Format for ANSWERING REVIEWERS

May 30, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: ESPS Manuscript NO 9290-review).

Title: Current approach to relapsed acute lymphoblastic leukemia in children

Autho: Jose L. Fuster

Name of Journal: *World Journal of Hematology*

ESPS Manuscript NO: 9290

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

(1) First reviewer. "This review is not well organized. Statements should be divided at least to 3 parts**;** one is for the contributing factors resulting in a relapse, second the prognostic factors of the patients with relapsed ALL, and third the treatment of the patients with relapsed ALL. In the manuscript, similar statements such as early relapse and late relapse are redundantly made everywhere. It is recommended that all definitions such as early relapse, late relapse, BM relapse, CNS relapse, other extramedullary relapse, CR1, CR2, etc. are first presented as a Table in the Basic concept section, and not mentioned repeatedly in the text." **A new table including basic concepts definition has been added. According to another reviewer's recommendation, the Basic Concept part has been reduced to contain just the definitions, and the implications and outcome issues are now included in another section (prognostic factors).**

(2) First reviewer. "Also, it is possible to prepare a Table to summarize all clinical as well as biological data clarified to date for early and late relapses, which helps readers understand easily." **A new table including different clinical and biological aspects of early and late relapses has been included. According to another reviewer's recommendation, the biology part has been shortened.**

(3) First reviewer. "In addition, the entire manuscript is better restructured as follows; I Abstract; II Introduction; III Basic concepts of ALL relapse; IV Contributing factors for ALL relapse: 1. Clinical, 2.

Biological; V Prognostic factors (affecting factors on the outcome) in patients with relapsed ALL: 1. Length of first complete remission, 2. Site of relapse, 3. Immunophenotype, 4. Minimal residual disease, 5. Other prognostic factors; VI Treatment for relapsed ALL: 1. Risk (HR, IR, SR)-adjusted selection of treatment, 2. Reinduction, 3. Post remission therapy- SCT vs. continuation of chemotherapy, 4. Local therapy for extramedullary ALL, 5. Treatment for second and subsequent relapses; VII Outcome of relapsed ALL; VIII New perspective; IX Summary and conclusions. With such restructuring measures, lots of redundancies could be deleted to make the entire manuscript be shortened and much concise." **The manuscript has been restructured as recommended.**

(4) First reviewer. Also, the expression of "most patients did" almost in every page should be more precise like "what % of the patients did". **These expressions have been substituted as possible for specific figures (percentages).**

(5) First reviewer. "Table 1 should include the year when the study was done, to clarify if the therapeutic results improved more recently**." The year of each study has been added (this table does not contain therapeutic results with different trials but the relative incidence of the site of relapse).**

(6) First reviewer. "Definition of Risk groups (SR, IR, HR) are better described in a Table, comparing initial risks for patient at onset and risks for relapsed ALL patients, because readers may confuse which the author talks. For example, the term HR relapse in line 3 from the bottom of page 18; does this mean the patients relapsed at initially at HR? Or did the relapsed patient be defined as HR at the time of relapse? Another example, in page 19; Within the NOPHO study, patients with late BM relapse but with initial HR features, Does what initial HR mean?" **A new table including prognostic factors affecting the incidence of relapse at primary diagnosis has been added. Risk stratification after relapse has been updated in table 5.**

(7) First reviewer. "The author employs both EFS as well as pEFS, and OS and pOS. It is not clear how the author switches those terms from one to the other." **The terms pEFS and pOS have been deleted from the text.**

(8) First reviewer. "Finally, if algorithm showing how to treat relapsed ALL is shown as a Figure, readers may welcome to understand the author's idea in tackling this very complicated problems." **A simplified algorithm has been added (figure 1).**

(9) Second reviewer. "The manuscript needs a revision to avoid and correct some grammatical and spelling errors." The manuscript has been revised an corrected by an English language editing professional support institutionally provided.

(10) Third reviewer. "Fuster review the current approach to relapsed ALL in children. This is an important topic in pediatric oncology. The review is extensive and generally well written. However, the review is very long and sometimes difficult to follow. The same data can be given in a much shorter and more concise manner and avoiding the multiple redundancies. For example the Basic Concepts part can be devoted just to the definitions that would be used later in the review without their implications as the outcome of different prognostic factors is later discussed." **The Basic Concept part has been reduced to contain just the definitions; the implications and outcome issues are now included in another section (prognostic factors). The text regarding the prognostic factor, the biology and treatment sections have been shortened.**

(11) Third reviewer. "The Biology part can be shortened just to shortly review the different models for relapse and the data supporting them." **The biology part has been shortened. According to another reviewer's recommendation, a new table (table 3) including different clinical and biological aspects of early and late relapses has been included.**

(12) Third reviewer. "The role of SCT versus chemotherapy in different risk is also given repetitively and can be given in just one section." **The text regarding post-remission therapy has been reduced and refined in order to avoid redundancies.**

(13) Third reviewer. "CAR therapy can also be shortly discussed as a novel therapeutics." **CAR therapy is now mentioned in the "new perspectives section" with the addition of two novel references (references number 80 and 94).**

(14) Fourth reviewer. "Congratulations. The subject of this paper is truly important and worth a presentation. The chief challenge of this article is that the article is too long which makes its content difficult to follow." **The basic concept part has been reduced to contain just the definitions; the biology part and the text regarding the prognostic factors and post-induction therapy have been shortened as well.**

(15) Fourth reviewer. "The structure of the manuscript is well-prepared; however, it is better to be more organized with smaller number of subtitles." **The text has been restructured following the specific**

recommendations kindly suggested by other reviewer.

(16) Fourth reviewer. "In addition, in my opinion, author should, in some situations, especially in tables, besides the references, mention the author's name and the date of its publication." **The author's name and the year of each study has been added in table 1, 3 and 4.**

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Hematology*

Sincerely yours,

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