

inside **blood** commentary

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Comment on Taub et al, page 3304

Looking up for AML in Down syndrome

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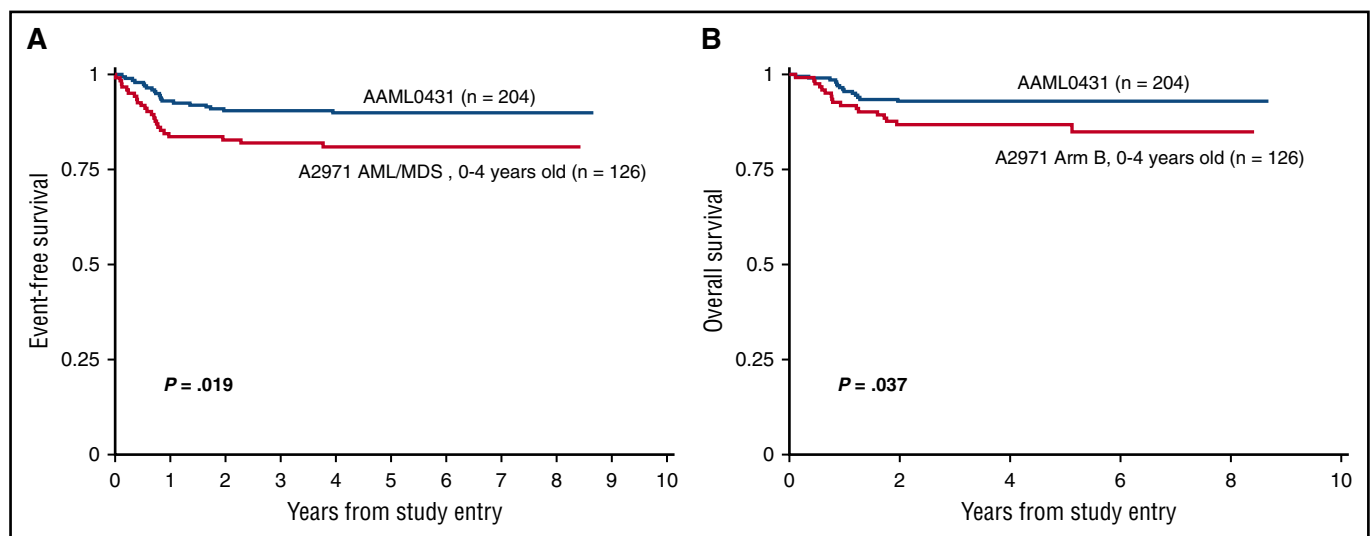
In this issue of *Blood*, Taub et al report improved survival with reduced-intensity therapy and the prognostic significance of end-induction residual disease from the largest prospective trial to date in children with myeloid leukemia of Down syndrome (ML-DS): the Children's Oncology Group AAML0431 study.¹

Children with trisomy 21/DS represent a clinically and genetically unique subset of pediatric patients with AML, with patients <4 years of age having a 500-fold increased risk of developing the disease.² Taub et al report improved event-free survival and overall survival in a prospective cohort of children with DS that examined the impact of early intensification of cytarabine therapy and reduction of cumulative anthracycline dosing in children diagnosed between age 0 and 4 years (see figure).

ML-DS is characterized by somatic mutations in the hematopoietic transcription factor *GATA1*, with cooperative effects of aberrant gene expression associated with trisomy 21.³ Myeloblasts from ML-DS patients are particularly sensitive to cytosine arabinosides because of the proximity of *GATA1* to the cytidine deaminase promoter.⁴ To determine whether this effect could be exploited without excess toxicity, patients in the 0431 study received intensified high-dose

cytarabine therapy during the second induction therapy block. This treatment phase had the longest median time to neutrophil recovery (37 days), highest incidence of febrile neutropenia (29.7%), and highest frequency of sterile site bacterial infections (22.6%), highlighting the very real need for close monitoring, continued improvements in supportive care, and a better understanding of impaired host defense in ML-DS patients. Three nonrelapse deaths occurred as a result of human metapneumovirus infection, consistent with the European experience with ML-DS in which viral infections accounted for the majority of infection-related mortality.⁵ These observations should generate further study about differences in T-cell reconstitution and antiviral immunity in children with ML-DS.

If, as they say, the sword of truth bears 3 edges (yours, mine, and the truth), we must carefully consider how the trident of organ toxicity, infection, and antileukemia cytoreduction is wielded in this population. Children with DS have a significantly increased risk of congenital heart disease, with



Survival curves comparing (A) event-free survival and (B) overall survival in children ages 0 to 4 years with Down syndrome treated on the Children's Oncology Group AAML0431 trial (dark blue) vs the legacy Pediatric Oncology Group A2971 AML/MDS study (red).

approximately 50% of all patients manifesting congenital structural lesions.⁶ It is not uncommon for them to receive a leukemia diagnosis after having received complex surgical repair or already being on long-term medical management to support cardiac function. This has substantial implications for the direct cardiotoxicity of anthracycline chemotherapy⁷ and the ability of these patients to meet the increased cardiac demands of infection and chemotherapy-induced anemia. The 0431 results reported here indicate that improvements in event-free survival and overall survival are maintained with a 25% reduction in total cumulative anthracycline dosing. Children with significantly reduced baseline cardiac function were excluded from the study, however. Continued longitudinal monitoring of survivors will determine whether other maneuvers to intensify therapy in the 0431 study, including cytarabine intensification and the introduction of etoposide, will introduce other long-term comorbidities.

The prognostic significance of high-resolution minimal residual disease (MRD) assessment has been demonstrated in pediatric AML patients without DS⁸ and was a secondary aim of the 0431 study. The authors conclude that end-induction MRD was a predictor of disease-free survival, with 92.7% survival in MRD-negative (defined as <0.01% blasts per 10 000 cells by flow cytometry) vs 76.2% in MRD-positive patients. Additional questions remain regarding how MRD levels can best be used to improve outcomes in MRD-positive patients. Identifying and intensifying therapy for patients who would not have otherwise been classified as high risk is of particular importance in ML-DS, because excess mortality from hematopoietic stem cell transplantation may limit options for children who relapse.⁹

With treatment modifications based on the known interactions of *GATA1* with chemotherapy-associated gene regulation resulting in improved survival, what lies on the horizon for pediatric ML-DS? As with other subtypes of pediatric leukemia, next-generation molecular profiling of ML-DS myeloblasts to identify novel oncogenic drivers and in the discovery of epigenetic regulatory elements such as micro-RNAs that drive myeloid leukemogenesis¹⁰ will surely define the leading edge of targeted therapy and ensure a brighter future for children with ML-DS.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

REFERENCES

1. Taub JW, Berman JN, Hitzler JK, et al. Improved outcomes for myeloid leukemia of Down syndrome: a report from the Children's Oncology Group AAML0431 trial. *Blood*. 2017;129(25):3304-3313.
2. Kolb EA, Meshinchi S. Acute myeloid leukemia in children and adolescents: identification of new molecular targets brings promise of new therapies. *Hematology Am Soc Hematol Educ Program*. 2015;2015:507-513.
3. Wechsler J, Greene M, McDevitt MA, et al. Acquired mutations in *GATA1* in the megakaryoblastic leukemia of Down syndrome. *Nat Genet*. 2002;32(1):148-152.
4. Ge Y, Jensen TL, Stout ML et al. The role of cytidine deaminase and *GATA1* mutations in the increased cytoside arabinoside sensitivity of Down syndrome myeloblasts and leukemia cell lines. *Cancer Res*. 2004; 15:64(2):728-735.
5. Hassler A, Bochennek K, Gilfert J, et al. Infectious complications in children with acute myeloid leukemia and Down syndrome: analysis of the prospective multicenter trial AML-BFM 2004. *Pediatr Blood Cancer*. 2016;63(6): 1070-1074.
6. Bergström S, Carr H, Petersson G, et al. Trends in congenital heart defects in infants with Down syndrome. *Pediatrics*. 2016;138(1):e20160123.
7. Krischer JP, Epstein S, Cuthbertson DD, Goorin AM, Epstein ML, Lipshultz SE. Clinical cardiotoxicity following anthracycline treatment for childhood cancer: the Pediatric Oncology Group experience. *J Clin Oncol*. 1997; 15(4):1544-1552.
8. Buldini B, Rizzati F, Masetti R, et al. Prognostic significance of flow-cytometry evaluation of minimal residual disease in children with acute myeloid leukaemia treated according to the AIEOP-AML 2002/01 study protocol. *Br J Haematol*. 2017;177(1): 116-126.
9. Hitzler JK, He W, Doyle J, et al; CIBMTR Pediatric Cancer Working Committee. Outcome of transplantation for acute myelogenous leukemia in children with Down syndrome. *Biol Blood Marrow Transplant*. 2013;19(6): 893-897.
10. Shaham L, Vendramini E, Ge Y, et al. MicroRNA-486-5p is an erythroid oncomiR of the myeloid leukemias of Down syndrome. *Blood*. 2015;125(8):1292-1301.

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CLINICAL TRIALS AND OBSERVATIONS

Comment on Uffmann et al, page 3314

Down syndrome and AML: where do we go from here?

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It is well documented that young children with Down syndrome (DS) have both a 500-fold increased incidence of acute myeloid leukemia (ML-DS) and a decreased tolerance of intensive chemotherapy. In this issue of *Blood*, Uffmann et al present the results of a large, multicentered, international, nonrandomized trial reducing the etoposide exposure while preserving the excellent outcomes reported in previous trials.¹ This trial builds on international experience demonstrating that most young children with ML-DS may be cured with less intensive therapy, and confirms that there remains a significant subset of patients for whom we have limited therapeutic options.

Constitutional trisomy 21 results in the increased expression of genes located on chromosome 21, including the oxidative metabolism enzymes of cystathionine β synthase (CBS) and carbonyl reductase (CR). Overexpression of CBS favors ara-C conversion to ara-CTP, increasing incorporation of the toxic nucleoside analog into DNA. Overexpression of CR increases catabolic reduction of anthracyclines to cardiotoxic alcohol metabolites. CBS and CR conspire with other genes on chromosome 21,

including superoxide dismutase, to yield fundamental alterations in drug metabolism that enhance the sensitivity of both leukemia and nonleukemia cells to cytotoxic therapies in children with DS.² As nicely summarized in Table 4 of Uffman et al, various international cooperative groups have effectively tested the hypothesis that the altered drug metabolism in ML-DS cells and the altered capacity for DNA repair in normal DS cells both permit and necessitate reduced exposures to cytotoxic therapies for optimal survival benefit.