Chapter 2
Acute Lymphoblastic Leukemia

Daisuke Tomizawa and Nobutaka Kiyokawa

Abstract Acute lymphoblastic leukemia (ALL) accounts for a quarter of malignant neoplasms in children and adolescents. With continuous effort on developing risk-stratified multi-agent chemotherapy through cooperative clinical trials worldwide, survival rate of childhood ALL increased from less than 10% in the 1960s to approximately 90% nowadays. Recent advance in genomic analyses is rapidly increasing our understanding of the pathobiology of ALL, which may lead to a development of novel molecular targeted therapy and finally to overcome the disease in future.

2.1 Introduction

Acute lymphoblastic leukemia (ALL) is a malignant disorder of lymphoid progenitor cells and the most common type of malignant neoplasms in children and adolescents. Development of multi-agent chemotherapy and risk stratification based on leukemia biology and early treatment response have improved the overall cure rate of childhood ALL to 80% or higher, which is one of the most successful story in the history of human medicine (Table 2.1) [1–12]. In this chapter, advances in the pathobiology and clinical management of ALL in children will be described.
<table>
<thead>
<tr>
<th>Study group</th>
<th>Trial</th>
<th>Years</th>
<th>ALL subtypes</th>
<th>No. of patients</th>
<th>Age</th>
<th>EFS, % (year)</th>
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<td>66.0 (4)</td>
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*EFS* event-free survival, *OS* overall survival
2.2 Epidemiology

Registry of the Japanese Society of Pediatric Hematology (currently, the Japanese Society of Pediatric Hematology and Oncology) covers more than 90% of the population under age 20 with hematological malignancies in Japan. 2463 patients are diagnosed as ALL between 2006 and 2010, that is, approximately 500 new cases are diagnosed every year [13]. As annual number of childhood cancer in Japan is estimated as 2000–2500, ALL accounts for 20–25% of all childhood cancers and 72% of all childhood leukemias. Male/female ratio is 1.3:1, and the peak incidence of ALL occurs between 2 and 5 years old. Immunophenotypically, 86% is B-cell precursor, 11% is T cell, 2% is mature B cell, and 1% is unknown.

Several inherited syndromes are known to be associated with an increased risk of ALL. Among all, most well recognized is Down syndrome which is 10–20 times more likely to develop ALL compared to non-Down syndrome children [14]. In addition, several rare germline mutations, such as PAX5 and ETV6, have been identified to be a genetic predisposition to B-ALL in familial leukemia kindreds [15, 16]. Although it has been long recognized that majority of ALL patients have no apparent clinical inherited factors, recent genome-wide association studies have identified several germline single-nucleotide polymorphisms (SNPs) in several genes (including IKZF1, ARID5B, CEBPE, CDKN2A, GATA3, etc.) that are associated with significantly higher risk of developing ALL [17–20].

Environmental factors, such as ionizing radiation, electromagnetic field, certain diets (e.g., bioflavonoids), seem to have little association in most of the ALL cases [21–23]. However, two infection-based hypotheses, Greaves’ “delayed infection” hypothesis and Kinlen’s “population-mixing” hypothesis that childhood ALL arise as a consequence of an abnormal immune response in susceptible individuals to common infections, are well supported by epidemiological data [24, 25].

2.3 Pathobiology

It is considered that ALL occurs as a consequence of malignant transformation of an abnormal single lymphoid progenitor cell via multi-step genetic alterations. It is not entirely clear how and when these genetic events take place. However, it is believed that causation of ALL is by chance, and normal allelic variation in inherited genes or inherited ALL predisposing syndromes in a small portion of cases, and exposures to various exogenous and endogenous factors all contribute to leukemogenesis [26].

Identification of genetic abnormalities plays a pivotal role in understanding the biology and treatment of ALL. Cytogenetic analysis by karyotyping which was established in 1960s and by fluorescence in situ hybridization (FISH) in 1980s is still necessary in the modern diagnostic evaluation in ALL. However, newer array-based technologies enabled us to analyze global gene expression, DNA copy numbers, SNPs, and methylation status. In addition, recent advance in genome-wide sequencing which include whole-genome sequencing, transcriptome sequencing
(RNA-seq), and whole-exome sequencing have helped us to approach the true nature of ALL. Although these novel genomic techniques are still used as research discovery tools, it is expected that they would be increasingly utilized for clinical applications in the near future.

Recurrent genetic alterations in ALL include aneuploidy (changes in chromosome number) and structural abnormalities. The molecular and clinical features of specific alterations are discussed below (Fig. 2.1).

### 2.3.1 Aneuploidy

Ploidy (number of chromosomes of a cell) could be determined by direct counting of the chromosome numbers in a metaphase karyotype preparation by G-band technique. Clinically, high hyperdiploidy is defined as chromosome number greater than 50 and hypodiploidy as less than 45 chromosomes. DNA index (DI) is an alternative method of measuring DNA content by flow cytometry; DI is 1.0 in normal diploid cells, while it is 1.16 or higher in high hyperdiploid cases.

#### 2.3.1.1 Hyperdiploidy

High hyperdiploidy accounts for 20–30% of childhood ALL. There is a distinct pattern of chromosomes gained at each modal number of chromosomes: most commonly gained is chromosome 21 (ch21), followed by ch4, chX, ch10, ch6, ch14, ch18, and ch17 [27]. Previous clinical studies have demonstrated that certain combination of gained chromosome are associated with better prognosis: “double
trisomy” of ch4 and ch10 in the Pediatric Oncology Group (POG); “triple trisomy” of ch4, ch10, and ch17 in Children’s Oncology Group (COG); trisomy of ch11 and ch17 in the Tokyo Children’s Cancer Study Group (TCCSG) [27–29]. Although prognostic significance of specific gained chromosomal combination is inconsistent among different study groups, high hyperdiploidy itself is associated with CD10-positive B-cell precursor phenotype, low leukocyte (WBC) count, younger age at diagnosis, and excellent prognosis.

2.3.1.2 Hypodiploidy

In contrast, hypodiploidy accounts for only 1% of childhood ALL and is a strong predictor of poor prognosis [30, 31]. Recent genomic analysis has identified TP53 mutations in 91% of low-hypodiploid ALL (32–39 chromosomes) [32]. Surprisingly, the mutation was also present in germline in 43% of the cases, which is a hallmark of Li-Fraumeni syndrome. Occasionally, there are cases with “masked hypodiploidy,” which occurs as a result of doubling of a hypodiploid clone [33]. Caution is needed because they do not appear to be different from non-masked hypodiploidy in clinical and prognostic features but could be misdiagnosed as “hyperdiploidy” harboring opposite prognosis.

2.3.2 Structural Chromosomal Abnormalities

Structural chromosomal abnormalities, most commonly translocations, are frequently observed in childhood ALL. They are considered to be initiating events in leukemogenesis. Several occur in utero, nearly 100% of MLL-AF4, similar to hyperdiploid cases, and 75% of ETV6-RUNX1, but none of TCF3-PBX1 [34]. This is supported by evidences of the high rate of concordance of leukemia in monozygotic twins and the prenatal origin of ALL demonstrated directly by the detection of unique fusion in neonatal blood spots on Guthrie cards who later developed ALL [35, 36]. Generally, two functional classes of translocations exist. One is juxtaposition of oncogenes with regulatory regions of actively transcribed genes causing its dysregulated target gene expression, such as c-MYC to immunoglobulin gene in Burkitt’s lymphoma/leukemia. Another is fusion of the genes at the translocation breakpoints to encode a novel chimeric protein with oncogenic function, ETV6-RUNX1, TCF3-PBX1, BCR-ABL1, rearrangements of mixed-lineage leukemia (MLL or KMT2A) gene, etc.

2.3.2.1 ETV6-RUNX1 (TEL-AML1)

t(12;21)(p13;q22.1) accounts for 15–20% of childhood ALL. It is cryptic in most cases and could be detected by FISH or real-time quantitative polymerase chain reaction (PCR). The translocation results in fusion of two hematopoietic transcription factor genes, ETV6 (formerly known as TEL) and RUNX1 (AML1).
ETV6-RUNX1 appears to arise in utero, but the fusion solely itself is not sufficient to cause the leukemia and subsequent events are required to full progression [37]. Children with ETV6-RUNX1 ALL is associated with excellent outcome similar to high hyperdiploid ALL [38].

2.3.2.2 TCF3-PBX1 (E2A-PBX1)

\(t(1;19)(q23;p13.3)\) is the second most common translocation and accounts for 5% of childhood ALL. The translocation results in the fusion of two transcription factor genes, TCF3 (formerly known as E2A) and PBX1. TCF3-PBX1 ALL appears to be pre-B cell phenotype with positive cytoplasmic \(\mu\). It was once associated with poor prognosis but has lost its prognostic significance in the context of modern ALL chemotherapy especially that contains high-dose methotrexate [39]. However, TCF3-PBX1 is associated with higher risk of central nervous system (CNS) relapse [40].

There is a rare subtype of TCF3 gene involved ALL with fusion partner hepatic leukemia factor (HLF) gene which arise from \(t(17;19)(q22;p13)\). TCF3-HLF only occurs in less than 1% of childhood ALL but has unique characteristics such as hypercalcemia, an increased risk of disseminated intravascular coagulation (DIC), and, moreover, very poor prognosis [41].

2.3.2.3 KMT2A (MLL) Gene Rearrangements

KMT2A (MLL) gene, located at chromosome band 11q23, encodes a histone methyltransferase that is involved in epigenetic regulation of blood cell development via expression of multiple Hox genes [42]. Rearrangements of MLL occur as a result of balanced chromosomal translocations that fuse the MLL gene to one of more than 70 known partner genes. The most common in ALL is MLL-AF4 (KMT2A-AFF1) derived from \(t(4;11)(q21;q23)\), followed by MLL-ENL (KMT2A-MLLT1) from \(t(11;19)(q23;p13)\), and MLL-AF9 (KMT2A-MLLT3) from \(t(9;11)(p22;q23)\) [43]. MLL rearrangement is particularly common in ALL in infants (age <1 year old), which accounts for nearly 80% of the cases and associated with CD10-negative pro-B cell phenotype, high leukocyte count at diagnosis, and very poor prognosis (Table 2.2) [44–48]. ALL with MLL rearrangements have very few additional somatic mutations, one of the lowest of any sequenced cancers [49].

2.3.2.4 BCR-ABL1

\(t(9;22)(q34;q11.2)\) results in formation of Philadelphia (Ph) chromosome, which is one of the first leukemic translocations described. Ph encodes BCR-ABL1, an activated tyrosine kinase. It is the most common translocation in adult ALL (25% of the cases) but less common in children (less than 5% of the cases). Ph-positive (Ph+) ALL was one of the most difficult to cure ALL with only 30–40% event-free survival (EFS) rate despite intensive chemotherapy and allogeneic hematopoietic stem cell
Table 2.2 Results of the recently reported trials for infants with ALL

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<th>ALL subtypes</th>
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<th>No. of patients received Allo-SCT in 1CR</th>
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<td>Koh et al. [48]</td>
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CCG Children’s Cancer Group, COG Children’s Oncology Group, JILSG Japan Infant Leukemia Study Group, JPLSG Japanese Pediatric Leukemia/Lymphoma Study Group

CR complete remission, EFS event-free survival, HSCT hematopoietic stem cell transplantation, MLL-g germline MLL gene, MLL-r rearranged MLL gene, OS overall survival

transplantation [50]. However, introduction of imatinib, a selective tyrosine kinase inhibitor (TKI), has revolutionized the therapy for Ph+ ALL (Table 2.3) [51–54].

2.3.2.5 Philadelphia (Ph)-like ALL

Ph-like or BCR-ABL1-like ALL is a newly recognized entity, harboring similar gene expression profile to Ph+ ALL but without BCR-ABL1 fusion gene [55, 56]. Recent genomic analyses have revealed diverse range of genetic alterations that activate tyrosine kinase signaling in 90% of the cases. The most commonly identified alterations are rearrangements involving ABL1, ABL2, CRLF2, CSF1R, EPOR, JAK2, NTRK3, PDGFRB, PTK2B, TSLP, or TYK2 and sequence mutations involving
Table 2.3 Results of the recently reported trials for children with Philadelphia chromosome positive ALL in the TKI era

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<th>Subgroups</th>
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<th>No. of patients received Allo-SCT in 1CR</th>
<th>DFS, % (year)</th>
<th>OS, % (year)</th>
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<td>All</td>
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<td>72.1 (4)</td>
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<td>Good-risk with imatinib</td>
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<td>37</td>
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<td>32</td>
<td>61.7 (4)</td>
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<td>Poor-risk</td>
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<td>COG</td>
<td>AALL0031 (cohort 5)</td>
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<td>Chemotherapy + imatinib</td>
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<td>70 (5)</td>
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<td>Schultz et al. [52]</td>
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<td>ALL-Ph04</td>
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<td>All</td>
<td>42</td>
<td>26</td>
<td>54.1* (4)</td>
<td>78.1 (4)</td>
<td>Manabe et al. [53]</td>
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</table>

COG Children’s Oncology Group, JPLSG Japanese Pediatric Leukemia/Lymphoma Study Group
Allo-SCT allogeneic hematopoietic stem cell transplantation, ICR first complete remission, DFS disease-free survival, OS overall survival, BMT bone marrow transplantation

FLT3, IL7R, or SH2B3 [57]. Importantly, “ABL-class” kinases (ABL1, ABL2, CSF1R, and PDGFRβ) could be targeted with TKI such as imatinib and dasatinib and alterations that activate JAK-STAT signaling (JAK1, JAK2, JAK3, CRLF2, EPOR, TSLP, and IL7R) with JAK inhibitors [58].

2.3.2.6 iAMP21

ALL with intrachromosomal amplification of chromosome 21 (iAMP21) is characterized by amplification of a portion of ch21, which could be detected by FISH analysis using a probe for the RUNX1 gene that reveals five or more copies of the gene (or three extra copies on a single abnormal ch21 in metaphase FISH) [59]. It occurs in 2% of childhood ALL and is associated with poor prognosis [60].

2.3.2.7 IKZF1, CRLF2, and JAK

Except for MLL-rearranged ALL in infants, many of the subtypes have multiple additional genetic alterations in general. These alterations commonly target genes encoding proteins involved in cell signaling, tumor-suppression functions, and lymphoid differentiation.
Most commonly targeted genes involved in B-lymphoid development are *PAX5* and *IKZF1* that are mutated in 31% and 15% of children with B-ALL, respectively. Notably, recurrent deletions and inactivating mutations in *IKZF1*, which encodes the hematopoietic transcription factor IKAROS, are associated with very poor prognosis in B-ALL [56]. Genetic alterations of *IKZF1* occur more frequently in high-risk cases, including Ph+ ALL and Ph-like ALL [62].

Cytokine receptor-like factor 2 (CRLF2) forms a heterodimeric cytokine receptor with interleukin-7 receptor α (IL7Rα) that mediates B-cell precursor proliferation and survival via activation of downstream JAK/STAT pathways. Rearrangements of *CRLF2* gene as *IGHa-CRLF2* or *P2RY8-CRF2* result in CRLF2 overexpression and found in 5–8% of pediatric ALL, 10–15% of adult ALL, and more than 50% of Down syndrome ALL [63–65]. It has been reported as poor prognostic factor but still controversial.

*JAK2* mutations are found in 18–35% of Down syndrome ALL cases and 11% of non-Down high-risk *BCR-ABL1*-negative ALL cases [66]. The mutation cause constitutive JAK-STAT activation. There is overlap among *IKZF1* and *CRLF2* alterations [67].

### 2.3.2.8 ETP-ALL

In contrast to genetic alterations discovered in B-ALL, many of the genetic alterations in T-ALL have not been found to have prognostic value yet. However, one subset of T-ALL with unique biology, early T-cell precursor (ETP) ALL that accounts for 10–15% of pediatric T-ALL, is recognized as a new entity [68]. ETP-ALL was originally identified by its unique gene expression pattern and immunophenotype with very early T-cell progenitor features: absence of T-cell markers CD1a and CD8; dim or absent CD5; combined with cytoplasmic, but not surface, CD3; and positive for one or more myeloid/stem cell markers (CD34, CD117, HLA-DR, CD13, CD33, CD11b, or CD65). By whole-genome sequencing, gene mutations similar to myeloid leukemias including RAS signal pathways were identified [69].

### 2.3.2.9 Genetic Alterations at Relapse

Genomic studies of matched diagnosis and relapsed ALL sample pairs have revealed that only 42% of the cases had evolved from diagnosis clone (8% was same and 34% was clonal evolution from diagnosis clone), but majority (52%) was rather evolved from ancestral clones, and the remaining 6% was genetically distinct secondary leukemia [70]. By further sequencing studies, mutations including *CREBBP*, *TP53*, and *NT5C2* were identified [71–74]. Focal deletion and sequence mutations in *CREBBP* were found in 19% of children with relapsed B-ALL. The mutation causes impaired histone acetylation and transcriptional regulation of *CREBBP* targets, thus impairing the normal *CREBBP*-mediated transcriptional response to glucocorticoids and possibly results in steroid therapy resistance of the relapsed clone.
NT5C2 encodes as 5’-nucleotidase enzyme that is involved in metabolisms of 6-mercaputopurine. Its mutation causes increased enzyme activity and resistance to nucleoside analog therapy. TP53 alterations were identified in 12% of relapsed B-ALL and 6% of relapsed T-ALL cases in the Berlin-Frankfurt-Münster (BFM) study, which was enriched compared to the initial diagnosis samples and was associated with poor response to the therapy and inferior outcome.

2.4 Clinical Management

2.4.1 Clinical Presentation

Anemia, thrombocytopenia, and/or neutropenia are typically observed among ALL patients, which reflect failure of normal hematopoiesis; pallor, fatigue, bleeding (e.g., petechiae or purpura), and fever (usually as leukemia-related rather than infection) are often present. Hepatosplenomegaly, lymphadenopathy, and bone pain are frequently manifested. Although not common at the time of initial diagnosis, involvement of extramedullary sites such as CNS, testis, and skin might be present simultaneously. Duration of these symptoms may vary from days to months; however, one may face life-threatening “oncologic emergency” situation at initial presentation, superior vena cava syndrome/superior mediastinal syndrome in T-ALL patients, disseminated intravascular coagulation, tumor lysis syndrome (renal failure, elevated levels of serum uric acid, potassium, and/or phosphate), and CNS hemorrhage or thrombosis induced by hyperviscosity syndrome, both often associated with hyperleukocytosis (>100,000/μL in peripheral blood), etc.

2.4.2 Diagnostic Procedures

Diagnosis of ALL is established by morphological detection of more than 25% leukemic blasts in bone marrow by aspirated bone marrow smears. It is preferable to perform bone marrow biopsy in case of dry tap. In addition to morphological examination, immunophenotyping, karyotype, and genetic analyses are essential for ALL diagnosis.

Evaluation of extramedullary leukemia, especially involvement in CNS, is necessary. CNS status at diagnosis is defined as follows: CNS1, no detectable blast cells in cerebrospinal fluid (CSF); CNS2, fewer than five leukocytes per μL with detectable blasts; and CNS3, the presence of overt CNS leukemia [75]. Although CNS2 had an adverse prognostic impact on CNS relapse in previous pediatric ALL trials, it has lost its prognostic effect in contemporary trials that include more effective systemic and CNS-directed treatment. Traumatic lumbar puncture at diagnosis is an issue, because it could cause iatrogenic CNS leukemia by mixing patients’ CSF with bloods with abundant circulating blasts, thus lead to increased risk of
CNS relapse [76, 77]. In order to reduce the risk of traumatic lumbar puncture at diagnosis, correction of thrombocytopenia and coagulopathy prior to the procedure, keeping patients steady under deep sedation, and immediate administration of intrathecal therapy (e.g., methotrexate) after the collection of CSF are strongly recommended [78].

2.4.3 Treatment

Principle of ALL treatment is based on “total cell kill” theory, an attempt to eradicate every leukemic blast inside the patient’s body. This is mostly accomplished by multi-agent combination chemotherapy including CNS-directed therapy. Hematopoietic stem cell transplantation (SCT) is additionally combined in a small portion of cases with very high risk of relapse. Risk stratification, means of optimizing therapy for the patients by evaluating relapse risk with known prognostic factors, has also contributed to improve survival rate in children with ALL.

Treatment algorithm of pediatric ALL proposed in the guideline of the Japanese Society of Pediatric Hematology and Oncology is shown in Fig. 2.2. Mature

![Algorithm of treatment for children with ALL. Ph+ ALL Philadelphia chromosome-positive ALL, PPR prednisone poor responder, PGR prednisone good responder, WBC leukocyte count, CNS central nervous system, MRD minimal residual disease, TKI tyrosine kinase inhibitor, Allo-SCT allogeneic hematopoietic stem cell transplantation. [Adapted from Clinical Guideline for Pediatric Leukemia and Lymphoma (ver.3) Japanese Society of Pediatric Hematology and Oncology]](image-url)
B-cell ALL or Burkitt ALL, usually presented with French-American-British (FAB) L3 blasts, surface antigen expression of kappa or lambda detected by flow cytometry, and presence of cytogenetic abnormalities of t(8;14)(q24;q32), t(2;8) (p11-p12;q24), or t(8;22)(q24;q11), should be treated separately with short intensive non-Hodgkin lymphoma-oriented chemotherapy [79–81]. Ph+ ALL with t(9;22)(q34;q11.2) or \textit{BCR-ABL1} is currently treated with TKI-combined chemotherapy, thus should be treated independently [51, 52, 54]. Infants (age at diagnosis below 1 year old) with ALL are another special subgroup requiring specific care [44, 48, 82]. The rest of the children with ALL should be treated with appropriate risk-stratified therapies.

\subsection{2.4.3.1 Prognostic Factors}

Prognostic factors are the factors that are predictive of disease outcome and are usually used to tailor therapy (“risk-stratified therapy”) with the intention to minimize toxic events for patients with better prognosis and to maximize the treatment effect for patients with poorer prognosis. The currently well-recognized prognostic factors could be categorized into three groups.

\subsubsection{Clinical Features at Initial Diagnosis}

WBC count, which reflects tumor burden, and age at initial diagnosis have been traditionally used as most reliable prognostic factors. The NCI-Rome criteria defined patients with WBC <50,000/μL and age 1–9 years old as “standard risk” and patients with either WBC ≥50,000/μL or age ≥10 years old as “high risk” [83]. Even in the context of modern therapies, WBC count and age continue to be significant prognostic factors especially in B-ALL; however, its importance became limited in T-ALL. Infants younger than 1 year old are a special group with worse prognosis; among infants, younger age at diagnosis (e.g., age <6 months old) is an independent poor prognostic factor [44].

\subsubsection{Biologic and Genetic Features}

As discussed in the pathobiology section, a number of recurrent genetic alterations are associated with the outcome of children with ALL. High hyperdiploidy and \textit{ETV6-RUNX1} are associated with a favorable outcome. In contrast, hypodiploidy, \textit{MLL} rearrangement, \textit{BCR-ABL1}, and recently Ph-like ALL and ETP-ALL are associated with high-risk clinical features and a poor outcome.
Early Treatment Response

After 4–6 weeks of initial remission-induction chemotherapy, 97–98% of the children with ALL achieve morphological remission. In other words, only 2–3% of the cases experience induction failure, and their prognosis is poor with overall survival rate of only 32% in a large international retrospective cooperative study [84].

Early clearance of leukemic blasts within 1–2 weeks of initial induction is predictive of good prognosis. “Prednisone response” established by the BFM group, evaluating residual leukemic blasts in peripheral blood following 7 days of prednisone monotherapy with single intrathecal methotrexate injection, clearly segregates good responder (≥1000 blasts/μL, 91% of the pediatric ALL cases) with 87% EFS rate and poor responder (<1000 blasts/μL, 9% of the cases) with 55% EFS rate in 6 years [85]. Because of the principles that children with ALL should be treated with combination chemotherapy and that response should be evaluated in bone marrow, Children’s Cancer Group (CCG) defined rapid early responder (25% or fewer bone marrow blasts) and slow early responder (more than 25% bone marrow blasts) evaluated on days 8 or 15 of induction therapy that was also predictive of favorable and poor prognosis, respectively [86].

In recent years, measurement of minimal residual disease (MRD) using flow cytometry detecting aberrant combinations of leukemic cell-surface antigen or PCR amplification targeting leukemic clone-specific rearrangement of immunoglobulin heavy chain (IgH) or T-cell receptor (TCR) genes is superseding morphological response [87, 88]. These techniques are able to detect submicroscopic levels of residual leukemia, one leukemia cell per 10^3–10^4 normal cells in flow-MRD and one per 10^4–10^5 cells in PCR-MRD. With MRD-guided therapy, outcome of poor prognostic subgroups such as Ph-like ALL or ETP-ALL could be significantly improved [89, 90]. Thus, MRD is currently utilized as the most powerful tool to predict prognosis in childhood ALL therapy. In German and Italian cooperative study, Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP)-BFM ALL 2000, all the children with ALL were stratified to either of the three risk groups (low-, intermediate-, and high-risk) only by treatment response indicators: prednisone response, state of bone marrow remission after the end of induction, and IgH/TCR-targeted PCR-MRD results after end of induction and end of early consolidation [1]. This study showed different MRD kinetics relevant to the outcome between B-ALL and T-ALL patients: significantly higher proportion of T-ALL patients showed slower blast clearance than B-ALL patients, and risk of relapse was strongly associated with MRD level of end of early consolidation in T-ALL, while it was with MRD level of end of induction in B-ALL [2]. In approximately 10% of the cases, the PCR target cannot be identified, thus MRD is not measurable. In contrast, flow-MRD is applicable to larger proportion of patients with other advantages such as less expensiveness and faster availability. In fact, study groups in North America (e.g., COG, St. Jude Children’s Research Hospital) are using flow-MRD in their ALL trials [91]. However, newer
technologies such as next-generation sequencing-based methods identifying MRD with specific molecular signatures might solve all the technical issues problematic in the current methods such as availability, sensitivity, and rapidity [92].

### 2.4.3.2 Chemotherapy for ALL

Chemotherapy is a mainstay of ALL treatment. History of ALL chemotherapy begins from the first description of temporary remission of leukemia by folic acid antagonist, aminopterin, reported by Sidney Farber in 1948 [93]. Since then, most of the chemotherapeutic agents that are still in current clinical use, such as 6-mercaptopurine, methotrexate, prednisone, dexamethasone, cyclophosphamide, vincristine, cytarabine, L-asparaginase, and daunorubicin, have been developed before the 1970s. By the use of these conventional drugs, along with recognition and introduction of multi-agent combination chemotherapy, CNS-directed therapy, post-induction intensification, and risk stratification, through step-wise efforts of clinical trials worldwide, have improved the outcome of children with ALL (Table 2.1).

ALL chemotherapy typically spans 2–3 years and consists of three phases; remission-induction therapy and post-remission therapy consisted of consolidation and maintenance therapy. CNS-directed therapy is included throughout the therapy except maintenance phase.

**Remission-Induction Therapy**

The aim of remission-induction therapy is to achieve morphological remission, defined as less than 5% blasts in bone marrow with regeneration of normal hematopoiesis and no evidence of residual extramedullary disease, which could be achieved in 97–98% of the cases. The therapy generally spans 4–6 weeks and consists of glucocorticoid (prednisone or dexamethasone), vincristine, asparaginase, intrathecal therapies (methotrexate with or without cytarabine and corticosteroid), and optional use of anthracyclines (the most common, daunorubicin).

Prednisone (40–60 mg/m² per day) is the most commonly used glucocorticoid; however, substitution with dexamethasone has been of strong interest, because dexamethasone has five- to sixfold higher cytotoxic potency than prednisone in *in vitro* assays, longer plasma half-life, and better cerebrospinal fluid penetration. In the CCG study for NCI standard-risk ALL and the UK study comparing prednisone (40 mg/m² per day) versus dexamethasone (6 or 6.5 mg/m² per day) during induction showed higher EFS rate in the dexamethasone arm mainly owing to lower CNS relapse [94, 95]. However, in the Japanese TCCSG study for non-high-risk ALL comparing prednisone (60 mg/m² per day during induction and 40 mg/m² per day during post-remission) and dexamethasone (8 mg/m² per day during induction and 6 mg/m² per day during post-remission) showed no difference in remission, EFS, OS, and CNS relapse rates [96]. In the AIEOP-BFM ALL 2000 trial, all the patients were randomized to
receive either 60 mg/m² per day of prednisone or 10 mg/m² per day of dexamethasone [97]. In this study, dexamethasone led to significant reduction in relapse risk, showing largest effect on extramedullary relapse, but was counterbalanced by significant higher induction-related death rate in the dexamethasone arm, thus led to no survival difference. However, subgroup analysis showed higher survival advantage of dexamethasone arm in T-ALL patients with good early response to prednisone prophase. Finally, in the COG trial for NCI high-risk B-ALL, dexamethasone (10 mg/m² per day) for 14 days showed better EFS rate in younger age (1–9 years old) patients who received high-dose methotrexate in second randomization compared to prednisone (60 mg/m² per day) for 28 days but showed no benefit for older patients (10 years old or older) with excess rate of osteonecrosis [98]. Although glucocorticoid is an essential key drug for ALL treatment, it is associated with adverse events, such as infection, osteonecrosis, psychosis, etc., and generally higher using dexamethasone [99]. Dexamethasone seems to be beneficial in the patients with lower risk of relapse (such as young patients or good early treatment responders), but caution is needed for use in higher dose (e.g., 10 mg/m² per day) for older patients.

Asparaginase is another essential key drug for ALL treatment, and there are currently three preparations available, Escherichia coli (E.coli), Erwinia chrysanthemi, and polyethylene glycosylated (PEG) E. coli derived. These three preparations have different cytotoxicity and half-lives (both, PEG > E. coli > Erwinia); therefore, optimizing dose and schedule is crucial to maintain asparagine depletion thus leading to obtain therapeutic effect [100]. In the contemporary ALL treatment in North America and Europe, PEG is favorably used because of longer half-life and potentially lower immunogenicity [9]. However, in countries where PEG is not available, native E.coli asparaginase is used. Erwinia is generally reserved for patients who develop hypersensitivity reactions [101]. Major adverse events of asparaginase are coagulopathy, acute pancreatitis, and hypersensitivity. The rate of thrombosis in pediatric ALL treatment is approximately 5%, and most of the events occur during induction phase [102, 103]. Attempts to prevent thrombotic events such as prophylactic antithrombin replacement and use of low-molecular heparin are frequently done as clinical practice; however, there is no clear evidence of efficacy in these interventions. Asparaginase-induced acute pancreatitis generally occurs during induction phase and could be fatal [104]. Re-treatment with asparaginase even with different preparations is not recommended because probability of recurrence is very high. The most critical and frequently observed asparaginase-related adverse event is hypersensitivity, which is observed in 20–30% of the cases throughout ALL treatment with native E.coli preparation (most often observed in re-induction phase). Intramuscular injection could reduce antibody production compared to intravenous injection; however, once hypersensitivity reaction occurs with either native or PEG E.coli preparations, it should be replaced with Erwinia. Even without clinical symptoms, antibody production could cause “silent inactivation” of administered asparaginase. In that sense, measurement of serum asparaginase activity would be a useful tool to monitor the therapeutic effect and alter asparaginase treatment, if necessary, especially during the post-remission phase [105].
Addition of anthracycline to three-drug induction (corticosteroid, vincristine, and asparaginase) is utilized in many study groups including the BFM. In some groups such as COG and the UK, anthracycline is not used for NCI standard-risk patients [3, 106]. Because use of anthracyclines could cause late cardiotoxic events even in patients with cumulative dose of less than 300 mg/m², anthracycline reduction or omitting is a preferable option for children with ALL [107]. However, the groups treating patients with three-drug induction are commonly using vincristine/dexamethasone pulse in maintenance phase instead. Therefore, reduction of certain elements should be considered in the balance of intensity of the total therapy.

Consolidation Therapy

Following remission induction, 6–8 months of intensive combination chemotherapy is administered aiming to consolidate remission status.

In the BFM regimen, an early intensification course (designated as protocol IB) follows directly after the four-drug induction (protocol IA), alternating with combination of cyclophosphamide, 6-mercaptopurine, cytarabine, and intrathecal therapies (IT). This strategy was introduced by Hansjörg Riehm and his colleagues in the 1970s adopting the Goldie-Coldman hypothesis (a mathematical model predicting the likelihood of mutations leading to drug resistance) that the best chance of cure would be to use all effective non-cross-resistant drugs in the early phase of the treatment before the leukemia cells acquire resistance [108]. COG applies early intensification strategy only for the NCI high-risk cases because they could not prove its efficacy over the less-intensive consolidation with vincristine, 6-mercaptopurine, and IT-methotrexate for the standard-risk patients in the CCG 105 study [109].

After the early consolidation course, interim maintenance course follows. BFM group introduced high-dose methotrexate (HD-MTX, 5 g/m²/dose) administered over 24 h followed by folinic acid rescue combined with 6-mercaptopurine and IT-methotrexate (protocol M) to intensify this course since BFM86 study [110]. In contrast, CCG had developed another strategy designated Capizzi methotrexate (Capizzi-MTX), with lower, escalating doses of intravenous methotrexate of 100–300 mg/m² through short infusions without folinic acid rescue followed by asparaginase. In COG AALL0232 study, randomly assigned HD-MTX arm demonstrated superior outcome compared to Capizzi-MTX for NCI high-risk B-ALL [98]. However, in COG AALL0434 study for T-ALL patients, Capizzi-MTX was superior to HD-MTX [111]. Irrespective of different approaches of intensification, the aim is to accumulate higher methotrexate polyglutamates, the active metabolites of methotrexate, in leukemic cells, which is associated with higher antileukemic activity. Accumulation varies widely between ALL subtypes: low in TCF3-PBX1, T-cell, and ETV6-RUNX1 ALL (thus, might benefit from higher dose of methotrexate) and high in hyperdiploid B-ALL cases [112].

Before entering maintenance therapy, a delayed intensification or re-induction course (designated as protocol II in BFM) mimicking BFM protocol I (IA and IB) is administered: prednisone is substituted by dexamethasone, daunorubicin by doxorubicin to dosorubicin...
bicin, and 6-mercaptopurine by 6-thioguanine. Delayed intensification course was also introduced by Riehm, adopting the Norton-Simon hypothesis (a hypothesis that a tumor is composed of populations of faster-growing chemosensitive cells and slower-growing chemoresistant cells) that the initial regimen must be effective enough to eradicate the low residual chemosensitive leukemia and substitution of some agents with non-cross-resistant agents to eradicate the remaining chemoresistant leukemia [113]. Delayed intensification course has been proven to be an essential element of ALL therapy for all the patients regardless of risk group stratified.

However, for the patients with unfavorable risk (e.g., poor prednisone responders), BFM standard regimen yielded EFS rate of lower than 50% even with addition of high-dose cytarabine and ifosfamide in BFM86 study [110]. Therefore, BFM introduced multiple courses of short intensive block therapy derived from their relapsed ALL study in consolidation phase since the study of BFM90, although its benefit is unclear [114]. In contrast, CCG investigators chose to intensify their consolidation phase with known ALL key drugs with limited hematologic toxicities, such as vincristine, asparaginase, and methotrexate, thus established “augmented BFM” therapy, which significantly improved the outcome of unfavorable risk patients [115].

Maintenance Therapy

Historically, maintenance therapy was introduced to prolong remission period achieved after induction phase. However, the therapy which lasts 2 years or longer consisting of oral intake of daily 6-mercaptopurine and weekly methotrexate with or without pulses of vincristine and dexamethasone is still an essential element in the context of contemporary intensive chemotherapy. There are several trials that attempted to shorten the duration of maintenance, but all failed: BFM group randomized 24-month and 18-month total duration, and shorter duration arm showed inferior outcome; TCCSG L92-13 study, evaluating 1-year total duration therapy in all risk groups, ended up with 59% EFS rate in 5 years, which was inferior to the historical control [116, 117]. Interestingly, the retrospective revisiting analysis of L92-13 study by Kato et al. has discovered the subgroups that might benefit from short duration maintenance: female, TCF3-PBX1, and ETV6-RUNX1 [118].

It is quite common to encounter patients with 6-mercaptopurine intolerances causing severe myelosuppression that results in frequent treatment disruptions and sometimes in risk of life-threatening infections. Recent pharmacogenomics studies have uncovered its mechanisms in part. The most well studied is genetic polymorphisms of thiopurine S-methyltransferase (TPMT) gene. TPMT catalyzes S-methylation of thiopurines to inactive methylated metabolites. As a result, patients with heterozygous or homozygous TPMT deficiency, which accounts for approximately 10% of Caucasian population, are associated with 6-mercaptopurine intolerance [119]. However, mutant alleles of TPMT are rare in Asian population (1.6% in Japanese). Recent studies identified germline polymorphisms of nucleoside diphosphate-linked moiety X-type motif 15
(NUDT15) gene, found in one third of Japanese population, to be associated with 6-mercaptopurine intolerance as well [120, 121]. Decreased enzymatic activity of mutant NUDT15 leads to excess levels of intracellular thiopurine active metabolites, thus results in cytotoxicity. Polygenic dosing algorithm that incorporates these pharmacogenomics data would provide personalized thiopurine therapy in the near future.

2.4.3.3 CNS-Directed Therapy

Control and prevention of CNS leukemia is a key component of ALL therapy. Cranial irradiation (24 Gy) has dramatically improved survival rate of children with ALL in the 1960s and 1970s, but it was associated with an increased risk of secondary CNS tumors, various endocrinopathies, growth impairment, and neurocognitive effects [122, 123]. As a result, CNS irradiation dose is reduced to 12–18 Gy and limited to only patients with higher risk of CNS relapse in the contemporary ALL therapy. CNS and hematological relapses are competing events; therefore, intensification of both systemic chemotherapy (high-dose methotrexate, asparaginase, and dexamethasone) and intrathecal chemotherapy plays important roles to prevent CNS relapse. With these intensifications, St. Jude Children’s Research Hospital has succeeded in eliminating cranial irradiation for all the children with ALL in their frontline therapy [8].

2.4.3.4 Hematopoietic Stem Cell Transplantation

Allogeneic hematopoietic stem cell transplantation (SCT) is still an option for children with very high risk of relapse, but its role continues to be limited in the context of contemporary treatment. Allo-SCT is no longer routinely recommended for children with Ph+ ALL due to the development of TKI-combined chemotherapy, and indication for infants with ALL is controversial [124]. For those receiving allo-SCT, post-transplant leukemia-free survival seems not to be affected by stem cell sources [125–127]. In terms of conditioning regimen, use of total body irradiation is generally recommended except for infants because of its higher therapeutic effect on preventing leukemia relapse [128, 129]. Finally, MRD status before SCT is a strong predictor of post-SCT relapse [126].

2.4.3.5 Special Subcategories

Down Syndrome ALL

Children with constitutive trisomy 21 or Down syndrome (DS) is associated with higher risk of developing B-ALL, but not during infancy, compared to non-DS children. Biologically, prevalence of common abnormalities in non-DS ALL, such as
ETV6-RUNXI, high hyperdiploidy, BCR-ABL1, or MLL-AF4, is low, and overexpression of CRLF2 is found in more than half the cases as previously described [64]. DS patients with ALL have higher cumulative incidence of relapse and treatment-related mortality, especially infection related, resulting in lower EFS and OS rates than non-DS ALL patients [130, 131]. Therefore, caution is needed not to reduce chemotherapy dosages excessively, but at the same time, careful management of infections is necessary throughout therapy including maintenance.

Adolescent and Young Adults with ALL

Historically, adolescents and young adults (AYA; age 15 years old or higher) with ALL had inferior EFS and OS rates compared to children. This is in part because of higher prevalence of unfavorable risk ALL (e.g., T-cell and Ph+) and lower prevalence of favorable risk ALL (e.g., ETV6-RUNXI and high hyperdiploid) in AYAs. However, recent clinical studies have shown feasibility and significant improved outcomes in AYAs with ALL treated with pediatric ALL protocol [132–134]. Hence, the consensus has been established that AYA patients should be treated based on pediatric ALL regimen.

2.5 Future Challenges

More than 80% of children with ALL are currently cured; however, this was accomplished by identification of optimal dosing and schedules of chemotherapeutic agents that have developed before the 1970s, not by identification of novel innovative agents. One of the major challenges in pediatric ALL would be to increase the cure rate of patient subsets with dismal prognosis that is unlikely to be improved with contemporary therapy. Owing to rapid progress in genomic analysis, there has been a tremendous increase in understanding of ALL biology in the past few years, and its application is currently ongoing. One of the most successful examples is the introduction of TKI in the treatment of Ph+ ALL, although optimal agents, dosing, and combination chemotherapy are still not determined [54]. There is substantial number of novel agents under evaluation: TKI (imatinib, dasatinib) for Ph-like ALL [58], epigenetic modifiers (DNA methyltransferase inhibitors, histone deacetylase inhibitors, DOT1L inhibitor) for MLL-rearranged ALL [135, 136], proteasome inhibitors (bortezomib) [137], monoclonal antibodies (rituximab, epratuzumab) [138], monoclonal antibodies conjugated with immunotoxins or chemotherapeutic drugs (moxetumomab, inotuzumab ozogamicin) [139], bispecific T-cell engager antibodies (blinatumomab) [140], chimeric antigen receptor (CAR) T-cell therapy [141], etc. It is expected that the genomic landscape of ALL would be fully unmasked in the near future and that the integration of discovered genomics into contemporary therapy would progress in order to realize precision medicine which would result in further improvement in the outcome of childhood ALL.
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