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Molecular Targeted Therapy for Growth Factors in Hepatocellular Carcinoma

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1. Introduction

Treatments for HCC are classified into local and systemic therapies. Various local treatment modalities, such as resection, local ablation, transcatheter arterial chemoembolization (TACE), and liver transplantation, are available at present. The most suitable treatment modality for HCC is selected according to the tumor stage, grade of liver dysfunction, and performance status of the patient [1,2]. Although the local approaches have been demonstrated to yield good outcomes in patients with earlier-stage disease, the usefulness is limited to patients with early-stage HCC [3]. TACE is the most widely used for patients with HCC who are not suitable candidates for curative surgical resection or local ablation therapy, and have preserved liver function (Child-Pugh class A or B). Randomized clinical trials (RCTs) and meta-analysis of RCTs on TACE have shown that this treatment modality yields a statistically significant improvement of survival in properly selected candidates, e.g., patients with multinodular asymptomatic tumors [4,5].

Despite the local therapies mentioned above yielding successful outcomes at first, the patients often develop recurrences or disease progression subsequently. Locoregional treatments for intra- and/or extrahepatic tumors in HCC patients with extrahepatic metastases may yield some survival benefit; the reported 3- and 5-year survival rates are 31.0, 9.2 and 4.5%, respectively, in patients administered locoregional treatments [6]. However, the survival rate is often dismal in patients with extrahepatic metastases, with the median survival time in HCC patients with metastases being 4.6 months. Despite the poor survival of patients with major vascular invasion, no effective treatment(s) has been established for these patients [3]. Thus, systemic therapy is needed to improve the survival of patients with advanced HCC, including those with major vascular invasion and/or extrahepatic metastases.

Chemotherapy is applied for patients with advanced HCC patients who are TACE-refractory or show major vascular invasion and/or extrahepatic metastases. Various studies have investigated the usefulness of combined therapy with anthracycline antitumor antibiotic agents, cisplatin and/or fluorouracil, with the reported response rates ranging from 14% to 26% and median overall survival (OS) ranging from 8.9 to 11.6 months [7-9]. However, despite the better response in phase III trials to

combination chemotherapy as compared to doxorubicin monotherapy, no standard chemotherapy was identified that could clearly prolong the survival [10]. On the other hand, in Japan, various hepatic arterial infusion chemotherapy regimens have been applied for patients with very advanced HCCs, such as those with extensive portal vein tumor thrombosis, and for some of these regimens, responses rates of more than 40% have been reported [11,12]. However, so far, no standard regimen has been identified based on large prospective clinical trials that can clearly prolong the survival in patients with advanced HCC.

Some growth factors and various signal transduction pathways have been identified in HCCs, and various targeted agents have been investigated for the treatment of patients with HCC. These therapies may target not only tumor cell proliferation, but also angiogenesis. Sorafenib is a small-molecule multikinase inhibitor that inhibits kinases such as Raf kinase, vascular endothelial growth factor receptor (VEGFR), and platelet-derived growth factor receptor (PDGFR)-β tyrosine kinases. It is the first agent that was demonstrated to yield survival benefit in patients with unresectable advanced HCC [13,14]. Subsequently, various targeted agents have been investigated for the treatment of HCC in various stages of progression. On the other hand, various characteristic toxicities of molecular targeted agents, such as hand-foot syndrome or hypertension, have been reported [13,14,15]. It is important to understand the efficacy and safety of molecular targeted therapy to gauge their true benefit.

2. Systemic therapy using targeted agents for advanced HCC

2.1 Summary of pivotal trilas of sorafenib

Sorafenib is a small-molecule multikinase inhibitor that inhibits kinases such as Raf kinase, vascular endothelial growth factor receptor (VEGFR), and platelet-derived growth factor receptor (PDGFR)-β tyrosine kinases [16]. In a phase I study of sorafenib conducted in 69 patients with solid malignant tumors, diarrhea was the most commonly encountered treatment-related adverse event, and the dose-limiting toxicities were diarrhea, fatigue, and skin toxicities, namely, hand-foot syndrome and rash [17]. The maximum tolerated dose was found to be 400 mg bid continuous and the recommended dose of sorafenib for future studies was also 400 mg bid as a continuous dosing schedule. In regard to the efficacy, even a partial response (PR) was observed in only one of the 45 patients treated continuously with sorafenib at doses of $\geq$ 100 mg bid, who was a patient of HCC treated with the drug at 400 mg bid. In this phase I study, six HCC patients were assessable for efficacy, of which one showed PR, 4 showed stable disease (SD), and one showed progressive disease (PD). Based on these preclinical results and the results of the phase I study of sorafenib, a phase II study was performed in 137 patients with advanced HCC [18]. Although the response rate was low (2.2%), the time-to progression (TTP) and overall survival (OS) were more promising (Table 1).

Based on these results, a large randomized controlled trial (RCT) of sorafenib versus placebo (the SHARP trial) was conducted in patients with advanced HCC and good liver function (Child-Pugh A)[13]. Six hundred two patients were randomized into two arms, namely, the sorafenib arm and the placebo arm (Table 1). The TTP was 5.5 months for sorafenib and 2.8

months for placebo, and the hazard ratio in the sorafenib arm was 0.58 (95% CI: 0.45-0.74; p<0.001). The median OS was 10.7 months in the sorafenib arm and 7.9 months in the placebo arm, and the hazard ratio for OS in the sorafenib arm was 0.69 (95% CI: 0.55-0.87; p<0.001). Thus, sorafenib was the first systemic chemotherapeutic agent demonstrated to prolong survival in patients with advanced HCC.

Agent	Study setting	n	Response rate	Median TTP	Median OS	p-value (HR, 95%CI)	Author (year)
Sorafenib	Phase II	137	2%	4.2 mo	9.2 mo	-	Abou-Alfa (2006) [18]
Sorafenib	Phase I	27	4%	4.9 mo	15.6 mo	-	Furuse (2008) [19]
Sorafenib	Phase III	299	2.3%	5.5 mo	10.7 mo	P < 0.001 (0.69, 0.55-0.87)	Llovet (2008) [13]
Placebo		303	0.7%	2.8 mo	7.9 mo		
Sorafenib	Phase III	150	3.3%	2.8 mo	6.5 mob	P = 0.0155 (0.67, 0.49-0.93)	Cheng (2009) [14]
Placebo		76	1.3%	1.4 mo	4.2 mo		

TTP, time-to progression; OS, overall survival; HR, hazard ratio; CI, confidence interval

Table 1. Clinical trials of sorafenib for hepatocellular carcinoma.

In the SHARP trial, approximately 90% of the patients enrolled were from Europe or Australia. The differences in the efficacy and safety was a concern in relation to the application of sorafenib as a global standard therapeutic agent for advanced HCC, as the etiology and treatment strategies for HCC vary among regions in the world. Therefore, to confirm the efficacy and safety of the drug in Asian populations, a RCT of sorafenib was conducted in the Asia-Pacific region (the Asia-Pacific trial)[14]. The dosing schedule of sorafenib was the same as that used in the SHARP trial, namely, continuous administration of 400 mg bid, and the patients were randomized 2:1 to sorafenib or placebo. The median OS, which was the primary endpoint, was 6.5 months for sorafenib and 4.2 months for placebo, and the hazard ratio for OS in the sorafenib arm was 0.67 (95% CI: 0.49-0.93; p=0.0155) [14].

Despite the equivalent hazard ratio for OS and TTP in the two RCTs, the median OS and TTP were very poor in the Asia-Pacific trial as compared with that in the SHARP trial. This was considered to be attributable to the differences in the patient characteristics, such as the poorer performance status (69% of ECOG PS) and more advanced stage of the cancer in the latter trial (96% with BCLC stage C, 52% with lung metastases).

Since patients enrolled in the SHARP trial and Asia-Pacific trial were limited to those with good liver function (Child-Pugh A), the usefulness of sorafenib needed to be examined in

patients with Child-Pugh class B, or moderate liver dysfunction. In a phase II study of sorafenib, 38 out of the 137 patients enrolled were classified into Child-Pugh class B [18]. This study revealed some variability in the AUC and Cmax values, which were slightly greater in the Child-Pugh class B patients than in the Child-Pugh class A patients, however, the differences were not significant [18]. In Japan, a phase I study of sorafenib was conducted to investigate the pharmacokinetics, safety and efficacy of the drug in Japanese patients with advanced HCC; the study included an equal number of Child-Pugh class A and B patients [19]. In regard to the differences in the pharmacokinetics between the Child-Pugh class A and B patients, although both the area under the concentration-time curve for 0-12 h and the maximal concentration in the steady state were slightly lower in the Child-Pugh class B patients than in the Child-Pugh class A patients, there were no major differences in the incidence or grade of drug-related adverse events between the Child-Pugh class A and B groups; however, hypertension, hand-foot skin reactions, and rash were reported more frequently in the Child-Pugh class B group [18]. Especially, grade 3-4 adverse events of elevated bilirubin, ascites, and encephalopathy occurred at a greater frequency in Child-Pugh class B patients than in the Child-Pugh class A patients [20]. Thus, the efficacy or safety of sorafenib in HCC patients categorized as Child-Pugh class B are not clear yet.

The most commonly reported toxicities of sorafenib are transient elevation of lipase and/or amylase, rash/desquamation, hand-foot skin reaction, diarrhea, anorexia, weight loss, alopecia, and voice changes. The reported drug-related adverse events of grade 3 or greater severity are diarrhea, hand-foot skin reaction, hypertension and rash.

2.2 Indications of sorafenib in the treatment of HCC

The Barcelona Clinic Liver Cancer (BCLC) staging classification has been employed as a guide for treatment selection in HCC patients [21]. Based on the results of RCTs of sorafenib, BCLS Stage C (advanced stage), which includes portal invasion, lymph node metastasis, and/or distant metastasis, has been reported as a suitable criterion for the selection of sorafenib. The Japanese consensus-based treatment algorithm also recommends treatment for HCC according to the tumor stage and degree of impairment of liver function [2]. In this algorithm, sorafenib is recommended as the first-line therapy for advanced HCC patients classified as Child-Pugh class A, who show extrahepatic spread or major vascular invasion and/or are TACE-refractory.

2.3 Recent trials using new targeted agents

Phase I, phase II studies have been conducted to investigate the usefulness of various new targeted agents for the treatment of advanced HCC (Table 2). Some large phase III studies of new targeted agents alone or such agents in combination with sorafenib vs. sorafenib alone have also been conducted. Some multikinase inhibitors, such as sunitinib, brivanib and linifanib, that have shown promising antitumor activity against HCC in phase II studies [22-25] have been investigated in head-to-head study comparisons with sorafenib (Table 3). Some phase III studies comparing sorafenib in combination with another molecular targeted agent or cytotoxic agent vs. sorafenib alone are also under way.

Agent	Study setting	n	Response rate	Median TTP/PFS	Median OS	Author (Year)
Sunitinib	Phase II	37	2.7%	5.3 mo	8.0 mo	Faivre (2009) [22]
	Phase II	45	2.9%	3.9 mo	9.3 mo	Zhu (2009) [23]
Brivanib	Phase II	55	7.3%	2.7 mo	10.0 mo	Park (2011) [24]
Linifanib	Phase II	44	6.8%	3.7 mo	9.3 mo	Toh (2009) [25]
Everolimus	Phase I/II	28	4%	3.8 mo	8.4 mo	Zhu (2010) [26]
TSU-68	Phase I/II	35	2.9%	2.1 mo	13.1 mo	Kanai (2010) [27]
Sunitinib	Phase III	529	6%	4.1 mo	8.1 mo*	Cheng (2011) [28]
Sorafenib		554	6%	4.0 mo	10.0 mo	

TTP, time-to progression; PFS, progression-free survival; OS, overall survival
*hazard ratio 1.31 (95% confidence interval: 1.13-1.52), P = 0.0019

Table 2. Clinical trials of new molecular targeted agents for hepatocellular carcinoma.

Study setting	Agent
1. First-line chemotherapy	sunitinib, brivanib, linifanib
2. Second-line chemotherapy	brivanib, everolimus, ramcirumab, axitinib*
3. Combination with TACE	sorafenib, brivanib, TSU-68
4. Adjuvant therapy after resection or ablation	sorafenib

TACE, transarterial chemoembolization
* randomized phase II study

Table 3. Molecular targeted agents developing in randomized clinical trials

The estimated time-to progression in patinets treated with sorafenib ranges from 2.8 to 5.5 months and some patients may accrue benefits of second-line chemotherapy after being labeled as sorafenib-refractory. Some large phase III studies of new targeted agents, such as brivanib, everolimus and ramcirumab, as second-line treatment have also been conducted (Table 3).

Among these phase III studies, the results of a phase III study comparing sunitinib with sorafenib was reported in 2011. The trial did not show any survival advantage of sunitinib

in pateints with advanced HCC; in fact, the survival in the sunitinib group was inferior to that in the sorafenib group (Table 3) [28].

3. Combined molecular targeted therapy with local therapy

3.1 Combination with TACE

Transcatheter arterial chemoembolization is widely applied for the treatment of HCC as one of the standard treatments along with resection and local ablation. One-third of all patients with primary HCC are treated by TAE/TACE as the first-line treatment [2]. However, the Nationwide Follow-up Survey by the Liver Cancer Study Group of Japan (LCSGJ) revealed that the 5-year survival rates for resection, ablation and TACE were 59.2%, 48.4% and 29.7%, respectively, for single tumors, and 46.4%, 37.3% and 23.0%, respectively, for two tumors; thus, the efficacy in terms of survival prolongation of TACE was limited as compared with that of resection and ablation [2]. It is difficult to obtain complete necrosis of tumors by TACE, and the reported objective response rate to TACE ranges from 15%-55% [29]. Thus, to improve the efficacy of TACE, combined use of TACE with molecular targeted therapy has been investigated.

Regarding the increment of the serum VEGF level associated with TACE, it was reported that the serum VEGF increased within 1 to 2 days after TACE and recovered by one month later; also, an association between the serum VEGF level and the prognosis after TACE in HCC patients has been reported. Therefore, it may be reasonable to suppress the effects of VEGF by VEGFR inhibitors to improve the survival benefit yielded by TACE in patients with HCC [30].

The first trial of combined TACE with molecular targeted agents was a placebo-controlled phase III study of sorafenib (post TACE study) conducted in Japan and Korea [31]. The primary endpoint was the TTP, and to prove the assumption that the median TTP would be 50% higher in the sorafenib than in the placebo group. The median TTP in the sorafenib and placebo groups was 5.4 and 3.7 months, respectively (hazard ratio (HR), 0.87; 95% confidence interval, 0.70-1.09; P = 0.252). Although the TTP in the sorafenib group was better than that in the placebo group, the drug yielded no statistically significant prolongation of the TTP after TACE. This study was designed before the results of the SHARP and Asia-Pacific trials of sorafenib were reported, and only patients who responded to TACE were included as the subjects of this study. As a result, it took a median of 9.3 weeks from TACE to randomization, because the efficacy of TACE could only be evaluated by CT one month after the procedure, and a central review of CT findings was required.

Currently, many comparative studies between TACE plus a targeted agent and TACE alone are under way (Table 3). In these studies, administration of targeted agents is initiated before TACE or as soon as possible after TACE.

3.2 Adjuvant therapy with targeted agents after curative treatments

One of characteristics of HCC is the very high recurrence rate after regional therapies. Even for early-stage HCCs (smaller than 3 cm and 3 or less in number), the reported cumulative 1- and 5-year recurrence rates after resection are 24.5% and 74.3%, respectively [32]. There are two mechanisms of recurrence after curative treatments, that is, metastasis from the primary

HCC lesion and new multicentric development. Patients with HCC have microscopic lesions, and intrahepatic metastases often develop rather early after curative treatments. On the other hand, patients with HCC are also at a greater risk of multicentric hepatocarcinogenesis and de novo development of HCC tumors [33].

Thus, various adjuvant therapies have been investigated to suppress the risk of recurrence after curative treatments, including resection and ablation therapy. An acyclic retinoid, polyprenoic acid, was reported to prevent the development of second primary hepatomas after surgical resection or percutaneous injection of ethanol in a small randomized comparison trial [34]. Peretinoin, an acyclic retinoid, administered at the dose of 600 mg statistically significantly decreased the 2-year recurrence rate as compared with placebo in a large RCT, however, no improvement of the primary endpoint, that is, of the recurrence-free survival, was observed, therefore, the efficacy is still unclear [35]. It was reported that adoptive immunotherapy may also improve the recurrence-free outcomes after surgery for HCC [36], but it has not yet been applied for adjuvant therapy in the clinical setting because of the complicated method of its use. While interferon or vitamin K have been suggested as having potential activity for suppressing recurrence, so far, no standard adjuvant therapy regimen including these agents has been established [37-39].

In a prospective study consisting 57 patients with HCC who underwent resection, high expression levels of PDGFR-α and PDGFR-β were independently associated with decreased survival [40]. Molecular targeted agents are expected to suppress the recurrence rate of HCC after curative treatments. Sorafenib is also currently under investigation as an adjuvant therapy after curative treatment(s).

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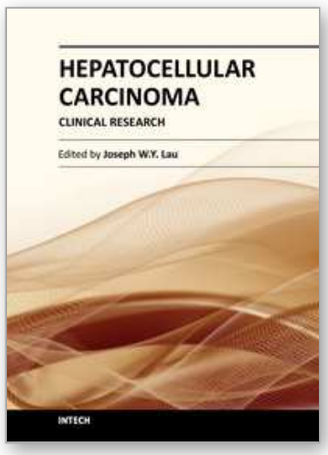

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This book covers the clinical aspects of hepatocellular carcinoma. This book is a compendium of papers written by experts from different parts of the world to present the most up-to-date knowledge on the clinical aspects of hepatocellular carcinoma. This book is divided into three sections: (I) Diagnosis / Differential Diagnosis; (II) Surgical Treatment; (III) Non-surgical Treatment. There are 19 chapters covering topics from novel diagnostic methods to hepatic lesions mimicking hepatocellular carcinoma, from laparoscopic liver resection to major hepatectomy without allogeneic blood transfusion, from molecular targeted therapy to transarterial radioembolization, and from local ablative therapy to regional therapy. This volume is an important contribution to the clinical management of patients with hepatocellular carcinoma. The intended readers of this book are clinicians who are interested in hepatocellular carcinoma, including hepatologists, liver surgeons, interventional and diagnostic radiologists, pathologists and epidemiologists. General surgeons, general physicians, trainees, hospital administrators, and instruments and drug manufacturers will also find this book useful as a reference.

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