Acute leukemia in children with Down syndrome

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Down syndrome or constitutional trisomy 21 (OMIN#190685) was linked to leukemia for the first time in a case report published in 1930.[1] Since then, Down syndrome has been recognized as one of the most important leukemia-predisposing syndromes and patients with Down syndrome and leukemia have unique clinical features and significant differences in treatment response and toxicity profiles compared to patients without Down syndrome.

One of the challenges faced in treating children with Down syndrome and leukemia is balancing curative therapy against potential toxicities. As first reported by the Pediatric Oncology Group (POG) and later confirmed by several other cooperative treatment groups, Down syndrome children with acute myeloid leukemia (AML), and in particular the acute megakaryocytic leukemia (AMkL) subtype, have exceptionally high cure rates. In this group of patients, the reported event-free survival rates have ranged from 80 to 100%.[2-5] On the other hand, the outcome of Down syndrome children with acute lymphoblastic leukemia (ALL) has been historically considered worse than the outcome of ALL patients without Down syndrome.[6-8] In addition, Down syndrome children with leukemia are more prone to suffer from significant toxicity to chemotherapy, particularly methotrexate.[9,10] The causes of these remarkable differences are not completely understood. They are either due to the unique biological characteristics of the Down syndrome leukemia blast cell or are related to a gene dosage effect for chromosome 21-localized genes which are overexpressed secondary to the presence of an extra copy of chromosome 21.

Leukemogenesis of AMkL in patients with Down syndrome is associated with the presence of somatic mutations involving the *GATA1* gene.[11] GATA1 is a chromosome X-linked transcription factor which is essential for erythroid and megakaryocytic differentiation. The resultant effect of the mutations is the production of a shorter GATA1 protein, (designated GATA1s), which has altered transactivation capacity and contributes to the uncontrolled proliferation of immature megakaryocytes.[11,12] Trisomy 21 likely contributes to the development of *GATA1* mutations in Down syndrome. Chromosome 21-localized genes, including cystathionine-β-synthase (*CBS*) and zinc-copper superoxide dismutase (*SOD1*), are linked to abnormal intracellular folate metabolism, uracil accumulation and increased oxidative stress leading to DNA damage.[13]

Past studies have demonstrated that the high event-free survival rates of Down syndrome patients with AMkL are related to increased *in vitro* sensitivity of Down syndrome megakaryoblasts to cytarabine (ara-C) and daunorubicin,[14] due in part to the presence of *GATA1* mutations. The relationship between *GATA1* mutations and outcome is highlighted by the lower frequency of *GATA1* mutations in Down syndrome AML patients greater than 4 years of age, who have significantly lower event-free survival (<35%) and increased relapse rates compared to the majority of Down syndrome AML patients.[15,16] The presence of *GATA1* mutations and the generation of GATA1s result in interactions and modulation of the expression of different genes, such as the cytidine deaminase gene (*CDA*; localized to chromosome 1). CDA is involved in the irreversible hydrolytic deamination of ara-C to the inactive metabolite ara-U and *in vitro* studies have shown that CDA transcript levels are significantly lower in Down syndrome AMkL blasts than in non-Down syndrome AML cells.[17] Additionally, the expression of both chromosome 21-localized genes and *GATA1* target genes also differs between Down syndrome and non-Down syndrome AMkL blasts. The expression of anti-apoptotic proteins such as BCL2 (whose gene, *BCL2* is localized to chromosome 18) and HSP70 (whose gene, *HSP70*, is localized to chromosome 5) is lower in Down syndrome AMkL blasts than in non-Down syndrome blasts, suggesting that Down syndrome megakaryoblasts are more susceptible to chemotherapy-induced apoptosis.[18] Gene dosage effects are also associated with the increased sensitivity of Down syndrome megakaryoblasts to AML chemotherapy agents. Overexpression of *CBS* has been correlated with *in vitro* generation of ara-CTP, the active intracellular ara-C metabolite, and subsequent increased ara-C sensitivity in Down syndrome AMkL blast cells.[14]

The increased *in vitro* sensitivity to chemotherapy observed in Down syndrome patients with AML does not extend to those with ALL.[19,20] Down syndrome lymphoblasts do not demonstrate greater sensitivity than non-Down syndrome cell lines to various chemotherapy agents.[19] This biological characteristic can potentially account for the inferior outcome to therapy described in Down syndrome children with ALL in comparison to the outcome in non-Down syndrome children.[6-8] However, no significant differences in cytotoxicity to chemotherapy were found between fibroblasts from patients with or without Down syndrome.[20] Other factors may account for the variation in chemotherapy response and toxicity and the molecular bases that contribute to these differences are not completely understood.

The most common cytogenetic abnormalities in non-Down syndrome children with B-precursor ALL are high hyperdiploidy (>50 chromosomes, uniformly harboring extra copies of chromosome 21) or the *TEL/AML1* (*ETV6/RUNX1*) fusion resulting from the translocation t(12;21) (p13;q22). In a recent study by the Children's Oncology Group (COG), children with ALL and Down syndrome had significantly lower frequencies of *ETV6/RUNX1* than children without Down syndrome (2.5% *versus* 24%, $P<0.0001$) and hyperdiploidy (with trisomies of chromosomes 4 and 10) (7.7% *versus* 24%,

P=0.0009); *ETV6/RUNX1* and hyperdiploid ALL with trisomies of chromosomes 4 and 10 have both been associated with very high event-free survival rates.[21] Interestingly, *GATA1* mutations have never been detected in cases of Down syndrome ALL,[11] highlighting its unique association with the Down syndrome AMkL phenotype. On the other hand, acquired gain-of-function mutations in the Janus kinase 2 gene (*JAK2*; localized to chromosome 9p24) are present in approximately 30% of cases of ALL in Down syndrome.[22,23] Abnormalities involving the *CRLF2* gene, which are associated with the activation of *JAK2* mutations, are also present in this group of patients.[24,25] The relationship between these findings and Down syndrome ALL leukemogenesis as well as response to chemotherapy is yet to be determined, though recent studies have shown that rearrangements of *CRLF2* are associated with a poor outcome in non-Down syndrome ALL patients.[26,27]

An important feature that may account for the increased morbidity and mortality seen in Down syndrome children with ALL is increased toxicity to chemotherapy drugs. Treatment-related toxicity, such as mucositis and infections, is both more frequent and more severe in ALL children with Down syndrome than in those without. Down syndrome children being treated with corticosteroids have an increased risk of developing hyperglycemia[28] and recent studies have highlighted the association of hyperglycemia during ALL induction therapy and infectious complications.[29] The COG reported a higher risk of infectious deaths for Down syndrome ALL patients during induction therapy with corticosteroids.[30]

It is known that Down syndrome children have increased toxicity to anthracyclines. A POG study involving 6,493 children treated with anthracyclines found that Down syndrome children had a relative risk of 3.4 of developing cardiac toxicity.[31] In the POG AML 9421 study, 17.5% of Down syndrome patients developed symptomatic cardiomyopathies, including three who died from congestive heart failure.[32] The increased risk of anthracycline-induced cardiac toxicity is potentially due to the localization to chromosome 21 of the superoxide dismutase (*SOD*) and carbonyl reductase 1 (*CBR1*) genes, which are involved in oxygen radical and anthracycline metabolism, respectively.

Importantly, Down syndrome children develop severe systemic toxicity such as myelosuppression, mucositis, and hepatoxicity after exposure to the antifolate agent, methotrexate, which suggests that Down syndrome cells have altered folate metabolism. The report by Buitenkamp *et al.* in this issue of the Journal addresses whether differences in pharmacokinetics could account for differences in drug sensitivity and toxicity seen in children with Down syndrome and ALL.[33] Methotrexate pharmacokinetics were analyzed retrospectively in children with ALL, comparing 44 with Down syndrome and 87 without the syndrome.[33] Using non-linear mixed effect modeling, no differences in methotrexate pharmacokinetics were found between patients with and without Down syndrome which could explain the significantly higher proportion of children with Down syndrome who experienced methotrexate-induced gastrointestinal toxicity. The authors concluded that the higher toxicities suffered by Down syndrome patients are probably related to pharmacodynamic differences of the gastrointestinal mucosa and that intermediate doses of methotrexate (such as 1-3 g/m^2) can be used safely in Down syndrome children with ALL.

Methotrexate is actively transported intracellularly via a transmembrane protein known as the reduced folate carrier. *SLC19A1*, the gene for this transmembrane protein, is localized to chromosome 21 and it is conceivable that an extra copy of chromosome 21 in cells with trisomy 21 results in greater uptake of methotrexate into various tissues potentially resulting in increased toxicity. Interestingly, in non-Down syndrome ALL patients with hyperdiploidy (in which there are frequently four copies of chromosome 21), increased generation of methotrexate polyglutamates likely contributes to the high event-free survival of this ALL subgroup.[34,35] In the Down syndrome group, the potential benefit of having three copies of chromosome 21 (including the *SLC19A1* gene) would potentially be offset by the systemic effects of methotrexate uptake into gastrointestinal tissues, while in cases of non-Down syndrome hyperdiploid ALL, the effects of greater methotrexate transport would be limited to the malignant cells and not present in the normal host tissues.

It is now clear that the mechanisms regulating the response to therapy and toxicity to different chemotherapy agents in the treatment of Down syndrome leukemia are multifactorial and they offer a powerful model to improve our understanding of the mechanisms of chemotherapy sensitivity. In the case of Down syndrome AML, additional studies are necessary to determine whether the intensity of AML therapy can be reduced while maintaining the high event-free survival rates. Furthermore, it is not known why a small proportion of Down syndrome AML patients relapse or have refractory disease even in the presence of the classic AMkL phenotype though lacking *GATA1* mutations.[36] In the case of Down syndrome ALL, it will be important to determine whether JAK2 inhibitors can be used in those patients who harbor *JAK2* mutations and whether new treatment protocols can be developed to reduce treatment-related toxicity.

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