Editorial Commentary

# The efficacy of homoharringtonine in pediatric acute myeloid leukemia: findings from the Chinese Children's Leukemia Group-AML 2015 Study

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Acute myeloid leukemia (AML) is a complex disease accounting for 15% to 20% of pediatric leukemia cases (1). Previous research has reported event-free survival (EFS) rates ranging from 53% to 63% and overall survival (OS) rates ranging from 63% to 74% in pediatric AML (2). 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 (3-6).

The Chinese Children's Leukemia Group-AML 2015 study, led by Jing Li, evaluated the effectiveness and safety of different treatment protocols for pediatric AML (7). Notably, this comprehensive, multicenter, open-label study spanning 35 centers across China explored the use of two specific treatments: homoharringtonine (HHT also known as omacetaxine), commonly used in adult AML in China; and all-trans retinoic acid (ATRA), known for its efficacy in treating acute promyelocytic leukemia. 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.

This study is intriguing because it proposes alternative therapeutic approaches, such as the use of HHT, the use of etoposide in induction and the use of maintenance, that deviate from the established standard of care within the Children's Oncology Group protocols (AAML1831).

In this study, children with newly diagnosed AML were randomly assigned to either an HHT-based (H-arm) or an etoposide-based (E-arm) induction regimen. The first phase (Induction I) involved the administration of VP-16 (etoposide, 100 mg/m$^2$ daily) or HHT (3 mg/m$^2$ daily) on days 1 to 5. Additionally, daunorubicin was given at a dose of 40 mg/m$^2$ daily on days 1, 3, and 5, and cytarabine was administered at a dosage of 100 mg/m$^2$ every 12 hours on days 1 to 7. For the induction II phase (E arm, idarubicin plus cytarabine plus etoposide; H arm, idarubicin plus cytarabine plus HHT), idarubicin was administered once daily at a dose of 10 mg/m$^2$ on days 1, 3, and 5, substituting daunorubicin.

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Following induction therapy, all patients received 3 courses of consolidation therapy, which included various regimens: mitoxantrone plus cytarabine, HHT plus cytarabine, and cytarabine plus L-asparaginase. High-risk patients ineligible for hematopoietic stem cell transplantation received an additional course of HHT plus cytarabine (7).

For maintenance therapy, patients who did not undergo hematopoietic stem cell transplantation were randomly assigned to ATRA-based (AT-arm) or cytarabine-based (AC-arm) therapy for approximately 1 year. In the AT arm, therapy consisted of daily oral doses of ATRA (20–30 mg/m$^2$) for the first 2 weeks and daily oral 6-mercaptopurine (50 mg/m$^2$) for the following 10 weeks. In the AC arm, therapy consisted of intravenous cytarabine (40 mg/m$^2$) administered daily on days 1 to 4 every 4 weeks and oral 6-mercaptopurine (50 mg/m$^2$) given once daily throughout the entire maintenance period. Each cycle lasted 12 weeks, and patients completed four cycles. The primary endpoint of the study was the complete remission rate following induction therapy, and the secondary endpoints were the OS and EFS rates. Importantly, the study was initially designed as a multicenter, randomized, controlled trial, but it was changed to a multicenter, prospective, observational clinical trial due to an unexpected, 6-month HHT shortage. Consequently, some patients were redirected to the E arm during this period, and a subgroup of patients initially assigned to the AT arm was transferred to the AC arm upon parental request (7).

The study included 1,258 patients; 1,253 were included in the intent-to-treat analysis. Inclusion criteria included patients younger than 18 years of age with newly diagnosed AML, with no prior chemotherapy treatment, treated per CCLG-AML 2015 protocol. Exclusion criteria included diagnosis of acute promyelocytic leukemia, juvenile myelomonocytic leukemia, secondary AML, and patients not able to follow the treatment protocol. Notably, patients who received H-arm induction therapy demonstrated better outcomes than those who received E-arm induction therapy (complete remission rate, 79.9% *vs.* 73.9%, respectively; P=0.014). Furthermore, the H-arm patients displayed better outcomes than the E-arm patients in terms of their 3-year OS rates (69.2% *vs.* 62.8%, respectively; P=0.025) and 3-year EFS rates (61.1% *vs.* 53.4%, respectively; P=0.022). Interestingly, the 3-year EFS rates improved more in the *AML1-ETO*-positive patients in the H/AT arms than in those in the E/AC arms (73.6% *vs.* 52.8%, respectively; P=0.013). When assessing the patients who underwent maintenance therapy, no statistically significant differences in the 3-year EFS rates were observed among the various treatment arms (H/AC, 74.8%; E/AC, 72.9%; H/AT, 70.7%; and E/AT, 66.2%) (7).

## The use of HHT in patients with leukemia

HHT has not previously been incorporated into any Children's Oncology Group protocol for leukemia treatment, and its use may revolutionize treatment practices. Originating from the *Cephalotaxus* genus of conifers, HHT has been extensively used in China since the 1970s to treat adult AML and chronic myeloid leukemia. In the US, HHT is currently manufactured as Omacetaxine and it is Food and Drug Administration (FDA) approved for the treatment of chronic myeloid leukemia. Functioning as a cell cycle-specific agent, it exerts its antitumor effects by inhibiting protein synthesis, depolymerizing polysomes, and disrupting ribosomal function (8-10). Mechanistically, it hinders cell proliferation by impeding DNA and RNA synthesis, ultimately prompting tumor-cell differentiation and apoptosis. Furthermore, HHT could modulate signaling pathways by regulating the phosphorylation of protein tyrosine kinases (11). Research has suggested that combining HHT with cytarabine enhanced the therapeutic outcomes for Chinese adults with AML (8,9,11). In addition, the efficacy of HHT in combination with daunorubicin (DAH) or aclarubicin has been demonstrated in several large-scale trials for AML (8-10). 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 (12).

## The use of etoposide in induction therapy

Notably, in the Children's Oncology Group protocols, etoposide is no longer employed during induction in patients with AML. Etoposide primarily inhibits topoisomerase II, inducing DNA breaks in cancer cells and leading to apoptosis. It is most effective during the G2 and S phases of the cell cycle. Although it was once considered a crucial component of pediatric AML treatment, its unclear benefits and potential for causing secondary malignancies, raising concerns regarding long-term quality of life and cancer prevention in children, have resulted in its exclusion from many initial AML treatment regimens (3,13,14). Studies have shown no significant differences in efficacy

and toxicity when comparing treatment regimens with or without etoposide, leading to uncertainty about the drug's role in induction therapy. After the Medical Research Council (MRC) AML10 study conducted a randomized comparison between DAT (daunorubicin, cytarabine, thioguanine) and ADE (daunorubicin, cytarabine, etoposide) as induction chemotherapy for pediatric AML, questions regarding the uncertain role of etoposide began to emerge. The study revealed no significant differences in terms of efficacy and toxicity. Subsequently, the MRC AML15 protocol randomized 1,983 patients, with 994 receiving DA (daunorubicin and cytarabine) and 989 receiving ADE. Both arms demonstrated similar complete-remission rates, 30-day mortality rates, and long-term outcome measures. The 5-year OS rates were 36% for DA and 35% for ADE (P=0.9), and the 5-year relapse-free survival rates were 38% for DA and 35% for ADE (P=0.8). Furthermore, the 5-year relapse rates (RRs) were 52% for DA and 55% for ADE (P=0.9). Ongoing studies such as the COG AAML1831 study do not incorporate etoposide into their induction treatment protocols (3).

## Maintenance therapy

Li *et al.*'s study also investigated the efficacy of maintenance therapy through a secondary randomization of patients who did not undergo hematopoietic stem cell transplantation. Within Western medicine, the significance of maintenance therapy in AML remains uncertain. Presently, maintenance treatments are not established as the standard of care and are not integrated into the typical therapeutic approaches for adult or pediatric AML cases (6,15,16), except in two instances. In the AAML1031 study, sorafenib maintenance was incorporated for patients with *FLT3/ITD*-positive AML (17). Meanwhile, in the AAML1831 study, patients who are *FLT3*-positive receive gilteritinib as part of their maintenance treatment plan (18). Li *et al.*'s study introduces an intriguing perspective by proposing that maintenance therapy be included as part of the treatment strategy for pediatric AML, and it is particularly interesting that the study tested ATRA for this purpose in that, in Western countries, the drug is used solely for acute promyelocytic leukemia and not for other AML subtypes (19). 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.

Li *et al.*'s findings pose essential questions about pediatric AML treatment strategies in Western medicine. In the current landscape of pediatric AML, the inclusion of drugs into treatment regimens presents challenges, primarily because the population of pediatric patients with AML is limited and heterogeneous. The fact that, on average, researchers are only able to conduct 1 phase III randomized study every 5 years underscores the critical importance of selecting the most suitable drugs for such investigations. 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. With numerous new drugs in development, expecting HHT to be the chosen drug for new, randomized pediatric AML studies appears unrealistic. Smaller, targeted studies, particularly those in specific relapsed or populations with poor OS, may offer a more feasible approach. Further comprehensive research studies, commencing with these trials, will be imperative for gaining insights into the safety profiles and therapeutic efficacies of these drugs in Western pediatric patients with AML.

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