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Editors-in-Chief
World Journal of Meta-Analysis

Dear Editor:

Manuscript No.: 46560
Title: Prospects for immunotherapy as a novel therapeutic strategy against hepatocellular carcinoma

Dear Editor:

We wish to express our appreciation to the Reviewers for the insightful comment, which have helped us significantly improve the paper.

Reviewer 1:

Comment . *Some issues needed to be revised before publication. The authors introduced lots of unpublished results. They are of uncertainty. The manuscript is not carefully prepared. The errors are readily observed. "Systemic chemotherapy and has been ..." "Liver cirrhosis often create a ..." Some words are unclear. The authors said "Based on these results, large-scale clinical trials of tremelimumab against HCC were not conducted. " However, why were the large-scale clinical trials of tremelimumab against HCC not conducted? The authors did not clarify. Additionally, in the paragraph of 4-2. Anti-CTLA-4 antibody, the authors said "Instead, clinical trials for a novel combination therapy that combines anti-PD1/PD-L1 antibodies is underway in patients with advanced HCC." The words are seemingly wrongly placed. Some perspectives are wrong. "Sorafenib, an inhibitor of tyrosine kinase, is the only molecular targeted drug against HCC that is approved by the Food and Drug Administration (FDA)". Other inhibitors of tyrosine kinase approved should be learned. Some perspectives can be improved. The authors sadi "Many standard therapies are considered for HCC treatment today, including surgical therapy, radiofrequency ablation therapy (RFA), transarterial embolization (TAE), and systemic chemotherapy. Surgical hepatic resection is considered as ideal for early-stage HCC patients,.." Please see a recent publication to overview all meta-analysis regarding management of HCC (PMID: 27167195). This overview suggests that systemic chemotherapy is not considered as the standard therapy for HCC and that RFA and surgical resection seem to have comparable outcomes. Please learn the reference and improve your perspectives. Some sentences could be improved, "...immunotherapy is a promising strategy for HCC therapy". "...survival prognosis..." A scheme regarding mechanisms of immunotherpay for HCC should be drawn to increase the publication possibility.*

Response: We thank the Reviewer 1 for this pertinent comment. We agree that indication of these points is valid. In accordance with the Reviewer 1`s comment, we have improved this paper.

1. Some unpublished results are currently being submitted as an original article in another journal. Therefore, we only have described the results in this review.

We have changed the following some text from (p.11, line 24), (p.14, line 18), and (p.17, line 22):

“unpublished”

to

"in preparation"

2. We have modified some sentences.

We have changed the following text from (p.6, line 14):

"Systemic chemotherapy and has been reported to show a high frequency of adverse events and strong tolerance, with poor clinical effectivity[17]."

to

"Systemic chemotherapy, which is other treatment method, has been reported to show a high frequency of adverse events and strong tolerance, with poor clinical effectivity[17]."

In addition, we have changed the following text from (p.8, line 10):

"Liver cirrhosis often create a highly genotoxic environment with persistent inflammation and fibrosis, which could promote the onset of HCC."

to

"Liver cirrhosis is often a highly genotoxic environment with persistent inflammation and fibrosis, which could promote the onset of HCC."

3. The large-scale clinical trials of tremelimumab against HCC not conducted. However, the reason is unclear. Currently, a phase II / III clinical trial of combination therapy using tremelimumab and durvalumab is ongoing. We have modified this review as shown more clearly and concisely above.

We have deleted the following text (p.22, line 1):

"Based on these results, large-scale clinical trials of tremelimumab against HCC were not conducted. Instead, Also, clinical trials for a novel combination therapy that combines anti-PD1/PD-L1 antibodies is underway in patients with advanced HCC."

In addition, we have added the following text (p.22, line 22):

"In addition, a phase III clinical trial of these combination therapies as first line therapy in the advanced HCC patients is currently ongoing (NCT 03298451)."

4. We have modified this review to more closely describe molecular targeted drugs used in HCC therapy.

We have changed the following text from (p.6, line 19):

"Sorafenib, an inhibitor of tyrosine kinase, is the only molecular targeted drug against HCC that is approved by the Food and Drug Administration (FDA)."

to

"Sorafenib, an inhibitor of tyrosine kinase, is the first molecular targeted drug against HCC that is approved by the Food and Drug Administration (FDA)."

In addition, we have added the following text (p.7, line 2):

"Indeed, as novel molecular targeted drug against HCC, Regorafenib and Lenvatinib were approved by the FDA in April 2017 and August 2018, respectively."

5. We have modified this review considering the report of overview all meta-analysis regarding management of HCC (PMID: 27167195).

We have changed the following text from (p.5, line 24):

"Many standard therapies are considered for HCC treatment today, including surgical therapy, radiofrequency ablation therapy (RFA), transarterial embolization (TAE), and systemic chemotherapy."

to

"Currently, there are various options for HCC therapy, depending on the clinical stage."

In addition, we have added the following text (p.6, line 3):

Surgical hepatic resection and radiofrequency ablation therapy (RFA) is considered as ideal for early-stage HCC patients,

In addition, we have added the following text (p.6, line 12):

"Meanwhile, for patients with advanced HCC, transcatheter arterial chemoembolization (TACE) and molecular targeted drugs have been conducted."

6. We have modified some sentences.

We have deleted the following text (p.7, line 16):

"Therefore, immunotherapy is a promising strategy for HCC therapy."

In addition, we have changed the following text from (p.7, line 4):

"In any case, the development of a new therapeutic strategy with adequate antitumor efficiency and few adverse effects that can improve the survival prognosis in HCC patients would be urgent."

to

"In any case, the development of a new therapeutic strategy of HCC with adequate antitumor effect and few adverse events would be urgent."

7. We described a scheme regarding mechanisms of immunotherpay for HCC.

We have added Figure 1 and Figure legend in this paper (p.45 and 46).

In addition, we have added the following text (p.8, line 1):

which is a cancer-specific antigen we identified (Figure 1).

Reviewer 2:

Major concerns
Comment 1. *The authors should provide a clear and concise introduction.*

Response: We appreciate the Reviewer 2's comment on this point. In accordance with the Reviewer 2's comment, we have modified more clearly and concisely Introduction of this review.

Comment 2. *The authors described the results of those unpublished analyses and consider them as evidence for immunotherapy. Indeed, the authors are only allowed to state concrete evidence in this manuscript.*

Response: We appreciate the Reviewer 2's comment on this point. Some unpublished results are currently being submitted as an original article in another journal. Therefore, we only have described the results in this review.

We have changed the following some text from (p.11, line 24), (p.14, line 18), and (p.17, line 22):

"unpublished"

to

"in preparation"

Comment 3. *In patients with HCC, the expression of PD-L1 in tumour tissue and the expression of tumour-infiltrating lymphocytes have not been reportedly associated with the efficacy of immunotherapy. The authors should address these facts in this manuscript.*

Response: We appreciate the Reviewer 2's comment on this point. In accordance with the Reviewer 2's comment, we have modified this review.

We have deleted the following text (p.19, line 8):

"PD-L1 expression levels, number of tumor-infiltrating lymphocytes, and Number of mutations in the patient have been considered as biomarkers to predict the clinical efficacy of these immunotherapies."

In addition, we have added the following text (p.19, line 11):

"Also, it has been reported that PD-L1 expression levels could be involved in the clinical effect of immunotherapy in patients with non-small cell lung cancer, but these relevance has not been reported in those with HCC."

Comment 4. *The authors should address the problems and challenges of immunotherapy in this manuscript. For example, immunotherapy is not effective in all patients with HCC; how to promote the activation of T cells, improve the killing power and proliferation efficiency of immune cells on tumors, reduce the side effects of drugs on the liver.*

Response: We appreciate the Reviewer 2's comment on this point. In accordance with the Reviewer 2's comment, we have modified this review.

We have added the following text (p.23, line 22):

"Therefore, further understanding of therapeutic effect prediction and resistance mechanism for immunotherapy could be necessary."

In addition, We have added the following text (p.25, line 1):

"Meanwhile, immunotherapy has the possibility of causing immune-related adverse events different from conventional therapy, and more severe management may be required. Therefore, for optimization of immunotherapy, we believe that it is urgent to product more strict novel algorithms for treatment selection and management of HCC."

Minor concerns
Comment 1. *Minor language polishing is needed.*

Response: We appreciate the Reviewer 2's comment on this point. In accordance with the Reviewer 2's comment, we have modified some word in this review.

We wish to thank the Reviewers again for the valuable comments. We trust that the revised manuscript is suitable for publication.