**Peer Review File**

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**Reviewer A**

The authors described the efficacy of Homoharringtonine in pediatric AML.
The manuscript is well written. But you should describe some information in detail.

**Comment 1: You mentioned maintenance therapy. In AC arm, how long entire maintenance therapy? I mean how long given the cytarabine and oral 6MP?**
Reply: Thank you for your feedback. Maintenance therapy had a duration of 1 year (4 cycles lasting 12 weeks each).
Changes in the text: The 1-year duration is stated in page 2 line 50. We added "Each cycle lasted 12 weeks, and patients completed 4 cycles" to page 2 line 63.

**Comment 2: Why the results with HHT/AT was better than E/AC in the AML1-ETO positive patients? Would you please mention the reason what you think?**
Reply: Thank you for your comment. In AML1-ETO there is a frequent aberrant c-KIT expression. It has been described that HHT could down-regulate c-KIT expression, explaining this improved response.
Changes in the text: We added "HHT reduces the expression of c-KIT, potentially providing a therapeutic benefit for individuals with AML1-ETO, given the common occurrence of abnormal c-KIT expression in these instances. This may account for the enhanced EFS observed in AML1-ETO patients as mentioned earlier." Page 3 Line 100.

**Comment 3: Usually, HHT was used for CML and ATRA was used for APL.**
**When you used those drugs off-label for AML, how did you need ethical issues?**
**If you did apply for IRB, would you please describe it?**
Reply: Thank you for your comment. The reviewed study stated it was approved by ethics committee and clinical registration. No further details regarding IRB were provided in the original article.

**Reviewer B**

**Comment 1: Please state in the review whether homoharringtonine is still being manufactured for clinical use (I believe it is not, but I am not sure).**
Reply: Thank you for your comment. HHT is also called Omacetaxine, the brand name is Synribo and it was FDA approved in 2012 for CML. We currently use it in our institution for that indication.
Changes in the text: We added "In the US, HHT is currently manufactured as Omacetaxine and it is FDA approved for the treatment of Chronic Myeloid Leukemia." Page 2 line 90.

**Reviewer C**

This paper provides a comprehensive summary of the CCLG-AML 2015 study and highlights the differences in treatment approaches between China and Western countries. Overall, this paper is well-written, and suitable for publication with the incorporation of the following comments.

**[Major point]**

**1) Major Comment 1: Page 1, Line 20-23**

**The authors have described the current survival outcomes of pediatric AML. I consider that the current outcomes of pediatric AML are relatively inadequate in comparison to pediatric acute lymphoblastic leukemia. You should clarify the problems of AML treatment and the key strategies to address these issues.**

Reply: Thank you for your feedback. We believe current problems of AML treatment include chemotherapeutic resistance, toxicity secondary to therapy, impact of infrequent molecular signatures and epigenetic mutations, difficulty in patient recruitment in clinical trials, and delay in access to adult-type treatment protocols.

Change in text: We have added "Existing challenges in AML treatment encompass issues such as resistance to chemotherapy, therapy-related toxicity, the influence of infrequent molecular signatures and epigenetic mutations, challenges in recruiting patients for clinical trials, and delays in accessing treatment protocols designed for adults. Strategies to enhance this situation involve refining risk stratification through the use of more precise diagnostic tools like Next-Generation Sequencing (NGS), creating targeted therapies to reduce the toxicity associated with conventional chemotherapy, and adjusting the age criteria for enrollment in adult trials." In page 1 Line 21

**2) Major Comment 2: Page 3, Line117**

**The use of maintenance therapy for pediatric AML has remained unestablished, except for specific situations as you described. The cumulative dose of cytotoxic agents increases with the application of maintenance therapy. In this context, the benefit of maintenance therapy is uncertain, and the toxicity of drugs is a matter of concern. You should discuss this aspect of the CCLG-AML2015 study because they attempted to remove etoposide in the aspect of toxicity.**

Reply: Thank you for your comment. We have added a discussion regarding this matter.

Change in text: We added "Despite the reduction in toxicity achieved by eliminating the use of etoposide in the H arm, it is imperative to address the potential additional toxicity that may arise from maintenance therapy in these patients." Page 3 Line 138

**3) Major Comment 3: Page 3, Line131-**

**You have raised an important point in this section. You commented that focusing the new drugs to use in randomized study should be well considered and limited, because of the rarity of pediatric AML. While seeking potential in older drugs has its limitations, using novel agents in clinical trials also faces challenges in many countries. What, in your opinion, is crucial to acerate the drug development for pediatric AML? Please describe**

**your perspectives more specifically.**

Reply: Thank you for your comment. We think one crucial element to accelerate the drug development for pediatric AML is facilitating the enrollment in adult trials by decreasing the minimal age for enrollment.

Change in text: We added "One of the challenges in pediatric AML treatment is the lag in initiating clinical trials for children compared to adult trials. It is essential to address this issue by actively promoting the participation of older children in adult trials, thereby minimizing the existing gap." In Page 4 line 148

**[Minor point]**

**1) Minor Comment 1: Page 1, Line 31**

**Please consider changing the phrase "ATRA-based treatment" to "ATRA-based maintenance therapy" because ATRA was used as maintenance therapy in the CCLG-AML 2015 study.**

Reply: Thank you for your comment. We have made the suggested changes.

Change in text: "This study sought to clarify whether HHT-based induction therapy is safe and effective in pediatric AML and whether ATRA-based maintenance therapy is effective in patients with non–acute promyelocytic leukemia AML." Page 1 Line 36.

**2) Minor Comment 2: Page 2, Line 81**

**The sentence should be revised to eliminate the redundant comma:**

**"HHT has not previously been incorporated into any Children's Oncology Group protocol for leukemia treatment, , and its use may revolutionize treatment practices."**

Reply: Thank you for your feedback. The redundant comma was deleted.

Change in text: "HHT has not previously been incorporated into any Children's Oncology Group protocol for leukemia treatment, and its use may revolutionize treatment practices." Page 2 Line 88.

**3) Minor Comment 3: Page 3, Line 102-**

**You should cite the reference about studies comparing the efficacy of etoposide.**

Reply: Thank you for your feedback. The references have been added.

Change in text: Added references 13 and 14. Page 5 line 198

**4) Minor Comment 4: Page 3, Line 123-**

**You should cite the reference of each study about maintenance therapy, if the number of references is permitted.**

Reply: Thank you for your feedback. The references have been added.

Change in text: Added references 15 and 16. Page 5 line 205.