Author's response to reviews

Title: Prognostic significance of peripheral monocyte count in patients with extranodal natural killer/T-cell lymphoma

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Version: 2 Date: 23 February 2013

Author's response to reviews: see over
Dear Editor in chief,

We have enclosed our revised manuscript entitled **Prognostic significance of peripheral monocyte count in patients with extranodal natural killer/T-cell lymphoma** for consideration as Research Articles in *BMC cancer*.

We have revised the manuscript in response to the reviewers' comments. Attached please find the list of changes in the “Response to Reviewers” section of this cover letter. The changes made from the previous article file has been done using “track changes” in programs including MS Word or marked any changes in blue in the new document.

BMC Cancer is an open access, peer-reviewed journal that considers articles on all aspects of cancer research, which is quite attractive for our authors. Extranodal natural killer/T-cell lymphoma (ENKL) has heterogeneous clinical manifestations and prognosis. Monocyte, which is recently reported to be a surrogate marker of the tumor microenvironment and host immunity, has been found to induce the proliferation of natural killer (NK)/T lymphoma cells and to infiltrate lymphomas. This current study firstly evaluated the clinical relevance of the peripheral blood monocyte count in ENKL. We found that absolute monocyte count (AMC) at diagnosis was identified as a novel, powerful prognostic factor for survival in ENKL, independent of International Prognostic Index (IPI) and Korean prognostic index (KPI). The prognostic index incorporating AMC and absolute lymphocyte count (ALC, another surrogate indicator of host immunity) could be used to stratify all the patients with ENKL into different prognostic groups. When superimposed on IPI or KPI categories, the AMC/ALC index was better able to identify high-risk patients in the low-risk IPI or KPI category.

All authors have read and approved the manuscript. This manuscript is not under consideration elsewhere. There is none of financial support or relationship that may pose conflict of interest. Neither deviations nor any potential conflicts related to the exclusive nature of the publication. This study complies with the principles of the Declaration of Helsinki. The protocol of this study was approved by the Institutional Review Board (IRB) of Sun Yat-Sen University Cancer Center. Informed consent was obtained from all patients before the collection of patients information.

The manuscript is written and formatted in accordance with the latest Author Guidelines. A medical editor, who is an English native speaker and the member of American Medical Writers Association and the freelancer of MedCom Asia, Inc., has edited this manuscript to ensure the correct usage of grammar and syntax.

On behalf of the authors of this paper, I would like to confirm that this is our original unpublished work, and has not been submitted to any other journal for review.

Yours sincerely,
Response to Reviewers:

Manuscript ID: 1310986505869785
Prognostic significance of peripheral monocyte count in patients with extranodal natural killer/T-cell lymphoma

Reviewer(s)' Comments to Author:
Reviewer: Gisele Colleoni
Minor essential revisions
The authors wisely defend that this model has to be applied in independent cohorts. However, some discussion should be added about how this new, simple and worldwide feasible score could change current treatment approach of this tumor, including their opinion (based on review of the literature) if there is early indication of high-dose chemotherapy followed by autologous stem cell transplant in high-risk cases.

Response:
We thank the reviewer’s comment. We have added some discussion according to the reviewer’s suggestion in the “Discussion” section as follows:

The current management of newly diagnosed ENKL patients was mainly based on the involvement sites (localized or disseminated disease). In this series, although most of the ENKL patients with localized disease underwent chemotherapy combined with radiation, some patients in this subgroup had unfavorable prognosis. The AML/ALC index was helpful to identify patients with poor survival outcomes. Maybe the combined treatment modality is insufficient to cure the high-risk patients. Several retrospective studies suggested that high-dose chemotherapy followed by autologous hematopoietic stem cell transplantation (HD-AHSCT) showed promising results for patients with disseminated ENKL [43, 44, 45]. It is interesting to investigate the efficacy of HD-AHSCT in the high-risk patients with localized disease in future studies.

Reference:
43. Murashige N, Kami M, Kishi Y, Kim SW, Takeuchi M, Matsue K, Kanda Y,
Response:

We thank the reviewer’s kindly remind. The manuscript is written and formatted in accordance with the latest Author Guidelines. A medical editor, who is an English native speaker and the member of American Medical Writers Association and the freelancer of MedCom Asia, Inc., has edited this manuscript to ensure the correct usage of grammar and syntax.

Reviewer: Otavio CG Baiocchi

Minor essential revisions:

1- Methods: The authors stated that written informed consent was obtained from all patients before treatment. This is a retrospective study and, probably, written informed consent was not obtained from all patients prior entering this study. The authors should address this topic more clearly.

Response:

Thanks the reviewer’s kindly remind. Written informed consent of treatment (chemotherapy and/or radiotherapy) was obtained from all patients prior to therapy. All patients agreed to use their medical records for research. This above issue has been addressed clearly in the revised manuscript.

2- Results:

- A more detailed explanation of AMC discriminative cut-points (ROC curve analysis) should be provided.

Response:

Thanks the reviewer’s kindly remind. The more detailed explanation of AMC discriminative cut-points (ROC curve analysis) has been added in the “Results” section as follows:

The most discriminative cut-points of the AMC was $0.495 \times 10^9/L$ (area under the curve [AUC]: 0.63, 95% confidence interval: 0.534-0.726, $P = 0.011$), as determined
by receiver operating characteristics (ROC) analysis.

- The associations between patient’s clinical characteristics (age, B symptoms, LDH, stage, etc…) and AMC and AMC/ALC prognostic index are lacking in the manuscript. It would be very interesting to see these correlations in the manuscript.

  **Response:**
  Thanks the reviewer’s suggestion. The associations between patients’ clinical characteristics and AMC and AMC/ALC prognostic index were evaluated in the revised manuscript, as follows:
  Patients with high AMC at diagnosis tended to have poorer performance status ($P = 0.002$) and IPI >1 ($P = 0.022$). Patients with high risk AMC/ALC index seemed to have a higher rate of B symptoms ($P = 0.005$).

- A more detailed explanation of ALC discriminative cut-points ($1.10 \times 10^9/L$) should be provided.

  **Response:**
  Thanks the reviewer’s kindly remind. The more detailed explanation of ALC discriminative cut-points ($1.10 \times 10^9/L$) has been added in the “Results” section as follows:
  The most discriminative cut-points of the ALC were $1.145 \times 10^9/L$ (AUC: 0.601, 95% confidence interval: 0.512-0.690, $P = 0.027$), as determined by ROC analysis. Therefore, ALC $\leq 1.10 \times 10^9/L$, which was close to the most discriminative cut-point, was selected as the optimal cut-off value.

- All tables (specially Table 2 and 3) and all figures must be redone in order to make them more self-explanatory. Example: How many patients were analyzed in each figure? Define group 1, 2 and 3 in each figure.

  **Response:**
  Thanks the reviewer’s kindly remind. We have redone the tables and figures to make them more self-explanatory in the revised manuscript. The number of patients analyzed in each figure and group 1, 2 and 3 in each figure has also been listed in each figure legend in the revised manuscript.

3- Discussion:

- Please revise all references: Example: in the text …”Evidence that AMC is an adverse prognostic factor in NHL was recently provided by Wilcox et al. in patients with DLBCL and FL [25,26,36]”… Is reference 36 correctly placed?

  **Response:**
  Thanks the reviewer’s kindly remind. All the references have been checked and revised in the revised manuscript. Evidence that AMC is an adverse prognostic factor in NHL was recently provided by Wilcox et al. in patients with DLBCL and FL [25,26,36]”… The reference 36 has been deleted.

- The authors must clearly state limitations of this manuscript. Example: the limitations and pitfalls of retrospective studies.
Response:
Thanks the reviewer’s suggestion. The limitations of the retrospective analysis has been mentioned and discussed in the “Discussion” section, as follows:
In this series, the underlying positive or negative biases during the therapy or selection of patients were inevitable, due to the limitation of its retrospective nature. Future prospective studies are warranted to validate our results.