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Editorial

Hepatocellular carcinoma: Current situation and challenge

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Hepatocellular carcinoma (HCC) ranks the fourth cause of cancer-related death worldwide [1]. More than 50% newly diagnosed HCC patients are in China, while 70% of them are at advanced stage when they are diagnosed [2]. These patients have lost the opportunity of radical surgery and can only receive palliative care. Currently, the modality for these advanced stage HCC patients mainly include: targeted therapy, interventional therapy, chemotherapy, radiotherapy, and immunotherapy.

In terms of targeted therapy, sorafenib has been the first-line molecular targeted agent for HCC for a decade [3]. Many clinical trials attempting to develop new tyrosine kinase inhibitors (TKIs) agents failed to meet planned endpoints. In 2017, RESORCE trial made regorafenib the second-line treatment for HCC patients who progressed on sorafenib treatment [4]. REFLECT trial showed that the efficacy of lenvatinib is equivalent to sorafenib in term of overall survival (13.6 vs. 12.3 months) [5]. Lenvatinib was approved in HCC treatment on August 29, 2018 by China Food and Drug Administration. CELESTIAL phase 3 trial indicated that cabozantinib had survival benefit in sorafenib intolerant HCC patients [6]. Cabozantinib was approved as second-line treatment in HCC in 2019. However, whether sorafenib or lenvatinib is the first-line treatment has not reached a consensus.

Targeted therapy is often accompanied with obvious side effects and low efficacy. The precise screening based on next-generation sequencing technology benefits the patients. The concept of combination therapy gives us a novel strategy of treating advanced HCC patients. Combination therapy is more likely to counteract tumor heterogeneity. The TACTICS clinical trial combines transcatheter arterial chemoembolization (TACE) and sorafenib which showed favorable clinical outcome in advanced HCC patients [7]. Several clinical trials were carried out, such as combining targeted therapy with chemotherapy, radiotherapy, local regional therapy or immunotherapy. Some of them showed promising results while others did not. Application of targeted therapy and immunotherapy together is the most potential combination.

Cancer immunotherapy represented by immune checkpoint inhibitors (CPIs) has made substantial progresses since 2013 [8]. Compared to TKIs, CPIs have higher objective response rate and lower adverse effects which make them effective on solid tumors. Nivolumab and pembrolizumab are both antibodies specific for programmed death-1 (PD-1). The response rate of nivolumab for advanced HCC is 14.3% while pembrolizumab is 17%. The exciting results of two phase 2 trials (Checkmate-040 and KEYNOTE-224) made U.S. FDA promptly approve them as second-line therapy for advanced HCC patients with sorafenib resistance or intolerance. The cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) inhibitor also showed favorable response rate in advanced HCC patients [9]. It gives a hint that CPIs based therapy will play an important role in HCC treatment. The ongoing phase 3 clinical trial (CheckMate-459) comparing nivolumab and sorafenib may push CPIs to the first-line treatment of HCC.

Theoretically, anti-angiogenetic therapy has synergistic effects with immunotherapy [10]. The combination of CPIs and molecular targeted agents attracts broad attention in the treatment of HCC. A phase 1 study reported on *American Society of Clinical Oncology* in 2018 showed that combination of lenvatinib with pembrolizumab can get 42.3% response rate [11]. Adoptive cell transfer therapy (ACT) is another promising immunotherapy for HCC. It is an individualized therapy not limited by HCC clinical stage and can potentially deplete circulating tumor cells to prevent tumor recurrence. Although chimeric antigen receptor T-cell (CAR-T) immunotherapy can achieve very good results in hematological malignancies, its application in HCC is still limited. How to select tumor specific antigen and promote cell infiltration in tumor are crucial for treatment efficiency. Because CPIs can reduce adverse effect of CAR-T therapy, combination of CAR-T and CPIs may be a good choice for treating HCC. Undoubtedly, the landscape of HCC treatment is going to change drastically soon due to fast-growing different combination strategies.

Given the context of underlying liver disease of advanced HCC patients, we should also raise concern about the toxic effects of these combined treatments. On the other hand, how to evaluate perfect order and timing of combination treatment is also very important. As we can see, most of clinical trials were limited in sample size and lack of significant biomarkers to screen enrolled patients. Large-scale clinical trials based on precisely selected patients are urgently needed to verify ideal combination of HCC treatments.

Above all, we have made great progress in treating advanced HCC patients in the past decade. For these patients, we should

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choose a patient-centered, tolerated treatment balancing between improving the quality of life and clinical outcome. The future HCC treatment relies on combination therapy and multidisciplinary management.

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ZJY proposed and designed the study. LZ wrote the first draft. ZJY contributed to the interpretation of the study and to further drafts. ZJY is the guarantor.

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Ethical approval

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Competing interest

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