

Letter to the Editor

Comprehensive Consideration before the Decision-Making of the Systemic Treatment in Patients with Advanced Hepatocellular Carcinoma

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Dear Editor,

We read with great interest the article by Rimassa et al. [1] in the current issue of *Liver Cancer* entitled “Systemic Treatment Options in Hepatocellular Carcinoma”. In this review, the authors summarize the current systemic therapies for hepatocellular carcinoma (HCC) and give some viewpoints that could assist physicians in the treatment decisions for patients with HCC. Although the information outlined is quite complete and can be utilized in the majority of situations in real-life HCC therapy, please allow us to make some further discussions about the problems we may meet. Our humble remarks are as follows.

To begin with, we have to acknowledge that as a very heterogeneous malignancy, the inclusion criteria of current clinical trials about HCC are almost based on nonspecific indexes such as liver function and tumor stage, etc. Therefore, though molecular targeted agents such as sorafenib are approved as the first-line treatment for advanced HCC, the application of sorafenib therapy is still lacking biomarkers [2]. The exploit of biomarkers for patient selection is necessary. The protooncogene *c-MET* may participate in the development of HCC, and its overexpression is also relevant for tumor recurrence, microvascular invasion, and poor overall survival (OS), etc. MET-inhibiting agents such as tivantinib, based on their characteristics, are investigated for the targeted treatment of MET-overexpressed HCC. Several clinical trials are being conducted. However, the level of *c-MET* as a biomarker to predict the benefit is still unclear [2, 3].

In addition, though that sorafenib was approved as the first-line treatment for advanced HCC is widely accepted, the application of it is still limited due to various causes including primary or acquired resistance, intolerance of its adverse events, and the inability to afford the high expense, etc. [4]. Systematic cytotoxic chemotherapy as the conventional treatment is less effective and easily leads to drug resistance. It seems that with the quickly developing small-molecule targeted agents, the continuing exploit of systematic chemotherapy is useless. However, clinical trials comparing the efficacy between sorafenib and cytotoxic chemotherapy are rare. Therefore, systematic chemotherapy for advanced HCC can still be considered. For example, OXA, a highly efficient drug with a relatively low toxicity, has been used clinically. The OXA-containing FOLFOX4 was approved by the Chinese Food and Drug Administration. A multicenter, open-label, randomized phase III study comparing FOLFOX4 and doxorubicin suggests a trend toward improved OS with FOLFOX4, along with increased progression-free survival and response rate (NCT00471965). It discloses the potential benefit patients can gain from systematic chemotherapy. In addition, systematic therapy combined with sorafenib can also be accepted.

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With the expanding treatment landscape of molecular targeted agents (sorafenib, lenvatinib, regorafenib, cabozantinib, and ramucirumab) and immune checkpoint inhibitors (nivolumab and pembrolizumab), the understanding of patient-centered outcomes such as health-related quality of life (QoL) is increasing, which can assist physicians in the decision-making for treatment sequencing in patients with advanced HCC [5]. Though the treatment of HCC is broadened, it still has a poor prognosis in advanced HCC. Therefore, patient-centered outcomes such as QoL are warranted. Despite benefits patients can gain from systemic treatment, however, it also negatively affects patients' QoL due to adverse events, which may further decrease their perspective of health and the duration of treatment. Therefore, the application of QoL in real clinical practice is necessary. In addition, it can also act as a factor independent from traditional primary endpoints of OS in clinical trials. With the increasing understanding of the health-related quality of life of patients, the decision-making of physicians may depend upon outcome priorities, adverse events, as well as patients' acceptance of the drugs. Therefore, all of these factors should be considered.

In conclusion, although sorafenib still acts as the first-line treatment, we cannot neglect the importance of other systemic therapies. In the decision-making for HCC treatment, besides molecular targeted agents and immune checkpoint inhibitors, systematic cytotoxic chemotherapy and other therapies should also be well considered. Moreover, compared to the rapid advancement in the investigation of molecular targeted agents, our understanding of patient QoL is still relatively immature both in clinical therapies and trials. Further investigation to develop such an understanding is warranted. In general, systemic therapy for advanced HCC still needs to be further discussed.

Disclosure Statement

The authors have no conflicts of interest to declare.

Author Contributions

All authors participated in the discussion of the letter. Mingyu Chen and Jiahao Hu wrote the letter together.

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