

## Format for ANSWERING REVIEWERS



July 17, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 11345-edited.docx).

**Title:** Skin toxicity predicts efficacy to sorafenib in patients with advanced hepatocellular carcinoma

**Author:** Masako Shomura, Tatehiro Kagawa, Koichi Shiraishi, Shunji Hirose, Yoshitaka Arase, Jun Koizumi, and Tetsuya Mine

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

**ESPS Manuscript NO:** 11345

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

1 Format has been updated. We changed FIGURES before TABLES according to the format. Moreover we added COMMENT in the manuscript.

2 Revision has been made according to the suggestions of the reviewers. All revisions included in the text are in red-colored lettering.

**We would like to thank all reviewers for their comments that enabled us to make improvements in our work. Our answers to reviewers were in red-colored lettering in this report.**

**REVIEWER (1):** 02861202

Comments to the Author

This paper by Shomura et al. refers to skin toxicity as predictor of efficacy to Sorafenib in patients with advanced HCC. The paper is of interest since it gives important clues for better selection of patients who may benefit at best from treatment with Sorafenib. However it raises few issues that need to be addressed:

(1) Aside from HFSR, it would be interesting to know whether patients experienced some other skin reaction that required dose reduction or treatment discontinuation. In our practice, we experience more and more skin reaction different from HFSR, that require dose reduction and almost invariably treatment withdrawal. Since we now routinely advise patients on the use of moisturizers, steroid ointments etc., we see very few cases of HFSR. Were skin reaction other than HFSR included in the analysis as well? If so, there was any difference in terms of predictor of treatment efficacy, according to the type of skin reaction?

Thank you for your suggestion. In this study all subjects with > G2 skin toxicity presented HFSR. Because there were few patients with both rash and HFSR and no patients with rash alone, we could not analyze these categories of patients.

(2) The authors indicate the occurrence of genetic polymorphisms of VEGF and VEGFR2 as involved in the mechanism of HFSR. How would the authors comment on the possible mechanism of occurrence of skin reactions other than HFSR?

Thank you for your comment. As far as we know, the mechanism of rash such as erythema remains unknown. Some researchers have suggested that inhibition of Raf may play a role (Lancet Oncol 2005; 6: 491–500).

**REVIEWER (2):** 00181532

Comments to the Author

In this study, the authors reported that significant skin toxicity(>grade 2), younger age (<70 years), and absence of hypoalbuminemia were associated with better overall survival. Significant skin toxicity and nursing intervention were associated with longer treatment duration. The study is limited by its small cohort size and retrospective nature. A few minor comments are provided that need to be addressed.

Comments in the body of the paper

(1) Abstract: AIM ...hepatocellular carcinoma (HCC). METHODS:--~~hepatocellular carcinoma~~-HCC

Thank you for your suggestion. We have changed according to your comment.

(2) Abstract: RESULTS: From the end of two sentences seem to be redundant.

Thank you for your suggestion. We made abstract shorter according to your comment.

(3) Core Tip: Last sentence does not make sense and is difficult to understand. Recommend rephrasing the sentence.

Thank you for your suggestion. We removed last sentence according to your comment.

(4) INTRODUCTION: Sorafenib should be a multikinase inhibitor, not just a tyrosine kinase inhibitor.

Thank you for your suggestion. We have changed from "tyrosine kinase " to "multikinase" according to your comment.

(5) Nursing Intervention: Consider to merge last sentence with the first sentence in this section.

Thank you for your suggestion. We removed last sentence of Nursing Intervention according to your comment.

(6) Discussion: p10 Patients with a genetic predisposition to HFSR may be sensitive to the antitumor effects of sorafenib. "more sensitive" is better.

Thank you for your suggestion. We have changed "more sensitive" according to your comment.

(7) Add full name in footnote. TNM,AFP,DCP

Thank you for your suggestion. We have added those words full name in footnote of each table.

(8) FIGURE LEGENDS: Thus more severe skin toxicity contributed to longer survival. - Recommend using the words 'is associated with' since it is unclear if skin toxicity is an epiphenomenon.

Thank you for your suggestion. We have changed "is associated with" according to your comment.

**REVIEWER (3):** 02903968

I suggest the author review that paper and provide more patients descriptions about whether the nursing treatment model can cope with AEs problem or not.

Nursing intervention program were described in Materials and Methods. However according to your comment, we added the descriptions about nursing intervention in **RESULTS: Nursing intervention and treatment duration**.

37 are the small sample data and make this article lack credibility.

Thank you for your suggestion. We know that the sample size is small and described about this in the Discussion.

**REVIEWER (4):** 02526284

This study by Masako Shomura, et al. evaluated study the relationship between adverse events, efficacy, and nursing intervention for sorafenib therapy in patients with hepatocellular carcinoma. Although the authors concluded that skin toxicity was associated with favorable outcomes with sorafenib therapy for advanced HCC and that nursing intervention contributed to better adherence, which may improve the efficacy of sorafenib. However, the sample size of this study seems extremely small to draw any conclusion.

Thank you for your suggestion. As explained reviewer 3, we know that the sample size is small and described about this in the Discussion.

In addition, the selection criteria for sorafenib administration seem unclear.

Selection criteria were described in Materials and Methods and we believe that these criteria are generally accepted.

What kinds of treatment did other patients with similar HCC stage receive during 3 years?

Selection criteria were described in Materials and Methods and we believe that these criteria are generally accepted. Patients without sorafenib indication usually receive transarterial infusion of 5-FU or best supportive care.

All HCCs had enhancement? If some HCCs did not show enhancement on dynamic imaging, how could be used mRECIST for response evaluation?

Selection criteria were described in Materials and Methods and we believe that these criteria are generally accepted. All tumors were enhanced by contrast agent, which allowed us to evaluate the efficacy of sorafenib according to mRECIST.

3 References and typesetting were corrected

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

Sincerely yours,

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