Peer Review File

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Reviewer A

It is a fascinating study investigating the progression-free survival of patients with HCC treated with TACE/Anlotinib compared to those treated with TACE alone. Although the number of included patients is small and the follow-up period is short, the results are interesting enough.

Comments to authors

1. In the Introduction section, please ensure to add references for the studies mentioned in the last paragraph of page 3 and the first paragraph of page 4.

Reply 1: The paragraph reference has been added and the other references have been rearranged（see the last paragraph of page 3 and the first paragraph of page 4.）
Changes in the text: Add 11th reference ("Guo W, Chen S, Wu Z, et al. Efficacy and Safety of Transarterial Chemoembolization Combined With Anlotinib for Unresectable Hepatocellular Carcinoma: A Retrospective Study. Technol Cancer Res Treat 2020;19:1533033820965587. ")

2. Add the reference for the statement about the immunomodulatory properties of anlotinib on page 4 ("Additionally, anlotinib demonstrates immunomodulatory properties.....ultimately remodeling the therapeutic microenvironment.")

Reply 2: The paragraph reference has been added and the other references have been rearranged（page 4.）
Changes in the text: Add 7th reference ("He C ,Wu T ,Hao Y .Anlotinib induces hepatocellular carcinoma apoptosis and inhibits proliferation via Erk and Akt pathway[J].Biochemical and biophysical research communications, 2018, 503(4):3093-3099. ")

3. For the adverse events section and tables 2 and 3, please include the actual number of patients in addition to the percentages.

Reply 3: Tables 2 and 3 have been modified as required（Tables 2 and 3）
Changes in the text: In Table 2 and Table 3, the actual number of patients, in addition to the percentage, is shown

4. While the two groups of patients did not differ in terms of the Child-Pugh score, please also consider including the MELD and ALBI scores for comparison.

Reply 4: It is true that ALBI score can eliminate the subjective factors of ascites and hepatic encephalopathy in Child-Pugh score to a certain extent, and quantitatively analyze bilirubin and albumin to assess liver function more accurately, and MELD score to evaluate the

priority of liver transplantation of patients. However, in this study, there was no statistical significance in the above indicators between the two groups of patients. In addition, Child-Pugh score is the most commonly used in patients with cirrhosis and is easy to obtain clinically. Therefore, we give priority to Child-Pugh score after referring to other literatures. To improve the understanding of the treatment effects and to enable more granular comparisons, it would be valuable to include MELD and ALBI scores in future studies. These scores could help in stratifying patients based on liver function severity and predicting outcomes more accurately, thereby tailoring the therapeutic approach accordingly.

5. It would be helpful to explain the rationale behind including a proportion of BCLC-C stage patients, as TACE is typically recommended for BCLC-B patients. Additionally, please describe the characteristics of these BCLC-C patients.

Reply 5: The inclusion of BCLC-C stage patients in this study was grounded in the recognition that hepatocellular carcinoma (HCC) is often diagnosed at advanced stages, particularly in regions with high prevalence, such as China. While transarterial chemoembolization (TACE) is primarily recommended for patients in the intermediate stage (BCLC-B), there is growing interest in exploring its efficacy in combination with systemic therapies for more advanced stages, including BCLC-C. This study aimed to assess whether adding anlotinib,could enhance the efficacy of TACE in extending progression-free survival (PFS) and potentially improving overall outcomes for patients with intermediate and advanced HCC.

The study included patients with BCLC-C stage HCC who had specific characteristics:

Hepatic Function: Patients had Child-Pugh grade A or B liver function, ensuring adequate hepatic reserve to tolerate the treatment.

Karnofsky Performance Status (KPS): Patients had a KPS score of over 60, indicating they were in relatively good functional status despite the advanced stage of cancer.

Inclusion Criteria: The patients included were not suitable for surgical resection, either due to the extent of the disease or refusal of surgery. They had no prior treatment for HCC and were between the ages of 18 and 75 years.

6. Please provide an explanation for choosing the RESIST criteria over the m-RESIST criteria for evaluating treatment response.

Reply 6: The study chose to use the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria over the modified RECIST (mRECIST) criteria for evaluating treatment response. The RECIST 1.1 criteria provide a standardized method for assessing tumor response to treatment based on changes in the size of target lesions, which is widely accepted and applied across various types of solid tumors, including hepatocellular carcinoma (HCC). This standardization ensures consistency and comparability of results across different studies and clinical settings.

In contrast, the mRECIST criteria are specifically tailored for HCC, taking into account not only the size but also the viable (enhancing) portion of the tumor, particularly relevant in the context of treatments like transarterial chemoembolization (TACE) that induce necrosis rather than shrinking the tumor. However, the adoption of mRECIST can sometimes be more subjective and require specialized imaging expertise, which might not be uniformly available.

Given these considerations, the study's use of RECIST 1.1 criteria allows for a broader and more universally comparable evaluation of treatment efficacy, especially important in clinical trials aimed at broader applications and regulatory submissions.

7. It would be valuable to analyze and present any differences in progression-free survival and overall survival between the two groups when Child-Pugh A and Child-Pugh B patients were separately evaluated.

Reply 7: We couldn't agree with you more, but unfortunately，the available data does not provide a detailed breakdown of PFS and OS specifically for Child-Pugh A and B patients. Further analysis and extended follow-up would be required to draw more precise conclusions regarding the differential impact of the treatment on these subgroups：

（1）PFS

The study indicated that the combination of TACE with anlotinib significantly improved PFS compared to TACE alone. However, when stratifying the results by Child-Pugh class, detailed subgroup analysis specifically isolating Child-Pugh A and B patients was not explicitly provided. Nevertheless, the overall PFS was notably longer for the combination therapy group, suggesting a potential benefit across the spectrum of liver function statuses included in the study.

（2）OS

Similarly, the overall survival (OS) was not reached during the study period, with only early trends available. There was no specific breakdown of OS by Child-Pugh class. It is noted that OS is a critical endpoint that may require longer follow-up to fully assess differences between the treatment groups, especially considering the varying liver function statuses.

8. Clarify and explain the Anlotinib protocol better. It is a little bit confusing.

Reply 8: we have modified our text as advised (see Page 8, line 211)"

Changes in the text: Anlotinib hydrochloride was administered orally at a dose of 12 mg once daily, taken before breakfast. This treatment commenced 3 to 7 days after the initial transarterial chemoembolization (TACE) procedure. The timing was chosen to allow for adequate recovery from the TACE procedure and to minimize potential adverse interactions. If intolerable adverse effects were observed at the 12 mg dose, the daily dose was reduced to 10 mg. This

reduction aimed to maintain the therapeutic benefits of anlotinib while minimizing adverse effects. Should the adverse effects fully subside, the dose could be cautiously escalated back to 12 mg, ensuring patient safety and tolerability. Subsequent TACE treatments were administered only if the patient showed no signs of hepatic impairment. This assessment was based on comprehensive laboratory evaluations, including liver function tests such as aminotransferase and bilirubin levels. Ensuring stable liver function was crucial before proceeding with additional TACE sessions to prevent further liver damage. The continuation of anlotinib treatment was contingent on several factors:①Disease Progression: The treatment was stopped if the disease progressed.②Voluntary Withdrawal: Patients could choose to withdraw their consent for treatment at any time.③Intolerable Toxicity: The occurrence of severe adverse effects necessitated discontinuation.However, if the investigator deemed that the patient could still derive therapeutic benefit from anlotinib, the treatment was continued, even amidst the above considerations. This decision was made on a case-by-case basis, reflecting a personalized approach to treatment management.

9. Please specify the number of radiologists involved in evaluating treatment response using the RESIST criteria and indicate if there was any intra-observer and inter-observer variability.

Radiologist Involvement and Variability Assessment

Reply 9: We added Radiologist Involvement and Variability Assessment to the original method section. (see page8,line 224)

Changes in the text: In this study, two experienced radiologists independently assessed the imaging studies for treatment response using the RECIST 1.1 criteria. Both radiologists were blinded to the treatment allocations and patient outcomes to minimize bias in their evaluations.

Reviewer B

This manuscript is very interesting and a new idea as far as I am concerned.
Is it possible to continue this study by comparing patients with intermediate or advanced HCC by comparing HCC treatment with the combination of TACE with Anlotinib with TACE and Sorafenib for PFS outcomes?

Reply: It is very interesting and meaningful to continue this study by comparing the PFS results of HCC treatment with TACE combined with amlotinib and TACE combined with sorafenib, and we hope to continue to discover more survival indicators after this paper, which has highlighted the therapeutic value of TACE combined with amlotinib.