Reviewer’s report

Title: If it is in the marrow, is it also in the blood? An analysis of 1,000 paired samples from patients with B-cell non-Hodgkin lymphoma

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Reviewer: Armando López-Guillermo

Reviewer’s report:

In this manuscript, Mancuso et al. analyzed a high number of paired samples from bone marrow (BM) and peripheral blood (PB) in patients diagnosed with lymphoma. They found remarkable concordance between BM and PB by flow cytometry, with Waldenström disease being the histology with a higher number of discordant cases. The paper has some interesting information. However, there are some concerns regarding the design of the study (histological types included, comparison between flow cytometry in BM and PB, but little information on BM biopsy, etc) that can be summarized in the following aspects:

- The definition of concordance in the abstract and in the Methods section (page 6) (‘‘…the presence of a positive or negative result in BOTH BM-TP and BM-FC OR BM-FC and PB-FC.’’) is confusing. In fact, the authors analyzed 3 different parameters: BM trephine biopsy (that is currently the standard), BM flow and PB flow. The comparison between BM flow and PB flow is perfectly performed (in page 8 and in table 2), with a nice concordance of 95.2%. The comparison between BM biopsy and BM flow is more confusing probably because in table 2 the data on BM trephine biopsy is not informative on the concordance with BM flow. Perhaps a separate table would be of help in this sense. So, there are two different “concordances” and this should be clarified in the methods, results and abstract (i.e., in the current version of the abstract the sentence “discordant cases (ie presence of pathological B-lymphocytes in BM under the sensibility of the technique in the PB)” is confusing, since it is not clear if the authors are comparing PB flow with BM flow or with BM trephine biopsy or with both).

- An additional analysis that may have some interest would be to compare the data on BM trephine biopsy with the combination of BM plus PB flow cytometry. At the end, the aim of the study from the clinical standpoint would be to have a less aggressive technique to detect lymphoma infiltration in the bone marrow.

- The histological distribution is not the standard for a series of unselected non-Hodgkin’s lymphoma (35% FL, 24% DLBCL, etc), but rather suggest a selection, probably based on the availability of the samples. This is a potential bias of the study and should be at least commented in the Discussion section. In addition, another potential bias is the fact that only 31% of paired samples corresponded to patients at diagnosis. The selection of the samples probably is much higher in relapsed patients. On the other hand, the therapy used, including Rituximab, may significantly influence the results. These aspects should also be commented.
- No clinical data are provided, in terms of initial features, response or survival. This information would be very interesting, particularly in discordant cases.

- The reasons to explain the discordant cases are probably diverse and the data on CXCR4 herein presented are only a small part. Moreover, the information provided on CXCR4 expression is really scarce (there is no information on the number of patients analyzed for each histological subtype, whether or not the CXCR4 expression was different in BM or PB from the same patient, etc). Detailed information on CXCR4 expression would be the subject of a different paper.

- The discussion is too concise; some of the above mentioned limitations of the study should be at least commented in this section.

- Minor point: currently, Waldenström disease is not considered a specific entity in the WHO classification.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Needs some language corrections before being published

**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'