Format for ANSWERING REVIEWERS

September 30, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 4404-review.doc).

Title: Epirubicin, Cisplatin, 5-FU combination chemotherapy in sorafenib-refractory metastatic hepatocellular carcinoma

Author: Ji Eun Lee, Si Hyun Bae, , Jong Young Choi, Seung Kew Yoon, Young Kyoung You, Myung Ah Lee

Name of Journal: Epirubicin, Cisplatin, 5-FU combination chemotherapy in sorafenib-refractory metastatic hepatocellular carcinoma

ESPS Manuscript NO: 4404

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

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

 # Reviewer 1

1. The manuscript has to be read carefully by a native speaker in order to improve wording in some parts

→ We revised the manuscript by American Journal Experts, the editorial office recommends. .

2. A list of abbreviations is needed.

→ We made a list of abbreviations and added it the last page, "appendix"

BCLC	Barcelona-Clinical Liver Cancer
ECF	Epirubicin, cisplatin, 5-FU combination
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HR	Hazard ratio
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
OS	Overall survival
PD	Progressive disease
PR	Partial response
RECIST	Response evaluation criteria in solid tumors
SD	Stable disease

TACE	Transarterial chemoembolization
TTP	Time to progression

3. Abstract and Introduction: The aim of the study was not clearly stated. The primary endpoint was the overall survival time. This should be clearly pointed out. What does efficacy mean in this context?

→ As the reviewer pointed out, the primary end point was overall survival time. But we also tried to know the response rate, time to progression and benefit of this treatment regimen as well as overall survival time. These are usually called as 'efficacy' clinically in field of oncology, so we used this term.

We described 'clinical efficacy' instead of 'efficacy' to avoid confusing in the abstract & introduction session.

4. Statistical analysis: What exactly is the definition of partial response and stable disease? This could be included in table 2.

→ According to RECIST criteria, commonly used the criteria for the response evaluation of chemotherapy, *partial response* is defined as 30% or more decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. *Stable disease* is defined as neither sufficient shrinkage to qualify as partial regression nor sufficient to qualify as disease progression (20% or more increase in the sum of diameters of target lesions or, the appearance of new lesions), taking as reference the smallest sum diameters while on study.

We described the method of the response evaluation in the method part, and added the definitions to table 2 as reviewer's comment.

Ref) Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors (RECIST Guidelines). J Natl Cancer Inst 2000;92:205–16.

5. The legend of the table has to be put on the top of the table.

→ Thank you for the thoughtful review. Legends are replaced on top of the table.

6. Methods: What was the decision matrix to stop or continue treatment every 4 weeks?

→ We made a decision based on the toxicity, response, and the patients' tolerability every cycle. If the progressive disease by RECIST criteria or unacceptable toxicities were developed, we stop the chemotherapy. And

if the patient was not tolerable to chemotherapy, treatment was also stopped.

We described the criteria in the method session as follows:

" The treatment was continued until progressive disease or unacceptable toxicity was observed. If the patient failed to tolerate the chemotherapy, treatment was also stopped."

7. Results:

Table 1: What was the aetiology of the HCC cases? HBV, HCV, alcohol? please add.

→ We added the etiology in Table 1 & result session

Table 3 can be omitted and included in the text.

→ We omitted the Table 3 and the data of Table 3 were included in the result session as below.

"There was a significant association between the status of the primary liver mass at the start of treatment and the clinical outcome. Patients who presented a stable primary liver mass showed a better response than those who presented with a progressive primary liver mass (p=0.004)."

8. Discussion:

It has to be pointed out that the improvement of life expectancy by treatment is minimal in most cases. Thus, in counselling, qualitiy of life parameters should play an important role; this is not mentioned.

→ Yes, we totally agree with your opinion.

We could not evaluate quality of life parameter because we retrospectively analyzed the data.

Instead of it, we analyzed the change of pain score (visual analogue scale) from the medical record. The pain control is most important for the advanced cancer care, and it can be parameter of the quality of life improvement.

As you pointed out, we added the limitation of survival benefit and the pain score in the discussion as below.

"Although some selected patients showed a survival benefit in the present study, the overall survival increase was minimal across all patients. However, the change in the pain score according to 10-step numeric rating scale was 0.5 (range: -6 ~to 3, data not shown). Most patients had minimal pain that required a dosage increase in pain

killers throughout the treatment period. We were unable to evaluate the quality of life improvement because this was a retrospective analysis. However, the minimal change of pain score suggested that ECF treatment might have a positive effect on pain control in advanced HCC."

9. In addition to the statement of the authors it should be made clear that only a randomised controlled trial can provide reliable data

→ All authors agree that prospective, randomized trial is needed to confirm the results of current study. This is stated as follows:

"To confirm our results, a prospective, randomized trial with a large sample size is warranted."

Reviewer #2

1. Why they did not include drug that inhibits the MDR1 along with the combination chemotherapy.

→ We totally agree with the reviewer's suggestion. In the previous published data, MDR1 inhibition can enhance sensitivity to chemotherapy, but these studies have been conducted in cell line or animal study, not in human study. Therefore, we could not treat our patients with the MDR1 agents in clinical practice. In the background of clinical trial, it is worthy of try throughout the preclinical & phase I trial of combination with chemotherapy

We commented it in the discussion as below.

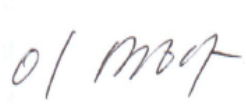
"The inhibition of MDR1 has been reported to enhance the sensitivity of chemotherapy in vitro or in animal model systems [23, 24, 25]. These data suggest that combining a MDR1 inhibitor with chemotherapy can be another direction for the treatment of HCC, besides the new agent targeting signal pathway or tumor angiogenesis. Unfortunately, there have been few human clinical trials using this approach, so more preclinical or clinical trials are needed."

2. The authors did not pay attention to Figure legend. They are very brief and difficult to understand. This need to be fixed before it is published. Also they are out of place.

→ We placed the legends on the top of tables and figures, and added the brief summary of tables and figures.

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

Sincerely yours,



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