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Letters to the editor

Critical commentary on camrelizumab-based triple therapy for unresectable hepatocellular carcinoma

Dear Editor:

The retrospective multicenter study by Jiang et al. [1] investigates the efficacy of camrelizumab combined with transcatheter arterial chemoembolization (TACE) and sorafenib or lenvatinib for unresectable hepatocellular carcinoma (HCC). While the results are encouraging, several important methodological and interpretative flaws limit the credibility and generalizability of their findings.

First, the study's design introduces substantial treatment allocation bias. Patients were not randomized, and treatment decisions were influenced by physician and patient preference, as well as economic factors. Although baseline characteristics were superficially balanced, the lack of adjustment for hidden confounders, such as comorbidities, tumor biology, and access to supportive care, severely threatens internal validity. Retrospective comparisons without propensity scoring or inverse probability weighting are increasingly considered suboptimal in contemporary oncologic research [2].

Second, the study inappropriately combines sorafenib and lenvatinib into a single comparator group. This masks important pharmacological and clinical differences between the two agents [3]. Given lenvatinib's superior progression-free survival compared to sorafenib in prior trials, any survival advantage attributed to the addition of camrelizumab may be skewed if more patients in the "double therapy" group received the less effective agent [4].

Third, heterogeneity in TACE technique and timing further weakens the conclusions. Although the authors describe conventional transcatheter arterial chemoembolization (c-TACE), procedural variability between centers is inevitable, especially without strict protocol enforcement. Moreover, the undefined timing of camrelizumab initiation relative to TACE likely introduced variations in immune microenvironment priming [5].

Additionally, the modest difference in progression-free survival (7.2 vs. 5.2 months) — despite being statistically significant — might lack clinical relevance in the context of treatment-related toxicities and cost. Furthermore, the lack of significant improvement in objective response rate (ORR) and disease control rate (DCR) raises questions about whether the observed survival benefit stems from true antitumor activity or other unmeasured factors such as patient selection.

Finally, the small sample size and exploratory subgroup analyses (e.g., HBV-related HCC) should be viewed cautiously. Overinterpretation of subgroup results from underpowered cohorts is a well-known pitfall in oncologic studies.

In conclusion, Jiang et al. provide early evidence suggesting a potential benefit of camrelizumab-based triple therapy. However, the methodological weaknesses and inherent biases of this study necessitate confirmation through large-scale, prospective randomized trials before changing clinical practice.

Author contributions

INH conceptualized the idea. INH wrote the main manuscript text.

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Declaration of competing interest

None.

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