Author's response to reviews

Title: Inflammatory (B) symptoms are independent predictors of myelosuppression from chemotherapy in Non-Hodgkin Lymphoma (NHL) patients - analysis of data from a British National Lymphoma Institute phase III trial comparing CHOP to PMitCEBO.

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Inflammatory (B) symptoms are independent predictors of myelosuppression from chemotherapy in Non-Hodgkin Lymphoma (NHL) patients - analysis of data from a British National Lymphoma Institute phase III trial comparing CHOP to PMitCEBO. Rohini Sharma, David C Cunningham, Paul Smith, Graham R Robertson, Owen Dent and Stephen J Clarke

Dr Sabina Alam
Assistant Editor
BMC-series journals

Dear Dr Alam,

Thank you for providing the responses from the reviewers. Reviewers 1, 2 and 4 are happy with the article and have not requested further changes or clarifications. Reviewer 3 has asked some very insightful questions that we have attempted to address below and through changes in the text. I hope we have now addressed his concerns and that you find our article suitable for publication.

Regards

Stephen Clarke

Reviewer 3: David J Straus
Reviewer's report:

Discretionary Revisions:

- This may not be an important point, but Table 1 does mix pre-treatment characteristics with toxicity during treatment by grade (not “stage”). Why could they not be separate tables for clarity?

We have created 2 tables from the previous one.

Minor Essential Revisions:

- The criteria for grading toxicity should be cited.

We have cited the web address for the NCICTC toxicity grading criteria within the text.

Major Compulsory Revisions:

- Since prophylactic use of GCSF is now standard of care in this population of elderly patients treated with this type of treatment, it noteworthy in Table 4, that the use of GCSF in this study seem to have a “protective effect” (p. 8) on the association of B symptoms with leucopenia. This makes the clinical importance of the observed association of B symptoms with leucopenia questionable. This should be addressed in the Discussion.

We have added the following paragraph to the discussion which we hope will satisfy this concern: “This study was principally undertaken to provide a clinical "proof of principle" of our previous pre-clinical and clinical findings that the presence of an inflammatory response predicts for slower hepatic clearance of cytotoxic drugs and
increased toxicity. The data will not have a major immediate impact on the management of patients with NHL, as prophylactic G-CSF is already routinely used in this condition, and our data confirm that this provides a protective effect against leucopenia.”

- The inclusion of the comments about the lack of association of B symptoms with response rates or survival also raises questions about the clinical importance of the association of B symptoms with toxicity. Evidently this lack of association of B symptoms as a surrogate for inflammation with response rates and survival does not confirm other reports in the literature. All of this also deserves comment in the Discussion.

We have added the following text to address this concern: “Also, in this cohort, the presence of inflammatory symptoms did not adversely impact survival, which again raises questions about the immediate clinical significance of our findings. However, this may have been due in part to our desire to include only patients on whom full data sets were available for the assessment of toxicity and could have excluded patients who experienced early disease progression. Furthermore, multiple previous investigators have established that B symptoms are associated with worse progression free and overall survival in NHL (6-10).”

- The questionable clinical importance of the association B symptoms with myelosuppression, especially with the apparent abrogation of this association with the prophylactic use of GCSF, makes the case for the use of agents to block inflammatory cytokines in these patients less than compelling.

We take on Dr Straus’ comments and feel we have addressed his concerns about overstating the clinical importance of our findings in regard to the management of lymphoma in the additional sentences. However, we would like to emphasise that we used lymphoma patients as the means by which to test the hypothesis that inflammation is associated with worse chemotherapy toxicity because of the strong association between B symptoms and elevated inflammatory proteins. Our principal focus is drug toxicity and not lymphoma. Inter-patient variability in toxicity from chemotherapy is a major cause of morbidity and mortality from chemotherapy. This is the issue we are trying to address and hence the comments about future interventions that might reduce variability in toxicity.

One other suggestion is to discuss the strengths and limitations of the study in Discussion. The following sentences are now included in the discussion: “The study has some limitations. Firstly, it was an unplanned reanalysis of prospectively collected data, and the presence of inflammation was only assessed clinically as correlative blood samples for measurement of inflammatory proteins were not available. In addition, it was not possible to assess the impact of B symptoms on the incidence of neutropenia, febrile neutropenia, toxicity related hospitalisation, treatment related death and dose delay or reduction, as these data had not been reliably recorded. Such associations and correlation with plasma inflammatory markers should be evaluated in future studies.”