New genetics and diagnosis of childhood B-cell precursor acute lymphoblastic leukemia

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Abstract

Over the last 50 years, while significant advances have been made in the successful treatment of childhood leukemia, similar progress has been made in understanding the genetics of the disease. In childhood B-cell precursor acute lymphoblastic leukemia (BCP-ALL), the incidences of individual chromosomal abnormalities are well established and cytogenetics provides a reliable tool for risk stratification for treatment. In spite of this role, a number of patients will relapse. Increasing numbers of additional genetic changes, including deletions and mutations, are being discovered. Their associations with established cytogenetic subgroups and with each other remain unclear. Whether they have a link to outcome is the most important factor in terms of refinement of risk factors in relation to clinical trials. For a number of newly identified abnormalities, appropriately modified therapy has significantly improved outcome. Alternatively, some of these aberrations are providing novel molecular markers for targeted therapy.

Introduction

In childhood B-cell precursor acute lymphoblastic leukemia (BCP-ALL), the incidences of individual chromosomal abnormalities are well established, with high hyperdiploidy and the translocation, t(12;21)(p13;q22), together comprising more than 50% of cases. Other abnormalities, for example the translocation, t(9;22)(q34;q11), and rearrangements of the MLL gene, are rare in childhood BCP-ALL. It is also known that the distribution of chromosomal changes varies according to age, with teenagers and young adults having the highest incidence of ill-defined abnormalities. Particularly in BCP-ALL, chromosomal abnormalities remain strong independent indicators of risk of relapse.

Structural chromosomal abnormalities in BCP-ALL

Those structural abnormalities 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-RUNXI 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-RUNXI 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-PBX1 were originally regarded as poor risk on some treatment protocols, but on modern therapy they are classified as standard risk.5 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 chromosome abnormalities in BCP-ALL

Significant numerical abnormalities include high hyperdiploidy (51-65 chromosomes), near-haploidy (24-29 chromosomes) and low hypodiploidy (24-29 chromosomes). High hyperdiploidy accounts for approximately 30% of childhood BCP-ALL and is characterised by the gain of specific chromosomes. It is 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 leukemogenesis 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 RB1.11,12 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.13 In particular, the association of IKZF1 deletions with a poor prognosis14,15 requires further validation in prospective, independent and unselected trial-based patient cohorts.

What can be the impact of discovering a new genetic abnormality?

Intrachromosomal amplification of chromosome 21-iAMP21

The cytogenetic subgroup, iAMP21 (intrachromosomal amplification of chromosome 21), was identified during routine screening for the presence of the ETV6-RUNXI fusion by fluorescence in situ hybridization (FISH).16,17 Patients are negative for the ETV6-RUNXI fusion, while in addition to the two normal copies of the ETV6 signal, show multiple RUNXI signals (3 or more additional signals) with this probe. In metaphase, one signal is located to the normal chromosome 21, while the others are seen in tandem duplication along an abnormal chromosome 21.18 In interphase, the signals are clustered together, except for one signal representing the normal chromosome 21, which is usually located apart. Cytogenetics, multiple colour FISH and high resolution genomic arrays have shown that the morphology of the abnormal chromosome 21 is highly variable between patients, with multiple, complex genomic rearrangements, and that the commonly amplified region always includes the RUNXI gene.19-20 This abnormality was originally described as poor risk on standard therapy,17,18,21,22 although the outcome has since been shown to be protocol dependent.23,24 Thus its accurate detection is important to guide therapy, at least in some protocols. Currently FISH with probes directed to RUNXI remain the only reliable detection method. Studies are continuing to determine the mechanism(s) underlying this unusual abnormality in order to develop an improved diagnostic test.

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IGH@ translocations

Translocations involving IGH@ at 14q32 are emerging as a significant subgroup in childhood BCP-ALL, at an incidence of approximately 8%. Translocations involving IGH@ with five genes from the CEBP gene family, ID4, and the cytokine receptor to erythropoietin, EPO, have recently been described.25-28 It is of interest that they occur more frequently in adolescents and, although numbers are small, they appear to have an inferior outcome.

Recently, a cryptic translocation, t(X;14) (p22;q32) or t(Y;14) (p11;q32), involving IGH@ and CRLF2 in the pseudosatellitoid region (PAR1) of the sex chromosomes,29 and a deletion within PAR1, giving rise to the P2RY8-CRLF2 fusion, have been reported.29-32 They lead to overexpression of CRLF2 at both the transcript and protein levels, 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 signalling pathway and they are particularly common in Down syndrome ALL.30,31,33 Activation of this pathway has been associated with a worse prognosis in adults and children in some trials,34,35 although not in others.36 Nevertheless, it has been highlighted as an important consideration for targeted therapy. Following further validation, the detection of CRLF2 alterations may become a necessary diagnostc test.

In childhood ALL, interest in mutations within genes involved in key cellular pathways is heightening as deep-sequencing techniques are becoming established.37 A number of associations with other genetic changes are already known, such as the link between mutations of genes within the RAS signalling pathway and high hyperdiploidy.38,39 Activation of this pathway has been associated with a worse prognosis in adults and children in some trials,40,41 although not in others.42 Nevertheless, it has been highlighted as an important consideration for targeted therapy. Following further validation, the detection of CRLF2 alterations may become a necessary diagnostic test.

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