Advances in the Treatment of Childhood Acute Lymphoblastic Leukemia

Hyery Kim

Division of Pediatric Hematology/Oncology, Department of Pediatrics, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

In recent decades, survival rates for childhood acute lymphoblastic leukemia have improved remarkably, as demonstrated by risk-stratified, prospective multicenter studies. Treatment protocols have evolved and become better matched to both prognostic factors and treatment responses. Recently, new molecular prognostic factors have been discovered in leukemia genomic studies. New tumor subtypes with independent gene expression profiles have also been characterized. Furthermore, therapies targeted to specific candidate mutations are being identified to broaden therapeutic options for patients with poor prognoses. Many new drugs are in clinical trials and immunotherapy is attracting significant interest for the treatment of recurrent or refractory disease in childhood acute lymphoblastic leukemia.

Key Words: Childhood, Precursor cell lymphoblastic leukemia, Prognosis, Survival

Introduction

Acute lymphoblastic leukemia (ALL) is the most common pediatric malignancy, which constitutes approximately 25% of cancer diagnoses among children younger than 15 years of age. In the past ALL was incurable, but now the survival rate is improved to 80-90% [1]. Improved supportive care, treatment stratification based on prognostic factors, and an improved understanding of biology of leukemia through nationwide and international collaborations have contributed to this dramatic improvement.

The age-standardized incidence rate of ALL in Korean children is approximately 28 per million in children under 14 [2] with 1,103 cases identified in 2008-2012 [3]. The relative survival rate of ALL in Korea was reported to be 75.2% in 2008-2012 [3], with event-free survival (EFS) of 78.5% and overall survival (OS) of 81.9% in a single-center study [4].

A current focus in research on childhood ALL is to refine prognostic factors and to develop novel therapies for relapsed/refractory patients while minimizing therapy-related, long-term complications.
Cytogenetics and Genomics of Childhood ALL

1) B-cell ALL

The genomics of childhood ALL have been extensively investigated, with multiple characteristic subtypes defined [5]. The incidence of recurrent cytogenetic abnormalities in ALL varies according to age at diagnosis, which could account for the difference in overall treatment outcome between children and adults (Fig. 1). Cases with recurrent genetic abnormalities are now categorized as distinctive diagnostic subtypes in the World Health Organization classification revised in 2016 (Table 1).

Multiple recurrent chromosomal abnormalities have prognostic significance, particularly in precursor B-cell ALL (BCP-ALL). ETV6-RUNX1 fusions and high hyperdiploidy are associated with favorable outcomes, while others with the Philadelphia chromosome [t(9;22)(q34;q11.2)], hypodiploidy, rearrangements of the MLL (KMT2A) gene, and intrachromosomal amplification of the AML1 gene (iAMP21) have been associated with a poor prognosis [6].

High hyperdiploidy, defined as 51 to 65 chromosomes per cell or a DNA index greater than 1.16, occurs in 20% to 25% of cases of BCP-ALL, but very rarely in T-cell ALL.

Fig. 1. Subclassification of precursor B acute lymphoblastic leukemia by age groups (reproduced from the data of Gu Z et al. Nat Genet 2019;51:296-307).
Table 1. 2016 World Health Organization (WHO) classification system for childhood ALL

<table>
<thead>
<tr>
<th>Classification</th>
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<tr>
<td>B-lymphoblastic leukemia/lymphoma</td>
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<tr>
<td>• B-lymphoblastic leukemia/lymphoma, not otherwise specified (NOS).</td>
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<tr>
<td>• B-lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities.</td>
</tr>
<tr>
<td>• B-lymphoblastic leukemia/lymphoma with t(9;22)(q34.1;q11.2); BCR-ABL1.</td>
</tr>
<tr>
<td>• B-lymphoblastic leukemia/lymphoma with t(11q23.3); KMT2A rearranged.</td>
</tr>
<tr>
<td>• B-lymphoblastic leukemia/lymphoma with t(12;21)(p13.2;q22.1); ETV6-RUNX1.</td>
</tr>
<tr>
<td>• B-lymphoblastic leukemia/lymphoma with hyperdiploidy.</td>
</tr>
<tr>
<td>• B-lymphoblastic leukemia/lymphoma with hypodiploidy.</td>
</tr>
<tr>
<td>• B-lymphoblastic leukemia/lymphoma with t(5;14)(q31.1;q32.3); IL3-IGH.</td>
</tr>
<tr>
<td>• B-lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3); TCF3-PBX1.</td>
</tr>
<tr>
<td>• Provisional entity: B-lymphoblastic leukemia/lymphoma, BCR-ABL1–like.</td>
</tr>
<tr>
<td>• Provisional entity: B-lymphoblastic leukemia/lymphoma with iAMP21.</td>
</tr>
<tr>
<td>T-lymphoblastic leukemia/lymphoma</td>
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<tr>
<td>• Provisional entity: Early T-cell precursor lymphoblastic leukemia.</td>
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</table>

[7] Patients with trisomies of chromosomes 4, 10, and 17 (triple trisomies) have a favorable outcome, as demonstrated in both Pediatric Oncology Group (POG) and Children’s Cancer Group (CCG) analyses [8].

Children with hypodiploidy (<44 chromosomes) have a notably poor prognosis progressively worsening with the extent of decrease of chromosome numbers [9]. A retrospective analysis reported an 8-year EFS of 38.5% and OS of 49.8% in this subgroup [9]. In low-hypodiploid ALL, genetic alterations involving RB1, TP53, and IKZF2 are common. The TP53 alterations observed in low-hypodiploid ALL are also present in nonleukemic cells in approximately 40% of cases, suggesting that these are germline mutations and there is underlying Li-Fraumeni syndrome [10].

ETV6-RUNX1; t(12;21)(p13.2;q22.1), formerly known as TEL-AML1, is present in 20-25% of cases of BCP-ALL but is rarely observed in T-cell ALL [11]. However, even within this favorable group, patients with National Cancer Institute (NCI) high risk features or minimal residual disease (MRD) positivity at the end of induction had significantly lower survival than others [12].

Rearrangements involving the MLL gene (also known as KMT2A) on chromosome 11q23; t(11q23,3) are observed in approximately 5% of childhood ALL, but in up to 80% of infants with ALL. However, they are rarely detected in children older than one year [13]. The prognosis of these patients is relatively poor with only half of the cases being cured by conventional chemotherapy. Patients with t(4;11) (q21;q23) are usually infants with high white blood cell (WBC) counts and central nervous system (CNS) involvement; they typically respond poorly to initial chemotherapy [14].

The TCF3-PBX1; t(1;19)(q23;p13.3) rearrangement occurs in approximately 5% of childhood ALL cases. The t(1;19) had been associated with inferior outcome, but the adverse prognosis can be largely abrogated by more aggressive chemotherapy [15]. Patients with t(1;19) were reported to have a comparable outcome to others, but have a higher risk of CNS relapse, suggesting that more intensive CNS therapy may be necessary for these cases [16].

The t(17;19) resulting in TCF3-HLF fusion occurs in less than 1% of pediatric ALL cases. These patients have extremely poor prognosis [17].

DUX4 rearrangements are found in approximately 5% of standard-risk and 10% of high-risk pediatric BCP-ALL [18]. About 50% of DUX4-rearranged cases have focal intragenic deletions involving ERG, and 35% to 40% have IKZF1 alterations. Patients with DUX4 rearrangements who lack ERG deletion appear to have a favorable prognosis [18].

PAX5 encodes a paired box DNA-binding transcription factor that regulates B lymphoid lineage commitment and maturation. In a recent study by Gu et al. [19], PAX5 alteration (PAX5alt) was redefined with integrated genomic analysis. Also PAX5 p.Pro80Arg was shown to be profoundly deleterious and led to arrest in maturation at the pro- to pre-B-cell stage. This subtype is also notable for loss of function of the PAX5 allele. PAX5 p.Pro80Arg and PAX5alt cases have intermediate to poor outcomes in chil-
Childhood Acute Lymphoblastic Leukemia

Intrachromosomal amplification of chromosome 21 (iAMP21) is a recurrent genetic abnormality found in up to 2% of pediatric ALL cases, and is associated with older age at onset and increased risk of relapse [20]. Several studies suggest that treatment of iAMP21 patients with high-risk chemotherapy regimens obviates its adverse prognostic significance and the need for hematopoietic stem cell transplantation (HSCT) [21,22].

Deletion of IKZF1, which encodes the lymphoid transcription factor IKAROS is present in approximately 15% of BCP-ALL; it is a frequent event in BCR-ABL1-positive ALL and Down syndrome ALL (DS-ALL) [23-25]. IKZF1 deletion and alteration of TP53 have been identified as factors that significantly worsen prognoses. However, recent results from the Associazione Italiana di Ematologia e Oncologia Pediatrica (AIEOP)-Berlin-Frankfurt-Münster (BFM) study revealed that IKZF1 deletion was not an independent prognostic factor in the MRD negative group, but concomitant deletions in CDKN2A, CDKN2B, PAX5, or PARD in the absence of ERG deletion (IKZF1Ph group) were the MRD-dependent very-poor prognostic factors [26]. The Malaysia-Singapore group published results of two consecutive trials in which IKZF1-deleted ALL patients achieved improved outcomes after receiving higher risk group therapy [27].

The Philadelphia chromosome t(9;22)(q34;q11.2) (Ph+) is present in approximately 3% of children with ALL and leads to production of a BCR-ABL1 fusion protein with tyrosine kinase activity. Historically, the Philadelphia chromosome t(9;22)(q34;q11.2) was associated with a poor prognosis, and its presence had been considered an indication for allogeneic HSCT in patients in first remission [28]. Inhibitors of the BCR-ABL1 tyrosine kinase, such as imatinib mesylate, are effective in patients with Ph+ ALL.

BCR-ABL1-negative patients with gene expression profiles similar to those of BCR-ABL1-positive patients have been referred to as BCR-ABL1-like (Ph-like) [29]. Ph-like ALL accounts for 10% to 20% of pediatric ALL patients, increasing in frequency with age (Fig. 1), and has been associated with IKZF1 mutation or deletion. A previous study indicated that patients with Ph-like ALL have a poor prognosis, with a 5-year EFS of 58% [24]. However, in a Children’s Oncology Group (COG) study in an NCI standard risk group, there was no difference in OS between patients with Ph-like ALL and others [30]. Moreover, in a study from St. Jude Children’s Research Hospital (SJCRH), the adverse prognostic significance of this subtype was abrogated when patients were treated with MRD based risk-directed therapy [31].

The hallmark of Ph-like ALL is activated kinase signaling, with 50% of patients having CRLF2 genomic alterations and half of those having concomitant JAK mutations [29]. Many other cases of Ph-like ALL present with translocations involving genes encoding kinases, including ABL1, ABL2,
CSF1R, JAK2, and PDGFRB. Recently, some Ph-like ALL patients have been suggested as candidates for targeted therapy. Currently, clinical trials are ongoing in Ph-like ALL patients with ABL1-class rearrangements (ABL1, ABL2, CSF1R, PDGFRB) using tyrosine kinase inhibitors (TKIs) such as dasatinib, and in those with JAK-STAT signaling abnormality (JAK2, CRLF2, EPOR) using JAK inhibitors such as ruxolitinib [24,29].

2) T-cell ALL

Multiple chromosomal translocations have been identified in T-cell ALL that results in deregulated expression of target genes. In most cases, chromosome rearrangements between transcription factors (e.g., TAL1/TAL2, LMO1/LMO2, LYL1, TLX1, TLX3, NKL2-I, HOXA, and MYB) and one of the T-cell receptor loci are found [32].

Notch pathway signaling is frequently activated by NOTCH1 and FBXW7 gene mutations in T-cell ALL, and these are the most commonly mutated genes in pediatric T-cell ALL [32]. NOTCH1-activating gene mutations and significantly higher frequencies of alterations in genes associated with cytokine receptors, RAS signaling, hematopoietic development, and histone modification. The transcriptional profile of ETP-ALL shows similarities to that of normal stem cells and myeloid leukemia stem cells [36]. ETP-ALL has a poor outcome, although this is alleviated by current risk-adapted therapy [37,38].

3) Early T-cell precursor ALL

Early T-cell precursor (ETP) ALL is a distinct form of leukemia characterized by reduced expression of the T-cell markers CD1a, CD8, and CD5, with aberrant expression of myeloid or stem-cell markers [35]. Compared with other T-cell ALL cases, patients with ETP-ALL had a lower frequency of NOTCH1 mutations and significantly higher frequencies of alterations in genes associated with cytokine receptors, RAS signaling, hematopoietic development, and histone modification. The transcriptional profile of ETP-ALL shows similarities to that of normal stem cells and myeloid leukemia stem cells [36]. ETP-ALL has a poor outcome, although this is alleviated by current risk-adapted therapy [37,38].

Pharmacogenetics

Germline polymorphisms in patients with ALL can alter genes encoding drug metabolizing enzymes, drug transporters, or drug targets and thus can influence the efficacy and/or toxicity of antileukemic agents. Thiopurine methyltransferase (TPMT), which methylates 6-mercaptopurine (6-MP) metabolites, is known to be one of the most critical genes in the pharmacogenetics of ALL [39]. Patients with a nonfunctional variant allele of TPMT have lower TPMT enzyme activity: consequently, 6-thioguanine nucleotide (6-TGN) accumulates to high levels, causing hematopoietic toxicity. Recently, a single-nucleotide polymorphism in nucleoside diphosphate-linked moiety X-type motif 15 (NUDT15) has been associated with thiopurine-induced myelosuppression [40,41]. The NUDT15 encoding enzyme dephosphorylates the 6-MP active metabolite and prevents their incorporation into DNA, thereby negating cytotoxic effects of 6-MP. However, when there are potentially deleterious polymorphisms in NUDT15, the usual doses of 6-MP can cause extensive DNA damage and drug toxicity. These findings led to guidelines for individualized 6-MP dosing according to TPMT or NUDT15 genotype [42].

Risk Stratification and Prognostic Factors

Children with ALL are treated according to risk groups, which are defined by both clinical and laboratory features. Through risk-based treatment, patients with favorable characteristics can be spared more intensive and toxic treatment, while a more aggressive therapeutic approach can be provided for patients who have a lower probability of long-term survival.

For COG trials, factors used to determine the intensity of induction include immunophenotype, steroid pretreatment, the presence or absence of Down syndrome, the presence or absence of extramedullary disease, and the NCI risk group classification, which stratifies risk according to age and WBC count (Table 2).

For BFM trials, risk groups have been stratified primarily by treatment response. In addition to prednisone prophase
response, treatment response is assessed through MRD measurements at two time points: end-induction (week 5) and end-consolidation (week 12). Patients with either the t(9;22)(q34;q11.2) or the t(4;11)(q21;q23) are considered high risk, regardless of their early response. Also, infants with MLL rearrangements, as well as any ALL patients with hypodiploidy, or initial induction failure are regarded as a very high risk group. Patients who achieve complete remission but have a slow early response to initial therapy, including those with a high absolute blast count after a 7-day steroid prophase, and patients with high MRD levels at the end of induction or later time points are also considered as very high risk group.

### Treatment Response

Traditionally, the main prognosis factors have been clinical features at diagnosis, molecular biological characteristics of leukemic blasts, and early response to treatment. Among these, the most critical is the response to treatment [43].

#### 1) Minimal residual disease determination

MRD is defined as the frequency of leukemic cells remaining after treatment. It has been measured by PCR assays of unique Ig/T-cell receptor gene rearrangements or fusion transcripts, or by flow cytometry assays using leukemia-specific immunophenotypes. With such techniques, the limit of detection has been one leukemia cell in 10^5 normal cells (10^-5). Newer methods involving high-throughput sequencing of Ig/T-cell receptor gene rearrangements can increase the sensitivity of MRD detection to one in 10^6 normal cells (10^-6).

End-induction MRD is used by almost all groups as a factor used to determine the intensity of post induction treatment, with patients with higher levels (MRD > 10^-3 to 10^-4) designated to receive more intensive therapies [44]. Patients who have a standard or intermediate risk at diagnosis, but have high levels of end-induction MRD, have been shown to have a poor prognosis and treated as a high-risk group.

MRD levels obtained at later time points (10 to 12 weeks, end-consolidation) have also been shown to be important. Patients with high levels of MRD at this time point have significantly inferior EFS relative to that of other patients [45]. For patients with B-cell ALL, evaluating MRD at two time points (end-induction and end-consolidation) can be important, but for T-cell ALL, an association between end-induction MRD level and relapse risk has not been found. An AIEOP study indicated that MRD at a later time point (week 12) might be a better prognostic factor for

### Table 2. Important prognostic factors in pediatric acute lymphoblastic leukemia

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Favorable prognostic factor</th>
<th>Adverse prognostic factor</th>
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<tbody>
<tr>
<td>Age at diagnosis</td>
<td>1-10 yr</td>
<td>&lt; 1 yr or ≥ 10 yr</td>
</tr>
<tr>
<td>Initial WBC count</td>
<td>&lt; 50,000/μL</td>
<td>≥ 50,000/μL</td>
</tr>
<tr>
<td>Sex</td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>Immunophenotype</td>
<td>B-cell</td>
<td>T-cell</td>
</tr>
<tr>
<td>Cytogenetics</td>
<td>ETV6-RUNX1, hyperdiploidy, chromosome trisomies</td>
<td>BCR-ABL1, MLL (KMT2A) rearrangements, hypodiploidy</td>
</tr>
<tr>
<td>Genomics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early response to treatment</td>
<td>Good response (&lt; 1,000 blasts/μL)</td>
<td>Poor response (≥ 1,000 blasts/μL)</td>
</tr>
<tr>
<td>Response of prophase glucocorticoid</td>
<td>M1 (&lt; 5% blasts) marrow at induction day 7 or 14</td>
<td>M2 or M3 (≥ 5% blasts) marrow at induction day 7 or 14</td>
</tr>
<tr>
<td>Early response during induction</td>
<td>&lt; 0.01% or undetectable</td>
<td>Persistent ≥ 0.01%</td>
</tr>
<tr>
<td>End-of-induction MRD</td>
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MRD, minimal residual disease.
T-cell ALL [46].

MRD measurements have also been used to identify subsets of patients with an extremely low risk of relapse. The COG reported a very favorable prognosis (5-year EFS of 97%) for patients with a precursor B-cell phenotype, NCI standard risk, CNS1, and favorable cytogenetic abnormalities (high hyperdiploidy with favorable trisomies or the ETV6-RUNX1 fusion) who had less than 0.01% MRD levels at both day 8 (from peripheral blood) and end-induction [12].

2) Peripheral blood response to steroid prophase

Early treatment response can be measured by the clearance of peripheral blasts after one week of prophase steroid. Patients with a reduction in peripheral blast count to less than 1,000/μL after a 7-day induction prophase with prednisone and one dose of intrathecal methotrexate have a more favorable prognosis than do patients whose peripheral blast counts remain above 1,000/μL [47]. Measurement of this early response to prednisone prophase is usually incorporated to determine treatment stratification in BFM trials.

**Treatment**

At first, combination chemotherapy induced remission in 80 to 90% of patients. However, the disease relapsed in almost all patients, especially in the CNS, with survival rates of 10 to 20% [48]. Survival increased considerably with the addition of craniospinal or cranial irradiation and intrathecal (IT) chemotherapy [49].

A breakthrough in therapy for childhood ALL was the development of an intensive 8-drug, 8-week induction and consolidation regimen including cranial irradiation, introduced by Rjehm et al., in 1970-1976 [50]. This regimen, which is now called protocol I, became the basis for the BFM regimen, which is the basis for current ALL treatment. Protocol I in BFM studies has been described as induction (Ia) and consolidation (Ib) in COG trials. According to subsequent trials, results were best when the protocol included an 8 week “rest” period of maintenance therapy between protocols I and II, called the interim maintenance phase in COG trials [51].

1) Induction

The goal of induction is to reduce the number of leukemic cells from about 10^{12} to 10^9, to reduce the frequency of leukemic blasts among total nucleated cells in bone marrow to less than 5%, and to restore normal hematopoiesis (remission). Induction therapy lasts 4 to 6 weeks and includes steroids (prednisolone or dexamethasone), vincristine, asparaginase, anthracycline (optional; usually in high risk group), and intrathecal chemotherapy.

Among steroids, dexamethasone has a longer half-life, increased affinity for steroid receptors, and better penetration into the CNS than does prednisolone. According to the AIEOP-BFM ALL 2000 trial, the relapse risk was significantly lower in the dexamethasone group (10.8% vs. 15.6%), but the benefit of dexamethasone was partially balanced by a considerably higher induction-related death rate (2.9% vs. 0.9%) [52]. In a COG high risk group trial (AALL0232), dexamethasone benefited younger children but provided no benefit and was associated with a higher risk of osteonecrosis among participants 10 years and older [53]. In the EORTC CLG 58951 randomized trial, although dexamethasone decreased the incidence of CNS relapse, dexamethasone and prednisolone were equally effective and had a similar toxicity profile [54].

Three different asparaginase preparations are currently used for the treatment of patients with ALL, Native *Escherichia coli* (E. coli) asparaginase and polyethylene glycolated (PEG)-asparaginase, are derived from the bacterium *E. coli* [55]. The third preparation, *Erwinia* asparaginase, is derived from the bacterium *Erwinia chrysanthemi*. The distinct bacterial origins of *Erwinia* give it a unique immunogenic profile, showing no cross-reactivity with native *E. coli* or PEG-asparaginase. *Erwinia* asparaginase is indicated for patients with ALL who have developed hypersensitivity to *E. coli*–derived asparaginases, PEG-asparaginase has the longest half-life, and *Erwinia* has the shortest of the three [56]. Due to the shorter half-life of *Erwinia* asparaginase, patients who switch to this formulation should receive a higher dose at higher frequency to maintain therapeutic levels of asparagine depletion.
Adverse events caused by asparaginase, including pancreatitis, hypersensitivity, hyperglycemia, hypertriglyceridemia, coagulopathy, and thrombosis are often severe and occasionally life-threatening. Furthermore, neutralizing antibodies sometimes develop without clinical symptoms (silent inactivation) and reduce asparaginase activity and anti-leukemic effects. Individualized dosing based on nadir serum asparaginase activity has been shown to improve outcomes [57]. For patients with neutralizing antibody, Erwinia can be an alternative and PEG-asparaginase can suppress allergy and inactivation.

Regarding the efficacy of each asparaginase preparations, PEG-asparaginase showed a lower incidence of silent antibodies, the absence of antibodies that cause rapid clearance, similar safety profile, and similar EFS relative to the native form [58]. Erwinia asparaginase was associated with a lower incidence of toxicity than the native E. coli preparation, but also had an inferior 5-year EFS [59].

2) Consolidation and intensification

After induction, patients are classified into risk groups based on their early response (e.g., prophase steroid response, end-induction MRD) and cytogenetics of leukemia. Treatment includes 6 to 8 months of intensive combination chemotherapy that is designed to consolidate remission by eradicating drug-resistant residual leukemic cells and prevent development of overt CNS leukemia.

In the BFM studies, an intensified consolidation (protocol Ib) that includes cyclophosphamide and cytarabine was followed for one month immediately post-induction. Afterward, consolidation has been improved for the augmented BFM regimen with the introduction of vincristine and asparaginase during periods of myelosuppression and the increase to a two-month block. The intensified protocol Ib is one of two major components of the augmented BFM regimen, which has significantly improved outcomes for the high risk group [60,61].

Protocol II was developed from the 8-week BFM protocol I and uses drugs similar to those used in remission induction (Protocol Ia) and consolidation (Protocol Ib). Protocol II has been described as delayed intensification including protocol Ila (re-induction) and IIb (re-consolidation). Between Protocols I and II, repeated courses of methotrexate (MTX) are administered either through short intravenous (IV) infusion or at high doses over 24 hours followed by leucovorin rescue (i.e., Protocol M) [62]. Currently, for the interim maintenance phase in COG trials, vincristine and escalating IV MTX without leucovorin rescue have been chosen for standard risk patients [63], while high-dose MTX with leucovorin rescue was introduced for high risk patients [53].

For high risk patients, intensification with including additional doses of vincristine and PEG-asparaginase, as well as repeated interim maintenance and delayed intensification phases could be administered [64]. Elimination or truncation of some of the intensification phases for lower-risk patients can be implemented to minimize acute and long-term toxicity.

3) Maintenance

For maintenance, patients receive low-intensity anti-metabolite-based therapy for 18 to 30 months. This therapy consists of daily oral 6-MP or thioguanine and weekly oral MTX. Some regimens, including COG trials, also include periodic 5 to 7-day pulsed doses of steroids and vincristine. CNS prophylaxis should continue during maintenance therapy. During maintenance, patients’ compliance is a critical issue. Noncompliance or high variability of metabolite levels within each patient, caused by varying drug doses and periods of treatment interruption, may result in increased risk of relapse [65].

4) CNS-directed therapy

Cranial irradiation dramatically reduced relapses, including CNS relapses. However, because of late complications including secondary neoplasms, cognitive disorder, and endocrinopathy, it has been replaced by IT therapy and high dose MTX. According to a study from SJCRH, the cumulative incidence of CNS relapse has fallen as low as 4% with increased use of IT triple therapy without prophylactic cranial irradiation [66]. In Korea, Lee et al, reported that risk group-based intensification without cranial irradiation, regardless of CNS involvement at diagnosis, successfully reduced CNS relapse to 2.3% [4]. In current practice, cranial
irradiation is only administered to CNS-involved patients in most protocols [67].

Generally, the first IT chemotherapy is administered on the first day of induction. However, traumatic lumbar puncture (TLP) with blasts has been reported to occur in 5.6-14.5% in ALL patients [68]. TLP contaminated with blasts has also been shown to be a risk factor for CNS relapse; thus a strategy for preventing TLP is essential [69]. A Taiwan group modified CNS-directed therapy by adding delayed triple IT upon clearance of circulating blasts to minimize TLP, and with the omission of cranial irradiation in all patients [70]. They reported that those modifications on treatment compromise neither survival nor CNS control.

5) Hematopoietic stem cell transplantation (HSCT)

HSCT is indicated in children with ALL in whom the probability of EFS with chemotherapy alone remains unsatisfactory. Primary induction failure is rarely seen in pediatric ALL (<2% incidence) but continues to be a strong indication for HSCT during the first complete remission (CR1), as it is one of the most unfavorable prognostic factors, with a long term survival rate of 32% in one study [71].

MLL (KMT2A) rearrangement is associated with relatively poor prognoses, but there are controversies on the absolute indication of HSCT especially in infant ALL with MLL rearrangement. Many multicenter study groups consider patients older than one year with t(4;11)(q21;q23) as candidates for HSCT at CR1. For infant ALL, the Interfant group suggested that HSCT offered an advantage for a subgroup of infants with MLL-rearranged ALL; those aged less than 6 months with poor response to steroids or with extreme hyperleukocytosis [13].

Children with hypodiploidy (<44 chromosomes) have a particularly poor prognosis, so HSCT at CR1 is indicated [72]. However, data from a small series of patients suggest that children with hypodiploid ALL and negative end-induction MRD may be cured through risk-based chemotherapy alone [73]. Another COG study reported that, while outcomes after chemotherapy alone were still suboptimal for hypodiploid ALL, HSCT in CR1 did not confer a survival benefit, thus indicating the need for alternative therapeutic strategies in this subset of patients [72].

Patients with T-ALL and poor MRD clearance at end-consolidation are considered candidates to receive an allograft in CR1. For relapse cases, although cases with late relapse and isolated extramedullary relapse have a better prognosis than other types of relapse, HSCT is commonly recommended for relapsed patients during the second remission [74].

Indication for HSCT in pediatric ALL is changing, with the development of novel immunotherapeutic approaches, so decisions on HSCT should be made carefully, considering the risk of effects and complications (Table 3).

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<th>Indication</th>
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<td>Infant at diagnosis</td>
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<td>High-risk CR1 including:</td>
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<tr>
<td>• Philadelphia chromosome positive ALL</td>
</tr>
<tr>
<td>• MLL rearrangement</td>
</tr>
<tr>
<td>• Persistent minimal residual disease, especially T-cell phenotype</td>
</tr>
<tr>
<td>Primary induction failure with subsequent CR1</td>
</tr>
<tr>
<td>First relapse&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>CR2 and beyond</td>
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<sup>a</sup>Patients with very early isolated extramedullary relapse, early isolated bone marrow relapse, any very early bone marrow relapse of precursor B-cell ALL or any bone marrow relapse of T-ALL should receive hematopoietic stem cell transplantation. CR1, first remission; ALL, acute lymphoblastic leukemia; CR2, second remission.

### Table 3. Indications for hematopoietic stem cell transplantation in childhood acute lymphoblastic leukemia

<table>
<thead>
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<th>Treatment of Specific Subgroups</th>
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<td>1) T-cell ALL</td>
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Historically, patients with T-cell ALL have had a worse prognosis than children with precursor BCP-ALL. In a review of a large number of patients treated in COG trials over 15 years, T-cell immunophenotype still proved to be an adverse prognostic factor on the basis of multivariate analyses [75]. However, with current treatment regimens, outcomes for children with T-cell ALL are now improving and approaching those achieved for children with BCP-ALL as EFS of 88.7-90.1% [76,77]. Most trials have classified T-cell ALL patients as a high risk group, so high-dose MTX
and asparaginases have been used to treat T-cell ALL [78].
A recent report from the COG AALL0434 trial which used prophylactic cranial irradiation indicated a better DFS for patients who were randomly assigned to the escalating MTX without a leucovorin arm than for patients randomly assigned to the high-dose MTX arm (91.5% vs. 85.3%) [77].
The use of prophylactic cranial radiation in the treatment of T-cell ALL is declining, so irradiation is limited to patients with very high risk features or CNS3 disease. Currently, prospective trials using upfront nelarabine or bortezomib with combination chemotherapy are ongoing in T-cell ALL.

2) Philadelphia chromosome positive ALL (Ph+ ALL)

The Philadelphia chromosome t(9;22)(q34;q11.2) is present in approximately 3% of children with ALL and leads to the production of a BCR-ABL1 fusion protein with tyrosine kinase activity. This subtype of ALL is more common in older children with BCP-ALL and is associated with high WBC counts, with the incidence increasing to about 25% in young adults with ALL.

The prognosis for Ph+ ALL has been completely revolutionized by the introduction of frontline imatinib. In 2014, COG reported comparable DFS between patients with the combination of imatinib and intensive chemotherapy and patients with HSCT [79]. The European EsPhALL group tested whether imatinib (administered discontinuously) given in the context of intensive chemotherapy improves outcomes for pediatric Ph+ ALL patients. A more recent study based on the use of the second-generation TKI dasatinib combined with intensive chemotherapy and reserving HSCT for high-risk patients and for those with a matched family donor, showed comparable 5-year EFS between the two groups [80]. These data suggest that HSCT can be avoided in a low risk group of Ph+ ALL in CR1. Currently, an international collaborative study is being conducted using EsPhALL based intensive chemotherapy and COG based continuous imatinib.

A recent Chinese randomized study compared outcomes between upfront imatinib and dasatinib with combination chemotherapy in pediatric Ph+ ALL patients. It reported significantly higher EFS in dasatinib arm (presented in the St. Jude VIVA Forum 2019).

3) Infant ALL

Infant ALL is uncommon, representing only 2% to 4% of cases of childhood ALL [81]. Because of their distinctive biological characteristics and high risk of relapse, infant ALL is treated using specific protocols for this subgroup. A common therapeutic strategy used to treat infants ALL is the inclusion of post induction intensification courses with high doses of cytarabine and MTX [14]. For infants with MLL gene rearrangement, the EFS rates have been reported in the 35% range. A very young age (≤90 days), poor early response, or extremely high presenting leukocyte count (≥200,000-300,000/μL), are factors predicting poor outcome in infants [82]. To overcome poor survival, intensified chemotherapy or HSCT are incorporated in most regimens.

4) Down syndrome-ALL (DS-ALL)

Children with Down syndrome are at 10-30% greater risk for developing acute leukemia than children with a normal karyotype [83]. Almost all DS-ALL patients have a precursor B cell phenotype. Several genetic events cooperate in the pathogenesis of DS-ALL, with trisomy 21 being an underlying factor. Overexpression of CRLF2 and JAK2 activating mutations can induce JAK-STAT signaling and promote leukemia [83]. Recent evidence has indicated that NRAS and KRAS mutations occur in some cases and deletions of PAX5 and IKZF in other [25].

Current therapy for DS-ALL offers similar treatment outcomes relative to those for children without DS. However, in general, there is increased morbidity associated with chemotherapy in children with DS. Relative intolerability to toxicity in DS-ALL leads to dose reduction in general, and might increase relapse rate in these patients [84]. Although HSCT remains a viable option for those at high risk or with relapsed ALL, the data on HSCT in patients with DS are limited, and its efficacy in relapsed patients with DS remains unclear.

5) Adolescents and Young Adults with ALL

Adolescents and young adults with ALL have been recognized as a high risk group for decades. Outcomes in almost all studies of treatment are inferior in this age group relative
to outcomes for children younger than 10 years [85]. The reasons for this difference include a more frequent presentation of adverse prognostic factors at diagnosis, including T-cell immunophenotype, Philadelphia chromosome positivity, and Ph-like disease, with a lower incidence of favorable cytogenetic abnormalities. In addition to more frequent adverse prognostic factors, patients in this age group have higher rates of treatment-related mortality and nonadherence to therapy. Current results have confirmed that older adolescents and young adults fare better on pediatric rather than adult regimens [86].

### Novel Therapy for Relapsed Patients

1) **Blinatumomab**

Blinatumomab is a bispecific T-cell engager antibody construct that directs CD3-positive effector memory T-cells to CD19-positive target leukemia cells. It was shown to be effective in children with relapsed or refractory CD19-positive BCP-ALL in an international, multicenter phase I/II study, showing 39% of CR within the first cycle and a median DFS of 4.4 months, increased to 7.5 months in the MRD-negative subpopulation [87]. Major adverse events included neurologic events (24%) and cytokine release syndrome (11%). According to a recent long-term follow-up of 70 pediatric patients, 22 (32%) treated at the recommended phase 2 dose were alive at their last follow-up visit [88].

2) **Inotuzumab**

Inotuzumab is an antibody-drug conjugate composed of a humanized IgG subtype 4 monoclonal CD22-targeted antibody linked to calicheamicin, an antitumor antibiotic. Promising results have been obtained in a cohort of heavily pretreated 51 children with relapsed or refractory ALL treated on a compassionate use basis; 67% of patients achieved CR, and the majority (71%) of the responders were MRD negative. Therefore, this observation provides a strong basis for implementing a prospective, multicenter, phase I/II study [89]. For adverse events, no patient developed sinusoidal obstruction syndrome (SOS) during inotuzumab therapy as observed in some adults; however, 11 of 21 (52%) patients who underwent HSCT following inotuzumab developed SOS.

3) **Chimeric antigen receptor (CAR) T cells**

Chimeric antigen receptors are receptor proteins that have been engineered to give autologous T cells the ability to target a leukemia-specific protein, CD19-CAR T cells are currently the most advanced T-cell therapy tested in clinical trials on patients with BCP-ALL. Initial clinical reports and clinical trials have demonstrated a 70-90% complete remission rate [90,91], with durable remissions obtained in patients with relapsed/refractory ALL who were considered incurable. Durable remissions after CAR-T infusion lasted over 6 months with 80% probability and 12 months with 59% probability [90].

Significant side effects of CAR-T cell therapy include prolonged B-cell aplasia and cytokine releasing syndrome (CRS). CRS is a form of systemic inflammatory response syndrome, and a common side effect observed with immune-modulating antibody therapies and CAR-T therapies. The degree of CRS corresponds to the leukemia burden at treatment. For moderate to severe CRS, the use of immunosuppressive agents like corticosteroids may be necessary, but judgment must be used to avoid negating the effect of drugs intended to activate the immune system. Tocilizumab, an anti-IL6 monoclonal antibody, has been used to treat severe CRS. In this era of CD19-directed immunotherapies, CD19-negative relapse in BCP-ALL is a significant problem, occurring in up to 20% of patients after therapy [92]. Two proposed mechanisms of CD19-negative relapse have been suggested: loss of the CD19 epitope and lineage switching [93]. Currently, a method for detection of CD19-negative relapse has not been identified, and anti-CD22 agents and dual CAR-T cells are being investigated for treatment.

### Conclusions

Collaborative group trials have refined the molecular classification of ALL and have substantially improved strategies for personalized treatment by identifying new targets for therapeutic intervention. These collaborative studies should continue to solve many issues relevant to Ph+ ALL, Ph-like ALL, infant ALL, and relapsed/refractory ALL, as
well as reducing long-term toxicities from treatment. Effective immunotherapies and cellular therapies will continue to be developed, especially for patients with no known genetic lesions that are responsive to available molecule-targeted therapy.

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