Hepatic Oncology

Systemic therapy for hepatocellular carcinoma: why do we keep failing?

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Sorafenib, a multi-kinase inhibitor targeting VEGF receptor, PDGF receptor and Raf kinase has demonstrated a statistically significant improvement in overall survival in patients with advanced hepatocellular carcinoma (HCC) [1,2]. Since this demonstration, a number of other systemic agents (e.g., sunitinib, erlotinib, brivanib, linifanib, everolimus and ramucirumab) were tested as first-line or second-line therapy but failed, and sorafenib remains the only approved systemic agent for HCC since 2007 [3–8].

Biomarkers for right patient

Although substantial progress has been made [9,10], the molecular pathogenesis and the driver target of HCC are still unclear. In some cancers, driving mutations have been found and matched targeted agents have been developed (e.g., imatinib in chronic myeloid leukemia, trastuzumab in breast cancer and crizotinib in non-small-cell lung cancer); however, identification of driver targets in HCC is still challenging. Lack of driver targets results in lacking of a biomarker-enriched patient selection of HCC clinical trials. However, in contrast to, for

example, gefitinib significantly prolonged the survival of non-small-cell lung cancer patients with EGFR mutations compared with patients without EGFR mutations (EGFR mutations, 7.0 months; no EGFR mutations, 4.1 months; HR: 0.16; 95% CI: 0.05–0.49) [11,12]. Although sorafenib has survival benefits in unselected patients with advanced HCC, relevant clinical factors and biomarkers for predicting response to sorafenib have still not been identified [13,14]. The lack of biomarker-driven patient selection in clinical trials may explain at least in part their failure to show benefits of new drugs. A recent randomized Phase II trial showed similar overall survival rates for tivantinib, a c-MET tyrosine kinase inhibitor and a placebo (tivantinib, 6.6 months; placebo, 6.2 months; HR: 0.90; 95% CI: 0.57–1.40) in a second-line setting of unselected HCC patients, but significantly higher overall survival and time to progression rates in tivantinib-treated patients with high compared with low MET expression (overall survival: high MET, 7.2 months; low MET, 3.8 months; HR: 0.38; 95% CI: 0.18–0.81; time to progression: high MET, 2.7 months; low MET, 1.4 months; HR: 0.43; 95%

KEYWORDS

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CI: 0.19–0.97) [15]. Biopsy for biomarker research must be conducted prior to enrollment in future clinical trials in advanced HCC.

Fine-tuning for better outcomes

When comparing two treatments of molecularly targeted agents, stratification with clinical characteristics is important. Advanced stage of HCC includes wide-heterogeneous patients in the aspect of liver function, tumor size, tumor number, vascular invasion, extrahepatic metastasis and tumor differentiation. Small differences in patient characteristics may influence trial outcome. A recent study investigating prognostic factors for survival in HCC patients who failed first-line systemic therapy reported that patients with macrovascular invasion upon progression had worse prognosis than those with extrahepatic spread only [16]. Despite comparable extrahepatic spread, HCC patients in the placebo group of a second-line brivanib trial had more frequent vascular invasions than did patients receiving brivanib (31 and 18%, respectively), which may account in part for the negative results of this trial [6]. Designating macrovascular invasion and extrahepatic spread as separate variables may also be applicable in the first-line setting. In addition, tumor differentiation or stemness might affect trial outcomes. The hepatic lineage (i.e., hepatocyte, cholangiocytes, progenitor cells, stem cells) can acquire stem cell properties and become a cancer stem cell [17]. Hepatic cancer stem cells may contribute to the morphological and biological heterogeneity characteristics of HCC, which may be related with relapse after therapy and distant metastasis [9].

Underlying hepatitis & cirrhosis matters

Patients with HCC usually have three diseases – underlying chronic hepatitis, cirrhosis and the tumor itself. Heterogeneity of underlying etiology should be considered. Sorafenib has shown to be more effective in patients with hepatitis C virus infection than in those with hepatitis B virus infection [13]. In patients with hepatitis C virus infection, overall survival is significantly shorter in patients who received sunitinib [3]. Better stratification is also essential. Cirrhosis means hepatic altered drug metabolism and clearance. The Child–Pugh classification system for cirrhosis patient is useful in clinical practice for categorizing patients according to the severity of hepatic impairment, but it lacks the sensitivity to assess drug metabolism in patients

with liver disease [18]. Although most clinical trials consist of patients with well-preserved liver function (Child–Pugh class A), drug-related adverse events may outweigh antitumor effects. Despite favorable secondary outcomes such as higher rates of progression-free survival and time to progression, sunitinib-treated patients experienced more adverse effects than did sorafenib-treated patients, which may explain why they had lower overall survival rates than did sorafenib-treated patients [3]. A recent study showed a different outcomes of sorafenib treatment according to the Child score A5/A6 [19] and suggests a necessity of stratification with Child A5/A6 for clinical trials.

Issues for design & analysis

Even when patients with advanced HCC experienced disease progression after first-line systemic therapy, their prognosis was better than expected (median overall survival, 7.5 months) if they had well-preserved liver function (Child–Pugh class A) [16]. In HCC, even with extrahepatic spread, overall prognosis is largely dependent on preexisting advanced intrahepatic HCC [20]. For patients with good hepatic reserve, an individualized multidisciplinary approach focusing on control of advanced intrahepatic HCC may help [20,21]. Moreover, metastasectomy for selected patients whose liver function is preserved and whose intrahepatic tumor is under control may also be beneficial [22]. The primary end point of Phase III trials for advanced HCC is usually overall survival. It is possible that recent clinical trials included post-progression subsequent treatments and that these treatments improved overall survival if the patients retained sufficient hepatic reserve. Additionally types of progression (i.e., intrahepatic progression, vascular invasion or extrahepatic metastasis) showed different outcomes of second-line treatment [23]. Analyses of the results of post-progression subsequent treatments, if any, are necessary since the treatments may have affected overall survival, a primary end point in most of the recent Phase III trials.

Another important issue in the second-line setting may be the progression pattern on prior sorafenib treatment; the primary resistance and the secondary resistance. The disease control rate is related with the primary resistance and the median time to progression could be related with the secondary resistance. In the aspect of tumor biology, two types of resistance to

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prior sorafenib treatment might have different molecular characteristics. Stratification with progression pattern has to be taken into account to succeed the clinical trials.

Phase II trials should be conducted with a randomized design. The failures of recent Phase III clinical trials may also be largely due to a lack of efficacy. Most drugs have been tested in small-sized (less than 50 patients), single-arm Phase II trials [24,25]. It is reasonable to conduct randomized Phase II clinical trials to reduce selection bias and improve predictability to determine whether the agent should be carried forward into a Phase III trial.

Conclusion

Post-sorafenib molecular-targeted agents tested in randomized controlled Phase III trials failed to match or surpass the survival benefits of sorafenib. An 'all-comers' approach rather a well-stratified and/or biomarker-selected

approach could obscure the potential benefits of new drugs; therefore, identification of driver mutations in hepatocarcinogenesis is indispensable. Future trials should be conducted on a biomarker-enriched population with better stratification and after determining maximum tolerated doses in Phase I clinical trials of patients with hepatic impairments. Such trials will increase their probability of success and improve the overall survival of patients with advanced HCC.

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