Author’s response to reviews

Title: Role of cytarabine in paediatric acute promyelocytic leukemia treated with the combination of all-trans retinoic acid and arsenic trioxide: a randomized controlled trial

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Author’s response to reviews:

Dear Editor:
Thank you very much for your letter and the reviewer’s comments (BCAN-D-17-01706, Role of cytarabine in paediatric acute promyelocytic leukemia treated with the combination of all-trans retinoic acid and arsenic trioxide: a randomized controlled trial.). Based on your comment and request, we have made the corrections. We have made underline changes in the sections of the revised text. Here below is our description on revision according to the comments.

Answers to Reviewer reports:

Scott C Kogan (Reviewer 1)

Thank you very much for your suggestions. Here are our responses to your comments.

Suggestions for revision.

Q : 1. Line 208. The authors intended “Induction therapy” here, not ”Introduction therapy.”

A : Line 208. It had been corrected as “Induction therapy”.

Q : 2. Line 255. Suggested revision “During consolidation, no blood product was required in the no-Ara-C group.

A: Results section. Line 260. It had been corrected as ”During consolidation, no blood product was required in the no-Ara-C group.”.

Q:3. Lines 268-269. Suggested revision. After the third consolidation cycle (i.e. the first cycle of DNR/DA), a complete remission (molecular) was achieved in all patients (Fig. 1). Suggest to omit the last sentence of this paragraph beginning ”All of the patients tested...” on line 271 as repetitive and not needed.

A : Results section. Line 272-273. It had been corrected as “After the third consolidation cycle (i.e. the first cycle of DNR/DA), a complete remission (molecular) was achieved in all patients (Fig. 1).”

The last sentence of this paragraph beginning ”All of the patients tested...” on line 271 had been omitted.

Q:4. Lines 294-297. Not entirely clear whether the authors mean that the median levels are not significantly different or mean that the groups are not significantly different. Correct as written? If correct as written, authors should state that the groups are not significantly different (by either one-sided t-test or similar appropriate analysis).

A: Results section. Line 293-296. It had been corrected as: The arsenic levels in the nails obtained from patients who had ceased treatment for 3-12 months (median, 264.2 ng/g; range,
117-24 240 ng/g) were higher than the levels in the controls (median, 198.8 ng/g; range, 33.6-588.1 ng/g). But statistical analyses revealed no significant difference between the two groups (P=0.215).

Q:5. Line 512. Spelling of "enrollment" should be corrected.
A: Line 512. It had been corrected.

Q:6. Figure 1: It could be of use to the reader to indicate the protocol planned days from first initiation of induction to the start of each of the 4 cycles of consolidation and to the beginning of maintenance.
A: The planned days had been added in Figure 1.

Answers to Reviewer reports:

Alix Seif (Reviewer 2):

Thank you very much for your suggestions. Here are our responses to your comments.

Suggestions for revision.

Major critiques:

Q: - Were patients with presenting WBC ≥10 more likely to have FLT3-ITD or mutations, as previously described? Were the children who presented with severe symptoms in either of these high-risk groups?

A: We had added the detail in the results section line 203-205. “There were no significant difference in FLT3-ITD mutation between the patients with WBC >10×10⁹/L and WBC ≤10×10⁹/L (P=0.310).”

Results section line 211-213 “There were no significant difference in the rate of severe symptoms between the patients with WBC >10×10⁹/L and WBC ≤10×10⁹/L (P=0.225).”

Q:- For patients who transferred to the no-AraC group either just before or mid-treatment, it appears the analysis groups them with the no-AC group. For a randomized trial, it would be preferable to analyze them according to an intent-to-treat analysis, particularly for those who were randomized to receive AraC and couldn't tolerate it due to hematologic toxicity.
A : We had added the note of intent-to-treat analysis in the text. All the things had been highlight with red and underline.

Methods, line 139-140, we added, Due to the open label character of the study, survival analysis was performed on an intention-to-treat (ITT) and a per-protocol (PP) basis.

Results section, line 253-258, we added, There were no significant differences in baseline characteristics between the Ara-C and no-Ara-C groups on a PP basis analysis (Table 2). Also, there was no significant difference (P>0.05) between the two groups on an ITT basis analysis in baseline characteristics (data not shown). In addition, there was no difference in EFS, DFS and OS between the two groups on an ITT and a PP basis analysis. Based on the actual application of the treatment, we compared the hematology toxicity between the two groups.

Discussion section, line 329-330, we added, In our study, there was no difference in outcomes between the Ara-C group and the no Ara-C group on an ITT and a PP basis analyses.

Q: Line 260 - this sentence is redundant, as the authors report the data for these events in the previous sentence. I would suggest presenting a statistical measurement to demonstrate whether the groups were in fact different. Rather or perhaps in addition to presenting the lowest WBC count over the study period, the number of days of neutropenia would be of interest.

A: Results section, line 263-265. The number of days of neutropenia had been added. The median days of neutropenia was 0 day (range, 0 to 9 days) in the no-Ara-C group and 6 days (range, 0 to 13 days) in the Ara-C group, respectively (P=0.000).

Minor critiques:

Q: Line 136 - median follow-up time should be presented under results and not methods

A: It had been deleted from methods and added to the line Line 193-194 in results section. “The follow-up of the patients was updated in May 2017 and included a median of 36 months (range, 5 to 83 months).”

Q: Line 240 - The phrasing "Consolidation therapy was administered in all patients who achieved CR" implies some patients did not achieve CR, which is not true. Depending on the intent of this sentence, the authors could perhaps state "Consolidation therapy was administered in all patients except for the patient who ended therapy early."

A: Line 240. It had been corrected as “Consolidation therapy was administered in all patients except for the patient who ended therapy early.”
Merry Christmas and Happy new year!

Thank you for your comments. If something should be done, please contact us without hesitate.

Sincerely yours,

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