Editor-in-Chief
World Journal of Gastrointestinal Oncology
December 26, 2023

Ref.:
Manuscript NO.: 88673
Efficacy and Predictive Factors of Transarterial Chemoembolization Combined with Lenvatinib Plus PD-1 inhibition for Unresectable Hepatocellular Carcinoma
submitted to *World Journal of Gastrointestinal Oncology*

Dear editor,

Thank you for your kind letter and detailed comments on our manuscript entitled " *Efficacy and Predictive Factors of Transarterial Chemoembolization Combined with Lenvatinib Plus PD-1 inhibition for Unresectable Hepatocellular Carcinoma*" The constructive comments have enabled us to improve our work. In the decision letter to our previous submission (**Manuscript NO.: 88673**), you suggested we make revisions on our manuscript. We believe we can respond appropriately to the reviewer' comments.

We have carefully answered the questions raised by the reviewer. The changes made in the article were highlighted in yellow. Appended to this letter are reproduced comments and our point-by-point responses to the question raised by the reviewer. We have verified the geographical information and the name of commercial products that keep them up to date, and went over the detailed information of bibliography.
We hope that our revised manuscript is qualified for further consideration of publishing in World Journal of Gastrointestinal Oncology. Please feel free to contact us if you have any questions.

Kindest regards, yours sincerely

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Response to the Comments

Reviewer #1:
Scientific Quality: Grade C (Good)
Language Quality: Grade C (A great deal of language polishing)
Conclusion: Major revision
Specific Comments to Authors:

1. **Materials and methods: there was no mention about the operator(s) of TACE and whether one or more interventional radiologists performed the procedures.**

Response: Thank you for your helpful suggestion, and we are sorry for not making it clear. There were two interventional radiologists who performed TACE procedures more than 15 years. We have described it and marked yellow in the text.

2. **There is no mention regarding the timing of follow-up e.g when AFP was repeated in relation to TACE?**

Response: Thank you for your helpful suggestion, and we are sorry for not making it clear. AFP was repeated every 4 weeks. The corresponding part was marked yellow in the text.

3. **No mention on what basis patients received different types of PD-1 antibody? Was it random or selected?**

Response: Thank you for your helpful suggestion. The types of PD-1 antibody was finally depended on patients' own choices according to offered guideline recommendation, individual financial condition, and so on. The corresponding part was marked yellow in the text.

4.Exclusion criteria should include:

(1) poor patient compliance (such as failing to visit the clinic as scheduled, leading to incomplete data); (2) medical comorbidities, including severe cardiac, pulmonary, renal, or coagulation dysfunction; (3) previous treatment with other targeted drugs or PD-1 immunotherapy

Response: Thank you for your helpful suggestion. We have added this part into exclusion criteria. The corresponding part was marked yellow in the text.

5.Treatment-related toxicity: with the majority being grade 1-2 [There is no mention of the grading of side effects and its reference].

Response: Thank you for your helpful suggestion. All AEs during the combination therapy were recorded and evaluated based on the Common Terminology Criteria for Adverse Events Version 5.0 [1] and standard laboratory examinations.

6.Discussion: one of the drawbacks is that being single-centre rather than multicentre analysis.

Response: Thank you for your helpful suggestion. This a single-center study which may lead to selection bias. We had pointed it out in limitation part (marked yellow), and we could further expand our study population following multicenter design.

7.Informed consent was obtained from all individual participants included in the study.

If the study was retrospective, how consent has been taken. It is better to mention that all patients consented to undergo TACE before the procedure and consented to receive the medications after discussion of side effects and alternatives.

Response: Thank you for your helpful suggestion. This a retrospective study and all patients consented to receive TACE before operation and combined medications after discussion of side effects and alternatives. We have revised the corresponding part and marked yellow in the text.

8.From Table S2, the percentage of patients who received further treatment after TACE is about 85 % and this definitely will affect the OS (we had the longest median OS of 26.43 months).

Response: Thank you for your helpful suggestion. Considering the long OS of 26.43 months, the analysis of subsequent treatment may be one of the reasons that affect the OS. We have discussed in the text and marked yellow.

9.From table 2: PR + PD = 72 patients however, from table S2, the number of patients who received Subsequent treatment after TACE+Lenvatinib+PD-1 combination = 87 patients

Is there any explanation why 15 patients with no evidence of PR or PD required further treatments?

Response: Thank you for your helpful suggestion. In the table 2, we assessed the best overall response (CR, PR, SD, PD), which is the best recorded therapeutic effect from the start of treatment until disease progression or recurrence. Our results showed that PR + SD + PD = 92. There were 87 patients received subsequent treatment. Some patients kept their beat overall response till the follow-up ended, however, the other patients' conditions went worse during follow-up, such from PR to PD due to new lesions found. So these kind of patients need to receive subsequent treatment for further disease control.

10.The discussion did not include similar studies and compare the results of this study versus others.

Important articles to help:

1. **Cai M, Huang W, Huang J, Shi W, Guo Y, Liang L, Zhou J, Lin L, Cao B, Chen Y, Zhou J and Zhu K (2022) Transarterial Chemoembolization Combined With Lenvatinib Plus PD-1 Inhibitor for Advanced Hepatocellular Carcinoma: A Retrospective Cohort Study. Front. Immunol. 13:848387. doi: 10.3389/fimmu.2022.848387**
2. **Qu S, Zhang X, Wu Y, Meng Y, Pan H, Fang Q, Hu L, Zhang J, Wang R, Wei L and Wu D (2022) Efficacy and Safety of TACE Combined With Lenvatinib Plus PD-1 Inhibitors Compared With TACE Alone for Unresectable Hepatocellular Carcinoma Patients: A Prospective Cohort Study. Front. Oncol. 12:874473. doi: 10.3389/fonc.2022.874473**
3. **Wang J, Zhao M, Han G, Han X, Shi J, Mi L, Li N, Yin X, Duan X, Hou J, Yin F. Transarterial Chemoembolization Combined With PD-1 Inhibitors Plus Lenvatinib Showed Improved Efficacy for Treatment of Unresectable Hepatocellular Carcinoma Compared With PD-1 Inhibitors Plus Lenvatinib. Technol Cancer Res Treat. 2023 Jan-Dec;22:15330338231166765. doi: 10.1177/15330338231166765. PMID: 37161343; PMCID: PMC10185979.**
4. **Zou X, Xu Q, You R, Yin G. Correlation and efficacy of TACE combined with lenvatinib plus PD-1 inhibitor in the treatment of hepatocellular carcinoma with portal vein tumor thrombus based on immunological features. Cancer Med. 2023 May;12(10):11315-11333. doi: 10.1002/cam4.5841. Epub 2023 Mar 23. PMID: 36951443; PMCID: PMC10242346.**

Response: Thank you for your helpful suggestion. All these four articles included TACE+PD1+Lenvatinib cohort and then assessed their efficacy. Compared with previous work, our study had the longest OS (26.43 months). As for enrolled number of patients receiving TACE+PD1+Lenvatinib, these studies only had small study population, less than 70 patients, but we included 102 patients. We have discussed in the text and marked yellow.

Reference

[1] NCI. National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v5.0. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. 2017. Accessed November 8, 2018.

Reviewer #2:
Scientific Quality: Grade A (Excellent)
Language Quality: Grade A (Priority publishing)
Conclusion: Accept (High priority)
Specific Comments to Authors:
Good manuscript

Response: Thank you for your helpful comments.