Author's response to reviews

Title: Treatment strategy for reducing the risk of rituximab-induced cytokine release syndrome in patients with intravascular large B-cell lymphoma: a case report and literature review

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Author's response to reviews: see over
Dear Professor Kidd:

Thank you for your invitation to resubmit our manuscript titled “Treatment strategy for reducing the risk of rituximab-induced cytokine release syndrome in patients with intravascular large B-cell lymphoma: a case report and literature review” for publication in BMC Medical Case Reports.

We have carefully considered the reviewers’ comments and have adjusted our manuscript accordingly. Point-by-point responses to these comments are listed below. We hope that you will find the revised manuscript suitable for publication.

Yours sincerely,

KATSUHIRO MAKINO
RESPONSES TO REVIEWER #1

**Comment #1:** In the introduction part, would recommend outlining the fact the fact that overall the risk of serious adverse events (SAEs) associated with the use of Rituximab are in general very rare. It is due to the increased frequency of usage for a myriad of conditions that adverse events are now more commonly reported (copy of our review attached for your reference).

**Response:** Thank you for this suggestion. We have altered the text accordingly, as can be seen below:

> However, this compound has been associated with severe and unpredictable complications including cytokine release syndrome (CRS), systemic inflammatory response syndrome (SIRS), and death [4, 5]. Similar side effects have been reported during the treatment of other forms of cancer, such as acute lymphocytic leukemia and chronic lymphocytic leukemia [6, 7].

was changed to

> However, 84%–95% of patients who receive a rituximab-based regimen experience treatment-related adverse events; approximately 90% of these are of mild to moderate severity, and most involve flu-like symptoms (fever, chills, nausea, and asthenia)[4]. The general overall risk of serious adverse events after rituximab administration is very low, but the compound has been associated with severe and unpredictable complications, including cytokine release syndrome (CRS), systemic inflammatory response syndrome (SIRS), and death [5, 6]. Similar side effects have been reported during the treatment of other forms of cancer, such as acute lymphocytic leukemia and chronic lymphocytic leukemia [7, 8]. The frequency of use of rituximab has been increasing as it is now applied to a myriad of conditions, and adverse events are more commonly reported [9].

**Comment #2:** When mentioning the efficacy of various regimens, it would be useful to mention the actual rates in terms of remission and the improvement with the addition of rituximab to these regimens.

**Response:** We added the following text to the manuscript:

> The R-CHOP regimen comprises rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone. The complete response (CR) rate is reportedly higher for patients with IVLBCL who have undergone chemotherapy with rituximab (R-chemotherapy group) compared with those who have not (chemotherapy group): in one study, a CR was achieved by 82% of patients in the R-chemotherapy group and by 51% of those in the chemotherapy group.
Comment #3: With respect to the random biopsies, were there any lesions or suspected areas that were biopsied and why that was chosen as the approach would be helpful.

Response: We added the following sentences to the manuscript:

These areas were selected for ease of access.

Comment #4: With respect to the mentioning of the R-CHOP regimen, please mention what it comprises.

Response: Please see the response to comment #2.

Comment #5: The conclusions are very interesting and clinically useful. However, the recommendations are still based on different cases/series and the numbers, though considerable, are still small. Therefore, it should be mentioned in the conclusion that this would need to be verified by prospective randomized controlled trials.

Response: We added the following sentence to the manuscript:

However, these data have been derived from a small number of patients, and future prospective studies of the timing of rituximab administration are warranted.

Comment #6: Also in this study, the pt had received some steroids earlier and thus the prednisone/prednisolone was not given as part of the chemotherapeutic regimen. However, we do know that some of the severe allergic reactions are markedly reduced with premedication with IV steroids right before the chemotherapeutic regimens; which somewhat are on the same clinical spectrum as CRS. As to how this would change the incidence of these reactions from Rituximab would also be worth mentioning in the discussion.

Response: We added the following paragraph in response to this comment:

It has also been reported that patients who have not undergone steroid therapy and/or chemotherapy before receiving the first dose of rituximab show a tendency to develop adverse events related to its infusion, more so than those who have undergone these treatments beforehand. We did not use steroids immediately before the injection of rituximab in the present case, but it could have been helpful in preventing an infusion reaction.

Comment #7: The only other thing that should be added to the case report before publication is to explicitly outline the search strategy for the literature review in more detail; as to how many papers were retrieved and how many studies were selected. A table of the studies selected and their patient characteristics in more detail would indeed be very useful and would add to the value of the case report since this adverse event is very rare.
Response: We added the following paragraph in response to this comment:

A total of 29 (58%) of the 50 patients received steroid therapy and/or chemotherapy before the first dose of rituximab. In the 1\textsuperscript{st} R-group, 14 of the 25 patients received rituximab on the first day of treatment, and 9 (64\%) of these developed an infusion reaction. Five of these 9 patients developed hypoxia in association with the rituximab infusion, including Grade 3 severe hypoxia in two. All patients except for our present case recovered without complications. On the other hand, in the 2\textsuperscript{nd} R-group, 10 of the 25 patients received rituximab on the second to seventh day of treatment, and 2 (20\%) of these developed an infusion reaction up to Grade 2.

We also added Table to provide more detailed information on the reports of adverse events among these patients.

RESPONSES TO REVIEWER #2

Comment #1: The authors proclaimed to review the previous cases.

Response: We have altered the text as shown below.

"We report the case of a patient diagnosed with an Asian variant of IVLBCL, who died from SIRS during the first course of chemotherapy that included rituximab."

to

We here report the case of a patient diagnosed with Asian variant IVLBCL who died from SIRS during the first course of a chemotherapy regimen that included rituximab; we also present a review of the literature associated with rituximab use among patients with IVLBCL.

Comment #2: There is little information regarding the reviewed cases.

Response: Please see the response to comment#7 from reviewer #1.

Comment #3: In table I the reviewed cases should be presented as individual cases or at least as classes of cases with the relevant details.

Response: Please see the response to comment#7 from reviewer #1.

Comment #4: In the conclusion part of the abstract they summarized: "The results of this study reveal that the incidence of adverse reactions can markedly decrease"… - this is not study, so these are not results. A similar approach was mentioned in the discussion:” Our analysis suggests that”… They may draw conclusions, but they have to present the arguments for that, especially in the discussion.
Response: We changed “study” to “data”, as in “Our data reveal that the incidence of adverse reactions to rituximab can be markedly decreased ...”

Comment #5: The case was written as by medical student and not by trained physician, especially the case report which was too long.

Response: We deleted some of the extraneous detail in the case report section.

Comment #6: The English language should be revised.

Response: The article has been reviewed by a native English editor.