Prof. Li-Jun Cui

Science Editor, Editorial Office

Baishideng Publishing Group Inc

March 3, 2018

Dear Prof. Li-Jun Cui:

On behalf of my co-authors, we thank you very much for giving us an opportunity to revise our manuscript. We also thank the editorial board member and reviewers for their careful review and constructive, encouraging, and thoughtful comments. We have carefully addressed the concerns of the reviewers in the manuscript. The amendments are highlighted in blue (format for manuscript) and yellow (the reviewers' comments /suggestions) in the revised manuscript, and our point-by-point responses to these concerns are detailed at the end of this letter. I am pleased to re-submit our revised manuscript titled **"** Effect and safety of sorafenib in patients with intermediate hepatocellular carcinoma who received TACE: A retrospective comparative study **"** (**Manuscript NO: 37831**) for consideration for publication as an original research article in *World Journal of Clinical Cases*.

I believe that this manuscript is appropriate for publication in *World Journal of Clinical Cases* because this study confirms that sorafenib plus TACE treatment for intermediate-stage HCC significantly prolonged the mOS of patients compared to TACE treatment alone. Moreover, this new treatment approach showed tolerable toxicity.

We confirm that this manuscript has not been published and is not under consideration for publication elsewhere. We have no conflicts of interest to disclose. We also declare that all authors have read and approved the final version of the manuscript. Please direct all correspondence about this manuscript to Prof. Lin Wang, whose contact information is given below.

We would like to express our great appreciation to you and reviewers for comments on our paper. Looking forward to hearing from you.

Thank you and best regards.

Yours sincerely,

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Responses to the comments from the editorial board member and reviewers:

Reviewer #1: (**Reviewer's code:** 00742121)

Major comments:

1. Cohort studies should be prospective. Hence, the last part of the title should be changed: "A retrospective cohort study" should be changed to "A retrospective comparative study"

As the reviewer suggested, we have changed the title to "Effect and safety of sorafenib in patients with intermediate hepatocellular carcinoma who received TACE: A retrospective comparative study"

2. Abstract, Background, line 1: HCC is not "the most common and malignant cancer in the world"; please rephrase.

We agreed with the reviewer that HCC is not the most common and malignant cancer in the world. We changed to "HCC is a common digestive tract malignancy." (*page 4, line 8*).

3. Abstract, Results, line 1: It is really questionable whether the authors should use only "median overall survival" or other measures of survival as well (e.g. overall survival rate). This comment also applies to the "Results" section of the main text.

Because of the limited word in the Abstract. Meanwhile, OS is the primary endpoint of the study. We put the OS in the Abstract, Results. while the other measures of survival are described in the "Results" section of the main text.

4. Abstract, Conclusion, lines 2-4: The sentence beginning with "To achieve a better…" is not a conclusion. Hence, it should be either removed or rephrased.

As the reviewer suggested, we removed "To achieve a better prognosis," (Abstract, Conclusion, *lines 2-4*)

5. Introduction, 1st paragraph: The epidemiological data provided in this paragraph are in part inaccurate and thus misleading: HCC is the 5th most common cancer and the 2nd cause of cancer-related mortality worldwide but only in men; in women it is only 9th and 6th, respectively. Furthermore, the authors should add some more information regarding geographical variations of HCC around the world (see: Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin. 2015;65:87-108).

We further read the literature before the amendment:

HCC is the fifth most common cancer among males and is also the second leading cause of cancer-related mortality; there are 9 and 6, respectively，among females around the world [1]. China, the incidence and deaths of HCC account for more than 50% of HCC cases in the world, is still facing the great challenge of disease burden caused by liver cancer[2].

6. Page 3, line 15: This study is a retrospective comparative study, not a systematic review; the term systematic review refers to secondary analyses of published studies.

As the reviewer suggested, we have changed "a systematic review" to "a retrospective comparative study".

7. - Page 4, line 14: "treated as" should be changed to "were included in".

We agreed with the reviewer that "treated as" have changed to "were included in".

8. - Page 4, line 15: "were treated as" should be changed to "were included in".

We agreed with the reviewer that "were treated as" have changed to "were included in".

9. Page 7, last paragraph entitled “Treatment responses”: This paragraph should be re-written in order to make comparisons of treatment responses between the two groups of patients more visible: CR of one group vs. CR of the other, PR of one group vs. PR of the other etc.

As the reviewer suggested, we have re-written this paragraph as follow.

Response evaluation was performed according to mRECIST criteria for all enrolled patients, as presented in Table 5. Sorafenib combined with TACE group and the TACE alone group were CR (12/38 31.6% vs 4/29 13.8%), PR (11/38 28.9% vs 8/29 27.6%), SD (10/38 26.3% vs 7/29 24.1%), PD (5/38 13.2% vs 10/34 34.5%), ORR (60.5% vs 41.4%) and DCR (86.8% vs 65.5%), respectively. The differences were statistically significant between treatment groups for these outcomes ($P < 0.05$).

10. Page 10. Line 2: The acronyms ORR and DCR should be written in full.

As the reviewer suggested, we chang “ORR” and “DCR” to “objective response rate” and “disease control rate”.

11. - Page 10: As mentioned earlier, the authors should discuss the main weakness, i.e. retrospective study design, as well as the strengths of the study, preferably just before the last paragraph, which presents the main conclusions of the study.

As the reviewer suggested, we have re-written this part as follow.

However, considering the design of this study is a small-scale retrospective comparative analysis, there is a need for well-designed multi-center, randomized, controlled trials to further explore the factors that affect the prognosis of survival. Additional areas that need to be studied include whether TACE affects the patient's liver function and if this will affect sorafenib treatment and repeated TACE can induce systemic therapy (i.e, sorafenib molecular-targeting therapy) resistance, which in turn may increase tumor recurrence and metastasis. In order to improve the survival and quality of life of patients with HCC, sorafenib combined with the timing of TACE is also important. In addition, clinical work can explore

the optimal combination of sorafenib and TACE, especially the best time for the TACE procedure to reduce the adverse reactions and increase patient compliance.

In conclusion, our results confirm that sorafenib plus TACE treatment for BCLC-B HCC significantly prolonged the mOS of patients compared to TACE treatment alone. Moreover, this new treatment approach showed tolerable toxicity. This study provides important information for clinicians who are interested in using sorafenib plus TACE therapies to treat BCLC-B HCC.

Reviewer #2: (03537089)

The study needs minor revision see the revised article

1.Comment: I think the study volume is small and the follow up is not enough

After applying the PASS software, we perform a statistical evaluation to calculate α and 1-β. The estimates are in full compliance with $\alpha < 0.05$, $1-\beta > 0.8$.

Further examination of the literature confirmed that liver cancer overall survival time was poor, and we follow-up time a median follow-up time which was 23.0 months.

2. **MATERIALS AND METHODS**

Sorafenib plus TACE treatment

Sorafenib was administered when the liver function was close to normal, following the first TACE. Patients received a dose of 400 mg sorafenib twice daily[20]. However, the dose was adjusted according to the severity of toxicity. Dose reduction was made according to the product characteristics and international recommendations (Ref). Treatment with sorafenib was maintained until clinical and/or radiological progression, until intolerable adverse effects (AEs) occurred, until death, or until patient refusal[21]. All patients treated with sorafenib plus TACE were evaluated for clinical characteristics and toxicity management every 4 weeks(Ref). TACE was repeated every month if target lesions were detected as a treatment response of partial response (PR) or stable disease (SD), without deterioration of liver biochemistry(Ref).

Transarterial chemoembolization

TACE used the traditional technology [22]. Iodized oil, an embolic agent, and chemotherapy drugs (100-150 mg oxaliplatin combined with 0.75-1.0 g fluorouracil) were combined into a suspension. The use of iodized oil as a drug carrier allows the treatment to have an affinity for the tumor, allows the introduction of chemotherapy drugs into the cancer tissue, and plays a lasting role in embolization chemotherapy (Ref).

As the reviewer suggested, we have added "and/or" and the references in this part. As follow:

Sorafenib was administered when the liver function was close to normal, following the first TACE. Patients received a dose of 400 mg sorafenib twice daily[22]. However, the dose was adjusted according to the severity of toxicity. Dose reduction was made according to the product characteristics and international recommendations[3]. Treatment with sorafenib was maintained until clinical and/or radiological progression, until intolerable adverse effects (AEs) occurred, until death, or until patient refusal[24]. All patients treated with sorafenib plus TACE were evaluated for clinical characteristics and toxicity management every 4 weeks[22]. TACE was repeated every month if target lesions were detected as a treatment response of partial response (PR) or stable disease (SD), without deterioration of liver biochemistry[4].

Transarterial chemoembolization

TACE used the traditional technology[26]. Iodized oil, an embolic agent, and chemotherapy drugs (100-150 mg oxaliplatin combined with 0.75-1.0 g fluorouracil) were combined into a suspension. The use of iodized oil as a drug carrier allows the treatment to have an affinity for the tumor, allows the introduction of chemotherapy drugs into the cancer tissue, and plays a lasting role in embolization chemotherapy[5].

3. **Statistical analysis**

The main outcomes evaluated included overall survival (OS) and toxicity. Additional outcomes included objective response rate (ORR) and disease control rate (DCR). OS refers to the time from when a patient is eligible for the first treatment until death for any reason, and a patient who survived the data cut-off date or a patient who was lost in the study would have the date of the last contact as the survival endpoint*(this is bias).*

As the reviewer suggested, we have changed the sentence "OS refers to the time from when a patient is eligible for the first treatment until death for any reason, and a patient who survived the data cut-off date or a patient who was lost in the study would have the date of the last contact as the survival endpoint" to "OS was calculated from treatment to death from any cause. OS is the primary endpoint of the study"

4. As the reviewer suggested, we removed "These data are presented in" (RESULTS, Baseline characteristics, *line 4*), and "and VEGF" (DISCUSSION, *line 14*), and "Figure 1. Kaplan-Meier survival cure for the sorafenib plus TACE and the TACE alone group." (Figure and table legends, *line 8*).

5. As the reviewer suggested, we added "has" (DISCUSSION, *line 2*), and "that" ((DISCUSSION, *line 14*), and "or patient death" (MATERIALS AND METHODS, Case data extraction, *line 1*) and "and/or" (MATERIALS AND METHODS, Sorafenib plus TACE treatment, *line 3*) and "or patient death" ((MATERIALS AND METHODS, Patients, *line 4*).

6.Sorafenib has made significant progress in clinical practice, and it is an effective treatment for advanced HCC, with good measures of safety and tolerance[25]. The development of sorafenib has changed the traditional treatment regimen of HCC and has given patients new hope. Sorafenib is currently the only evidence-based, molecule-targeted treatment in the world that can significantly prolong the survival time of advanced HCC patients[26] *Are you sure??.*

However, whether sorafenib can be used for BCLC-B HCC or with TACE as an adjunctive adjuvant therapy after radical treatment is inconclusive*(Ref)*

As the reviewer suggested, we have revised. As follow:

Sorafenib has made significant progress in clinical practice, and it is an effective treatment for advanced HCC, with good measures of safety and tolerance[-6]. The development of sorafenib has changed the traditional treatment regimen of HCC and has given patients new hope. So far, sorafenib is the only agent approved by the U. S. Food and Drug Administration (FDA) for the first-line therapy of patients with advanced HCC. However, whether sorafenib can be used for BCLC-B HCC or with TACE as an adjunctive adjuvant therapy after radical treatment is inconclusive[6]. (DISCUSSION, *paragraph1*)

7. The survival curves of this study showed that in the first 20 months, the experimental group has a shorter survival time than the control group (Figure 1). The rationale for this observation is that the Kaplan-Meier survival analysis is a comparison of survival rates by the curve, rather than at a certain point in time. Some studies show that sorafenib targeting is effective at inhibiting tumor angiogenesis and that the prolonged use of sorafenib is reflected gradually so after a period of treatment in the sorafenib plus TACE group, the gap between the survival curve of combined treatment and TACE alone group was widened[43]. Short-term sorafenib use may increase tumor invasion and metastasis, which are common problems related to VEGF inhibition. The early outcome of the experimental group was slightly worse than the control group, but the later outcome of the experimental group was significantly better than the control group(the previous observations need more explanation).

We have re-written this part according to the Reviewer's comments. As follow:

The survival curves of this study showed that in the first 20 months, the experimental group has a shorter survival time than the control group (Figure 1). The rationale for this observation is that the Kaplan-Meier survival analysis is a comparison of survival rates by the curve, rather than at a certain point in time. Some studies[48,7] show that sorafenib targeting is effective at

inhibiting tumor angiogenesis and that the prolonged use of sorafenib is reflected gradually so after a period of treatment in the sorafenib plus TACE group. Disease progression is often due to the heterogeneity of the tumor or the emergence of resistance in treatment. Patients with high tumor heterogeneity tend to develop PD early in treatment, whereas resistant patients often appear during treatment. Short-term sorafenib use may increase tumor invasion and metastasis, which are common problems related to VEGF inhibition. The early outcome of the experimental group was slightly worse than the control group, but the later outcome of the experimental group was significantly better than the control group. ***(***DISCUSSION, ***paragraph 4)***

Reviewer #3: (00183339)

This paper investigated Effect and safety of sorafenib in patients with intermediate hepatocellular carcinoma who received TACE. The manuscript is well presented and of interest. The study was done well and their results can contribute to knowledge of this topic.

We thank you for your recognized and encourage.

We tried our best to improve the manuscript and made some changes in the manuscript. These changes will not influence the content and framework of the paper. And here we did not list the changes but marked in blue and yellow in revised paper.

We appreciate for Editors/Reviewers' warm work earnestly, and hope that the correction will meet with approval.

Once again, thank you very much for your comments and suggestions.

The comments of the editorial board member and reviewers are highly insightful and constructive. We believe that the changes based on your comments have greatly improved the

quality of our manuscript. We appreciate your consideration of this manuscript and look forward to hearing from you soon.

Sincerely yours,

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