Author's response to reviews

Title: Pharmacokinetics and safety of cyclophosphamide and docetaxel in a hemodialysis patient with early stage breast cancer: A case report

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Author's response to reviews: see over
Dear Prof. Roselyn Remoto and Reviewers:

Thank you for your letter and for the reviewers’ comments concerning our manuscript entitled “Pharmacokinetics and safety of cyclophosphamide and docetaxel in a hemodialysis patient with early stage breast cancer: A case report” (ID: 7334735291418091). The comments are valuable and were very helpful in revising and improving our paper, as well as helped provide guidance for our researches. We have gone through the comments and have revised our manuscript accordingly. The manuscript has been polished by an English language editor. And we have removed the patient consent form from the manuscript as required. We hope that the revisions meet with approval. Revised portions are marked in red in the paper. The main corrections in the paper and the responses to the reviewer’s comments are as follows:

Reviewer #1

Major comments:

1. The analytical method performance should be included as the assay was adapted from others. Linearity, limit of detection and variability in the lab performing the assays should be reported.

Response: Thank you for your comments. We have added the essential information about the analytical method performance in the revised paper, including linear correlation coefficient, limit of detection and variability for cyclophosphamide and docetaxel (line 16~19 of page 6).

2. The results include AUC from 0-infinity- however patients underwent dialysis with after hour 48. Does the AUC from 0 to infinity include the post dialysis sample? Please clarify the methods.

Response: The AUC from 0-infinity was calculated according to the data of 48 hours, by excluding the post dialysis sample. In order to clarify the methods, some revisions...
were made.

3. The assay the investigators used did not measure the active cyclophosphamide metabolite (4 hydroxycyclophosphamide) even though the assay they reference did – this limitation should be expanded upon and its implication to the interpretation of the data.

**Response:** Thank you for your comments. We have added some discussion of the limitation (line 26~29 of page 9).

4. It is stated that therapy was tolerated “without severe adverse reactions” however there was grade III leukopenia. This statement should be revised to reflect this grade of toxicity and what grade toxicity would be considered severe (ie greater than grade II?) Simply because degree III toxicity occurs in 10% of patients does not mean that it is not a severe reaction.

**Response:** Thank you for your comments. In the original paper, the term “severe” meant “no additional severe adverse reaction occurred relative to patients receiving TC regimen in normal condition”. In patients with normal renal function, a previous study reported that the incidence rates of grade III leukopenia was approximately 10%, and the ADR was controllable. The case reported in this study was similar. In order to clarify the term “severe”, certain revisions were made (page 7).

5. Additional information about hemodialysis should be included (duration, type of filter, etc).

**Response:** Thank you for your question. We have added the essential information on hemodialysis including duration, type of filter (line 28~30 of page 5).

6. The findings for dialysis removal should be discussed with what was previously known.

**Response:** Thank you for your comments. We have revised the discussion section by including data from the previous literature on the dialysis removal of
cyclophosphamide and docetaxel (line 3–13 of page 9).

Minor comments:
1. The text page 6 line 28 – auc units are uM/h, however units elsewhere are mcg/ml (figures and tables) – please be consistent with use of units – no need to convert uM/h in the text when concentration time plot is ug/ml (or provide the conversion).

Response: Thank you for your comment. We have revised the AUC units in the revised paper.

Reviewer #2
Major Compulsory Revisions:
1. Remove conclusions no efficacy in abstract and conclusion. This case report cannot assess efficacy. Similarly the claims on safety should be tempered because a case report only provides limited safety evidence (that it is safe in some people, without defining what fraction).

Response: Thank you for your comments. We have revised the abstract and the conclusion in the revised paper to make the claims more tempered.

Minor essential revisions:
1. "Degree I thrombocytopenia, degree III leukopenia" in abstract and p7 L7 appear to refer to grade. Should describe them as grade 1, grade 3 and provide the grading criteria (e.g. NCI CTCAE v4).

Response: We have made changes in the revised paper.

2. p5 L13 should read "hemodialys is every 48 hours, and has produced no urine"

Response: We have made changes in the revised paper.

3. p8 L2 "Marion et al." should read Haubitz et al.

Response: We have made changes in the revised paper.
4. p8 L12 "as an implosive therapy" doesn't make sense. Suggest you restate.

**Response:** We have made changes in the revised paper.

5. p8 L26-27 per cyclophosphamide package insert the hemodialysis may or may not clear this drug depending on the particular type. If you are going to talk about how it effects cyclophosphamide clearance, it would be important to know details of the hemodialysis methods.

**Response:** Thank you for your question. We have added essential information on hemodialysis including duration and type of filter, and have revised related discussion (line 28~30 of page 5).

These changes will not influence the content and framework of the paper, and were marked in red in electronic revised paper. We appreciate the Editors/Reviewers’ inputs, and hope that the responses meet with approval.

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

Yours sincerely, Peng Shen, Jian Chen

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