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.

**Authors:**

Rohini Sharma (r.sharma@imperial.ac.uk)
David C Cunningham (David.Cunningham@rmh.nhs.uk)
Paul Smith (p.smith@ctc.ucl.ac.uk)
Graham R Robertson (grobertson@med.usyd.edu.au)
Owen Dent (owen.dent@netspeed.com.au)
Stephen J Clarke (sclarke@med.usyd.edu.au)

**Version:** 2 **Date:** 13 February 2009

**Author's response to reviews:** see over
Response to Reviewers’ Comments – Stephen Clarke

Reviewer's report – 1.
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.
Version: 1 Date: 19 December 2008
Reviewer: Donald C McMillan
Reviewer's report:
The present study uses an indirect approach to address the hypothesis that systemic inflammation predicts response to chemotherapy. By not making direct measurements of this means that much of the introduction and discussion is taken up with linking inflammatory symptoms with systemic inflammation and leucopenia with treatment related toxicity. Therefore, although the study is large, well described and well carried out the results are of limited value. As a consequence much of the discussion is speculative and the concluding paragraph has nothing to do with the study. I would suggest that the report is shortened and the authors avoid speculative statements
Level of interest: An article of limited interest
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests

Response – we would have liked to have been able to measure plasma concentrations of inflammatory markers in this patient cohort, but that was not possible. However, in NHL, unlike any other malignancy, inflammatory symptoms have been shown repeatedly to be associated with elevated plasma markers of inflammatory proteins including IL-6 and CRP. They are also an accepted adverse prognostic indicator in NHL and consequently are routinely assessed by treating physicians. Therefore, we do not think their use as an indicator of an ongoing tumour induced inflammatory response is inappropriate. If it had been any other tumour type, then we would support the assertions of this reviewer. Consequently, we have not altered the text based on the comments of this reviewer.

Reviewer's report – 2.
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.
Version: 1 Date: 28 January 2009
Reviewer: Umberto Tirelli
Reviewer's report:
Major compulsory revisions: In the manuscript there is no mention of toxic deaths and of other important side effects like fatigue. There is no mention in the paper on the relationship between myelotoxicity and CR rate and overall survival.
Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: Yes, but I do not feel adequately qualified to assess the
statistics.

Declaration of competing interests:
I declare that I have no competing interests

Response – these are extremely valid points. We limited our review to those parameters that were reliably reported in the study. There were significant gaps in the reporting of fatigue and in the indication of treatment related deaths and dose reductions and delays due to toxicity. Therefore, we did not feel able to adequately comment on these issues, however we plan to evaluate these issues in a future dataset. In terms of response rate and survival, there was no statistical difference between patients with A and B symptoms and we have included a sentence to this effect in the manuscript.

Reviewer's report – 3.
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.
Version: 1 Date: 3 February 2009
Reviewer: Miles Prince

Reviewer's report:
This is a well written report, comprehensively addressing an important question. The authors should comment in the Discussion that this finding should now be tested in a prospective fashion.
Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests.

Reviewer's report
Response – we have included a sentence about future prospective studies to evaluate this hypothesis in the discussion.

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.
Version: 1 Date: 3 February 2009
Reviewer: David J Straus

Reviewer's report:
This is a provocative report testing a novel hypothesis that B symptoms at diagnosis and the associated elevations in inflammatory cytokines like IL-6 may increase toxicity of chemotherapy, particularly leucopenia and anemia in elderly patients treated with combination chemotherapy for diffuse large B-cell lymphoma. There is no statement as to whether or not presence of B symptoms at diagnosis had any impact on event-free or overall survival in the clinical trial that was analyzed. The association of B symptoms with toxicity would be less important if there was no adverse effect on these outcomes. Exactly when and how often toxicities during treatment were measured is not clear in this analysis. Were the toxicities measured after cycle 1 of chemotherapy or during any cycle of chemotherapy? Did they measure how often these toxicities occurred in each patient? This might have an impact on
the interpretation of these findings. For example, if toxicity occurred only after cycle 1 or the first few cycles of chemotherapy and B symptoms promptly resolved with treatment, was there less toxicity in subsequent cycles? The way in which the toxicity is reported should be clarified (total toxic events? chemotherapy cycle 1 toxic events? total number of each toxic events per patient?). Also, since prophylactic GCSF is now standard practice even with cycle 1 chemotherapy, it is not clear whether B symptoms would be associated with increased leucopenia with this treatment policy.

Specific Comments:
Table I mixes pretreatment characteristics and toxicity during treatment. These should probably be in 2 separate tables. Again, it is unclear how toxicity is being reported. p. 8, typo: They must really mean that severe leucopenia occurred more frequently in patients who did not receive GCSF. The tables are not cited correctly in the text. P. 6: Table 4 show the associations of anemia and thrombocytopenia with pretreatment characteristics, not Tables 5 and 6. P. 9: There are no Tables 7 and 8. These must refer to Tables 5 and 6. Level of interest: An article whose findings are important to those with closely related research interests.

Response – the toxicities recorded are for the entire treatment course – we have clarified this issue in the methods. The toxicity data were included in Table 1 for 2 reasons. Firstly, we wished to limit the number of tables and secondly, we thought it appropriate to list all parameters that were essentially “baseline” data for the current study. Therefore, we have left these data in Table 1. We have added a statement about response and survival. We cannot comment about disappearance of B symptoms with treatment as this symptom was only assessed at baseline. The reviewer does not appear to appreciate that G-CSF was only administered to 50% of patients as it was a second randomization in the study. We have corrected the specific issues raised.

Also, please could you include the following important information to your revised manuscript:

***Trial registration number: The data reported in this study have been taken from the trial listed as Reference 16 in your manuscript. Please could you clarify if the original trial has a registration number? If it does, then please include the trial registration number at the end of the abstract.
Done – the trial registration number was ISRCTN98741793

***Competing interests - Please include a 'Competing interests' section between the Conclusions and Authors' contributions. If there are none to declare, please write 'The authors declare that they have no competing interests'.
Done

***Authors' contributions - Please include an Authors' contributions section before the Acknowledgements and Reference list.
The following section has been included:
RS carried out liaison with the BNLI to obtain the dataset for the manuscript
and was responsible for preparing an initial version of the manuscript.
PS and DC were responsible for providing the UK side of the BNLI liaison and for providing data, answering data queries and reviewing the manuscript.
OD was responsible for the statistical analysis and providing input into the later versions of the manuscript.
GR and SC initiated and jointly supervised the project.
All authors read and approved the final manuscript.