The Acute Lymphoblastic Leukemias of Down Syndrome (DS-ALL)

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Abstract
Children with Down Syndrome have a markedly increased risk for acute lymphoblastic leukemia (DS-ALL). These leukemias are exclusively of the B cell precursor phenotype and occur in a similar age to “common” sporadic ALLs with the strike absence of infant leukemia. Recent studies reveal that DS-ALLs are heterogeneous and differ from sporadic ALLs. Only about a fifth of DS-ALLs carry the common cytogenetic aberrations typical to sporadic ALL. Genomic rearrangements leading to the expression of a cytokine receptor, CRLF2, are detected in 60% of DS-ALL in comparison with 10% of sporadic ALLs. These abnormalities are often associated with acquired mutations in the JAK-STAT pathway. In general, the prognosis of DS-ALL is inferior to sporadic ALL mainly because of increased treatment toxicity. However recent data challenge this view and suggest that the inferior outcome may be mainly related to the genetic properties of the leukemic cells and that excessive chemotherapy dose reductions may not be appropriate for these patients. The common activation of the CRLF2-JAK-STAT signaling pathway in DS-ALLs suggests a future for targeted therapy with JAK inhibitors for DS-ALLs.

Pathogenesis
The excess of ALLs in DS raises several general questions:

a) Are these leukemias unique to DS (like the ML-DS) or do children with DS have a general increased risk for childhood “common” B cell precursor ALL?

b) What is the nature of the acquired somatic genetic events that cooperate with constitutional trisomy 21 in the evolution to ALL? Since most children with DS do not develop leukemia, such progression events are necessary for leukemogenesis. Almost all the ML-DS have an acquired mutation in the megakaryocytic transcription factor GATA1 11-12. Does a similar cooperative genetic event, unique to DS, exist in DS-ALL?

c) What is the role of trisomy 21? Which are the genes on trisomy 21 that confers increased risk for ALL?

While ML-DS is a unique disease (that has now a special WHO classification code) recent studies demonstrate that DS-ALL is a...
heterogeneous disease suggesting complex pathogenesis. This is clearly evident in the gene expression patterns. Unlike the usual genetic subtypes of childhood ALL that are clearly clustered in distinct subgroups by gene expression profiling, DS-ALLs do not fall into one clear diagnostic cluster. Thus the term "DS-ALL" may be a misnomer – there are different ALLs in DS.

Although the immunophenotype of DS-ALL is of a typical childhood BCP-ALL, there is a significantly lower prevalence of the common genetic subtypes of B cell precursor ALL (BCR/ABL, TEL/AML1 and Hyperdiploid ALL (HHD)) in DS-ALL. This was confirmed in two recent large studies – a retrospective database of the iBFM study group consisting of 215 DS-ALLs compiled from several cytogenetics laboratories and a prospective systematic diagnostic genetic testing of childhood ALL in Children's Oncology Group (COG) trials during the last decade. Both suggest that only up to one fifth of DS-ALLs carry the two most frequent genetic anomalies, HHD and TEL/AML1, characterizing about 60% of sporadic childhood BCP-ALL. However, if one take into account the 20 fold increased risk of ALL in DS, then there may be an absolute increase in the incidence of these common subtypes of childhood leukemias in DS.

It emerges that the majority of the DS-ALLs differ from the sporadic ALLs containing excess chromosome 21. The most common cytogenetic abnormality in DS-ALL is an extra chromosome X, observed in close to half the patients. Additional copy of chromosome X is usually present in HHD sporadic ALL however the combination of trisomy 21 and extra chromosome X as a single cytogenetic abnormality seems unique to DS-ALL, and suggest a, yet unknown, collaborating event between gene(s) on chromosome 21 and X.

Figure 1.
Somatic genetic events cooperating with constitutional trisomy 21 in initiation of leukemias. The myeloid leukemias of DS (ML-DS) are universally characterized by an acquired mutation in GATA1. The lymphoid leukemias (DS-ALL) are more heterogeneous. About 20% of DS-ALLs carry similar aberrations of sporadic ALLs, namely TEL/AML1 translocation or hyperdiploidy (HHD). Most of DS-ALLs have cooperating events that are relatively unique to DS. About 60% have an aberrant expression of CRLF2 often associated with JAK2 mutations. It is likely that additional somatic mutations are necessary for progression from the pre-leukemic phase to full blown leukemias.
Such a collaborating event has recently been discovered. Genomic aberrations causing the expression of cytokine receptor CRLF2 are present in about 60% of DS-ALLs but only in up to 10% of sporadic childhood ALL. CRLF2 encodes one chain of the receptor to TSLP, a cytokine involved in allergic and inflammatory disorders. It signals into the cells via the JAK-STAT pathway. The importance of the activation of this pathway to survival of the leukemia cells is underscored by the frequent occurrence of activating mutations in the kinases JAK2 or JAK1 or in the CRLF2 receptor itself. The presence of activation of the JAK-STAT pathway in the majority of DS-ALLs, expressing CRLF2, suggest that these leukemias may be candidates for therapy with the novel JAK2 inhibitors that are being explored in early clinical trials for myeloproliferative neoplasms.

The role of the trisomy 21 has remained a mystery. There is high interest in the pathogenesis of DS-ALL also because trisomy 21 (or sometimes tetrasomy 21) is the most common acquired somatic chromosomal abnormalities in sporadic ALL. It is mostly found in HHD-ALL a subtype of ALL characterized by more than 50 chromosomes, always involving chromosome 21. Hence it is tempting to speculate that constitutional and somatic trisomy 21 may facilitate leukemogenesis in a similar fashion and therefore the study of DS ALL may have direct implications for sporadic childhood ALL. Indeed gene expression analysis demonstrates that level of expression of chromosome 21 genes is similar in HHD and DS ALLs.

Yet, as have been recently demonstrated, HHD and DS ALLs differ significantly for example by the abnormal expression of CRLF2 and the associated mutations in JAK2. Importantly there are fundamental differences between constitutional and somatic trisomies that could explain the uniqueness of DS leukemias. The former exists in all body cells from the time of conception, whereas the latter is acquired and exists only in the transformed cells. Thus constitutional trisomy can predispose to cancer in a variety of ways. It may exert a direct activity in a cell autonomous manner enhancing the risk of transformation or affecting the differentiation of (fetal) B cell progenitors. Alternatively, the trisomy could promote leukemia because of aberrant effects on immediate micro-environment, for example on the bone marrow’s or fetal liver’s stroma cells that regulate proliferation and differentiation of hematopoietic stem cells. More complex may be the influence of the trisomy on the macro-environment. For example, viral infections and the immunological response have been suggested to have a role in the pathogenesis of childhood common ALL. The markedly increased risk of ALL in DS could also be caused by the immunodeficiency, altered immunological environment and the increased infection rate that characterize DS.

Why aberrant expression of CRLF2 is so much common in DS-ALL compared with sporadic ALL is unknown. Perhaps CRLF2 expressing cells are selected by increased production of TSLP in the bone marrow of children with DS, but this has not been shown yet. Another possibility is that a prolonged arrest in early B cell developmental stages in which the V(D)J recombination machinery is active might explain the chromosomal aberrations involving CRLF2 or other translocations to the IgH locus that are more frequent in DS-ALL, such as the t(8;14)(q11;q32). Consistent with this hypothesis are the aberrant expression of DNA damage genes in DS-ALL suggesting the presence of lymphocytic specific genomic instability.

Clinical course and therapy

Unlike ML-DS that is uniquely sensitive to chemotherapy, in particular to ARA-C, the prognosis of DS-ALL is less favorable in most of the clinical trials. Marked toxicity manifested by increased mucositis, infections and death during intensive periods of chemotherapy is observed. DS patients may be especially sensitive to the toxic effects of Methotrexate, a drug that is not used in AML, due to the excess activity of the folate transporter coded by a gene on chromosome 21. However, severe toxicity is also observed to anthracyclines and to the marked immunosuppressive effect of ALL therapy.

Importantly, marked reduction of chemotherapy may be a mistake in DS-ALL. A Children’s Cancer Group study demonstrated a surprisingly good survival in children with DS-ALL treated by...
risk adjusted intensive chemotherapy protocols Event-free (56% vs. 74%; P < .001) and disease-free (55% vs. 73%; P < .001) survival at 10 years was significantly lower in the standard-risk DS-ALL population compared with ALL in non DS, but not in high-risk DS-ALL population (event-free survival, 62% vs. 59%; P = .9; disease-free survival, 64% vs. 59%; P = .9), and these differences persisted regardless of treatment era (early era [1983-1989] vs. recent era [1989-1995])31. These observations have been recently confirmed by analysis of COG trials. It demonstrated that the major cause of the poorer outcome of DS-ALL is the lower prevalence of the good prognostic sentinel cytogenetic lesions, namely TEL/AML1 fusion and trisomies of chromosomes four and ten.

These results suggest that intensification of therapy for patients with DS-ALL is needed to maintain outcome comparable with those of ALL in non DS patients. Similarly a recent survey of 8 children with DS-ALL who underwent bone marrow transplantation reported that relapse and not treatment related toxicity were the major causes for treatment failure. Indeed the only surviving patients were those that were treated by myeloablative chemotherapy 32.

Thus the clinician faced with a patient with DS and ALL has difficult choices. Intensive chemotherapy is likely to cause life endangering toxicity but may also be required for cure, especially if the leukemia lacks the ETV6-RUNX1 translocation or hyperdiploidy. There may be a light in the end of this tricky maze. The activation of the CRLF2-JAK-STAT signaling pathway in the majority of DS-ALLs suggests a therapeutic potential for JAK inhibitors. If confirmed in clinical trials, this therapy will target the unique biological properties of ALLs in children with DS.

References


