Molecular Targeted Therapy for Hepatocellular Carcinoma: Where Are We Now?

Seven years have passed since sorafenib was approved as a systemic chemotherapeutic agent that improves survival in patients with advanced hepatocellular carcinoma (HCC). Despite numerous studies over subsequent years aimed at developing novel molecular targeted agents, no new drugs have produced positive results to date. Because of the difficulties faced in developing novel agents, the patients selected for drug development trials have shifted from those with similar hepatic functions and tumor stages, as in conventional trials, to those with homogeneous biological characteristics based on biomarkers. In addition, a promising new strategy in the development of treatments for HCC is the emerging field of immuno-oncology. However, to reduce medical costs, it is necessary to take a broad perspective to drug development by, for example, incorporating new concepts such as a master protocol system.

Unmet Needs in Clinical Practice

The multikinase inhibitor sorafenib was the first oral molecular targeted agent to show survival benefits in patients with advanced HCC [1, 2]. As a result, sorafenib has become the standard treatment option in patients with advanced HCC with extrahepatic spread and/or vascular invasion [3, 4]. Because the treatment efficacy of sorafenib is relatively modest, and toxicity can be an issue in some patients, a number of clinical trials have been conducted aimed at developing more potent and less toxic molecular targeted agents to address unmet clinical needs for first-line and second-line treatments, for combination/adjuvant therapies with transarterial chemoembolization (TACE) [5–10], and for adjuvant therapies after curative treatment. However, the trials conducted thus far to develop novel agents for the treatment of HCC have all been unsuccessful, underlining the unique difficulties involved in drug development for HCC.
Clinical Trials for Different Disease Stages

Clinical trials have been conducted to find solutions to the above-mentioned unmet needs for the treatment of HCC at various disease stages. For early-stage HCC, agents for adjuvant therapy after surgical resection or radiofrequency ablation have been tested; for intermediate-stage HCC in which TACE is indicated, several agents that may improve TACE efficacy have been tested; and for advanced-stage HCC, for which sorafenib is the standard of care, several first- and second-line agents have been tested.

**Early-Stage HCC**

The Sorafenib as Adjuvant Treatment in the Prevention of Recurrence of Hepatocellular Carcinoma (STORM) study was aimed at suppressing HCC recurrence after curative therapy such as resection [11] or ablation [12, 13]. However, no significant difference was seen in recurrence-free survival between the sorafenib and placebo arms of the study [14]. Peretinoin, an acyclic retinoid agent for oral administration, has a structure similar to vitamin A and functions as a transcription activator and an inducer of differentiation. Therefore, it was hypothesized that peretinoin might suppress HCC in its precancerous stage by inducing apoptosis and might also inhibit carcinogenesis through the induction of differentiation. A phase II/III study investigating the inhibitory effect of peretinoin on HCC recurrence had a negative outcome because of a dosage problem [15]; however, another trial with an adjusted dosage is currently ongoing as a phase III trial.

Validation of the efficacy of this agent would be a step toward establishing prevention of recurrence. However, the use of molecular targeted agents will raise new problems that will need to be addressed, such as higher medical expenses for preventing tumor recurrence and determining the duration and purpose of preventive treatments.

**Intermediate-Stage HCC**

TACE is recommended for intermediate stage HCC; however, TACE is not a curative therapy, and therefore residual tumor remains and recurrence will inevitably occur. Combination therapy with TACE and anti-angiogenic agents is not just a simple combination of two treatment types. Anti-angiogenic agents inhibit the hypoxia-induced angiogenesis that immediately follows TACE, thereby greatly suppressing tumor recurrence and regrowth and potentially extending the duration of tumor suppression by TACE. This means that TACE will be performed less frequently, thereby helping to maintain liver function.

Globally, many clinical studies have used sorafenib as post-TACE adjuvant chemotherapy [16]. The Sorafenib or Placebo in Combination with Transarterial Chemoembolization for Intermediate-Stage Hepatocellular Carcinoma (SPACE) study, a phase II clinical trial of sorafenib that used drug-eluting beads loaded with doxorubicin [17], achieved its primary endpoint of time to radiologic progression, but the outcome was considered clinically insignificant and was thus essentially a negative result. Large-scale studies such as the Eastern Cooperative Oncology Group (ECOG) 1208 and TACE2 studies were terminated because insufficient numbers of cases were recruited. The Transcatheter Arterial Chemoembolization Therapy in Combination with Sorafenib (TACTICS) study conducted in Japan is the only large-scale study currently underway for this type of treatment.

Negative outcomes have also resulted for agents other than sorafenib, e.g., in the Brivanib Versus Placebo as Adjuvant Therapy to Trans-Arterial Chemoembolization in Patients with Unresectable Hepatocellular Carcinoma (BRISK-TA) study, a phase III study on brivanib [an inhibitor of vascular endothelial growth factor receptor (VEGFR) and fibroblast growth factor receptor (FGF)R] [18], and in the Orantinib in Combination with Transcatheter Arterial Chemoembolization in Patients with Unresectable Hepatocellular Carcinoma (ORIENTAL)
study, a phase III study on orantinib [an inhibitor of VEGFR, platelet-derived growth factor receptor (PDGFR), and FGFR].

**Advanced-Stage HCC**

A large number of trials have been conducted to develop molecular targeted agents that are more effective and less toxic than sorafenib for use as first-line therapy in advanced-stage HCC. However, these studies using sunitinib, brivanib, and linifanib could not prove superiority or noninferiority to sorafenib [19–21]. A phase III study of lenvatinib as first-line treatment is currently underway, and the results are eagerly awaited.

Studies using brivanib, everolimus (an inhibitor of mammalian target of rapamycin), or ramucirumab (a human monoclonal antibody against VEGFR-2) as second-line therapy in sorafenib-refractory or sorafenib-intolerant cases were unable to show the superiority of these agents over placebos [22–24]. Ramucirumab was highly effective in patients with high alpha-fetoprotein (AFP) levels [24], and therefore a phase III study of ramucirumab is currently underway in patients with advanced HCCs and AFP levels ≥400 ng/ml.

Other ongoing studies are evaluating the efficacies of three agents: regorafenib, which inhibits various kinases such as VEGFR, PDGFR, FGFR, TIE2, KIT, RET, and RAF; refametinib, which inhibits mitogen-activated protein kinase kinase (MEK); and tivantinib, which inhibits cMET.

As stated above, many drug development trials have ended with negative outcomes. A number of potential causes have been proposed to explain this fact, including drug toxicity and/or unsuitable trial design.

**Trial Design**

In general, to avoid bias in patient randomization, studies have clearly defined allocation factors. Possible issues associated with HCC patients include the handling of portal vein tumor thrombus and extrahepatic spread. All currently ongoing studies have been designed to allocate patients based on the presence of portal vein tumor thrombus, extrahepatic spread, or neither of these factors. In patients with HCC, portal vein tumor thrombus indicates extremely poor prognosis, and it seems that study outcomes are affected by handling portal vein tumor thrombus similarly to extrahepatic spread. If more patients with portal vein tumor thrombus are assigned to the real drug group, and thus more patients with extrahepatic spread are assigned to the placebo group, this creates a disadvantageous situation in the real drug group. This actually occurred in a trial of second-line therapy with brivanib [22]. Therefore, portal vein tumor thrombus and extrahepatic spread should be handled as independent allocation factors.

The period between post-treatment progressive disease and death is referred to as post-progression survival (PPS); therefore, progression free survival (PFS) + PPS = overall survival (OS). In general, even when a significant difference is observed in PFS, this difference will be negated if PPS also becomes progressively longer. Locoregional therapy is a very effective treatment for HCC, which makes HCC different from all other solid cancer types. Although molecular targeted agents are administered when locoregional therapy is no longer applicable, locoregional therapy is often performed again as post-trial treatment if molecular targeted agents are ineffective. This rarely happens with other cancers, demonstrating that it is largely unique to HCC, for which extremely effective locoregional therapies such as radiofrequency ablation or TACE are available. These post-trial treatments can extend PPS and inevitably minimize differences in the primary endpoint, OS [25].
Studies include patients intolerant to sorafenib among the subjects allocated for second-line therapy, which could also enhance the effect of post-trial treatment. Patients who were non-responsive to sorafenib likely had poor liver function and/or other systemic conditions. In contrast, in sorafenib-intolerant patients who experienced adverse effects, drug therapy was likely terminated after administering only a small amount of sorafenib, and therefore the tumor would have hardly progressed, leaving the patients in an extremely good condition and inevitably increasing the likelihood of various post-trial treatments, especially locoregional therapy. With this in mind, studies on second-line therapy should be performed only with patients who were refractory to sorafenib. In a currently ongoing study of regorafenib as second-line therapy, sorafenib-intolerant patients were excluded from the study (because the structural formula and toxicity profile of regorafenib are almost the same as those of sorafenib), and the results are awaited with interest.

Because of the presence of underlying chronic liver disease such as cirrhosis, the effect of not only the tumor itself but also the effect of liver function should be considered when predicting the prognosis of patients with HCC. Although the subjects of clinical studies on HCC are primarily Child-Pugh A, prognoses vary greatly between patients with a score of 5 and those with a score of 6. It may be necessary, therefore, to include Child-Pugh scores 5 and 6 as allocation factors.

**Enrichment Trial Design Based on Biomarker Selection**

Compared with other solid cancers, HCC is an extremely heterogeneous tumor. In particular, hepatitis virus-related HCC is associated with multicentric tumor occurrence, and the tumor characteristics can even vary nodule by nodule in the same patient. Furthermore, outcome greatly depends on liver function. Consequently, the effects of molecular targeted agents in recruited patients often vary in different HCC nodules. Indications for inclusion in clinical trials include Child-Pugh classification and tumor stage. Overall, it may look as if a homogeneous population has been selected, but in reality, patients are often a biologically heterogeneous group of individuals. Accordingly, patient selection needs to be narrowed down based on biological/genomic mutation homogeneity [26], which requires the use of biomarkers [27], as was done in the study of the cMET inhibitor tivantinib. Patients with high expression levels of cMET, a hepatocyte growth factor receptor, have poor prognoses, but a phase II study reported that tivantinib was efficacious only in patients with high cMET levels [28]. A placebo-controlled phase III study is currently underway to evaluate the effect of tivantinib in HCC tumors strongly expressing cMET. However, this does not solve the problem of nodule-dependent biomarker heterogeneity among tumor tissue samples from an individual patient. This problem makes it impossible to avoid sampling errors. Currently underway is a study of the MEK inhibitor refametinib using a RAS mutant as a biomarker. The abovementioned problems might be resolved when more effective serum biomarkers have been identified.

**Emerging Strategy: Immune Check Point Inhibitor**

Attention has recently focused on an antibody against programmed cell death-1 (PD-1), an immune checkpoint inhibitor. A presentation at the 2015 American Society of Clinical Oncology Annual Meeting reported excellent outcomes obtained with anti-PD-1 monoclonal antibody in a phase I study on HCC, demonstrating two cases of complete response and
seven cases of partial response, with a response rate of 23% [29]. Globally, a phase I expansion cohort study on HCC started this summer, 2015 and there are high expectations for this antibody. However, because of its extremely high cost, when used in clinical practice it may cause healthcare costs to soar. Therefore, it will be necessary to find a biomarker that selects the optimal patient subgroup and to carefully evaluate the agent from the perspective of pharmaceutical value and medical economics.

**Master Protocol Design**

It is extremely expensive to conduct clinical studies for drug development, and considerable effort is involved in recruiting patients. In the United States, a novel treatment approach for lung cancer (squamous cell carcinoma), called the Lung Cancer Master Protocol, was initiated in 2014 [30]. In this approach, subjects are screened against cancer-related gene mutations and are allocated to an appropriate clinical study based on the screening results, thereby facilitating the recruitment of patients and reducing the costs of developing effective drugs. Because medical economics necessitate that patients be assigned to receive appropriate agents, the results obtained by this program will certainly contribute to reducing medical costs. The approach will also clearly benefit patients with HCC, and therefore it is desirable to incorporate this program into the treatment of HCC as soon as possible. To make this approach successful, the cooperation of many pharmaceutical companies will be required. The cooperation of public agencies is also vital to instigate such an integrated public–private project.

**Conclusion**

The current status and future perspectives of systemic therapy for HCC were reviewed. To help minimize the difficulties associated with the development of novel drugs, the subjects selected for drug development clinical trials have been moving away from HCC patients with similar hepatic functions and tumor stages, as in conventional trials, to patients with homogeneous biological/genomic mutation characteristics based on biomarkers. To prevent medical costs from soaring, a broad perspective should be taken toward drug development by incorporating new concepts such as biomarker-driven trials or even the master protocol system.

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