February 12, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 14190-edited.doc).

**Title:** Is sorafenib the almighty therapy for the patients with advanced hepatocellular carcinoma invading portal vein?

**Author:** Su Jong Yu, Yoon Jun Kim

**Name of Journal:** *World Journal of Hepatology*

**ESPS Manuscript NO:** 14190

The manuscript has been improved according to the suggestions of reviewers:

1. Format has been updated.

2. Revision has been made according to the suggestions of the reviewer

Thank you for your kind advice for our manuscript entitled "**Is sorafenib the almighty therapy for the patients with advanced hepatocellular carcinoma invading portal vein?**" (**14190**). We also appreciate the constructive comments from the reviewers. These comments are most valuable for us in preparing a more concise manuscript. We have revised the manuscript according to the reviewer's suggestions. The revised portions in the manuscript have been highlighted (underlined and in blue).

Specific responses to reviewer's comments are described below:

## Reviewer #2936280's Comments:

This work proposes a review on various treatment strategies for the patients with hepatocellular carcinoma and portal vein invasion. It is a topic of interest to the researchers in the related areas but the paper needs very significant improvement before acceptance for publication. My detailed comments are as follows:

1. The title of the paper is very misleading because the data shown in the manuscript are not directly related to the safety or efficacy of sorafenib in patients who have HCC with PV invasion. Review on the directly relevant references will be more helpful for the reader.

**Author's Response:** We appreciate the reviewer's comment. To avoid misunderstanding, we'd like to amend the title of this paper as follows: Effective treatment strategies other than sorafenib for the patients with advanced hepatocellular carcinoma invading portal vein.

2. The author should accentuate his own opinions in this manuscript, rather than a simple list of documents. Try to discuss the best individualized treatment plan for different patients with hepatocellular carcinoma and portal vein invasion in this paper in more clear, write one section to define the problem.

**Author's Response:** We appreciate and totally agree with the reviewer's comment. We added the section of "Individualized treatment plans for different patients" on page 16 of revised manuscript as follows:

**6. Individualized treatment plans for different patients**

For HCC patients with PVTT with Child-Pugh class B, portal hypertension, or Eastern

Cooperative Oncology Group (ECOG) 2, sorafenib would be best option as recommended in BCLC guideline. For HCC patients with PVTT with Child-Pugh class C, portal hypertension, or ECOG > 2, we have to treat these patients with best supportive care. For HCC patients with PVTT with Child-Pugh class A, no portal hypertension, and ECOG 0-1, we could treat these patients with individualized treatment plans, as follows:

**1) Single HCC (≤ 2cm) with PVTT**

In this setting, we could consider surgical resection as best options other than sorafenib. Alternatively, TACE and EBRT could be other good options.

**2) Single HCC (> 2cm) with PVTT**

For single HCC larger than 2cm with PVTT, we still consider surgical resection as best option for patients with resectable tumor, reserved hepatic function and sufficient post-operative remnant hepatic volume. If tumor size is 10cm or less, TACE and EBRT could be alternative options. For single huge HCC larger than 10cm with PVTT, sorafenib would be 1$^{st}$ line option.

**3) Multiple (maximal tumor size ≤ 2cm) with PVTT**

If maximal tumor size is 2cm or less, we could adopt TACE as best option for multiple HCC. Sorafenib would be another best option for these patients.

**4) Multiple (maximal tumor size > 2cm) with PVTT**

In this setting, sorafenib would be 1$^{st}$ line option. However, we could still consider TACE as alternative option if maximal tumor size is 10cm or less and tumor extent ≤ 50% of liver volume.

3. Since outcomes of therapies can be quite different across tumor stages and different location and extent of PVTT, the author should review the available evidence supporting the potential roles of different treatment strategies in the different stages of HCC.

**Author's Response:** When we added the section of "Individualized treatment plans for different patients" on page 16 of revised manuscript, we suggested different treatment options according to different tumor stage, reserved hepatic function, presence or absence of portal hypertension, and performance status.

4. The authors have shown the survival benefits of the various treatment strategies in patients with advanced HCC with PVTT. However, it should also be noted that the other three important parameters, efficacy, tolerance and cost, are taken into consideration.

**Author's Response:** We totally agree with the reviewer's comment. We additionally noted tolerance profiles in each section of treatment strategies. However, it is hard for us to note cost profile because almost authors did not perform cost effectiveness analyses in their published articles. It is important to take into consideration these important parameters in the near future studies.

5. The conclusion section should include the general treatment recommendations for patients with HCC and PVTT. There are, however, too many references in this manuscript.

**Author's Response:** We suggested general treatment recommendations in the conclusion section of the revised manuscript on page 18, line 7-18 as follow: For resectable single nodular HCC patients with PVTT, we could treat these patients with surgical resection as 1$^{st}$ line

treatment if they have Child-Pugh class A, no portal hypertension, and ECOG 0-1. TACE, EBRT, and sorafenib would be alternative treatment options for these patients. For multi-nodular HCC patients with PVTT, we could treat these patients with TACE or sorafenib if they have Child-Pugh class A, no portal hypertension, and ECOG 0-1. TACE would be 1$^{st}$ line if maximal tumor size is 2cm or less and sorafenib would be 1$^{st}$ line if maximal tumor size is greater than 2cm. For HCC patients with PVTT with Child-Pugh class B, portal hypertension, or ECOG 2, sorafenib would be best option. However, for HCC patients with PVTT with Child-Pugh class C, portal hypertension, or ECOG > 2, we should treat these patients with best supportive care as recommended in BCLC guideline.

## Reviewer #2527419's Comments:

**General Comments:**

This is a generally well-written manuscript, which reviewed various treatment strategies for patients with hepatocellular carcinoma (HCC) and portal vein tumor thrombosis (PVTT). I listed my comments as below:

**Comments:**

1. The author described several treatment strategies, including sorafenib, TACE, TARE, HAI chemotherapy, RFA, percutaneous laser ablation, surgery, external beam radiotherapy and combined treatment for patients with HCC and PVTT. Can the author make a table to summarize and compare the difference between these treatment strategies?

**Author's Response:** We appreciate the reviewer's comment. According to reviewer's suggestion, we made a table 2 to summarize and compare the difference between different strategies in the revised manuscript.

2. In page 5, line 13, please change EHS to extrahepatic spread (EHS).

**Author's Response:** We amended EHS to extrahepatic spread (EHS) on page 7, line 13 of revised manuscript.

Thank you again for publishing our manuscript in the *World Journal of Hepatology.*

Sincerely yours,

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