ANSWERING REVIEWERS

December 31, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 5390-editied_revised.doc).

Title: Chemotherapy for advanced hepatocellular carcinoma in the sorafenib age

Author: Koji Miyahara, Kazuhiro Nouso, and Kazuhide Yamamoto

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 5390

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.

For the first revision: answers to the reviwers No. 00008874, 00503526, and 00183339 (This section had already submitted)

(1) The reviewer (No. 00503526) suggested changing the title of the manuscript because the main topic of the manuscript is sorafenib. According to the reviewer's comment, we revised the title from "Recent developments in chemotherapy for treatment of advanced hepatocellular carcinoma" to "Chemotherapy for advanced hepatocellular carcinoma in sorafenib age".

(2) The reviewer (No. 00503526) claimed that our article did not contain new information. This manuscript is a review article meaning that the contents were the summary of recent published data. Therefore, it is not strange that the manuscript did not contain new information for well-studied specialists of the field. It does not weaken the importance of this manuscript so that the rest of the reviewers (No. 00183339 and 00008874) did not focus on the point.

For the second revision: answers to the reviwers No. 00928100, 00503516, 00680628, 00054369

(This section is for the current revision)

Answers to the reviewer (No. 00503516)

(1) The reviewer suggested adding information in the section describing the mechanisms of action of sorafenib. According the suggestion, we added a sentence "In addition, sorafenib also has been shown to induce apoptosis as direct effects on tumor cell[4]." in page 4, line 13. Accroding to this addition, we changed the reference number from No.28 to No.4.

Answers to the reviewer (No. 00680628)

Major Comments

(1) The reviewer suggested explaining about the time for permission for using sorafenib in the guidelines of international agencies. We have already mentioned this issue in page 5, line 2 as follows: "Sorafenib is recommended as a treatment in patients with i) extrahepatic lesions, ii) macrovascular invasion, or iii) those who do not response to TACE/arterial injection chemotherapy, when the liver function is Child-Pugh (CP) -A, in a consensus-based treatment algorithm for HCC (JSH Consensus 2010)[9]." and in page 5, line 6: "Patients recommended for sorafenib in this algorithm overlap with those recommended according to the European Association for the Study of the Liver (EASL), the European Organization for Research and Treatment of Cancer (EORTC)[10], the American Association for the Study of Liver Diseases (AASLD)[8], and the National Comprehensive Cancer Network (NCCN) Clinical Practice Guideline[11]."

(2) The reviewer questioned whether there is the interaction between sorafenib and other drugs. There is no study to answer the question so far. Alternatively, we have provided information about clinical trials of combination therapies: sorafenib with TACE in page 8, line 16, and Table 4; with HAIC in page 10, line 11; and sorafenib with erlotinib in page 10, line 22.

(3) The reviewer suggested adding a table for adverse events with the frequencies. According the suggestion, we added a new Table 3, and a sentence "Various adverse events were frequently observed during sorafenib therapy (Table 3)" in page 7, line 22.

(4) The reviewer suggested adding a table for OS and 95% (CI) in major clinical trials. According to the suggestion, we added a new Table 1, and a sentence "The recommendation was based on the results demonstrated in SHARP and AP trials (Table 1)." in page 5, line5.

Minor Comments

(1) The reviewer suggested rewriting a sentence in the first paragraph of abstract, because the meaning of the sentence was difficult to understand. According to the

suggestion, we changed the sentence from "Although it is difficult to know in advance who the responders will be using conventional characteristics of patients, …." to "Although it is difficult to know the responders in advance using conventional characteristics of patients, …."in Page 2, line 11.

(2a) The reviewer commented that the JSH also indicates sorafenib as an option for CP-B patients (reference 8) (the number of this reference was changed to 9 in the revised manuscript.) However, the referential manuscript stated "Sorafenib is only recommended for HCC patients with Child–Pugh A liver function." in the footnote of Figure3 in page 678. So, we deemed that sorafenib was ***not*** recommended for CP-B patients in the JSH Consensus 2010.

(2b) The reviewer recommended adding references to support our description "whereas, no clear evidence has been presented on safety of sorafenib in CP-B patients". To the best of our knowledge, the GIDEON study (reference No.12) presents the best evidence about this issue. But GIDEON is non-interventional and non-controlled study. In addition, the safety of sorafenib in CP-B patients have not been validated in randomized controlled studies. This report did not proof the evidence, so that we explained the fact as "no clear evidence has been presented on safety of sorafenib in CP-B patients". To make this clear, we inserted words ", based on randomized controlled trials," in page 5, line 12.

(2c) The reviewer suggested changing the capital letters to small letters in the following sentence: "The recent report in Global Investigation of therapeutic DEcisions in HCC and Of its treatment with sorafeNib (GIDEON)" in page 5, line 14. According the suggestion, we revised the sentence to "The recent report in Global investigation of therapeutic decisions in HCC and of its treatment with sorafenib (GIDEON)".

(2d) The reviewer suggested changing the reference 11 (the number of this reference was changed to 12 in the revised manuscript.) to the original paper (Int J Clin Pract, July 2012, 66, 7, 675–683. doi: 10.1111/j.1742-1241.2012.02940.x). Both of them are the results of GIDEON study, but the reference that we citeded in the manuscript presented the latest results of final analysis dealing with more than 3000 patients. In contrast, the published paper (Int J Clin Pract 2012) presented the results of the first interim analysis with 479 patients. The results of second interim analysis have also been published last month (Int J Clin Pract 2013, doi: 10.1111/ijcp.12352); however, the number of patients was only 1571. The results of final analysis have not been published as an original paper, but we deemed it more informative than that of interim analysis in this up-to-date review. The reviewer also mentioned that the description of the relationship between poor OS and CP grading was a problem because the effect of tumor-related factors could not be negligible. According to the reviewer's suggestion, we deleted the words at the last part of the sentence: ", and median overall survival (OS) was longer in CP-A (13.6 months) than CP-B patients (5.2 months)" in page 5, line 20.

(3) The reviewer questioned whether MVI represented "macroscopic vascular invasion" or "microvascular invasion". MVI represented "macroscopic vascular invasion" and we

have explained this abbreviation in page 6, line 4. This abbreviation was also used in reference No. 14 and 15.

(4) The reviewer suggested adding the word "TREATMENT" in a subtitle in page 6, line 15. According the suggestion, we added the word.

To all reviewers

Thank you for your reviewing.

Thank you for your kindness in advance.

Sincerely yours,

Koji Miyahara, MD, PhD

Department of Gastroenterology & Hepatology

Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences

2-5-1 Shikata-cho, Kita-ku, Okayama-city, Okayama 700-8558, Japan.

Telephone: +81-86-235-7219

Fax: +81-86-225-5991

E-mail: mkojisup@yahoo.co.jp