

Dear Editor and Reviewers,

Thank you very much for your letter and for the reviewers' comments concerning our manuscript titled "Posaconazole-associated severe hyperbilirubinemia in acute myeloid leukemia following chemotherapy: a case report and review of the literature" (ID: 42332). Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made correction which we hope will meet with approval. Revised portion are marked in yellow in the paper.

The main corrections in the paper and the responses to the reviewer's comments are as following:

Reviewer #1 (00506492):

1. Thank you for your nice comments on our article. Hopefully, the case report provides instructive points for other healthcare professionals.

Special thanks to you for your good comments.

Reviewer #2 (00503929):

1. Specific comments on originality: *The authors should be precise when reporting on the novelty of their study. In the manuscript, it is repeatedly stated that this complication of antifungal treatment is very rare. It is also repeatedly stated that their study is, to the best of their knowledge, the first report of this complication. It may not be obvious, but these two statements contradict each other. If something is stated to be very rare, this statement implies that it has occurred and been documented, even though it is very rare. If it has been observed, but not adequately documented, then it may be very rare, but incompletely described in the scientific literature. Then the authors, who knew beforehand that this complication existed, and that it was rare, undertook to make a thorough description of one such case. They are commended for having done so, but should make it clear that "the condition is usually very rare, and we have found no detailed description of it in the medical literature, so to the best of our knowledge, this is the first thoroughly documented case report of it."*

Response: Thank you for your reminding and corrections. We feel sorry that we were not very precise when reporting the novelty of the study. Actually, it is the first thoroughly documented case report with detailed description. So, according to your suggestions, we have deleted imprecise description in the section of Abstract and Introduction, and have re-written the novelty in the section of Conclusions as following: The condition is usually very rare, and we have found no detailed description of it in the medical literature. So to the best of our knowledge, this is the first thoroughly documented case report of it.

2. Specific comments on section organization: *Quantitative data should not be reiterated in the discussion, since they are expected to have all been included in the results section, to*

which reference can be made within the discussion.

Response: Thank you for your comments. It is really true as suggested that quantitative data should not be reiterated in the discussion. So we have just deleted all quantitative data of laboratory examination of the patient in the section of Discussion.

3. Specific comments on care of manuscript: *The manuscript contains a large number of typos, which must be corrected. It also contains incomplete phrases and cumbersome expressions which make it difficult for the reader to follow the scientific description. I have made the corresponding corrections in the accompanying copy of their manuscript [shown in boldface], and strongly recommend the authors to incorporate these corrections in any revised version of their study.*

Response: Thank you for your careful checks and corrections. We feel sorry for our carelessness and poor writings. We have corrected the typos and incomplete phrases. And we do invite one of our authors who have lived in the U.S. for over 10 years and have obtained the Doctor of Pharmacy degree in the U.S. to help polish our article. Also, in order to make it easy for readers to follow the scientific description, we have added necessary figure to present the medication process. And we hope the revised manuscript could be acceptable for you.

4. Specific comments on scientific value: *I consider the discussion of the case to be useful and updated, especially as concerns the mechanisms of liver cell damage and the possible influence of drug binding to plasma proteins and of upregulated glucuronidation in determining the extent of hepatic injury.*

Response: Thank you for your nice comments on our article. Hopefully, the case report provides instructive points for other healthcare professionals.

5. Specific comments on ethical considerations: *Authorization to publish the findings seems to have been granted by the patients' relatives (degree of kinship non-specified). On the other hand, the fate of the patient beyond recovery of the liver damage is not described, so we are left without information as to why the patient himself did not use of his right to grant publication of the data. We think more detail on both aspects is required to establish that the study was unimpeachable from the point of view of medical publication.*

Response: Thank you for your reminding. Written informed consent containing liver damage was obtained from the patient himself before all procedures described in the report as well as for the use of the patient's clinical information for publication.

Special thanks to you for your good comments.

Reviewer #3 (01021289):

1. Specific comments: *It is hard to understand the time course change of jaundice with respect to medications that were administered. The authors should show the figure that demonstrate the time course change of jaundice relative to all the drugs used, so that the reader will be able to understand which drugs were associated with the elevation of bilirubin. The current*

manuscript is very hard to follow to understand which medication was associated with hyperbilirubinemia.

Response: Thank you for your reminding. We feel sorry we did not provide the figure that demonstrates the time course change of jaundice relative to all the drugs used. According to your suggestions, in order to make it easy for readers to follow the case description, we have added the necessary figure titled “Relationship of T-BIL and medication process” to demonstrate the time course change of T-BIL relative to all the drugs used.

2. Specific comments: *Discussion is too long. Since this is a case report, discussion should be more concise and shortened.*

Response: Thank you for your reminding and suggestions. According to your comments, we have shortened our discussion and make it more concise.

Special thanks to you for your good comments.

We appreciate for Editors/Reviewers’ warm work earnestly, and hope that the correction will meet with approval. If you have any question about this paper, please feel free to contact us.

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

We look forward to hearing from you at your earliest convenience.

Yours sincerely,

Fei DONG