Peer Review File

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Reviewer A

Authors provide a detailed and updated systematic review with meta-analysis for the topic - "hepatic arterial infusion chemotherapy and sorafenib for advanced hepatocellular carcinoma". It is a very thoroughly written manuscript with good attention to limitations, conclusions.
I had minor suggestions to make:
Comment 1:
- The authors have very well calculated the relative measures of outcomes, such as OS, PFS, DCR. It would be great if they could calculate absolute measures of efficacy as well for these comparisons so that we know whether HAIC increases overall survival by a few days vs months when compared to sorafenib
Reply 1: Special thanks to you for your good comments. It would be helpful for doctors or the patients to evaluate the direct effect of different treatment based on absolute measures. However, the absence of generally accepted methods to pool the absolute measures of the median overall survival makes it difficult. Moreover, the pooled estimates by using the median OS may be controversial, according to Cochrane handbook, "it is not appropriate to analyze time-to-event data using methods for continuous outcomes (e.g., using mean times-to-event), as the relevant times are only known for the subset of participants who have had the event. The most appropriate way of summarizing time-to-event data is to use methods of survival analysis and express the intervention effect as a hazard ratio." Ref: https://training.cochrane.org/handbook/current/chapter-06#section-6-8.
For the reasons above, absolute measures of the median overall survival were not presented in this article.

Comment 2:
- There have been multiple chemotherapies and immunotherapy approaches that have shown promise over recent time such as bevacizumab plus atezolizumab, nivolumab, etc. These should be mentioned within the introduction.
Reply 2: It is true as Reviewer suggested that immunotherapy approaches have emerged as a promising treatment for cancer. we have modified our text as advised (see Page 5, line 77). Thanks to you for your good comments.
Changes in the text: Page 5, line 77 "Recently, immunotherapies have emerged as a promising treatment for cancer, including liver cancer. Immunotherapies including Nivolumab and Pembrolizumab have been approved for advanced hepatocellular carcinoma by FDA (6). In addition, the combinations of atezolizumab and bevacizumab significantly improve overall survival as compared with sorafenib. Despite those encouraging results, the adverse effects remained high in both groups. Grade 3 or 4 adverse events occurred in 56.5% of patients who received atezolizumab–bevacizumab and in 55.1% of patients who received

sorafenib (7). Moreover, patients with history of autoimmune disease, coinfection with hepatitis B or hepatitis C virus had always been excluded for immune checkpoint inhibitor trials." was added.

Reviewer B

Comment 3

Authors showed a meta-analysis comparing HAIC and sorafenib for advanced HCC. Present work was well addressed and well written although similar works were already present. Authors compared the treatment effect of HAIC with that of sorafenib. But sorafenib is one of the approved TKIs for advanced HCC. Authors should discuss also other TKIs such as lenvatinib. Furthermore the possibilities of the combination therapies with HAIC and TKIs should also be discussed.

Reply 3: We are very sorry for our negligence of discussion of other TKIs and combination therapies with HAIC and TKIs. we have modified our text as advised (see Page 5, line 73; Page 12, line 254). Thanks to you for your good comments.

Changes in the text: Page 5, line 73 "Another novel multityrosine kinase inhibitor, lenvatinib, merely demonstrated a noninferior outcome with a median survival time of 13.6 months vs those of 12.3 months in sorafenib group (hazard ratio 0.92)" was added.

Page 15, line 299 "Recently, it has also been proposed that the combination of HAIC with tyrosine kinase inhibitors might benefit patients with advanced hepatocellular carcinoma through a synergistic anticancer effect. A randomized clinical trial comparing the efficacy and safety of sorafenib plus HAIC vs sorafenib for hepatocellular carcinoma with portal vein invasion found that sorafenib plus HAIC of FOLFOX improved overall survival and had acceptable toxic effects (35). Those clinical benefits of HAIC shown in this trial were consistent with our meta-analysis." was added.

Reviewer C

Yan et al have conducted a meta-analysis comparing HAIC versus sorafenib in aHCC patients. 18 studies including 1264 HAIC treated patients and 1041 sorafenib treated patients were analyzed. They found that HAIC was superior to sorafenib in terms of OS, PFS, OR, and DCR.

Comments 4:

Overall, the meta-analysis was conducted following the recommended guideline. The analysis was conducted following traditional statistical methods. However, I found that comparison of the baseline clinical characteristics between the two groups of patients was missing. To conclude that HAIC is better than sorafenib, one needs to show that the two groups are relatively compatible in cancer stages (BCLC stage, portal vein thrombosis/macrovascular invasion rate, and distant metastasis rate) as well as in liver functional class (Child-Pugh class A or B). Please provide these comparisons. If there are differences in these factors, you may need to adjust for these factors to see whether they affect your analysis.

Reply 4: we added the data of BCLC stage in each study and compared the baseline clinical characteristics between the two groups. The comparable data was marked using "*" as shown in Table 1. (See Page 27, Table 1). We further conducted a subgroup analysis to evaluate the

impacts of baseline characteristics on the analysis (see Page 13, Line 265; Page 32, Table 2). Due to the studies included were mostly retrospective or prospective cohort studies, the potential selection bias was also discussed (see Page 14, Line 286). Thanks to you for your good comments.

Changes in the text: Page 27, Table 1 “BCLC stage” was added.

Page 13, Line 265 were corrected as “HAIC remained to showed a benefit in OS of patients included in studies published after 2017 (HR: 0.496, 95%CI [0.263-0.936]， P=0.03), those conducted in countries other than Japan（HR: 0.464, 95%CI [0.248-0.867]， P=0.016, those with a small sample size (HR: 0.645, 95%CI [0.445-0.934], P=0.02), those that were of high quality (HR: 0.616, 95%CI [0.405-0.938], P=0.024), those that contained cases with macroscopic vascular invasion (MVI) only (HR: 0.566, 95%CI [0.437-0.732], P<0.001), and those in which cisplatin + 5-FU or mFOLFOX was used as the HAIC regimen, and those that contained cases with BCLC Stage C only (HR: 0.637, 95%CI [0.509-0.797], P<0.001).”

Page 32, Table 2 subgroup analysis of BCLC staging was added.