC. Several postulations have been made to account for this phenomenon, namely the plateau effects of anti-angiogenesis approach, the heterogeneity of HCC in terms of background hepatitis/cirrhosis and tumor biology, as well as the way how clinical trials are designed. Regardless of the underlying reasons, these results suggested that alternative strategies are necessary to further develop systemic therapy for HCC. Several new strategies are currently evaluated: for examples, molecular agents with activities against targets other than vascular endothelial growth factor receptor are being evaluated in on-going clinical trials. In addition, different approaches of targeted agents in combination with various treatment modalities, such as concurrently with another molecular agent, cytotoxic chemotherapy or transarterial chemoembolization, are being developed. This review aims to give a summary on the results of recently released clinical trials on TKIs, followed by discussion on some of the potential novel agents and

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INTRODUCTION

Following the approval of sorafenib for treatment of unresectable hepatocellular carcinoma (HCC), there has been a surge of interests in the clinical development of targeted agents for HCC. Despite intensive efforts being put on drug testing over the past 5 years, the outcomes of patients with advanced HCC remain poor. Recently, a number of novel multi-targeted tyrosine kinase inhibitors (TKIs) have completed phase III testing but all of the results have turned out to be negative^[1-3]. In addition, these large scale clinical trials persistently reported a median overall survival (OS) of 9 to 10 mo, indicating that the benefit of existing panel of TKIs has reached a plateau. Although these negative results appear discouraging to some, experience from these trials have shed insights to

Table 1 Results of completed phase III clinical trial on systemic agents for hepatocellular carcinoma

Clinical trial	Drug	Population	TTP (mo)	OS (mo)
1st line				
SHARP ^[89]	Sorafenib	19% HBV; 29% HCV	5.5	10.7
	Placebo	18% HBV; 27% HCV	2.8	7.9
Asian SHARP ^[90]	Sorafenib	71% HBV; 11% HCV	2.8	6.5
	Placebo	78% HBV; 4.0% HCV	1.4	4.2
SUN1170 ^[11]	Sunitinib	55% HBV; 21% HCV	4.1	8.1
	Sorafenib	53% HBV; 22% HCV	3.8	10.0
BRISK-FL ^[2]	Brivanib	44% HBV; 20% HCV	4.2	9.5
	Sorafenib	45% HBV; 21% HCV	4.1	9.9
Linifanib <i>vs</i> sorafenib ^[12]	Linifanib	49% HBV	5.4	9.1
	Sorafenib		4.0	9.8 (<i>P</i> = NS)
SEARCH ^[57]	Sorafenib + Erlotinib	NA	3.2	9.5
	Sorafenib		4.0	8.5 (<i>P</i> = 0.2)
Chemotherapy ^[62]	Doxorubicin	80% HBV; 8% HCV	NA	6.8
	PIAF	82% HBV; 4% HCV		8.7
2nd line				
BRISK-PS ^[3]	Brivanib	NA	4.2	9.4
	Placebo		2.7	8.2
			(<i>P</i> = 0.0001)	(<i>P</i> = 0.33)

HBV: Hepatitis B virus; HCV: Hepatitis C virus; NA: Not available; OS: Overall survival; TTP: Time to progression; NS: Non-significant; HCC: Hepatocellular carcinoma.

the design of new approaches in drug testing. In the current paper, we aim to give an update on the recent data on clinical trials using molecular targeted agents and discuss some of novel approaches for developing systemic agents for HCC.

UPDATE OF RESULTS OF CLINICAL TRIALS AT 2013

Phase III studies on anti-angiogenic TKIs

Sorafenib is a small molecule TKI which targets at multiple receptor kinases and signaling molecules, namely the vascular endothelial growth factor receptor (VEGFR), platelet derived growth factor receptor (PDGFR), B-Raf, Fms-related tyrosine kinase (FLT) and c-kit at nanomolar concentration^[4,5]. Sorafenib is generally considered an anti-angiogenic agent though its exact mechanism remains unclear. Following the positive results of clinical trials using sorafenib, a number of multi-targeted angiogenic TKIs have undergone clinical testing for the treatment of advanced HCC. These TKIs are characterized by their abilities to inhibit a wide spectrum of membranous receptors, mainly including VEGFR, FGFR (fibroblast

growth factor receptor) and PDGFR. The key results of completed phase III clinical trials on these agents are summarized in Table 1.

Sunitinib is the first anti-angiogenic TKI to compare with sorafenib in phase III trial. The targets of sunitinib include VEGFR, PDGFR, c-kit and FLT-3. Despite multiple targets of sunitinib, clinical experiences with the drug suggest that anti-angiogenesis is probably the major anti-neoplastic mechanism. Initial phase II studies reported potential activities of sunitinib in advanced HCC, with disease control rate ranging from 38% to 52%, and overall survival ranging from 8.0 to 9.8 mo^[6,7]. To validate the results of these studies, a multi-centered phase III clinical trial (SUN1170) was launched in 2008 to compare sunitinib to sorafenib as the first-line treatment for advanced HCC. The original design was aimed to recruit 1200 patients with randomization in 1:1 ratio into two arms, namely sunitinib 37.5 mg daily or sorafenib 400 mg twice daily. However, after accruing 1074 patients, the study was prematurely stopped when a preplanned safety analysis revealed a higher incidence of serious adverse events in the sunitinib arm^[1]. The primary endpoint, OS, of the sunitinib arm was 7.9 mo, which was significantly worse than the 10.2 mo in the sorafenib arm (*P* = 0.0014), while the time-to-progression (TTP) was similar between the two arms (sunitinib 4.1 *vs* sorafenib: 3.8 mo; *P* = 0.8312)^[1]. In terms of toxicity profile, sunitinib was associated with more grade 3 or above complications, including bleeding events (11.4%), thrombocytopenia (29.7%) and neutropenia (25.7%). The toxicity and inferior outcomes of patients treated with sunitinib have stopped further development of the agent in HCC.

Brivanib is a dual VEGFR and FGFR inhibitor^[8]. In preclinical models, the drug has been shown to have more potent anti-angiogenic effects than sorafenib, and the additional activity against FGFR is postulated to counteract the resistance mechanism to angiogenic agents targeting VEGF alone. In phase II clinical trials, brivanib has demonstrated reasonable activity in both first- and second-line setting with TTP of 2.8 and 1.4 mo, respectively^[9,10]. Two randomized phase III clinical trials were conducted to assess the agent in the first-line (BRISK-FL) and second-line (BRISK-PS) settings. BRISK-FL is a head-to-head randomized phase III clinical trial comparing brivanib to sorafenib as the first-line therapy in patients with unresectable HCC. The study enrolled 1155 patients who had not received any prior systemic treatment, and participants were randomized in 1:1 ratio to receive brivanib at 800 mg daily or sorafenib at 400 mg twice daily, with OS as the primary endpoint^[2]. The clinical trial has adopted a non-inferiority study design. According to the latest publication, the primary endpoint, OS non-inferiority between brivanib and sorafenib, was not met [brivanib: 9.5 mo; sorafenib: 9.9 mo; HR = 1.06; *P* = non-significant (NS)]^[2]. There were also no difference in TTP between brivanib and sorafenib (brivanib: 4.2 mo; sorafenib: 4.1 mo; *P* = NS)^[2]. In addition, brivanib appeared to be less well tolerated than sorafenib, as evidenced by higher rates of adverse events resulting in

Table 2 List of selected ongoing clinical trials on novel targeted therapy for hepatocellular carcinoma

Drug	Design	Phase	Status	NCT number
Single-agent TKI				
Dovitinib (TKI258)	Dovitinib <i>vs</i> sorafenib (1 st line)	Randomized phase II	Completed	NCT01232296
Carbozantinib	Carbozantinib <i>vs</i> placebo (2 nd line)	Phase III	Ongoing	NCT01908426
c-MET inhibitor				
Tivantinib	Tivantinib <i>vs</i> placebo (2 nd line)	Phase III	Ongoing	NCT01755767
INC280	INC280 (1 st line in c-MET expressing HCC)	Phase I / II	Ongoing	NCT01737827
Oncolytic poxvirus				
JX594	JX594 <i>vs</i> placebo (2 nd line)	Randomized phase II	Ongoing	NCT01387555
Glypican-3				
GC33	GC33 <i>vs</i> placebo (2 nd line)	Phase III	Completed	NCT01507168
mTOR inhibitor				
Everolimus	Everolimus <i>vs</i> placebo (2 nd line)	Phase III	Press release	NCT01035229
Temsirolimus	Temsirolimus (1 st or 2 nd line)	Phase II	Abstract	NCT01251458
CC-223	CC-223 in solid tumors including HCC	Phase I / II	Ongoing	NCT01177397
Arginine deprivation therapy				
ADI-PEG 20	ADI-PEG 20 <i>vs</i> placebo (2 nd line)	Phase III	Ongoing	NCT01287585
Combination				
Sorafenib	Sorafenib + doxorubicin <i>vs</i> sorafenib	Phase III	Accrual	NCT01015833
Sorafenib	TACE + sorafenib <i>vs</i> TACE (ECOG 1208)	Phase III	Accrual	NCT01004978
Everolimus	TACE + everolimus <i>vs</i> TACE	Randomized phase II	Accrual	NCT01379521
Axitinib	TACE + axitinib	Phase II	Accrual	NCT01352728
Bevacizumab and Erlotinib	Bevacizumab + erlotinib <i>vs</i> sorafenib	Randomized phase II	Accrual	NCT01180959

TACE: Transarterial chemoembolization; TKI: Tyrosine kinase inhibitor; HCC: Hepatocellular carcinoma; c-MET: c-mesenchymal-epithelial transition factor-1.

treatment discontinuation (brivanib: 43% *vs* sorafenib: 33%)^[2]. In the second-line setting, BRISK-PS compared brivanib to placebo in patients who were refractory or intolerant to first-line treatment of sorafenib. The trial has randomized 395 patients in 2:1 ratio to receive brivanib 800 mg daily or placebo along with best supportive care, with OS as the primary endpoint. Disappointingly, although TTP was significantly longer in the brivanib arm than placebo (4.2 *vs* 2.7 mo; $P = 0.0001$), providing a signal of potential activity of brivanib, the study failed to reach its primary endpoint of achieving benefit in OS

(brivanib: 9.4 *vs* placebo: 8.2 mo; $P = 0.33$)^[3].

Linifanib is an oral TKI with selective activity against VEGFR and PDGFR. Preclinical studies have reported potent activity of the agent on HCC xenografts. In a single-arm phase II study, linifanib was associated with a radiologic response rate of 9.1% and median TTP of 3.1 mo^[11]. These promising results have led to an international multi-centered phase III trial comparing linifanib to sorafenib. In this trial, a total of 1035 patients were randomized to linifanib at 17.5 mg daily or sorafenib at 400 mg twice daily. According to the preliminary results released at American Society Clinical Oncology (ASCO) Gastrointestinal Cancers Symposium in 2013, linifanib failed to demonstrate superiority or non-inferiority in terms of OS when compared with sorafenib (linifanib: 9.1 mo; sorafenib: 9.8 mo; $P = \text{NS}$)^[12].

Following the results of these studies, both brivanib and linifanib were generally considered not to be valid options for patients with advanced HCC.

EMERGING MOLECULAR TARGETS

In addition to the anti-angiogenic multi-targeted TKIs, there is a growing number of biologics that target at different molecular pathways. Some of these treatments act along molecules of intracellular signaling pathways while others are agents relying on the inhibition of non-signaling dependent mechanism (highlighted in Table 2). A number of agents have shown promising preliminary data for HCC, and these have been selected for more detailed discussion below.

c-mesenchymal-epithelial transition factor-1 inhibitor

c-mesenchymal-epithelial transition factor-1 (c-MET) is a membrane receptor that is essential for hepatocyte and tissue remodeling of liver after hepatic injury^[13,14]. The activation of c-MET is implicated in the proliferation, invasion and metastases of cancer cell^[15,16]. The expression of c-MET receptor protein occurs in 20% to 48% of human HCC samples^[17-20], and has been shown to be a poor prognostic factor in patients with HCC. In addition, the inactivation of c-MET could lead to regression of tumors in xenograft model and growth inhibition in HCC cell lines^[21]. Therefore, therapeutics aiming at the c-MET receptor is a rational approach for HCC. Two agents, namely tivantinib and cabozantinib, have undergone more advanced development. Tivantinib is an oral tyrosine kinase inhibitor of c-MET^[22]. A randomized phase II trial comparing the use of tivantinib *vs* placebo as the second-line treatment, showed that the TTP was slightly improved in the tivantinib arm (Tivantinib 1.6 mo; placebo 1.4 mo; $P = 0.04$). In particular, a more obvious improvement of TTP was noted in patients with tumors overexpressing c-MET (Tivantinib arm: 2.7 mo; placebo arm: 1.4 mo; HR = 0.38, 95%CI: 0.18-0.81, $P = 0.01$)^[23]. Currently, a phase 3 study is underway to compare tivantinib *vs* placebo in subjects with c-MET overexpressing HCC who have failed one prior systemic therapy (NCT01755767).

On the other hand, carbozantinib is an oral TKI with

activity against both c-MET and VEGFR-2. In a phase II randomized discontinuation clinical trial; patients were treated with cabozantinib and reassessed at 12 wk. Those patients with evidence of response would continue with cabozantinib while patients with stable disease were randomly assigned to cabozantinib or placebo. According to the results reported in the 2012 ASCO meeting, an impressive efficacy has been observed; the progression-free survival (PFS) was 4.4 mo while the median OS was 15.1 mo in the cabozantinib arm^[24]. This encouraging data has led to a planning of a phase III clinical trial testing the efficacy of cabozantinib in the second-line setting (NCT01908426). This phase III study is also planning to collect the tumor tissues to determine whether c-MET is a predictive marker, an aspect that has not been studied in the previous phase II study.

mTOR inhibitor

The phosphoinositide 3-kinase (PI3K)/Akt/mTOR axis is involved in multiple cellular processes including survival and proliferation^[25]. This signaling is initiated when membrane receptors are activated by binding of growth factors, which in turn recruit and activate the PI3K. The activation of PI3K will lead to a cascade of activation of downstream effectors leading to activation of mTOR. Comprehensive genomic analyses have shown that components of the PI3K/Akt/mTOR pathway are frequently deregulated in up to 50% of HCC^[26,27]. Therefore, targeting the components of this pathway, especially the downstream molecule mTOR, has been a research focus for development of therapeutics for HCC.

mTOR inhibitors, especially everolimus and temsirolimus, are being investigated in patients with HCC. In a phase I study of everolimus in 28 patients with advanced HCC, of whom over 70% were treated with more than one prior regimen, the maximum tolerated dose was 10 mg daily. At this dose, treatment with everolimus yielded a disease control rate of 44% and an overall survival of 8.4 mo^[28]. The drug was generally well tolerated with most common toxicities being fatigue and hyperglycemia^[28]. A phase III study comparing everolimus with placebo (EVOLVE-1) in patients who have failed or become intolerant to sorafenib has recently been completed (NCT01035229). At the time of writing, there has been a press release indicated that the EVOLVE-1 study failed to reach its primary endpoint of extending OS with everolimus^[29]. Further detailed results are expected in the near future. For temsirolimus, a phase I / II study in a heavily pretreated population of unresectable HCC has reported the maximum tolerated dose (MTD) of temsirolimus to be 25 mg every week; amongst the 36 patients recruited in the phase II portion, the disease control rate was 38.9%^[30,31]. A number of clinical trials have been designed to evaluate the combination of mTOR inhibitor with sorafenib (see section below: combinational treatment approach). Another mTOR inhibitor, CC-223, which possesses dual activity against mTORC1 and 2, is also undergoing phase I / II development in solid tumors including HCC (NCT 01177397).

Histone deacetylase inhibitor

The expression of tumor suppressor genes is influenced by coiling and uncoiling of DNA around histone, which is mainly mediated by histone acetylation. Acetylation of histone results in less condensed chromatin leading to expression of gene expression while histone deacetylases (HDACs) remove the acetyl groups from histones leading to condensed and transcriptionally silenced chromatin^[32]. Such histone modification is one of the major epigenetic mechanisms on gene regulation, and the HDACs are amenable to inhibition by HDAC inhibitors. This class of agents was initially investigated for hematological malignancies, and vorinostat and romidepsin have been approved for the treatment of peripheral T-cell lymphoma^[33,34].

For HCC, preclinical studies showed that treatment with HDAC inhibitor could induce apoptosis in HCC cell lines^[35-37]. A phase I / II clinical trial assessed HDAC inhibitor, belinostat, for treatment of advanced HCC. Amongst the 42 patients treated in the phase II portion, reasonable efficacy was demonstrated in a heavily pretreated population, with disease stabilization rate of 47.6% and PFS of 2.64 mo^[38]. Belinostat was well tolerated with lower than 10% grade 3 or above toxicities^[38]. More interesting findings come from the exploratory analysis on the role of HR23B to predict the clinical response. HR23B is a protein which is responsible for shuttling ubiquitinated cargos for proteosomal degradation. It has been suggested that the expression of HR23B is a potential predictive marker for response to HDAC inhibitor in hematological malignancies^[39,40]. In the aforementioned phase II trial on HCC, it was shown that tumors with high HR23B histoscores is associated with a higher rate of disease stabilization ($P = 0.036$)^[38]. Further studies are required to study the clinical role of HR23B as predictive biomarker in HCC.

Arginine deprivation therapy

In human cells, arginine is a non-essential amino acid, and arginine is synthesized from citrulline through a series of enzymatic reactions^[41]. However, HCC cells are known to be defective of a number of these enzymes including argininosuccinate synthetase (ASS) or ornithine transcarboxylase (OTC); as a result, there is impairment in the cellular ability to replenish the arginine once it is depleted, which subsequently leads to cell death^[42,43]. This mechanism of arginine deprivation is attractive because it could provide selective cytotoxic effect on tumor but not non-tumorous tissues.

At present, two classes of arginine degrading enzymes have undergone clinical testing, namely the ADI-PEG 20 and the PEG-BCT-100. ADI-PEG 20 is an arginine deaminase which depletes arginine level by converting it to citrulline and ammonia. Two phase II studies have been completed in HCC^[44,45]. The reported disease-control rate (DCR) and the mean OS were in the range of 30%-60% and 7-16 mo, respectively. This has led to the conduct of an international multi-centered study to compare the efficacy of ADI-PEG 20 vs placebo in the second-line set-

ting, following failure to sorafenib (NCT01287585).

PEG BCT-100 is a recombinant human arginase which degrades arginine by converting it to ornithine and urea^[46-49]. Compared to ADI-PEG 20, the agent has a theoretical advantage of having broader activity on HCC cells which express ASS but not OTC. Clinical trials in phase II setting are being planned.

Immunotherapy

HCC is an inflammation-associated cancer; analysis of the tumor microenvironment has suggested that local immune responses may be prognosticator of the disease^[50]. Specific anti-tumor T-cell responses can be detected in patients with HCC. Immune responses are regulated by molecules that provide co-stimulatory and inhibitory signals to T cells. Down regulation of T-cell activity upon binding to ligands on antigen-presenting cells and tumor cells affects peripheral tolerance and protection from autoimmune damage^[51]. The recent approval of ipilimumab for patients with melanoma and Sipuleucel-T for patients with prostate cancer, has highlighted the possibility of adopting immunotherapy in other malignancies including HCC^[52,53].

COMBINATIONAL TREATMENT APPROACH

The concept of combination of different agents or treatment modalities is attractive for the following reasons^[54]: (1) taking into consideration most of the single-agent therapies are associated with low radiologic response rate and the high HCC tumor heterogeneity, the concurrent use of compounds with synergistic activity may potentially improve the clinical outcome; and (2) the survival time of patients with advanced HCC is relatively short compared with other solid tumors, thus limiting the possibility of sequential treatments using individual agents. Obviously, one of the biggest obstacles for combination treatment is the concomitant compromised hepatic reserves present in most HCC patients with most of them suffering from cirrhosis. Therefore, carefully planned and dedicated early clinical trials are warranted to investigate the toxicity and efficacy of novel combinations in patients before proceeding to phase III development. Over the past few years, different ways of combinational treatment has been explored by various groups, and these are discussed below.

Combination of targeted agents

Most of developments have been based on combination of a novel class of targeted agent with sorafenib. At present, there are more than 20 clinical trials with such design. According to the recently available results, it appears that the difficulty of combining sorafenib with other targeted agent may be greater than expected. For examples, in a phase I / II study testing the combination of temsirolimus and sorafenib, the MTD of the combinational regimen was sorafenib at 200 mg twice daily and temsirolimus at 10 mg weekly, which was lower than that found in melanoma patients with hepatic dysfunction^[55].

In another phase I study on sorafenib and everolimus, the MTD of everolimus was only 2.5 mg daily, which was a significantly lower dosage than that required to achieve a biologically effective dose in human body^[56]. Similar problem is also experienced in the phase III SEARCH study comparing sorafenib-erlotinib *vs* sorafenib-placebo^[57]. In this trial, not only did the sorafenib-erlotinib not improve clinical outcomes, the combination was associated with shorter duration of treatment and higher withdrawal rate indicating poor tolerance.

There have been fewer studies on the combination with a non-sorafenib agent. At present, the most well studied regimen is the combination of erlotinib and bevacizumab. In a phase II single-arm study of 40 Caucasian HCC patients, Thomas *et al*^[58] reported a response rate of 25%, and a median PFS and OS of 9.0 mo and 15.7 mo respectively in an initial report. The results were subsequently updated in a final analysis, which demonstrated a median PFS and OS of 7.2 mo and 13.7 mo^[59]. However, another phase II study with the same combination failed to reproduce the survival data; the response rate was only 3.7% and the overall survival was 9.5 mo^[60]. A randomized phase II study comparing bevacizumab-erlotinib to sorafenib is currently underway to validate the efficacy of this combinational regimen (NCT01180959).

Chemotherapy plus targeted agent

Although chemotherapy has not been directly compared to placebo or sorafenib in randomized studies, chemotherapy has persistently been associated with a high radiologic response and a large magnitude in decrease of serum alpha-fetoprotein level^[61-63]. The recently published phase III data on EACH study comparing FOLFOX4 to doxorubicin chemotherapy has also suggested that FOLFOX chemotherapy is a potential option of systemic treatment for patients with advanced HCC, with radiologic response of over 8%^[64]. Theoretically, the addition of chemotherapy could overcome the weakness of cytostatic property of molecular targeted agents. To test this hypothesis, a randomized phase II clinical trial has been conducted to compare sorafenib (400 mg twice daily)-doxorubicin (60 mg/m² every 3 wk) combination *vs* doxorubicin (60 mg/m² every 3 wk). According to the trial results, there was an improvement of both OS (13.7 *vs* 6.5 mo; *P* = 0.006) and radiologic response rate (62% *vs* 29%) favoring the combination arm^[62]. However, this benefit was at a cost of increased toxicities in the combinational arm especially with increased rate of left ventricular systolic dysfunction (all grade 19% *vs* 2%). It remains unclear whether the cardiac toxicity is due to drug interaction or due to the synergistic toxicity conferred by VEGF inhibition with sorafenib. A phase III clinical trial is currently undertaken to study the efficacy and safety of the sorafenib-doxorubicin combination *vs* single-agent sorafenib in the first-line setting (NCT01015833).

Transarterial chemoembolization plus targeted agent

HCC is a highly vascular tumor and transarterial chemoembolization (TACE) could induce tumor hypoxia, there-

by provoke a post-treatment surge of angiogenic factors including VEGF that may occur as early as a few hours post TACE. The event may contribute to the revascularization of tumors and reduction of the efficacy of TACE^[65,66]. In addition, the peripheral rim of HCC tumors frequently escapes the cytotoxic effects of TACE because of tumor repopulation, and microscopic tumor progression is frequent during the interval between each treatment cycle of TACE^[67]. Combining anti-angiogenic drugs with TACE may potentially improve treatment outcomes^[68].

The concept of combining sorafenib and TACE was initially tested in a single arm phase II study in which sorafenib was started at 1 wk after TACE with drug-eluting beads. This reported a DCR of 95% and objective response rate of 58% according to European Association for the Study of the Liver criteria^[69]. However, the global SPACE study, designed to test the continuous administration of sorafenib during TACE, failed to demonstrate significant benefit favoring the combinational approach. In the clinical trial, patients were randomized into two arms: one arm undergoing continuous administration of sorafenib 400 mg twice daily together with TACE at specified intervals and another arm receiving placebo and TACE. The primary endpoint was time to radiologic progression (TTRP). According to the results released in the 2012 ASCO Gastrointestinal Cancers Symposium, the study has met its primary endpoint on the improvement of TTRP in the sorafenib arm as compared to placebo arm [median TTRP of sorafenib = 169 d *vs* placebo = 166 d; HR = 0.797, *P* = 0.072 (pre-specified *P* value for the one-sided Log-rank test was set at 0.15)]^[70]. However, there was no statistically significant difference in OS and response rate between the two arms. In view of the small difference in the TTRP and the lack of difference in OS, most of the clinicians do not consider the results of this trial to be encouraging.

The less impressive results of SPACE clinical trial have casted shadow on whether the combination of TACE and sorafenib is an effective approach. Other groups attempt to address the issue with different studies. For examples, a multi-centered phase III ECOG 1208 study is underway, testing the continuous use of sorafenib with TACE *vs* placebo (NCT01004978). This phase III clinical trial has very similar design to the SPACE trial. The clinical trial may help further determine whether the approach of concurrent administration of sorafenib together with TACE is effective for treatment of HCC. On the other hand, we are conducting a phase II clinical trial testing the use of axitinib in combination with TACE (NCT01352728). Axitinib is a more potent TKI of all three VEGFRs1-3, and its use could potentially inhibit the surge of VEGF levels after TACE at a greater extent than sorafenib. The clinical trial is expected to complete accrual in early 2014.

came from subgroup analyses: both geographical difference and hepatitis status have had significant effects on treatment outcomes^[71]. Patients with hepatitis C virus infection or patients of non-Asian ethnicity tend to derive more benefits from sorafenib than patients with hepatitis B virus or the Asian origins. This type of finding was also similarly observed in the subgroup analysis of the Asian SHARP trial^[71]. Different explanations including genetic background, molecular pathogenesis, aggressive approach using surgery/locoablative treatment between West and East, have been postulated. Regardless of the underlying postulations, the geographical location and the hepatitis status should be taken into consideration during the design of clinical trials in HCC. Preferably, a dedicated phase I / II clinical trial should be designed to evaluate new agents in hepatitis B and hepatitis C-related HCC subpopulations, in addition, the design of international multi-centered trial should consider stratification by geographical regions, in terms of East *vs* Non-East, in the randomization process.

Selection of suitable patients

It is evident that unresectable HCC population consists of a highly heterogeneous group of patients with a wide spectrum of survival ranging from a few months only to longer than 2 years^[72-74]. As a result, it is difficult to precisely estimate the survival of patients during the design of clinical trials that encompass a heterogeneous population. Different staging systems have been developed to define suitable patients for the administration and testing of systemic agents. At this juncture, the Barcelona Cancer Liver Clinic (BCLC) classification is the most frequently used staging system for clinical trials. It has to be noted that BCLC was initially designed for allocation of treatment rather than for prognostication of HCC. As a result, the staging system is suboptimal in identifying homogeneous group of patients in terms of prognosis and disease behavior. For examples, patients classified as BCLC stage C disease (*i.e.*, advanced disease defined as patients with Child's A or B liver function, having a performance status of 1 or above, and the presence of vascular invasion or extra-hepatic disease) has been assigned the target group for testing systemic agents. However, there have been studies suggesting that the BCLC system is inadequate in predicting the short-term outcome of patients or identifying a homogenous group of patients with advanced disease^[75,76]. Also, the treatment allocation as recommended by BCLC is considered too conservative by most Asian clinicians. For examples, most of the hepatobiliary cancer surgeons in Asia will not regard invasion of branch of portal vein as a definitive contraindication to surgical resection^[77,78]. In view of these limitations, a more precise staging system is necessary to identify a homogenous group of patients for testing systemic agents.

On the other hand, in Asia, because of the limited choice and the low efficacy of available systemic agents, patients with unresectable HCC confined to liver are often treated with multiple cycles of TACE before consid-

FUTURE DIRECTIONS

Design of clinical trial

One interesting point observed from the SUN1170 study

ering systemic agents, albeit limited efficacy^[79]. Given the increasing number of novel agents currently being tested that may potentially improved efficacy for HCC, studies are indicated to refine the TACE population and define the optimal timing to shift away from TACE when the treatment is no longer effective. For examples, there has been a recent study by the European group on the development of a scoring system to guide the retreatment with transarterial chemoembolization^[80].

Personalized treatment

Experiences from the lung and breast cancer fields have shown that success in clinical trials using targeted agents can only be improved if we are able to apply to appropriately selected patients whose tumors are “addicted” to a known driver gene or pathway. An ideal approach would be targeting individual agents in patients whose HCC tumors have the corresponding genetic mutations. With recent genomic sequencing showing that a genetic driver mutation, if present, occurs at a rate of lower than 5% in HCC, the chance of picking up a responder of a novel agent in an unselected population is much lower than 5%^[81-85]. This clinical challenge is evidenced by the persistently low response rate observed in multiple clinical trials on molecular targeted agents in unselected HCC populations, all of which have resulted in an overall survival that leveled off in the range of 9 to 10 mo (Table 1). Given the reported data on the role of c-MET expression and the potential use of HR23B to predict response of individual targeted agents, future clinical trials should be tailored towards identification of molecularly enriched patient population. Therefore, it is important to obtain pre-treatment tumor samples in the conduct of clinical trials. Owing to the invasive nature of tumor biopsy, a number of groups are currently studying the use of massive parallel sequencing to study the cancer genome in patients’ plasma samples, which could potentially obviate the need of needle biopsy^[86-88].

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