Editorial Commentary

BCLC stage C hepatocellular carcinoma: modern therapeutic strategies in the age of immunotherapy

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Comment on: Zhang TQ, Geng ZJ, Zuo MX, *et al.* Camrelizumab (a PD-1 inhibitor) plus apatinib (an VEGFR-2 inhibitor) and hepatic artery infusion chemotherapy for hepatocellular carcinoma in Barcelona Clinic Liver Cancer stage C (TRIPLET): a phase II study. Signal Transduct Target Ther 2023;8:413.

Keywords: Hepatocellular carcinoma (HCC); immunotherapy; hepatic arterial infusion chemotherapy (HAIC)

Submitted Mar 22, 2024. Accepted for publication Sep 29, 2024. Published online Oct 29, 2024.
doi: 10.21037/jgo-24-37
View this article at: https://dx.doi.org/10.21037/jgo-24-37

A recent issue of *Signal Transduct Target Ther* provides a thought-provoking study by Zhang and colleagues about a phase II trial about the use of camrelizumab [a programmed cell death protein 1 (PD-1) inhibitor] plus apatinib [a vascular endothelial growth factor receptor-2 (VEGFR-2) inhibitor] and hepatic artery infusion chemotherapy for hepatocellular carcinoma (HCC) in Barcelona Clinic Liver Cancer stage C (BCLC-C) (1). This trial contributes to the existing body of knowledge on treating patients with HCC in the BCLC-C category.

Primary liver malignancies ranked as the world's sixth most common cancer type and held the third highest position in cancer-related deaths (2,3). HCC represents 75–85% of all liver cancer cases. The last update by the BCLC group on prognosis and treatment strategies was recently published including some new recommendations, such as the use of transarterial radioembolization (TARE) in patients with a BLCL-B (4). The current approach for HCC involves classifying patients based on tumor burden and symptoms to predict prognosis. For patients classified as BCLC-C, systemic chemotherapy is often recommended. Even so, various effective treatment options are available for eligible patients in the first, second, and further lines of therapy (5).

Currently, the preferred initial treatment for unresectable or metastatic HCC is the combination of atezolizumab [an anti-programmed death-ligand 1 (PD-L1) agent] and bevacizumab [a vascular endothelial growth factor (VEGF) inhibitor] due to its enhanced survival advantages compared to sorafenib (6-8). This combination therapy shows increased PD-L1 on tumor cells and increased PD-1 expression on $CD4^+$ cells (9). Recently, it has been demonstrated that the combination of durvalumab and tremelimumab outperforms sorafenib in response rate (20% compared to 6%) and overall survival (OS) (with a median of 16.4 *vs.* 13.8 months) (10). However, this combination did not show an impact on progression-free survival (PFS), with medians of 3.78 and 4.07 months respectively. Tyrosine kinase inhibitors (TKIs) like sorafenib or lenvatinib remain options when other treatments are unsuitable (5).

Different strategies with anti-PD-1 antibodies have been described in the treatment of HCC patients previously treated with sorafenib. The CheckMate 040 study investigated the effectiveness and safety of various dosages of nivolumab in 262 participants, some of whom had been previously treated with sorafenib with an objective response rate (ORR) of 15% in the dose-escalation phase and 20% in the dose-expansion phase with nivolumab treatment (11). Additionally, the median OS was observed to be 15 months in

the dose-expansion phase. Two phase III trials, CheckMate 459 and KEYNOTE-240 (12,13), exploring nivolumab (*vs.* sorafenib) as a first-line treatment (median OS: 16.4 *vs.* 14.7 months) and pembrolizumab (*vs.* placebo) as a second-line therapy (median OS: 13.9 *vs.* 10.6 months), did not demonstrate statistical significance for their primary endpoints. KEYNOTE-394 trial adds to this understanding, evaluated the effectiveness of pembrolizumab in Asian patients with advanced HCC who had prior treatment with sorafenib, compared to a placebo (14). The results indicated statistically significant enhancements in OS, as well as PFS and ORR. Another trial, KEYNOTE-524, showed that lenvatinib combined with pembrolizumab was effective and safe in treatment-naïve unresectable HCC, but this was only assessed in the first-line setting (15).

CARES-310 (16), an international phase 3 trial conducted across 95 sites in 13 countries, focused on patients with unresectable or metastatic HCC without prior systemic treatment. Participants were either treated with camrelizumab intravenously every two weeks and daily oral rivoceranib (formerly apatinib, a VEGFR-2 inhibitor), or with oral sorafenib twice daily. The camrelizumab-rivoceranib combination showed an improvement in median PFS (5.6 *vs.* 3.7 months) and OS (22.1 *vs.* 15.2 months) compared to sorafenib, positioning it as a potential first-line treatment for this patient group. Recently, a phase I study by Xu *et al.*, and a phase II study called RESCUE (17), enrolled patients with advanced HCC, whether they were treatment-naïve or had been refractory/intolerant to first-line targeted therapy. The effectiveness and tolerability of the camrelizumab plus apatinib combination in the first-line group were similar to those observed with pembrolizumab plus lenvatinib and atezolizumab plus bevacizumab. Moreover, the efficacy of this combination strategy in the second-line group (ORR 22.5%) aligned with the Food and Drug Administration (FDA)-approved second-line combination, nivolumab plus ipilimumab [an anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4) antibody] (11). In Western countries, patients can be treated with a combination of nivolumab and ipilimumab. This regimen has demonstrated considerable effectiveness in early-phase trials, and its efficacy is awaiting confirmation from a phase III clinical trial that has already concluded (the CheckMate-9DW trial) (18).

Different randomized clinical trials have attempted to demonstrate the usefulness of different combinations of chemotherapy with the aim of improving oncologic outcomes in patients with advanced unresectable HCC. The addition of pembrolizumab to lenvatinib as first-line therapy for advanced HCC did not meet prespecified significance for improved OS and PFS *vs.* lenvatinib plus placebo (19). In the COSMIC-312 study, first-line cabozantinib plus atezolizumab did not improve OS *vs.* sorafenib (20). On the other hand, in RATIONALE-301 trial, tislelizumab demonstrated OS benefit that was noninferior *vs.* sorafenib, with a higher ORR, while median PFS was longer with sorafenib (21).

Hepatic arterial infusion chemotherapy (HAIC) is recognized for its direct delivery of chemotherapy to liver tumors, resulting in higher local drug concentration and reduced systemic side effects (22). At the moment, HAIC it is not currently a standard of treatment for patients with advanced HCC but combination treatment containing immunotherapy may be an area to develop. In a recent meta-analysis, the authors determined that for patients with inoperable HCC, HAIC may provide greater benefits than the conventional transarterial chemoembolization (TACE) therapy (23). The data showed that patients who were treated initially with HAIC experienced improved OS and enhanced PFS, when compared to those who underwent TACE.

In the treatment of advanced HCC, the use of hepatic arterial infusion chemotherapy of infusional fluorouracil, leucovorin, and oxaliplatin (HAIC-FO), combining oxaliplatin and fluorouracil, has been proposed by the Chinese Society of Clinical Oncology and the adapted Pan-Asiatic Guidelines of the European Society for Medical Oncology (24), especially when there is macrovascular invasion. A phase III trial, FOHAIC-1 (25), compared HAIC-FO and sorafenib in advanced HCC patients without prior systemic therapy. This study primarily included patients with significant intrahepatic tumor load and limited extrahepatic metastases and concluded that HAIC-FO was more effective than sorafenib in extending median OS (13.9 *vs.* 8.2 months). Tumor downstaging was observed in 16 patients (12.3% of 130) receiving HAIC-FO, including 15 who underwent curative surgery or ablation, resulting in a median OS of 20.8 months. He *et al.* (26) also reported similar downstaging benefits using HAIC-FOLFOX combined with sorafenib, and a study presented at the European Society for Medical Oncology in 2020 indicated higher resection rates in unresectable early- or intermediate-stage HCC patients treated with HAIC-FOLFOX (23.9%) compared to those receiving TACE (11.5%) (27). However, more research is needed to compare HAIC chemotherapy with the commonly used first-line immune checkpoint inhibitors, particularly in treating advanced high-risk HCC.

The TRIPLET study by Zhang *et al.* (1), explored the

efficacy of combining HAIC-FOLFOX with camrelizumab and apatinib. This single-arm phase II trial primary endpoint was to assess the ORR and PFS. A total of 35 patients were enrolled in the study. The results showed a higher ORR of 77.1% and a prolonged PFS of 10.38 months compared to other studies such as RESCUE (17) or CARES-310 (16), and also reported a significant percentage of patients achieving disease downstaging and candidates for curative treatments (17.1%) compared to FOHAIC-1 (12.3%) (25) or HAIC-FOLFOX (26) (12.8%).

Moreover, TRIPLET included patients with high-risk features like portal vein tumor thrombus and large tumor size, showing promising response rates in this subgroup. The study also assessed patient quality of life, noting an initial decline followed by improvement over time. Although there was a transient decline in patient quality of life within the initial four treatment cycles, it generally improved thereafter. Interestingly, it appeared that the improvement of quality of life (QoL) coincided with the control of disease. In addition, TRIPLET showed that the triple therapy could be well-tolerated, with adverse events aligning with known safety profiles.

As the authors point out, there are several limitations in this study that need to be considered. First, it is a phase II clinical trial without a control group, and that difficult to definitively attribute the observed improvements to the combined systemic therapy following HAIC. The sample size is limited and there is a possibility to concerns overestimating the ORR. To further evaluate the effectiveness of the triple therapy, a phase 3 randomized controlled trial is underway, comparing it with the combination of camrelizumab and apatinib in patients with HCC at BCLC-C. In addition, an important aspect of the TRIPLET study, in terms of its applicability to the global HCC population, is its focus on patients primarily infected with the hepatitis B virus (HBV), which is a leading cause of HCC in China. This contrasts with Europe, where HCC is more frequently linked to other causes like alcohol-related liver disease.

It is important to emphasize that the use of HAIC can be associated with liver function deterioration thus precluding the use of systemic agents (TKIs, immune checkpoint inhibitors or anti-VEGF) that require a preserved liver function (usually Child-Pugh A class). In future clinical trials, combination therapies using HAIC should be compared with a combination treatment strategy based on TKIs and immune checkpoint inhibitors (without HAIC). This combination has recently shown very promising efficacy and safety, in a comprehensive review analyzing the pathogenetic rationale of this combination treatment strategy and the risk of adverse events (immune-related adverse events or risk of liver function impairment), which requires optimal patient selection (28). This is a crucial point for future clinical trials comparing OS (which could also be affected by impaired liver function) and safety of treatment strategies with and without HAIC. In conclusion, the TRIPLET study demonstrates promising outcomes, surpassing those of preceding studies, by employing an innovative treatment combination that previously lacked extensive evidence. This leads us to consider the possibility of a new first-line therapeutic approach for treating the condition. However, further phase 3 clinical trial are needed to confirm these promising results.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Journal of Gastrointestinal Oncology*. The article has undergone external peer review.

Peer Review File: Available at https://jgo.amegroups.org/article/view/10.21037/jgo-24-37/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.org/article/view/10.21037/jgo-24-37/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Lopez-Lopez V, Sánchez-Esquer I, Ramírez P, Robles-Campos R. BCLC stage C hepatocellular carcinoma: modern therapeutic strategies in the age of immunotherapy. J Gastrointest Oncol 2024;15(5):2367-2371. doi: 10.21037/jgo-24-37