Author's response to reviews

Title: Retrospective comparison between a regular and a split-dose protocol of 5-fluorouracil, cisplatin, and mitoxantrone for the treatment of far advanced hepatocellular carcinoma

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Author's response to reviews: see over
Dear Dr Erik Alexandersson, Dr Diana Marshall, and Dr Zhao-Chong Zeng,
Thank you very much for your careful and thorough reviews of our manuscript. My colleagues and I greatly appreciate the comments and suggestions from the Reviewers.

We have revised our manuscript along the lines indicated by the Reviewers. All changes were marked in red in the revision. The following are the point-by-point responses to the comments:

Reviewer 1 and 2 suggest that the paper is acceptable.
We appreciate the help from these two reviewers.

Reviewer 3 suggests that all statistic methods are correct and appropriate. Two concerns that do not affect the validity of the article are raised:
1. Younger patients have worse prognosis.
2. The sample is small and should have further confirmation.

Ans: An independent large scale study conducted in Taiwan also showed that younger patients with advanced HCC had worse prognosis (reference 23). The possible explanation had been provided (page 11, lines 2-5). The small sample size of this study and the need for further confirmation were discussed (page 11, lines 24-31).

Reviewer 4 raised several issues for the statistical methods.
1. Number of death and post hoc power for statistical analysis should be given.
Ans: The number of death was clarified (page 7, lines 15-16). The power for several comparisons was given (page 7, lines 23-24; page 9, line 13).

2. Patients at risk for survival curves should be done.
Ans: The numbers of patients at risk were added as suggested (Figure 1 revised).

3. Strategy of multivariate Cox and logistic model is not described regarding the number of variables that could be included.
Ans: The strategy of multivariate analysis and number of variables were provided as suggested (page 8, lines 18-20; lines 31-32).

4. The reviewer suggested us to calculate of a propensity score to assess variables associated with split-dose treatment in order to take into account the bias associated with treatment choice.
Ans: In our patients, no significant difference was observed in basic clinicopathological data between the regular treated group and the split-dose treated group (Table 1). Logistic regression analysis also failed to identify any clinicopathological factor significantly associated with the choice of either protocol. Thus, propensity score matching analysis was not applied in this study. This point was clarified (page 7, lines 13-15).

5. The reviewer suggested us to clarify if deaths were used as events for OS (overall survival) and asked for the reason why PFS (progression free survival) was not used.
Ans: The methods of OS calculation had been provided (page 6, lines 9-10). All except 3 responders and 2 patients with progressive diseases were followed till death (page 7, line 15-16). In advanced HCC patients, the survival time was very short. Therefore clinically, overall survival is a better endpoint for evaluation of treatment efficacy (clarified in page 11, lines 11-14).

6. Discussion section should include more clearly limitation regarding number of patients and selection bias.
Ans: This was provided as suggested (page 11, lines 24-31).

7. The reviewer suggested us to provide BCLC and CLIP scores.
Ans. This was provided as suggested (page 4, lines 23-25; page 8; line 5 and 13-14; and Table 3).

8. Clearly state the exploratory purpose of the study.
Ans. This was given (page 4, lines 3-6).

We hope the paper is now acceptable.
Thank you again for handling our paper.

Sincerely,
Chau-Ting Yeh, MD, PhD