In childhood acute lymphoblastic leukemia (ALL), the incidences of individual chromosomal abnormalities are well established. It is also known that their distribution varies according to age. Especially in precursor-B ALL (BCP-ALL), they remain strong independent indicators of risk of relapse, while in T-ALL they contribute significantly to the understanding of the biology of the disease.

**Structural chromosomal abnormalities in BCP-ALL**

Among these abnormalities, those with the most significant impact for risk stratification for treatment are t(9;22)(q34;q11)/BCR-ABL1 and rearrangements of the MLL gene. In particular this applies to t(4;11)(q21;q23)/MLL-AFF1 (previously known as MLL-AF4). The prognosis of the other MLL partners may become significant in the future, particularly among infants. The detection of these two abnormalities provides the basic criteria for the classification of high risk groups which is applicable to all treatment protocols. Other significant structural abnormalities include t(12;21)(p13;q22)/ETV6-RUNX1 fusion, as well as t(1;19)(q23;p13.3)/TCF3-PBX1 fusion. However, these are not used in risk stratification on all protocols. The ETV6-RUNX1 fusion occurs in approximately 25% of younger children with BCP-ALL. These patients have an extremely good prognosis. Among patients with TCF3 rearrangements, those with TCF3-PBX fusion were originally regarded as poor risk on some treatment protocols, but on modern therapy they are classified as standard risk. In contrast the rare variant, t(17;19)(q22;p13)/HLF-TCF3 fusion, has a dismal outcome on all therapies. Thus its accurate identification is important.

**Numerical chromosomal abnormalities in BCP-ALL**

Significant numerical abnormalities include: high hyperdiploidy (51-65 chromosomes), near-haploidy (24-29 chromosomes), and low hypodiploidy (31-39 chromosomes). High hyperdiploidy accounts for approximately 30% of childhood BCP-ALL and is characterised by the gain of specific chromosomes.
associated with a good prognosis in children. Near-haploidy and low hypodiploidy are rare, comprising <1% each of childhood ALL. Their characteristic features are the gain of specific chromosomes onto the haploid chromosome set and, in the majority of patients, the presence of a population of cells with an exact doubling of this chromosome number. Both are linked to a poor outcome and are used to stratify patients as high risk.

Submicroscopic abnormalities in BCP-ALL

A significant discovery was the finding that the disruption of genes involved in B-cell development played an important role in leukaemogenesis in childhood BCP-ALL. Approximately 40% of these patients had abnormalities of genes involved in the B-cell developmental pathway: PAX5, TCF3, EBF1, LEF1, IKZF1 and IKZF3. Other genes frequently affected were those controlling cell cycle progression: CDKN2A, CDKN1B and RB1. Many of these deletions can be detected by FISH and/or genomic arrays. Whether there is a link between these genes and outcome has become a critical question. In particular, the association of IKZF1 deletions with a poor prognosis requires further validation in prospective independent and unselected trial based patient cohorts. Thus at present routine screening is not a recommendation.

Recently, a cryptic translocation, t(X;14)(p22;q32) or t(Y;14)(p11;q32), involving IGH@ and CRLF2 in the pseudoautosomal region (PAR1) of the sex chromosomes, and a deletion within PAR1, giving rise to the P2RY8-CRLF2 fusion, have been reported. They lead to overexpression of CRLF2, which has been defined as a novel, significant abnormality in BCP-ALL. CRLF2 alterations, including activating mutations of the CRLF2 receptor itself, are associated with activating JAK mutations resulting in constitutive activation of the JAK-STAT signaling pathway. Activation of this pathway has been associated with a worse prognosis in adults and children and has been highlighted as an important consideration for targeted therapy. Following further validation, the detection of CRLF2 alterations may become a necessary diagnostic test.

Chromosomal and genetic changes in T-ALL

The chromosomal changes found in T-ALL are different from BCP-ALL. Visible cytogenetic changes are seen in approximately 50% of T-ALL patients. Cryptic translocations, for example t(5;14)(q35;q32) involving TLX3, and deletions, such as TAL1, may be detected by FISH using appropriate probes, considerably increasing the abnormality detection rate. T-ALL, translocations involving the T-cell receptor loci are found in approximately 35% of T-ALL by FISH. They may result in oncogenes becoming juxtaposed to the promoter and enhancer elements of the TCR genes, leading to their aberrant expression and the development of T-ALL. Alternatively, aberrant expression of oncogenic transcription factors in T-ALL may result from loss of the upstream transcriptional mechanisms that normally down regulate the expression of these oncogenes during T-cell development. The formation of oncogenic fusion transcripts is rare in T-ALL. Translocations of this type include MLL fusions and PICALM-MLLT10, as well some rare rearrangements involving the tyrosine kinase gene, ABL1. Aberrant expression of one or more transcription factors is a critical component of the molecular pathogenesis of T-ALL. These include the class B basic helix-loop-helix (bHLH) genes TAL1, TAL2, LYL1, OLIG2 and MYC, as well as genes involved in transcription regulation, for example, the cysteine-rich LIM-only domain, LMO1 and LMO2 genes. Abnormalities also affect the homeodomain genes, TLX1 and TLX3, and members of the HOXA cluster. Mutations, particularly those involving NOTCH1 and FBXW7, are significant in T-ALL, together being found in approximately 70% of cases. Mutations and deletions of the X-linked tumor suppressor gene PHF6 and PTPN2 have recently been reported; the latter has been identified as a modulator of response to treatment. Chromosomal rearrangements and amplification of MYB at 6q23 has been found in approximately 8% T-ALL, which represents an interesting molecular target for therapy.

De Keersmaecker et al. classified the different T-ALL specific abnormalities into subgroups which defined four pathways based on different classes of mutations that: 1) provide a proliferative advantage; 2) impair differentiation
and survival; 3) affect the cell cycle; and 4) provide self renewal capacity. One interesting finding has been the strong interrelationships between the different types of abnormalities in T-ALL. The T-ALL specific oncoproteins may be upregulated by association with the promoter regions of either TRA/D@ or TRB@, as well as other genes, for example BCL11B (and CDK6). In addition to these abnormalities NOTCH1 mutations and deletions of CDKN2A may be present, indicating an interacting role for chromosomal abnormalities in T-ALL. Interlaced with these four major classes of mutations is the molecular classification, which has emerged from gene expression profiling. It has identified several gene expression signatures indicative of arrest at specific stages of thymocyte development; a LYL1 positive signature represents immature thymocytes (pro-T), TLX1 positive represents early cortical thymocytes and TAL1 correlates with late cortical thymocytes. Thus, gene expression profiling has improved our understanding of the biological heterogeneity of the disease, whilst revealing clinically relevant subtypes. In addition, molecular analysis has shown its capacity to elucidate significant pathways relevant to the future treatment of T-ALL. These findings have indicated that continued genetic analysis in T-ALL is important to further classify this heterogeneous disease.

References


