Reviewer's report

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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Reviewer: Alix Seif

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Zhang et al present results of their clinical trial for children with acute promyelocytic leukemia (APL), which randomizes children to receive or omit high-dose cytarabine (AraC) during consolidation cycles. Reduction of treatment intensity is a topic of clinical interest for children with APL, and multiple studies exist suggesting deintensification of either anthracyclines/anthracenediones and shortening duration of therapy may still be effective for children with this rare tumor.

The authors present the results of a small randomized clinical trial. Unfortunately, the novelty and impact of this paper are attenuated by two recent publications of large cooperative group trials describing the combination of ATRA and ATO to allow for the reduction of exposure to cytotoxic therapy (Kutny 2017 JCO 35:3021; Creutzig 2017 Pediatr Blood Cancer 64:DOI:10.1002/pbc.26461). Nonetheless, this paper presents the results of a randomized clinical trial and thus has merit. Furthermore, the presentation of ATO levels in multiple tissues over time adds novelty to other reports of clinical trial results. The paper is well written and well referenced.

Major critiques:

- 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?

- 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.
- 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.

Minor critiques:

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

- 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."

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

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If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

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