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Acute Lymphoblastic Leukemia: Genetic Events and Molecular Signatures

Yiguo Hu [1, 2]

[1] State Key Laboratory of Biotherapy, Collaborative Innovation Center for Biotherapy, West China Hospital, West China Medical School, Sichuan University, Chengdu, P. R. China.
[2]Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, U.S.A.
***Corresponding author:**
Yiguo Hu
State Key Laboratory of Biotherapy
West China Hospital, West China Medical School, Sichuan University
Chengdu, Sichuan 610041
P. R. China
Fax: (86)-28-85164060
Email: huyiguo99@gmail.com

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Abstract

Childhood or pediatric acute precursor B cell lymphoblastic leukemia (B-ALL) is the most prevalent hematological malignancy in children. Previous studies have revealed relationships between genetic lesions and the disease. In this review, I discuss our current understanding of the genetic lesions and molecular events in childhood B-ALL and the related therapeutic implications.

Keywords: ALL, Genetics, Translocations, Alterations, Mutations, Prognosis.

1. Introduction

Acute lymphoblastic leukemia (ALL), also called acute lymphocytic leukemia or acute lymphoid leukemia, is the most common malignancy in children. Approximately 25% of all pediatric cancers are ALL [1]. With recent advances in therapy, the five-year survival rate of children with ALL has greatly been improved to more than 85%, and recurrences are very rare [2].

The World Health Organization defines the diagnostic criteria for ALL as a precursor B cell acute lymphoblastic leukemia/lymphoma (B-ALL/B-LBL) or a T cell acute lymphoblastic leukemia/lymphoma (T-ALL/T-LBL). During the process of B and T cell differentiation, any genetic insult that blocks precursor B or T cell differentiation and drives their aberrant proliferation and survival may cause ALL. Of all the ALL cases, B-ALL comprises approximately 80-85%, while the remainder are T-ALL [3]. B-

ALL is an aggressive malignancy of small- to medium-size precursor B cells.

Although the primary genetic lesions that cause the vast majority of ALL are still unknown, a number of genetic abnormalities have been found in approximately 75% of childhood ALL cases, including chromosome number alterations, chromosome translocations that deregulate gene expression or create novel fusion genes, and specific gene mutations. Genetic alterations that are frequently detected in childhood B-ALL include translocations (such as t(12;21) [*ETV6/RUNX1*], t(9;22) [*BCR/ABL1*], t(1;19) [*TCF3/PBX1*], and *MLL*-involved t(4;11), t(9;11), t(11;19)), and mutations of genes involved in tumorigenesis or tumor suppression, apoptosis, and cell cycle regulation (such as *CRLF2*, *IKZF1*, *TP53*, and *FLT3*). Array and next generation sequencing technologies have advanced the classification of childhood ALL and elucidated new genetic targets involved in tumorigenesis and relapse [4-10]. Despite these advances, about 25% of ALL cases are not genetically classified [11].

Overall, genetic lesions initiate ALL or affect prognosis by altering expression of key transcription factors, chromatin-modifying factors, or oncogenesis signaling pathways, including the overexpression of oncogenes or the deletions of tumor suppressor genes. Here, I review the spectrum of genetic mechanisms of ALL progression and prognosis.

2. Translocations

2.1 ETV6-RUNX1 (t(12;21)

A translocation between chromosome 12 and 21, which fuses *ETV6* gene on chromosome 12 to *RUNX1* gene on chromosome 21, produces a new fusion protein, ETV6/RUNX1, formerly known as TEL/AML1 (Table 1). The t(12;21) translocation is detected in 20% to 25% of cases of precursor B-ALL but is rarely observed in T-ALL [12]. The t(12;21) occurs most commonly in children aged 2 to 9 years [13, 14], and Caucasian children have a higher incidence rate than Hispanic children [15]. Patients with the *ETV6/RUNX1* translocation are known to have a higher frequency of late relapses when compared to other forms of B-ALL [16, 17]. These relapsed patients have a better outcome than other relapsed leukemia patients [18, 19].

The ETV6-RUNX1 chimeric protein formed by the translocation event is comprised of the N-terminal portion of ETV6 protein and almost the entire RUNX1 protein. The fusion effectively enhances RUNX1 transcriptional repressor function [20]. Based on the studies of *ETV6/RUNX1* leukemogenic model, expression of the fusion protein alone is not sufficient to cause the disease [21, 22]. Additional secondary genetic alterations are required to trigger disease initiation and progression [23]. Gene profiling analysis revealed that ETV6-RUNX1 expression contributes to B-ALL by repressing gene expression [24].

Previous studies showed that RUNX1 can repress transcription of its target genes through recruitment of mSin3A/HDAC complexes [20]. The fusion with ETV6 converts RUNX1 to an HDAC-dependent, constitutive repressor and contributes to leukemogenesis by altering the expression pattern of RUNX1 target genes [20]. Target genes for those that are repressed by RUNX1 are distinct from those that are activated by RUNX1. RUNX1 needs to dimerize with CBFβ, a non-DNA-binding regulatory protein, to effectively bind to its DNA target sites [21, 25, 26].

Although the role the ETV6/RUNX1 fusion protein plays in leukemogenesis is not fully understood, many possible mechanisms have been suggested. For example, siRNA- or shRNA-mediated knockdown studies of the fusion gene indicate that *ETV6/RUNX1* expression supports the survival of leukemia cells by up-regulating heat shock proteins, survivin, and MDM2 and by activating the PI3K/AKT/mTOR signaling pathway [27-29].

2.2 Philadelphia chromosome

The Philadelphia chromosome (Ph) results from the translocation t(9;22). The *BCR/ABL1* fusion gene that is formed encodes an oncoprotein with constitutive tyrosine kinase activity. The Ph chromosome is present in approximately 10-15% of children ALL [11, 30].

It is more commonly detected in older children with precursor B-ALL [11].

Table 1: Genetic alterations in childhood B-ALL, prognosis, and involved signaling pathways

Genetic alterations	Common genes	Prognosis	Signaling pathways involved	References
Translocations				
t(12;21)(p13;q22)	*ETV6/RUNX1*	Good	mSin3A/HDAC complexes; *CBFβ*; PI3K/AKT/mTOR signaling; represses *RUX1* target genes	18;19;22;23
t(9;22)(q34;q11)	*BCR/ABL1*	Poor	*RAS*; *RAC*; *RAF-1*;*PI3k*; *BCL-2*; *NF-kB*; *JAK/STATs*	41,42, 43,44,45,46
t(4;11)(q21;q23)	*MLL/AF4*			
t(9;11)(p22;q23)	*MLL/MLLT3*	Poor	activating *Hox* genes; down-regulating *CDKN1B*; up-regulating *FLT3*; transcription elongation	59;60;61;62
t(11;19)(q23;p13)	*MLL/ENL*			
t(1;19)(q23;p13)	*TCF3/PBX1*	Intermediate	transcription factors; pre-BCR signaling; *JAK2* and *TP53* alterations; deletions of *IKZF1*	65;67;68;69
Genes alterations				
CRLF2, JAK2, and IKZF1 alterations	*CRLF2; JAK2, IKZF1*	Poor	overexpression of *CRLF2*; mutations of *JAK2*; deletions of *IKZF1*	3;70;71;73; 75-80
TP53 alterations	*TP53*	Poor	*TP53* mutations, deletion, or copy number alterations	88
PAX5 deletion or rearrangement	*PAX5*	unknown	co-incidentally with *ETV6* translocation and *JAK2* mutations	89-91
Ph-like ALL	*CRLF2; JAK2, IKZF1*	Poor	overexpression of *CRLF2*; mutations of *JAK2*; deletions of *IKZF1*;EBF1/PDGFRB signaling	8;27;28; 72-74;84; 85
Chromosome alterations				
Down sydrome (including iCAMP21)	*RUNX1; miR-802*	Poor	overexpression of *CRLF2*; mutations of *JAK2*; deletions of *IKZF1*;*RB1*;*CDKN2A*;*miR-802*;RUNX1 signaling	
High hyperdiploidy		Good		105-107; 109113
Hyperdiploidy (including near hyperdiploidy, low hyperdiploidy)		Poor	RTK signaling; RAS signaling; *IKZF3*; *TP53*, *RB1* and *IKZF2* alterations	116

According to previous studies, both the BCR and ABL1 portions in the BCR/ABL1 protein are essential for its signaling activity and the neoplastic transformation of cells. The extreme N-terminal portion of BCR encodes a coiled-coil oligomerization domain, which promotes BCR/ABL1 activation and is indirectly required for BCR/ABL1 cytoskeletal localization [31].

The C-terminal kinase portion of BCR binds to the ABL SH2 domain in a phosphotyrosine-independent manner [32]. This interaction is proposed to release the ABL kinase activity from negative regulation within BCR/ABL1. The tyrosine phosphorylation of BCR Tyr177 is required for BCR/ABL1 signal transduction pathways [33, 34]. For example, deletion of the BCR coiled-coil domain or mutation of Y177 to phenylalanine (Y177F) abolishes the BCR/ABL1 protein's capability to cause leukemia in mouse models [35]. These findings indicate that the full function of the coiled-coil region within BCR is required for BCR/ABL1 to cause leukemia. The phosphoserine-threonine-rich sequences between amino acids 192-242 and 298-413 in BCR are also essential for the oncogenic activation of BCR/ABL1 [32]. ABL1 tyrosine kinase activity is tightly regulated under physiological conditions [36]. The K1172 site in the ABL1 SH1 domain is essential for both of ABL1 and BCR/ABL1 kinase activity. Mutation of K1172 causes BCR/ABL1 to lose its kinase activity and most signal transduction functions [37]. Deletions of the SH2 domain has been shown to reduce the capability of BCR/ABL1 to transform fibroblasts [38]. The SH3 domain appears to play an inhibitory function. It is thought to bind to the proline-rich region at the center of ABL1 and cause a conformational change that leads to inhibition of its interaction with its substrates [39-41]. Syp83 and PTP1B form protein complexes with BCR/ABL1 and inhibit its phosphorylation [42]. Overexpression of PTP1B can impair BCR/ABL1 transformation activity in fibroblasts [43].

BCR/ABL1 expression triggers malignant transformation by altering target cell adhesion to stromal cells and extracellular matrix [44], constitutively activating mitogenic signaling [33], and reducing cell apoptosis [45]. These phenotypes are associated with enhanced expression and activation of many effectors, including RAS [46], RAC [46], RAF-1 [47], PI3K [48], BCL-2 [49], NF-□B [50], and STATs [51].

SRC family kinases play critical roles in Ph^+ B-ALL. BCR/ABL1 activates SRC family kinases by its kinase-independent activity [52]. Previous studies showed that in the absence of three members of SRC kinases (Hck, Lyn and Fgr), BCR/ABL1 could not sufficiently induce B-ALL [53]. Inhibition of SRC family kinases and BCR/ABL1 activities with dasatinib (a dual inhibitor of BCR/ABL1 and SRC family kinases) achieved therapeutic effect on Ph^+ B-ALL in a mouse model [52, 53]. Although Src family kinases play essential roles in BCR/ABL1 oncogenic activities on B-ALL, they alone are insufficient to transform B-lymphoid cells [54]. Historically, the Ph chromosome t(9;22) was associated with an extremely poor prognosis. Inhibitors of the kinase activity of BCR/ABL1 and SRC family members are effective in patients with Ph^+ B-ALL [55].

2.3 MLL translocations

Chromosome translocations involving the 11q23 region that contain the mixed lineage leukemia (*MLL*) gene are associated with approximately 8% of ALL cases [56]. These translocations include t(4;11), t(9;11), and t(11;19). ALL involving *MLL* gene rearrangement is generally associated with a high frequency of treatment-failure risk [57-60]. The t(11;19) translocation involving *MLL* and *MLLT1/ENL* is detected in both early B-ALL and T-ALL [61]. Patients with *MLL* gene rearrangement often have poor prognoses [61]. Interestingly, patients with deletions of the *MLL* gene have not been shown to have an adverse prognosis [62].

MLL is homologous to the *trithorax* gene of *Drosophilia melenogaster* and functions as a transcription factor and a DNA methytransferase. *MLL* is involved in translocations with >50 different genes [63, 64]. All the translocations involving the *MLL* gene affect the gene expression of the fusion genes during MLL, and this promotes leukemogenesis. The translocation of t(4;11) also deregulates the expression of the ALL fused gene on chromosome 4 (*AF4*), which is detected in 50–70% of infant leukemias. AF4 protein contains nuclear localization and guanosine triphosphate binding domains. MLL-AF4 fusion protein aberrantly activates *HOX* genes and contributes to leukemogenesis [65]. MLL-AF4 down-

regulates *CDKN1B* at its transcriptional level by binding the promoter region. This caused a reduction in the CDKN1B (p27kip1) protein level in an *in vivo* model [66]. Patients with *MLL* rearrangement also exhibit elevated expression of FMS-like tyrosine kinase 3 (FLT3) gene [67]. The t(11;19) translocation leads to the fusion of the *MLL* gene to 1/eleven-nineteen-leukemia (*MLLT1/ENL*). MLLT1/ENL is a part of the histone H3 Lys79 methyltransferase disruptor of telomeric silencing-like (Dot1L) complex, which plays a role in transcription elongation [68]. MLL-MLLT1 fusion protein aberrantly regulates the canonical Wnt-signaling pathway and contributes to childhood ALL [68].

2.4 TCF3/PBX1 translocation

The t(1;19) translocation is found in approximately 5% of childhood ALL cases. The t(1;19) translocation leads to the fusion of the *TCF3* gene on chromosome 19 to *PBX1* gene on chromosome 1 [69, 70]. The t(1;19) translocation is primarily associated with pre-B ALL [60]. The *TCF3*/*PBX1* [t(1;19)(q23;p13)] fusion is found in about 2-5% of cases of childhood *ALL [71]*. The t(1;19) translocation had been associated with inferior outcome in the context of antimetabolite-based therapy [72].

The fusion protein is comprised of the transactivation domains of TCF3 and a DNA binding domain of the homeobox protein PBX1. *TCF3* encodes E12 and E47 transcription factors, which are required for early lymphoid development. The translocation causes E12 and E47 protein levels to be reduced, and PBX1 to be converted into a transactivating factor [71, 73]. *TCF3*/*PBX1* functions as a potent oncogene. Gene profiling data showed that pre-BCR signaling genes are overexpressed in *TCF3*-*PBX1* positive B-ALL but not other cytogenetic subtypes B-ALL [74]. Mutations in the *JAK2* and *TP53* genes, as well as deletions of *IKZF1* gene, are also commonly observed in relapsed patients with *TCF3-PBX1* [75].

3. Cytogenetics/genomic alterations

3.1 Deregulations of CRLF2, JAK2, and IKZF1

Genomic alterations that leads to CRLF2 overexpression are detected in approximately 10% of B-precursor ALL cases [76, 77], and 60% of B-ALL in children with Down syndrome [77]. The *CRLF2* gene encodes a type I cytokine receptor that can heterodimerize with IL7 receptor subunit (IL7R). It is activated upon binding of its ligand, thymic stromal lymphopoietin (TSLP). Genomic rearrangements via intrachromosomal deletions centromeric or translocations to the immunoglobulin heavy chain locus lead to uncontrolled transcription of *CRLF2* [76-79]. Interestingly, *CRLF2* abnormalities are strongly associated with the presence of *IKZF1* deletions and *JAK* mutations [19, 77-80]

Approximately 25% of B-ALL patients harbor a *CRLF2*F232C mutation. This mutation occurs at the transition between the extracellular and transmembrane domains. *CRLF2*F232C promotes constitutive dimerization and ligand-independent signaling activity in the absence of both of TSLP and IL7R. Patients with wild-type *CRLF2 (*~40% of total B-ALL) often harbor a *JAK2R683G* mutation [78]. In these cases, *CRLF2* is believed to serve as a scaffold for the JAK proteins and their substrates. Strikingly, one report stated that 100% of B-ALLs harboring *JAK2* mutations also overexpress the *CRLF232C* mutation, suggesting that *CRLF2* serves an essential scaffold function for mutant JAK2 activity [81]. In the remaining B-ALL cases with *CRLF2* overexpression, neither *CRLF2* nor *JAK2* mutations are detected.

Growth factor-dependent myeloid and lymphoid cells can be transformed by CRLF2F232C alone, wild-type CRLF2 with mutant JAK2, or treatment of cells that express CRLF2/IL7R with TSLP. In each of the three scenarios, transformation renders the cells highly sensitive to JAK inhibitors. Only cells transformed by CRLF2/mutant JAK2 have constitutive JAK2 phosphorylation. This suggests that other JAK proteins, or additional kinases inhibited by these agents, mediate CRLF2F232C and canonical TSLP signaling [7].

Patients with B-ALL associated with overexpression of *CRLF2* have poor outcomes, indicating an unmet therapeutic need in this

population. Enzymatic inhibitors of JAK2 are being developed for clinical treatment of myeloproliferative neoplasms. These can also be used to treat B-ALL with rearrangements of *CRLF2* and other tumors with continually activated *JAK2* signaling. It is also important to mention that overexpression of *CRLF2* confers a *BCR/ABL*-like transcriptional signature [81]. This suggests a dependence on *CRLF2* signaling that could be targeted with kinase inhibitors. Several retrospective studies suggest that *CRLF2* alterations have poor prognoses [4, 76, 77, 79, 82].

IKZF1 deletions, including deletions of the entire gene and deletions of specific exons, are present in approximately 15% of B-ALL cases [83]. *IKZF1* deletions tend to occur in older children and are associated with higher WBC counts and poor outcomes [19, 84]. *KZF1* deletions are also present in a large proportion of *BCR/ABL1* cases [19, 85]. Moreover, ALL arising in children with Down syndrome appears to have elevated rates of *IKZF1* deletions [86]. *IKZF1* deletions are also common in cases with *CRLF2* genomic alterations and in Ph–like ALL [4, 11, 19]. Multiple reports have documented the adverse prognostic significance of an *IKZF1* deletion, and most studies have reported that this deletion is an independent predictor of poor outcome based upon multivariate analyses[4, 11, 19, 30, 87-90].

3.2 Ph-like ALL

Ph-like ALL refers to a small proportion of ALL cases that exhibit a gene expression profile similar to *BCR/ABL*1–positive ALL patients but are triggered by alternative genetic events [11, 30]. Ph-like occurs in 10% to 15% of pediatric ALL patients, who have a poor prognosis. Deletions or mutations of the *IKZF1 gene are* associated with approximately 40% of Ph-like ALL [9, 11, 30, 78, 90]. The hallmark of disrupted IKZF1 protein function is an activated kinase signaling cascade similar to *BCR/ABL*1–positive ALL. Still, about 50% cases contain *CRLF2* genomic alterations [79] and around 25% cases contain *JAK* mutations [80]. The remaining cases have been noted to have a series of translocations with a common theme of involving the *ABL1*, *JAK2*, *PDGFRB*, or *EPOR* genes [9]. Fusion proteins from these gene chimeras have been noted in some cases to transform cells but have responded to tyrosine kinase inhibitors both in vitro and in vivo [9], suggesting potential therapeutic strategies for these patient carrying these translocations. Point mutations in kinase genes, except for *JAK1* and *JAK2*, are rare in Ph-like ALL cases [78]. Transcriptome and whole-genome sequencing of Ph-like ALL identified more genetic alterations involving in several kinase signaling pathways, including *EBF1-PDGFRB*, which is comprised of the transcription factor *EBF1* (early B-cell factor 1) fused to the receptor tyrosine kinase *PDGFRB* (platelet-derived growth factor receptor β) [9, 91]. Several reports suggest that use of tyrosine kinase inhibitors to treat B-ALL patients harboring *EBF1-PDGFRB* rearrangement may be beneficial [92, 93].

3.3 TP53 alterations

TP53 alterations are detected in about 11% of patients with ALL. These alterations include amino acid mutations and/or copy number alterations. Approximately half of these alterations are observed at initial diagnosis, and half are newly observed at time of relapse [94]. Patients with *TP53* alterations are associated with poor outcomes [94].

3.4 PAX5 deletions and rearrangements

Genome-wide analysis reveals that mutations of PAX5 are observed in 32% of childhood B-ALL cases [84]. The *PAX5* gene encodes a transcription factor that belongs to the paired box gene family. It is necessary for normal hematopoietic development [95]. *PAX5* alterations also occur co-incidentally with other genetic alterations, such as *ETV6* rearrangements and JAK2 mutations [96]. A recent study results indicate that *PAX5 alterations may play a role in the in*herited susceptibility of B-ALL [97].

4. Chromosomal number alterations

4.1 Down syndrome

Children with Down syndrome (DS) (also called trisomy 21, due to affected individuals

owning a full or partial extra copy of chromosome 21) have higher risk of developing both ALL and acute myeloid leukemia (AML) [98, 99]. Approximately 2% to 3% of childhood ALL cases are associated with DS [100-102]. In childhood ALL with DS, *CRLF2* is highly expressed in about 50% to 60% of cases [80, 86, 103]. This is in stark contrast to what is observed in B-ALL children without DS, where over-expression of *CRLF2* is rarely detected (<10%) [19, 80, 103]. *IKZF1* deletions were observed in up to 35% of ALL patients with DS. Moreover, *IKZF1* deletions were associated with significantly diminished outcomes in these patients [86]. *JAK2* mutations were found in approximately 20% of ALL cases in children with DS [86, 103-106]. Nevertheless, there is no preliminary evidence to support the correlation between *JAK2* mutation status and 5-year event-free survival in ALL children with DS [103, 105].

A portion of ALL cases have been associated with a specific genomic alteration known as intrachromosomal amplification of chromosome 21 (iAMP21), which presents three or more copies of the *RUNX1* gene within amplified regions on chromosome 21 [107, 108]. This region contains *RUNX1* gene, *miR-802*, and genes responding to DS. Similar as ALL in DS, iAMP21 leukemia patients often exhibit concomitant genetic alterations of *IKZF1*, *CDKN2A*, *PAX5*, *ETV6*, and *RB1* [109]. Overexpression of *CRLF2* driven by the promoter of *P2RY8* is observed in 35% of childhood ALL associated with iAMP21 [110]. iAMP21 occurs in approximately 2% of B-ALL in older children and is associated with poorer outcomes and high risk for relapse [109].

4.2 High hyperdiploidy

Leukemia cells possessing 51 to 65 chromosomes per cell, or a DNA index greater than 1.16, are defined as high hyperdiploidy. High hyperdiploidly occurs in 20% to 25% of cases of B- ALL but very rarely in T-ALL [111]. This condition can be evaluated by measuring the DNA content of cells (DNA index) or by karyotyping. High hyperdiploidy is usually associated with clinically favorable outcomes and have a better prognosis [111-113].

Patients with trisomies of chromosomes 4, 10, and 17 (triple trisomies) have been shown to have particularly favorable outcomes, as demonstrated by the analyses from Pediatric Oncology Group (POG) and Children's Cancer Group (CCG) [114]. POG data also suggest that patients with trisomies of 4 and 10, regardless of their chromosome 17 status, have an excellent prognosis [115].

Near triploidy (68–80 chromosomes) and near tetraploidy (>80 chromosomes) are rarely found in ALL patients and appear to be biologically distinct from high hyperdiploidy [116]. It has not been determined whether near triploidy and tetraploidy are associated with a favorable prognosis [116, 117]. If patients with high hyperdiploidy are also associated with chromosome translocation involving oncogene overexpression, these patients commonly have poor outcomes. For instance, one study showed that approximately 8% of Ph^+ patients also had high hyperdiploidy [118], and the outcome of these patients was poor when compared to Ph^- high hyperdiploid patients.

4.3 Hypodiploidy

B-ALL patients with fewer than the normal number of chromosomes are defined as hypodipoidy. Examples include near haploid (24 to 29 chromosomes), low hypodiploid (33 to 39 chromosomes), high hypodiploid (40 to 43 chromosomes), and near diploid (44 chromosomes) [119]. Compared to non-hypodiploid cases, patients with near haploid or low hypodiploid have an increased risk of treatment failure [119, 120]. Overall, patients with fewer chromosomes have a worse outcome than those with more chromosomes [119].

The recurring genomic alterations that occur in cases of hypodiploidy differ between near haploid and low hypodiploid ALL cases [121]. Receptor tyrosine kinase (RTK) signaling, RAS signaling, and *IKZF3* are more commonly found in near haploid ALL. *TP53*, *RB1*, and *IKZF2* genetic alterations are more commonly found in low hypodiploid ALL [121].

Overall, a number of recurrent chromosomal abnormalities have been shown to have prognostic significance, especially in B-ALL.

Some chromosomal abnormalities are associated with more favorable outcomes, such as high hyperdiploidy (51–65 chromosomes)

4.4 Treatment and relapsed ALL

Chemotherapy is a first choice treatment for most ALL cases. The early response to chemotherapy by patients has strong prognostic significance. There are three phases of chemotherapy for ALL: induction, consolidation, and maintenance. Most patients also will be treated with intrathecal chemotherapy to help treat or prevent disease in the central nervous system (CNS). For some patients with ALL, a long-term course of chemotherapy is required to achieve remission. For these patients, bone marrow transplantation may offer a better alternative to achieve a cure or long-term remission. In these cases, a bone marrow or cord blood transplantation procedure is preceded by chemotherapy, with or without radiation, to destroy the diseased cells and bone marrow. Hematopoietic stem cells (HSCs) are then transplanted to replace disease-forming cells with healthy ones.

Induction therapy brings about a remission in most patients, but over time, some patients will relapse. Patients that relapse after chemotherapy can be treated with different chemotherapy drugs and/or more intense doses. For these patients, a HSC transplant is necessary, as a second round of chemotherapy is less likely to bring about long-term remission. In such cases, a bone marrow or cord blood transplant may be the best option for a cure or long-term remission.

Conclusions

Currently, genetic alterations in B-ALL have been well defined, but much work remains to be done. Next-generation sequencing of ALL genomes will help to identify mutations at nucleotide-level resolution and provide the clues necessary to identify novel genes associated with ALL.

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