Childhood B-acute lymphoblastic leukemia: a genetic update

Jennifer S Woo, Michael O Alberti and Carlos A Tirado*

Abstract

In the pediatric population, B-acute lymphoblastic leukemia (B-ALL) is the most prevalent childhood hematological malignancy, as well as the leading cause of childhood cancer-related mortality. Advances in cytogenetics utilizing array-based technologies and next-generation sequencing (NGS) techniques have revealed exciting insights into the genetic basis of this disease, with the hopes of developing individualized treatment plans for affected children. In this comprehensive review, we discuss our current understanding of childhood (pediatric) B-ALL and highlight the most recent genetic advances and their therapeutic implications.

Keywords: Pediatric B-ALL, B-precursor, B-cell, Genetics, Cytogenetics

Introduction

ALL is a malignant clonal proliferation of lymphoid progenitor cells, most commonly of the B-cell lineage (B-ALL). In the pediatric population, ALL accounts for 81% of childhood leukemias; leukemia overall accounts for one third of cancers diagnosed in children between ages 0–14 years [1]. In the United States, the majority of ALL cases occur in ages 1–4, with an incidence rate in this group of 8 per 100,000, and preponderance for males over females [1]. The long-term rates of event-free survival (EFS) for childhood B-ALL approach 90%, although infants are associated with poorer prognosis and lower EFS rates [2-4].

This review discusses our current understanding of childhood B-ALL and highlights recent genetic advances and their therapeutic implications. Genetic classification of B-ALL is paramount for risk stratification and in treatment evaluation, especially within the context of clinical trial enrollment. At the forefront of pediatric oncologic research is the Children’s Oncology Group (COG) in North America, as well as the International Berlin-Frankfurt-Münster (BFM) Study Group in Europe, whose work has played a significant role in disease-specific research and therapeutic developments. Treatment protocols, including clinical trials, are the mainstay treatment for children with hematological and solid tumor malignancies. Cytogenetics advances of B-ALL have led to the discovery of numerous additional genetic changes, including mutations involving key cellular pathways in lymphoid development, tumor suppression, and cell cycle regulation. Uncovering the prognostic significance of these genetic aberrations is fundamental for risk stratification and ultimately individualized treatment.

Clinical presentation

ALL is a disease of the bone marrow. Clinical suspicion for ALL arises with signs and symptoms reflective of bone marrow failure (pancytopenia) and/or extramedullary disease. The most common symptoms include fatigue, pallor, bone pain, arthritis, limping, easy bruising/bleeding, and/or petechiae. Physical examination may show lymphadenopathy and hepatosplenomegaly [5]. Extramedullary involvement may be seen in the central nervous system (CNS) with signs of increased intracranial pressure including headache [6]. In boys, testicular involvement may present as a testicular mass. Adverse prognostic factors include high leukocyte count on presentation, age <1 year or >10 years, and adverse cytogenetics [7,8].

Histology

Bone marrow aspirate studies show a preponderance of lymphoblasts with high nuclear to cytoplasmic (N:C) ratio, finely dispersed nuclear chromatin, and prominent nucleoli. On occasion, vacuolated cytoplasm and cytoplasmic...
pseudopods can be seen. Bone marrow core biopsies demonstrate diffuse replacement of normal marrow elements by uniform sheets of round to oval lymphoblasts with indented to convoluted nuclei [9] (Figure 1). No lower limit of blast percentage is required to establish the diagnosis, but most treatment protocols define ALL by the presence of greater than or equal to 25% blasts. By immunophenotype, B-lymphoblasts demonstrate universal positivity for B-cell markers including CD19, cytoplasmic CD79a, and cytoplasmic CD22; as well as positivity for surface CD22, CD24, PAX5 and TdT; with variable expression of CD10, CD20 and CD34 [9]. CD10 is often negative in infant ALL (age <1 year) with \textit{MLL} (11q23) gene rearrangements [10].

Recurrent genetic abnormalities
Approximately 75% of childhood ALL cases harbor recurrent genetic abnormalities, including aneuploidy or structural chromosomal arrangements, detected by conventional karyotyping and fluorescence \textit{in situ} hybridization (FISH) [11]. Translocations t(9;22)(q34;q11) [\textit{BCR-ABL1}], t(12;21) (p13q22) [\textit{ETV6-RUNX1 (TEL-AML1)}], hyperdiploidy, and translocation t(4;11)(q21q23) [\textit{MLL-AFF1(AF4)}] in infants, are found at the highest frequency in childhood B-ALL [11]. Other recurrent cytogenetic abnormalities include hypodiploidy and translocation t(1;19)(q23p13) [\textit{TCF3-PBX1 (E2A-PBX1)}] [11]. Advances in cytogenetics utilizing array-based technologies and NGS have uncovered additional submicroscopic DNA alterations affecting genes involved in normal hematopoiesis, tumor suppression, apoptosis, and cell cycle regulation, including \textit{IKZF1}, \textit{CRLF2}, \textit{PAX5}, and \textit{FLT3} (Table 1). Advanced techniques have revealed new insights into well-known recurrent abnormalities, and have more importantly elucidated new gene targets involved in aberrant hematopoiesis and relapse. Overall, the utilization of these newly identified genetic alterations has clinical utility for diagnosis, risk stratification, and targeted therapy.

Aneuploidy

\textbf{High hyperdiploidy}
High hyperdiploidy (51–65 chromosomes) is one of the most common cytogenetic abnormalities observed in childhood B-ALL (Figure 2). It is seen in 25-30% of total childhood B-ALL cases, with the highest frequency in the 1 to 4 year age range [12,13]. High hyperdiploidy is characterized by a nonrandom gain of chromosomes, including + X, +4, +6, +10, +14, +17, +18, and +21 [13,14]. The diagnosis confers a good prognosis in childhood B-ALL, with EFS rates of approximately 80% and overall survival (OS) rates of 90% (reviewed in [13]). Despite favorable outcomes, 20% of children relapse and 10% eventually succumb to the disease [15]. SNP array analysis of high hyperdiploid B-ALL has shown that almost 80% of cases display further genetic abnormalities in addition to characteristic chromosomal gains; although these additional aberrations have no definitive clinical ramification [14].

Recently, rare alleles of \textit{PRDM9} (which encodes a meiosis-specific histone H3 methyltransferase that controls

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{image.png}
\caption{Evaluation of a boy with abdominal pain, night sweats, increased fatigue, petechiae, and a white blood cell count of 113 × 10^3/μL. A. Bone marrow core biopsy (100x) showed diffuse replacement of normal marrow elements by uniform sheets of round to oval lymphoblasts with indented to convoluted nuclei. B. Touch preparation of core biopsy material showed lymphoblasts with high nuclear to cytoplasmic (N:C) ratio, finely dispersed nuclear chromatin, and prominent nucleoli. C-D. Peripheral blood smear (100x) showed lymphoblasts with high N:C ratio and cytoplasmic pseudopods.}
\end{figure}
Table 1 Recurrent genetic abnormalities in B-ALL, associated affected genes, and prognosis

| Aneuploidy                          | Common genes implicated | Prognosis         | Additional comment                                                                 | References |
|-------------------------------------|------------------------|-------------------|-------------------------------------------------------------------------------------|------------|
| High-hyperdiploidy                  |                        | Good              | FLT3 mutations can be seen in hyperdiploid B-ALL. Almost 80% of cases display further genetic abnormalities of no definitive clinical significance. | [14,93]   |
| Hypodiploidy                        |                        | Poor              | Concomitant alterations in RTK- and Ras-signaling (NF1), as well as IKZF3 (Aiolos) may be seen. | [22]       |
| Near-hypodiploidy                   |                        | Poor              | Concomitant alterations in TP53, RB1, IKZF2 (Helios) may be seen.                    | [22]       |
| Low-hypodiploidy                    |                        | Poor              | Concomitant alterations in TP53, RB1, IKZF2 (Helios) may be seen.                    | [22]       |

| Recurrent translocations             |                        |                   |                                                                                     |            |
| t(12;21)(p13;q22)                    | ETV6-RUNX1 (TEL-AML1)  | Good              |                                                                                     |            |
| t(1;19)(q23;p13)                     | TCF3-PBX1 (E2A-PBX1)   | Intermediate      |                                                                                     |            |
| t(9;22)(q34;q11)                     | BCR-ABL1 (Philadelphia chromosome; Ph+) | Intermediate | Associated with older age, higher leucocyte count, and more frequent CNS leukemia at time of diagnosis. | [34]       |
| MLL (11q23) rearrangements          |                        | Poor              | Almost exclusively seen in infant B-ALL. FLT3 mutations are often seen with MLL rearrangements. Epigenetic aberrancies, through microRNAs, are implicated in the pathogenesis of MLL-rearranged B-ALL. | [93,98]    |
| t(4;11)(q21;23)                      | MLL-AFF1(AF4)          | Poor              |                                                                                     |            |
| t(9;11)(p22;q23)                     | MLL-MLT3(AF9)          | Poor              |                                                                                     |            |
| t(11;19)(q23;p13.3)                  | MLL-ENL               | Poor              |                                                                                     |            |
| t(10;11)(p13-14;q14-21)              | MLL-MLT10(AF10)        | Poor              |                                                                                     |            |

| Additional genetic alterations       |                        |                   |                                                                                     |            |
| BCR-ABL1-like ALL                    | IKZF1, CRLF2, JAK mutations | Poor              | Defined by a similar GEP to Ph + B-ALL, but in the absence of the BCR-ABL1 rearrangement (t(9;22)). Rearrangements in CRLF2 or EBF1-PDGFRB, as well as concurrent JAK mutations, and/or IKZF1 (Ikaros) deletions/mutations may be seen. | [60,61,89] |
| JAK mutations, including JAK2 (9p24) | IKZF1, CRLF2, CDKN2A/B (p16) | Poor              | In the setting of BCR-ABL1-like B-ALL, JAK mutations are associated with concomitant IKZF1 (Ikaros) and CDKN2A/B (p16) alterations. JAK2 mutations are also associated with CRLF2 rearrangements, and have been described in 60% of Down syndrome-associated ALL. | [72-78]    |
| iAMP21                              | RUNX1, P2RY8-CRLF2      | Poor              | Occurs in older children with B-ALL. Associated with P2RY8-CRLF2, resulting in the overexpression of CRLF2. | [56,57]    |
| IgH@ (14q32) rearrangements          | IgH@ with multiple fusion partners | Poor              | Occurs in older children, adolescents, and young adults. Recurrent fusion partners include CRLF2, ID4, CEBP, and EPOR. | [46,51]    |
| FLT3 (13q12) mutations               | FLT3                   | Poor              | Seen in MLL-rearranged and hyperdiploid B-ALL.                                                                 | [93,94]    |
| PAX5 (9p13) rearrangements, deletions| PAX5 with multiple fusion partners | Unknown           | Reported rearrangements with multiple genes, including ETV6 and JAK2.                                | [75,91,92] |
| Relapsed all                         | CDKN2A/B, ETV6, IKZF1, CREBBP, NT5C2 | Poor              | 20% of total pediatric ALL relapse cases and 60% of high-hyperdiploid relapse cases harbor mutations in CREBBP. | [103,104,106-109,111] |
activation of recombination hotspots) have been reported to be associated with the development of high hyperdiploid and infant B-ALL [16,17]. Furthermore, it was even postulated that PRDM9 activity during the early stages of meiosis in the parental germline could lead to genomic instability and development of childhood B-ALL [16].

**Hypodiploidy**

Hypodiploidy is characterized by fewer than 46 chromosomes and is seen in 5-8% of total B-ALL cases [18,19]. The current high risk COG protocol AALL1131 denotes hypodiploidy as less than 44 chromosomes. The majority of hypodiploid B-ALL contain 45 chromosomes. The remainder of hypodiploidy cases are much rarer and include high-hypodiploid (40–44 chromosomes), low-hypodiploid (33–39 chromosomes), and near-haploid (24–29 chromosomes) groups [19,20]. In general, hypodiploidy with less than 40 chromosomes confers a poor prognosis. The 3-year EFS for near-haploid and low-hypodiploid B-ALL is 30% [19,20]. Hypodiploid cases have also been shown to undergo reduplication, resulting in a hyperdiploid karyotype (so called "masked hypodiploid ALL"), which may preclude the correct genetic classification and therefore render an inappropriate treatment regimen [20,21].

A recent genomic profiling study of hypodiploid ALL cases identified multiple recurrent genetic alterations, distinguishing near haploid from low-hypodiploid ALL [22]. Near-haploid ALL cases showed alterations targeting genes in receptor tyrosine kinase (RTK) signaling and Ras.
signaling (NF1) pathways, as well as high frequency alterations in the IKAROS gene family, particularly IKZF3 (Aiolos) which encodes for the zinc finger transcription factor AIOLOS [22]. Low-hypodiploid cases showed genetic alterations of TP53, RB1, and IKZF2 (Helios) [22]. In the TP53 mutated cases, non-tumor cells also harbored TP53 mutations, suggesting an inherited basis of disease and a possible manifestation of Li-Fraumeni syndrome (LFS) [23]. Both low-hypodiploid and near-haploid ALL showed activation of Ras-signaling and PI3K (phosphoinositide 3-kinase)-signaling pathways that were sensitive to PI3K inhibitors such as rapamycin in vitro, suggesting that PI3K inhibitors could be explored as a therapeutic treatment option [22].

Recurrent translocations

**ETV6-RUNX1 (TEL-AML1)**

The most common chromosomal rearrangement in B-ALL is t(12;21)(p13;q22), encoding for ETV6-RUNX1 (TEL-AML1) [11] (Figures 3, 4 and 5). It occurs in 25% of children with B-ALL and confers an excellent prognosis [24,25]. Both ETV6 and RUNX1 transcription factors are required for normal hematopoiesis [26,27]. The ETV6-RUNX1 fusion protein is thought to disrupt the normal expression of RUNX1-regulated genes by converting RUNX1 to a transcriptional repressor [28].

**TCF3-PBX1 (E2A-PBX1)**

The t(1;19)(q23;p13) rearrangement and its unbalanced variant der(19)t(1;19)(q23;p13) are commonly seen in B-ALL. This translocation is associated with the t(12;21) translocation in the HLA-DR gene, resulting in an unbalanced translocation between chromosomes 1 and 21, leading to the formation of the ETV6-RUNX1 fusion transcript.
ALL [11] (Figure 6). The resultant TCF3-PBX1 (E2A-PBX1) fusion protein is comprised of the transactivation domains of TCF3 and a DNA binding domain of the homeobox protein PBX1, converting PBX1 into a trans-activating factor and reducing expression of the TCF3 encoded transcription factors E12 and E47, required for early lymphoid development [29,30]. The translocation occurs in 6% of childhood B-ALL and is historically associated with poorer outcomes [31]. However, advances in treatment have improved clinical outcomes of children with this abnormality and the translocation is now thought to confer an intermediate prognosis [32].

**BCR-ABL1 (Philadelphia chromosome)**

B-ALL harboring the t(9;22)(q34;q11) translocation or ‘Philadelphia chromosome’ (Ph + B-ALL), encodes the fusion gene BCR-ABL1. This translocation is present in 3-5% of childhood B-ALL cases [33] and is associated with older age, higher leukocyte count, and more frequent CNS involvement at time of diagnosis [34]. The translocation fuses the 5′ sequence of the breakpoint cluster region (BCR) on chromosome 22 to the 3′ sequence of the ABL1 gene on chromosome 9. The resultant oncoprotein is a constitutively active nonreceptor tyrosine kinase, responsible for leukemogenesis. The BCR region contains two breakpoint areas, including a major BCR (M-bcr) area commonly seen in chronic myelogenous leukemia (CML), and a minor BCR (m-bcr) area seen in pediatric B-ALL. In 90% of childhood B-ALL cases, fusion genes created by breaks in m-bcr encode for a 190 kDa fusion protein (p190) [35].

The use of ABL1 tyrosine kinase inhibitors (TKIs), such as imatinib, has been revolutionary in the treatment of Ph + B-ALL. Once associated with dismal outcomes, use of TKIs combined with intensive chemotherapy has improved 3-year EFS in children and adolescents with...
Ph + B-ALL with no appreciable increase in toxicity [36]. The COG AALL0622 clinical trial, substituting the second generation TKI, dasatinib, for imatinib, is under investigation [37].

**MLL** gene rearrangements

MLL (mixed-lineage-leukemia) gene rearrangements at 11q23 are present in 80% of all infant B-ALL cases and 10% of all childhood B-ALL [38,39]. The **MLL** gene encodes for a protein with histone methyltransferase activity, which is essential for hematopoietic regulation of HOXA and MEIS1 gene expression [40]. The most common gene rearrangements include t(4;11)(q21;q23) encoding **MLL-AFF1** (AF4), t(9;11)(p22;q23) encoding **MLL-MLLT3** (AF9), t(11;19)(q23;p13.3) encoding **MLL-ENL**, and t(10;11)(p13-14;q14-21) encoding **MLL-MLLT10** (AF10) [41,42]. About 50% of **MLL** rearrangements show the t(4;11)(q21;q23) translocation. In general, **MLL** rearrangements are associated with adverse outcomes, with an EFS of approximately 35% [43], largely due to cellular drug resistance [44,45].

**IGH** translocations

Rearrangements of the immunoglobulin heavy chain locus (**IGH**) on chromosome 14q32 are rare in B-ALL, occurring in <5% of cases [46]. **IGH** rearrangements occur more frequently in adolescents and appear to have poor clinical outcomes. The most common **IGH** partners include **CRLF2** (cytokine receptor-like factor 2) at the pseudoautosomal region 1 (PAR1) of Xp22.3/Yp11.3 (resulting in overexpression of **CRLF2**) [47], **ID4** (inhibitor of DNA binding 4) at 6p22 [48], and members of the

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**Figure 5 Evaluation of a 7 year-old boy with B-ALL.**

A. Abnormal male karyotype with a deletion of 11q and trisomy 21. B. FISH analysis demonstrated an abnormal signal pattern consistent with **ETV6-RUNX1** (**TEL-AML1**) fusion, indicative of t(12;21) translocation, as well as +21q and 11q- (**MLL** deletion).
CEBP (CCAAT/enhancer binding protein) family [49,50]. Translocations between IGH@ and EPOR (erythropoietin receptor) at 19p13 have also been reported [51-53], with other remaining translocations appearing sporadic [46].

Intrachromosomal amplification of chromosome 21 (iAMP21)

iAMP21 is defined as the presence of three or more copies of the RUNX1 gene within a morphologically abnormal chromosome 21 [54,55]. Amplified regions on chromosome 21 are found within a 5.1 Mb region containing RUNX1, miR-802, and genes mapping to the Down syndrome critical region. iAMP21 occurs in approximately 2% of older children with B-ALL, and is associated with poorer outcomes when treated with standard therapy, and also increased risk for early and late relapse [56]. The five-year EFS is approximately 29%, with an OS of 71% [57]. Recent studies have shown that treatment of iAMP21 patients as high-risk provides a significant improvement in outcome [58]. One recurrent abnormality in iAMP21, seen in 35% of children with iAMP21, includes the P2RY8-CRLF2 fusion (created by a focal deletion at the PAR1 region at Xp22.3/Yp11.3) which results in the overexpression of CRLF2 [47]. Gain of the X chromosome, and abnormalities affecting the genes IKZF1 (Ikaros), CDKN2A, PAX5, ETV6, and RB1 have also been associated with iAMP21 [56]. Lastly, individuals born with the constitutional Robertsonian translocation rob(15;21)(q10;q10)c have a 2700-fold increased risk of developing B-ALL with iAMP21 [59].

Submicroscopic genetic alterations

The role of IKZF1 in BCR-ABL1 and BCR-ABL1-like ALL

“BCR-ABL1-like” B-ALL, seen in 15% of childhood B-ALL, has recently been defined by gene expression profiling (GEP). BCR-ABL1-like B-ALL shows a similar GEP to Ph + B-ALL, but in the absence of the BCR-ABL1 rearrangement [60,61]. These cases are associated with poor outcomes and increased relapse risk [62-64]. Deletions and sequence mutations in IKZF1 (Ikaros) at 7p13, which encodes for the lymphoid transcription factor IKAROS, are associated with approximately 70% and 40% of BCR-ABL1-positive and BCR-ABL1-like B-ALL, respectively [60,63]. Despite improvements in outcomes for children with Ph + B-ALL that has resulted from combination TKI and chemotherapy, recent studies have demonstrated that Ph + ALL harboring IKZF1 deletions are associated with unfavorable outcomes; irrespective of imatinib treatment [65]. In addition to frequent IKZF1 (Ikaros) abnormalities, up to 50% of BCR-ABL1-like ALL harbor rearrangements in CRLF2, with concurrent Janus kinase family (JAK) mutations [66,67]. BCR-ABL1-like ALL has also shown resistance to L-asparaginase, and to
a lesser extent, daunorubicin; although intensified therapy could give more suitable treatment options [60].

Additional BCR-ABL1-like ALL studies have shed light on the heterogenous pathogenesis of ALL. In 2013, a genome-wide association study (GWAS) of BCR-ABL1-like ALL identified a susceptibility locus for BCR-ABL1-like ALL (GATA3, rs3824662) [68]. This locus was shown to be associated with CRLF2 rearrangements, JAK mutations, and deletions in IKZF1 (Ikaros) [68].

Transcriptome and whole-genome sequencing of BCR-ABL1-like ALL has also identified other genetic alterations involved in the activation of kinase signaling, including EBF1-PDGFRB, comprised of the transcription factor EBF1 (early B-cell factor 1) and the receptor tyrosine kinase PDGFRB (platelet-derived growth factor receptor β), resulting from 5q33q33 microdeletion [53,69]. Several reports suggest that the use of TKIs to treat B-ALL harboring the EBF1-PDGFRB rearrangement may be of clinical benefit [70,71].

JAK mutations and CRLF2 rearrangements

The role of cytokine receptors and JAK family members are playing increasingly larger roles in B-ALL studies. The JAK family encodes four nonreceptor tyrosine kinases (JAK1, JAK2, JAK3, TYK2) involved in cytokine-mediated signaling (JAK-STAT pathway) [72]. Mutations occur in about 10% of high-risk childhood B-ALL cases [73]. In the setting of BCR-ABL1-like B-ALL, JAK mutations are also associated with concomitant IKZF1 (Ikaros) and CDKN2A/B alterations, and correlate with worse outcomes [74,75]. JAK2 mutations are also associated with CRLF2 rearrangements (as described above), and are described in 60% of Down syndrome (Trisomy 21)-associated ALL [76,77]. Approximately 40% of CRLF2-rearranged cases can harbor JAK2 mutations [78].

Abnormalities involving JAK2 (9p24) most often arise via point mutations involving the pseudokinase domain R683 [79,80]; however, rare cases of JAK2 rearrangements have also been identified [79,81,82]. In JAK2 rearrangements, dimerization or oligomerization of JAK2 is induced without ligand binding, resulting in constitutive activation of downstream pathways in leukemic cells. Alterations in CRLF2, (Xp22.3/Yp11.3), occur in up to 8% of unscreened childhood B-ALL cases and up to 15% of high-risk B-ALL patients [83-86]. CRLF2 rearrangements result in constitutive activation of the STAT5 pathway, resulting in leukemogenesis. Additionally, abnormal PI3K/mTOR pathway signaling has also been implicated [87].

The JAK2 inhibitor, ruxolitinib, has been shown to reduce tumor burden in xenograft mouse models harboring BCR-JAK2 [t(9;22)(p24;q11.2)] [88], and has demonstrated promising results in the treatment of CRLF2-rearranged, JAK2-mutated leukemic cells in vitro [87]. Additionally, the PI3K inhibitor, rapamycin, has been shown to control leukemic burden [88]. Clinical trial NCT01251965, utilizing ruxolitinib in refractory or relapsed ALL or AML (acute myelogenous leukemia), is currently ongoing.

More recently, another potential molecular target in JAK2-mutated B-ALL was revealed. In a mouse model, overexpression of mutant JAK2 led to downstream upregulation of prosurvival Bcl-2 gene family members, and combined use of the Bcl-2/Bcl-xL inhibitor ABT-737 with JAK2 inhibitors prolonged disease regression time [89].

PAX5 deletions and rearrangements

PAX5 (9p13), a member of the paired box gene family, is a transcription factor necessary for normal hematopoietic development [90]. In childhood B-ALL, mutations in PAX5 have been detected in 32% of cases by genome-wide analysis [75]. PAX5 rearrangements occur with incidence of about 2.5%, with numerous reported rearrangements including ETV6 (12p13) and JAK2 (9p24) [91]. Recently, a heterozygous germline PAX5 variant, c.547G>A, encoding p.Gly183Ser, was identified in two unrelated families with autosomal dominant B-ALL, suggesting that PAX5 mutations may play a role in the inherited susceptibility of B-ALL [92].

FLT3 mutations

FLT3 (fms-tyrosine kinase 3) on chromosome 13q12 is frequently mutated in MLL-rearranged and high hypodiploid B-ALL [93]. Infants with MLL-rearrangements have been shown to be sensitive to the FLT3 inhibitor, PKC412 (midostaurin), suggesting that multitarget kinase inhibition may present as novel therapeutic modalities [94]. COG study AALL0631, utilizing the FLT3 inhibitor lestaurtinib (CEP701) along with standard chemotherapy, is currently ongoing in infants with MLL rearrangements.

The role of epigenetics

The role of epigenetic regulation in B-ALL has gained considerable attention. In 2013, the first integrated genome-wide analysis in childhood ALL, incorporating cytosome methylation profiling, DNA copy number alterations (CNA) and GEP, was reported [95]. Recurrent epigenetic alterations were identified across all B-ALL subtypes studied, suggesting that certain epigenetic events are required for leukemic transformation [95]. Moreover, genes frequently affected by structural abnormalities were shown to be targets for aberrant DNA methylation [95]. Additionally, global histone modification profiling revealed a distinct molecular chromatin signature in several ALL cell lines, subsequently noted to harbor abnormalities in NSD2, encoding for a methyltransferase [96]. Targeted investigation of patient samples revealed approximately 7.5% of childhood B-ALL
harbored mutations in WHSC1/NSD2 (particularly p.E10 99K) but were enriched the B-ALL subtypes ETV-RUNX1 (20%) and TCF3-PBX1 (15%) [96]. More recently, NGS targeted exome profiling identified a number of epigenetic regulators, including CREBBP and SETD2, mutated in 25% of B-ALL samples at time of diagnosis [97]. Further analysis revealed that mutations in SETD2 were enriched in MLL-rearranged (22%) and the ETV-RUNX1 (13%) subtypes of B-ALL, and that over 50% of matched relapsed cases, regardless of subtype, demonstrated enrichment of mutations in epigenetic regulators (discussed more below) [97].

Epigenetic studies have also shown insights into our understanding of MLL-rearranged B-ALL. MicroRNAs (miRNAs), short noncoding RNAs involved in the regulation of signaling pathways of cell differentiation, proliferation, and apoptosis, have been shown to promote leukemogenesis through aberrant epigenetic activity [98]. The presence of these epigenetic aberrancies suggests that histone deacetylase (HDAC), DNA methyltransferase (DNMT), and/or histone methyltransferase (HMT) inhibitors may play a therapeutic role in MLL-rearranged B-ALL [99,100]. Notably, selective DOT1L HMT inhibitors, such as EPZ-004777, have been shown to selectively destroy MLL-rearranged cells in mouse models [101,102]. Clinical trial NCT01684150 is currently evaluating the use of the DOT1L HMT inhibitor, EPZ-5676, in adults with MLL-rearrangements.

**Relapsed ALL**

Despite overall progress in treatment, relapsed B-ALL has a dismal prognosis with an overall survival of 30% [103]. Several genetic subtypes and aberrations are associated with high treatment failure risk, including CDKN2A/B, ETV6, and IKZF1 (Ikars) mutations. Relapse occurs across the spectrum of all B-ALL subtypes, with some cases demonstrating acquisition of additional chromosomal abnormalities over time. In 2008, genome-wide analysis of matched samples from diagnosis and relapse identified different patterns of genomic CNA for samples at diagnosis and relapse, with that acquired abnormalities preferentially affected cell cycle regulation and B-cell development genes [104]. They determined that only 8% of relapse clones carried identical CNA to the diagnostic clone, while almost 90% of relapse clones evolved to acquire additional or some but not all CNA from the diagnostic clone [104], highlighting that relapse in ALL is variable and complex, but often a descendent of an ancestral clone to the principal de novo leukemia clone (reviewed in [105]).

Gene sequencing studies in 2011 [106] and 2012 [107], demonstrated 20% of total pediatric ALL relapse cases [106] and 60% of high-hyperdiploid relapse cases [107] harbor mutations in CREBBP, a transcriptional co-activator and histone acetyltransferase (HAT). Mutations in CREB BP have been shown to affect the regulation of glucocorticoid responsive genes. Because glucocorticoids are the cornerstone of B-ALL therapy, CREBBP mutations are thought to influence response to treatment and influence the likelihood for relapse [108]. In this regard, a recent study identified a selective enrichment of mutations in CREBBP and other epigenetic regulators (SETD2, KDM6A, MLL2, and MSH6) in relapsed and/or chemoresistant childhood B-ALL, which could suggest that epigenetic regulation plays a central role in clonal survival and ultimately chemotherapy resistance and relapse [97]. In addition to mutations in CREBBP and SETD2, relapse-specific mutations in the NT5C2 gene have been described in childhood B-ALL [109,110]. NT5C2 is a 5′ nucleotidase responsible for the inactivation of nucleoside-analog drugs, therefore conveying resistance to conventional therapeutic agents such as 6-mercaptopurine (6-MP) [109].

Although the true prognostic importance of these mutations at both diagnosis and relapse is unknown, therapies aimed at modulating epigenetic regulators in B-ALL is already in clinical development, as mentioned previously. Interestingly, CREBBP has also been shown to play a role in Wnt/β-catenin signaling, a pathway critical for the self-renewal of normal hematopoietic progenitor cells. In this regard, ICG-001, a novel small-molecule modulator of Wnt/β-catenin signaling that binds to CREBBP, leads to the differentiation of pre-B ALL cells and loss of self-renewal capacity, thereby sensitizing cells to chemotherapeutic treatment [111].

**Conclusions**

Advances in genetic technologies have enriched our current understanding of childhood B-ALL. Although conventional karyotyping and FISH technologies play a significant role in detecting numerous recurrent abnormalities, microarray-based techniques and NGS have revealed a multitude of new molecular targets that may prove useful in the diagnosis, risk stratification, and most importantly individualized treatment of this disease.

**Consent**

Written informed consent was obtained from the patient’s guardian/parent/next of kin for the publication of this report and any accompanying images.

**Competing interests**

The authors declare that they have no competing interests.

**Authors’ contributions**

All authors wrote, reviewed and approved the manuscript.

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