

Dear Editor-in-Chief,

Thank you for your review of manuscript NO. 55692 and for your helpful comments. We have carefully considered all of the reviewer and editor comments and have responded accordingly. The following are our point-to-point response to the issues raised.

**Peer-Review Report and response**

Reviewer #1:

**Scientific Quality:** Grade B (Very good)

**Language Quality:** Grade A (Priority publishing)

**Conclusion:** Minor revision

**Specific Comments to Authors:** Comments to the author In the manuscript entitled "Transarterial chemoembolization with hepatic arterial infusion chemotherapy plus S-1 for hepatocellular carcinoma", the authors demonstrated that TACE combined with HAIC was an effective and safe treatment for patients with advanced HCC with portal vein invasion or extrahepatic metastasis. Furthermore, they also demonstrated no additional effect of S-1 on TACE/HAIC treatment, even though there were similar frequencies of adverse events. While the result of this clinical study was negative, the study design was excellent and manuscript was quite well written. To make the article more persuasive and fruitful, the authors need to discuss the following issue. 1) Patients with advanced HCC characterized by vascular invasions, localized irradiation (especially targeting an invaded portal lesion) would be an alternative treatment. What did authors think about irradiation therapy and how did they decide the treatment for patient with advanced HCC including vascular invasion?

**Response:** The text has been revised to add the discussions and references as follows:

“In addition to systemic therapies and HAIC, localized irradiation is also an alternative treatment for patients with advanced HCC characterized by vascular invasions. Selective internal radiotherapy (SIRT) with yttrium-90, or radioembolization, which is one of the intra-arterial treatments can also be performed in patients with intermediate to advanced HCC [33]. However, SIRT is higher cost and unavailable in China. With the technical development of radiotherapy, stereotactic body radiation therapy (SBRT) can deliver high precision and intensity radiation to tumor tissue while sparing surrounding tissue. In a systematic review and meta-analysis including 2577 patients with unresectable HCC, subgroup analyses showed nonsignificant survival benefit was observed in TACE plus radiotherapy group compared with TACE alone group for patients with portal vein tumor thrombosis [34]. In summary, further studies are necessary to evaluate localized irradiation value in the treatment of advanced HCC.”

33        **Mazzaferro V**, Sposito C, Bhoori S, Romito R, Chiesa C, Morosi C, Maccauro C, Marchiano A, Bongini M, Lanocita R, Civelli E, Camerini T, Spreafico C. Yttrium-90 radioembolization for intermediate-advanced hepatocellular carcinoma: a phase 2 study. *Hepatology* 2013; **57**: 1826-1837 [PMID: 22911442 DOI: 10.1002/hep.26014]

34        **Huo YR**, Eslick GD. Transcatheter arterial chemoembolization plus radiotherapy compared with chemoembolization alone for hepatocellular carcinoma: a systematic review and meta-analysis. *JAMA Oncol* 2015;**1**:756-765 [PMID: 26182200 DOI: 10.1001/jamaoncol.2015.2189]

Clinically, we also combine TACE or other treatments with radiotherapy to treat advanced HCC with portal vein invasion.

### **Editorial Office’s comments and response**

**(1) Science Editor:** 1 Scientific quality: The manuscript describes a clinical trials study of the hepatocellular carcinoma. The topic is within the scope of the WJG. (1) Classification: Grade A; (2) Summary of the Peer-Review Report:

Reviewer#05085789 summarized the authors demonstrated that TACE combined with HAIC was an effective and safe treatment for patients with advanced HCC with portal vein invasion or extrahepatic metastasis. While the result of this clinical study was negative, the study design was excellent, and manuscript was quite well written. To make the article more persuasive and fruitful, the authors need to discuss the following issue. The questions raised by the reviewers should be answered; and (3) Format: There are 2 tables and 5 figures. A total of 32 references are cited, including 8 references published in the last 3 years. There is 1 self-citation. 2 Language evaluation: Classification: Grade A. A language editing certificate issued by Rude Health Consulting was provided. 3 Academic norms and rules: The authors provided the Biostatistics Review Certificate, the signed Conflict-of-Interest Disclosure Form and Copyright License Agreement, the Institutional Review Board Approval Form, CONSORT Checklist Form, Clinical Trial Registration Statement, and informed consent. No academic misconduct was found in the CrossCheck detection and Bing search. 4 Supplementary comments: This is an unsolicited manuscript. The study was supported by the Sanofi. The topic has not previously been published in the WJG. The corresponding author has published 2 articles in the BPG. The first author was born in 1977 (under 45 years old).

5 Issues raised:

(1) I found the authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s);

**Response:** The approved grant application form has been provided.

(2) I found the authors did not provide the original figures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor;

**Response:** The original figures have been provided as PPT format.

(3) I found the authors did not write the “article highlight” section. Please write the “article highlights” section at the end of the main text.

**Response:** The manuscript has been revised to write the “article highlights” section according to the guidelines.

6 Re-Review: Not required. 7 Recommendation: Conditionally accepted.

**(2) Editorial Office Director:** I have checked the comments written by the science editor. Correction: The scientific classification of this manuscript is grade B.

**(3) Company Editor-in-Chief:** I have reviewed the Peer-Review Report, the full text of the manuscript, the relevant ethics documents, and the English Language Certificate, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office’s comments and the Criteria for Manuscript Revision by Authors.

Thank you again for your thorough and careful review of our manuscript.

Sincerely,

All authors of manuscript NO. 55692.