Chemo-Free Therapy Improves Outcomes in Pediatric APL (EHA 2026)

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> Acute promyelocytic leukemia (APL) in pediatric patients has historically been managed with chemotherapy-containing regimens, which, while effective, carry significant long-term toxicities. The introduction of all-trans retinoic acid (ATRA) and arsenic trioxide (ATO) has enabled the development of chemotherapy-free protocols, offering a less toxic yet highly efficacious treatment approach for this specific subtype of acute myeloid leukemia.

KEY TAKEAWAYS

- The Pivot: Chemotherapy-free regimens using ATRA and ATO are now the standard of care for pediatric APL.
- The Data: Complete remission rates exceed 95% with ATRA/ATO, with significantly reduced long-term sequelae.
- The Action: Clinicians should prioritise ATRA/ATO-based, chemotherapy-free protocols for newly diagnosed pediatric APL patients.

Acute promyelocytic leukemia (APL) is a distinct subtype of acute myeloid leukemia (AML) characterised by a specific chromosomal translocation, t(15;17), leading to the PML-RARA fusion gene. This genetic alteration renders APL highly sensitive to differentiation-inducing agents such as all-trans retinoic acid (ATRA) and arsenic trioxide (ATO).1 Historically, treatment for pediatric APL involved regimens combining ATRA with intensive chemotherapy, which achieved high rates of complete remission (CR) and overall survival (OS). However, these chemotherapy-containing protocols were associated with substantial acute and long-term toxicities, including myelosuppression, infections, cardiotoxicity, and secondary malignancies, particularly concerning in a pediatric population with a long life expectancy.2 The clinical dilemma has been to maintain high efficacy while mitigating these adverse effects. The incidence of APL in children is relatively low, accounting for approximately 5-10% of all pediatric AML cases, making the optimisation of treatment strategies for this specific population particularly critical. Prior to the widespread adoption of ATRA and ATO, the prognosis for APL was considerably poorer, with high rates of early mortality due to coagulopathy and hemorrhage. The introduction of differentiation therapy marked a significant turning point in APL management, transforming it from a highly fatal disease to one with excellent outcomes.

What the study did

The EHA 2026 presentation synthesised data from multiple prospective clinical trials and real-world registries evaluating chemotherapy-free regimens for newly diagnosed pediatric APL. These studies primarily focused on

combinations of ATRA and ATO, with or without gemtuzumab ozogamicin (GO) for high-risk cases. The primary endpoints included complete remission rates, event-free survival (EFS), overall survival (OS), and the incidence of treatment-related toxicities. Patient cohorts typically included children and adolescents up to 18 years of age, diagnosed with confirmed APL based on cytogenetic or molecular detection of the PML-RARA fusion.3 Diagnostic confirmation involved fluorescence in situ hybridisation (FISH) or reverse transcription-polymerase chain reaction (RT-PCR) for the PML-RARA transcript. The chemotherapy-free regimens typically involved daily oral ATRA and intravenous or oral ATO administered in induction and consolidation phases, followed by a maintenance phase with ATRA alone or in combination with low-dose chemotherapy in some earlier protocols. The inclusion of real-world registries provided valuable insights into the applicability and effectiveness of these regimens outside of highly controlled clinical trial settings, reflecting broader clinical practice.

The trials consistently demonstrated that ATRA and ATO-based chemotherapy-free regimens achieved complete remission rates exceeding 95% in pediatric APL patients.4 For instance, one pooled analysis of 8 clinical trials, enrolling a total of 1,250 pediatric APL patients, reported a 5-year event-free survival rate of 92% (95% CI, 90%-94%) and a 5-year overall survival rate of 95% (95% CI, 93%-96%) with chemotherapy-free ATRA/ATO protocols.5 These outcomes were comparable to, and in some analyses, numerically superior to, historical chemotherapy-containing regimens.5 The mechanism of action for ATRA involves binding to the RARA portion of the PML-RARA fusion protein, inducing differentiation of leukemic promyelocytes into mature granulocytes, thereby reducing the leukemic burden. ATO similarly targets the PML-RARA fusion protein, promoting its degradation and inducing apoptosis and differentiation of APL cells.

Crucially, the toxicity profiles were significantly more favorable with the chemotherapy-free approach. The incidence of severe myelosuppression (Grade 3-4 neutropenia or thrombocytopenia) was reduced by 70% compared to chemotherapy-containing arms (P 0.001).6 Rates of febrile neutropenia and severe infections requiring hospitalisation were also substantially lower. Long-term sequelae, such as cardiac dysfunction, secondary AML, and neurocognitive deficits, were observed at significantly lower frequencies in patients treated with ATRA/ATO alone.6 Differentiation syndrome, a known complication of ATRA, was manageable with corticosteroids and temporary ATRA interruption, occurring in approximately 15-20% of patients across the trials.7 This syndrome, characterised by fever, respiratory distress, weight gain, and renal dysfunction, requires prompt recognition and management but is rarely fatal when treated appropriately.

For high-risk pediatric APL, defined by an initial white blood cell count greater than 10 x 109/L, the addition of a single dose of gemtuzumab ozogamicin to the ATRA/ATO backbone demonstrated improved outcomes without significantly increasing toxicity. One study reported a 3-year EFS of 88% in high-risk patients receiving ATRA/ATO/GO, compared to 80% with ATRA/ATO alone (HR 0.65; 95% CI, 0.48-0.89; P = 0.007).8 Gemtuzumab ozogamicin is an antibody-drug conjugate that targets CD33, an antigen expressed on myeloid leukemia cells, delivering a cytotoxic agent directly to the malignant cells.

Limitations of the presented data include the heterogeneity across some of the pooled studies regarding specific ATRA/ATO dosing schedules and supportive care protocols. While the evidence strongly supports the efficacy and safety of chemotherapy-free regimens, long-term follow-up beyond 5 years is still accumulating for some cohorts, particularly regarding very rare late effects. Future research may focus on optimising ATRA/ATO dosing, identifying

minimal residual disease (MRD) guided therapy, and exploring novel targeted agents for refractory cases. Further investigation into the optimal management of specific subgroups, such as infants with APL or those with concomitant medical conditions, also warrants attention. The consistent positive outcomes across multiple studies, however, firmly establish chemotherapy-free ATRA/ATO as the preferred first-line treatment for pediatric APL.9

CLINICAL IMPLICATIONS

The data presented at EHA 2026 unequivocally solidify the role of chemotherapy-free ATRA/ATO regimens as the standard of care for pediatric acute promyelocytic leukemia. For clinicians, this means a clear directive: move away from chemotherapy-containing protocols for newly diagnosed APL in children. The evidence is compelling, demonstrating not just comparable efficacy to older, more toxic regimens, but often superior outcomes with a dramatically improved safety profile. The reduction in severe myelosuppression and long-term sequelae translates directly into a better quality of life for young patients, a critical consideration in a disease with high support management of / may help patients with rates. Adherence to these protocols, including vigilant monitoring for differentiation syndrome, is paramount.

From a patient and family perspective, this represents a significant advancement. The prospect of treating a childhood cancer without the debilitating side effects of chemotherapy, such as hair loss, severe nausea, and the risk of secondary cancers, is immensely reassuring. It allows children to maintain a more normal life during treatment, with fewer hospitalisations and less disruption to schooling and social development. This shift in treatment paradigm underscores the importance of precise diagnosis of APL, as its unique biology allows for this targeted, less toxic approach, unlike other AML subtypes.

The pharmaceutical industry's role in ensuring access to ATRA and ATO, both relatively inexpensive and off-patent drugs, remains crucial. While there may be less incentive for novel drug development in this specific, highly treatable subtype, the focus should be on global availability and consistent quality. Guideline bodies, such as the Children's Oncology Group (COG) and the European Society for Medical Oncology (ESMO), should continue to reinforce these chemotherapy-free recommendations, ensuring widespread adoption and consistent application across diverse healthcare settings. The success in pediatric APL serves as a powerful example of how understanding disease biology can lead to truly transformative, less burdensome therapies.

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