

Acute lymphoblastic leukemia - Section 2

Advances in acute lymphoblastic leukemia genomics

Christine J. Harrison, Claire Schwab

Northern Institute for Cancer Research, Newcastle University, Newcastle-upon-Tyne, UK

Take Home Messages

- Genomic screening in B-other-ALL has identified a wide range of novel genetic subtypes.
- iAMP21-ALL, which originally emerged from B-other-ALL, now represents a distinct genetic subgroup, in which modified treatment has improved outcome.
- Among the Ph/BCR-ABL1-like poor risk patients, a subset have been identified with ABL-class fusions and poor response to conventional therapy, who respond to tyrosine kinase inhibitors.
- Continued screening for additional targetable genetic abnormalities will likely reduce toxicity and further improve survival.

Introduction

In childhood B-cell precursor acute lymphoblastic leukemia (BCP-ALL), the major cytogenetic subgroups are strongly associated with outcome. Their routine use in risk stratification for treatment has contributed to improved survival rates.¹ As examples, the t(12;21)(p13;q22)/*ETV6-RUNX1* fusion and high hyperdiploidy (51-65 chromosomes) are associated with an excellent prognosis, while t(9;22)(q34;q11)/*BCR-ABL1* fusion is a marker of poor outcome. Approximately 30% of patients with none of the major cytogenetic abnormalities, known as B-other-ALL, were regarded as intermediate risk, although patients were heterogeneous at the genetic level. One important example is iAMP21-ALL, characterized by a grossly abnormal chromosome 21.^{2,3} It was originally classified among B-other-ALL, but now represents a distinct cytogenetic entity (~2%) of older children (median age 9 years) with BCP-ALL. Its accurate identification is vital, as patients have a high relapse rate on standard treatment⁴ and intensification of therapy has greatly improved outcome.^{5,6} Genomic studies have elucidated the mechanism underlying the formation of the iAMP21 chromosome from breakage-fusion-bridge cycles and chromothripsis.⁷ Ongoing studies to decipher the genomic complexity of the iAMP21 chromosome will identify genes on chromosome 21 as potential targets for novel therapies, to reduce the toxicities of the current high risk treatment.

Below we describe a selection of novel abnormalities more recently identified within the revised B-other-ALL subgroup (Figure 1). They are presented in relation to their biological and clinical significance, with particular emphasis on relevance to treatment.⁸

Current state-of-the-art

B-other-ALL

A spectrum of genomic studies has more recently revealed a range of distinct, recurrent abnormalities among B-other-ALL, with approximate incidences diagrammatically represented in Figure 1. The poor risk subtype, Ph-like/*BCR-ABL1*-like ALL,^{9,10} accounts for up to 15% of B-other ALL. As a consensus gene expression profile for this group has failed to emerge, screening for the chromosomal and genetic abnormalities underlying the signature may prove to be more useful clinically.

Rearrangements of kinase genes have been identified within Ph-like-ALL:¹¹ notably those with ABL-class fusions (*ABL1*, *ABL2*, *PDGFRB* and *CSF1R*) and JAK-STAT signaling (including *CRLF2*-deregulation, truncating rearrangements of *EPOR*, *JAK2* fusions and genetic alterations of *IL7R*, *FLT3*, *SH2B3*, *JAK1*, *JAK3*, *TYK2* and *IL2RB*) may respond to alternative therapies.¹² Rearrangements of *CRLF2* are the most common (~10%) with relapse rate similar to the B-other cohort overall. Among the ABL-class fusions, *EBF1-PDGFRB* was the most frequent (~4%), with clinical and experimental evidence of successful response to tyrosine kinase inhibitors (TKI).¹² As patients with this fusion are usually refractory to induction therapies or have high levels of minimal residual disease,¹³ TKI treatment has become an important consideration when designing screening algorithms for childhood ALL. There is also increasing evidence that patients with *JAK2* rearrangements may benefit from treatment with the JAK inhibitors.¹¹

A distinct sub-group of B-other ALL with rearrangements and overexpression of *DUX4* has recently been reported to have a good outcome.^{14,15} Due to the small size of the rearrangement, repetitive nature of the gene, and its location within the subtelomeric regions of chromosomes 4 and 10, *DUX4* rearrangements are difficult to identify. Thus, transcriptome sequencing

currently remains the most reliable detection method. As accompanying *ERG* deletions occur exclusively within this sub-group, detection of *ERG* deletions may be used as a surrogate marker of *DUX4* abnormalities.

The clinical relevance of other emerging sub-groups, including fusions of *ZNF384*,¹⁶ *MEF2D*,¹⁷ *NUTM1*,¹⁸ rearrangements of *IGH*¹⁹ and *PAX5*²⁰ and patients with an *ETV6-RUNX1*-like gene expression profile¹⁴ is less clear, having been reported only in sporadic cases or studied in single cohorts.

Future perspectives

The continued screening for genetic abnormalities among B-other-ALL will hopefully lead to genomic classification of all cases. A spectrum of approaches is available for their detection, each with its merits and limitations. The choice of methodology is applied according to the expertise of the individual study group. Many of these abnormalities are rare, thus continued investigation at the biological and clinical level are essential to determine their true prognostic relevance and identification of appropriate targets for novel less toxic therapies. The specific treatment of patients responsive to TKI has been a breakthrough

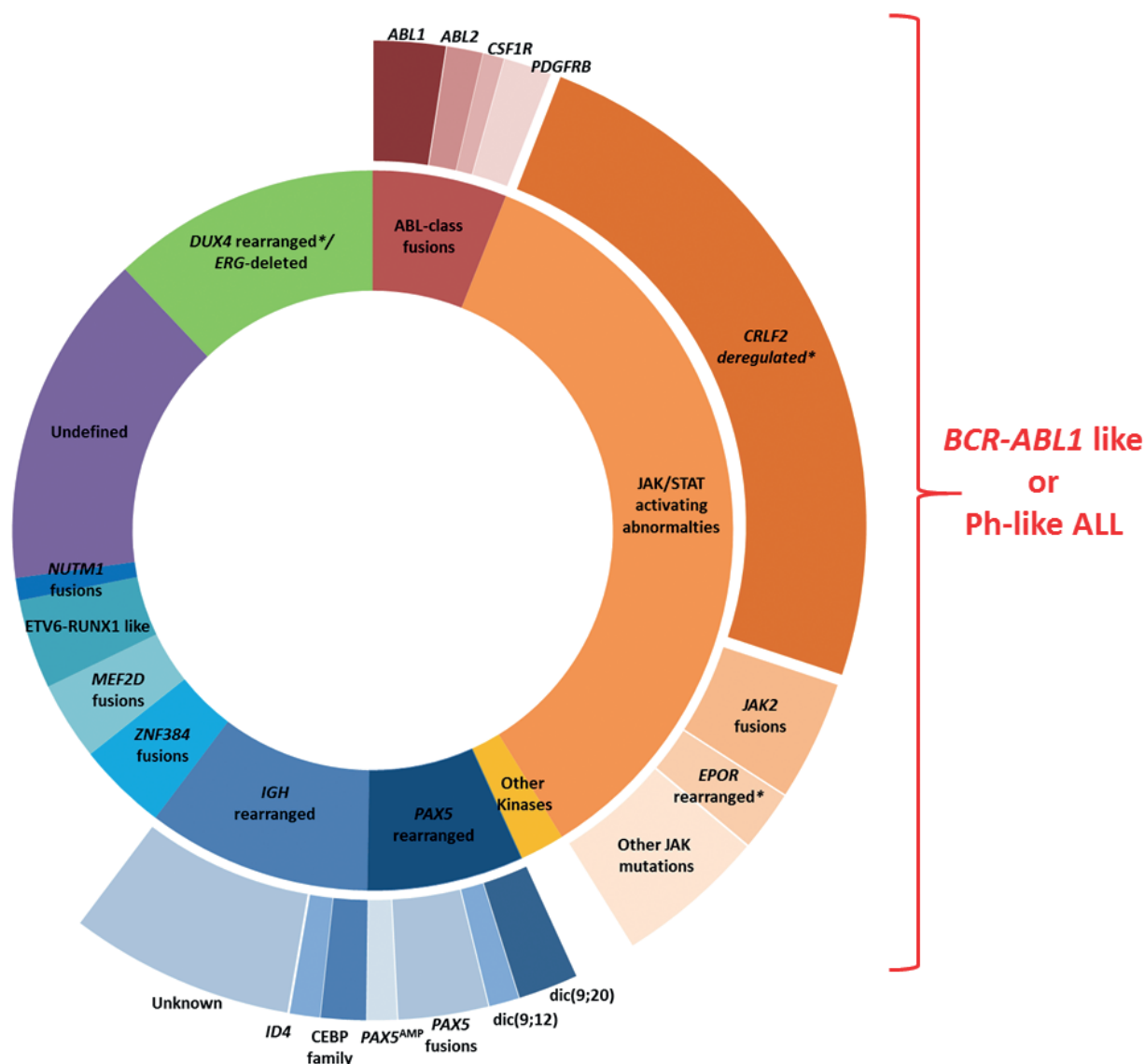


Figure 1. The range of genetic abnormalities comprising B-other ALL. The relative distribution of abnormalities is approximated from reports in the literature. Largely the color scheme indicates the associated prognosis, with orange (denoting Ph/BCR-ABL1-like) indicating a poor outcome, green indicating a good prognosis, while the remainder are classified as intermediate risk at this time. The proportion of cases currently undefined at the genomic level are indicated in purple.

which hopefully will be mirrored by targeted treatment of a wider range of abnormalities.

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