approximately 50% of all patients manifesting congenital structural lesions. 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 chemotherapy 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 DS 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.

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 leukemogenesis will surely define the leading edge of targeted therapy and ensure a brighter future for children with ML-DS.

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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?

Daisuke Tomizawa and E. Anders Kolb

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.

C onstitutional 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 catalytic 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 Uffmann 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.
The Children’s Oncology Group recently demonstrated that a reduction in the cumulative anthracycline dose by 25% improved survival compared with predecessor North American studies. Intrathecal chemotherapy was reduced from 7 doses to 2 in the Children’s Oncology Group, with no effect on CNS relapse. The Japan Pediatric Leukemia/Lymphoma Study Group eliminated high-dose cytarabine for a majority of patients, yielding a fraction of the cumulative cytarabine dose when compared with the other major ML-DS studies. For many years, the Japan Pediatric Leukemia/Lymphoma Study Group has used no intrathecal therapy without increased central nervous system relapse risk. In the International European trial, ML-DS 2006, Uffmann et al report that outcomes are preserved when reducing the etoposide exposure by more than 50%.

It is critical to all international cooperative groups that we find the optimal regimen to improve survival and reduce toxicity in these vulnerable children. Taken together, the North American, Japanese, and European groups have shown that cumulative doses of daunorubicin, cytarabine, etoposide, and intrathecal treatments can each be significantly reduced while maintaining excellent survival in young children with ML-DS, although there is still no consensus on the necessity for high-dose cytarabine and intrathecal therapy. To date, each group has been successful in reducing the cumulative doses in their chosen backbone, yet it will not be easy to continue to study dose reductions that improve or maintain a 90% event-free survival rate in this rare disease. Perhaps it is now time to consider how we can layer on targeted therapies with long-term goals of eliminating, where possible, cytotoxic therapies, and further improving long-term survival. It is important to remember that children with relapse ML-DS do not benefit from dose intensification and transplant. In other words, although it is true that the international community of AML groups has demonstrated that dose deintensification is appropriate for most newly diagnosed children with ML-DS, dose intensification of conventional therapy is not sufficient to salvage patients with ML-DS in relapse. The identification of new and more targeted therapies will be the only effective future strategy with the potential to improve outcomes further.

The international precision medicine strategy to date in ML-DS has been the targeted reduction in toxic therapy based on the unique pharmacogenomic features of children with DS. Future precision medicine strategies now need to turn to somatic events. Various groups have reported that minimal residual disease (MRD) at the end of induction, trisomy 8, non-M7 morphology, older age at diagnosis, and relapsed disease each predicts a poor outcome with conventional therapeutic approaches. There remains some inconsistency among the prognostic factors identified in different studies, but MRD is generally accepted as a poor prognostic marker that is present in up to 14% of patients. MRD at the end of induction may help to identify patients at highest risk for relapse and appropriate for the clinical investigation of targeted therapies. The reported somatic mutations in ML-DS confirm that epigenetic regulators, cell cycle check point regulators, the cohesion complex, CTCF, EZH2, the ras pathway, and the Jak pathway are all commonly mutated and/or targetable. Nonetheless, the development of targeted small molecules and immunotherapies still lags far behind the development pace seen in other leukemias. ML-DS represents a unique biologically defined subtype of AML in a unique and vulnerable host. As each of the international cooperative groups have recently identified minimally toxic and effective backbone therapies, it is the ideal time for collaborative efforts to develop strategies to evaluate more rationally targeted therapies for these children.

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**Clinical Trials and Observations**

Comment on Gardner et al, page 3322

**Equal opportunity CAR T cells**

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In this issue of Blood, Gardner et al report results of a phase 1 trial of 45 children and young adults with relapsed or refractory B-lineage acute lymphoblastic leukemia (ALL) who received a T-cell product of defined CD4/CD8 composition that was genetically modified with a CD19-4–1BB:ζ chimeric antigen receptor (CAR) lentiviral vector. The authors report successful product release in 93% of enrolled patients and an overall intent-to-treat (ITT) minimal residual disease–negative (MRD−) remission rate of 89%. Of note, 100% of patients who received cyclophosphamide-fludarabine lymphodepletion had an MRD− remission, further reinforcing the importance of...
Down syndrome and AML: where do we go from here?

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