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Pediatric Acute Lymphoblastic Leukemia: Recent Advances for a Promising Future

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Abstract

Acute lymphoblastic leukemia (ALL) is the most common pediatric cancer and accounts for approximately 75% of all cases of childhood leukemia. Both diagnostic and therapeutic advances have been instrumental in improving the outcomes of once a dreaded disease. Currently, approximately 90% of the children treated according to risk-directed and response-adapted therapy will be long-term survivors. The use of pediatric protocols for the treatment of adolescent and young adults (AYA) has also resulted in significant improvements in their long-term survival. New therapies including tyrosine kinase inhibitors (TKIs), monoclonal antibodies and CAR T-cell therapy are changing the approach to therapy for relapsed or refractory disease. We are approaching a time where therapy for all patients will be personalized with the use of genome-based characterization of disease and incorporation of drugs against actionable targets, ultimately leading to improved clinical outcomes and decreased toxicity of therapy. Still, certain subgroups including patients with relapsed disease, infant ALL, and those with certain cytogenetic/molecular variants, remain challenging to treat. This chapter is an overview of the recent advances in the ALL disease biology, newly identified prognostic factors and an overview of emerging therapeutic options.

Keywords: acute lymphoblastic leukemia, minimal residual disease, CAR T-cell therapy, monoclonal antibody, advances

1. Background

ALL is the most common childhood malignancy and accounts for approximately 30% of all childhood cancers and 75% of all cases of childhood leukemia [1, 2]. Each year, 3600 new cases of childhood ALL are diagnosed in the United States. Precursor B-ALL accounts for approximately 80–85% of the cases, while 15–20% are of the T-cell type [3]. The peak age group for ALL is 2–8 years, which accounts for approximately 80% of the childhood ALL burden. The incidence decreases from 90 cases per million in the 2-8-year age group to 30 per million beyond 8 years of age [3, 4]. ALL is more common in children compared to older age groups as shown in **Figures 1** and **2** [5].

The treatment of childhood ALL has evolved over the past 50 years. Successful development of multi-agent chemotherapy regimens, improved disease risk stratification as well as enhanced supportive care have been instrumental in improving survival (**Figure 3**) [6]. The ALL chemotherapy backbone has included various phases—remission induction, central nervous system-directed therapy, interim maintenance and continuation therapy—with essentially the same chemotherapy

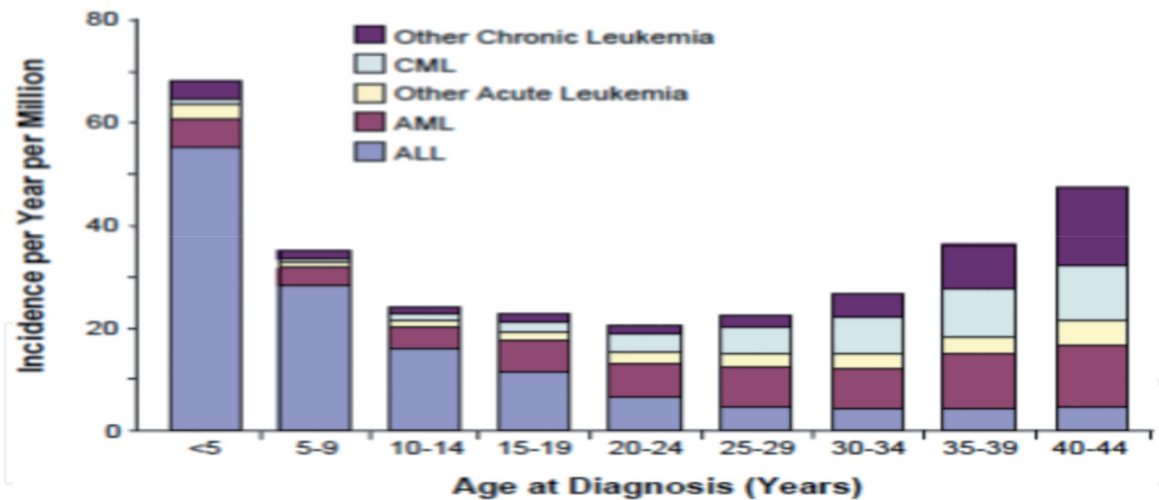


Figure 1. Incidence of leukemia by age, SEER 1975–1999 [6].

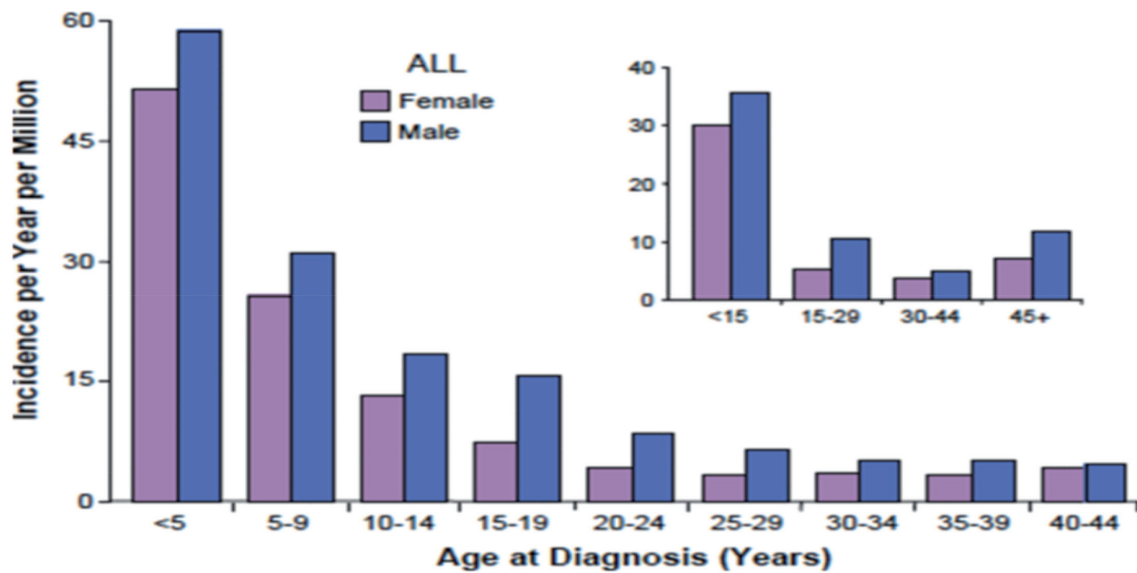


Figure 2. Incidence of acute lymphoblastic leukemia by age and gender, SEER, 1975–1999 [6].

drugs in use since the 1960s. Modifications in dosing, mode of administration and varying combinations have resulted in improvements in outcomes now reaching a plateau [7–10]. Certain subgroups continue to have a very poor outcome, including those patients with relapsed disease, infant ALL, and specific disease-related cytogenetic and molecular changes.

Childhood ALL differs from adult ALL in several ways. The overall survival (OS) of pediatric ALL has reached 90%, whereas adults still fare poorly at approximately 40% [10, 11]. Biologically, there is a higher frequency of poor prognostic subtypes like Philadelphia (Ph) positive and multi-lineage leukemia (MLL) rearranged leukemia in adults compared to children (7% vs. 1–2%) [12]. On the contrary, children have a higher frequency of favorable cytogenetics like hyperdiploidy and ETV6-RUNX1 as their leukemia drivers [12]. The majority of children with ALL are treated at specialized centres and as part of clinical trials, unlike adults. Additionally, pediatric protocols have a greater dose intensity and deliver therapy guided by degree of myelosuppression. Adults generally tolerate treatment less well, resulting in increased treatment related toxicity

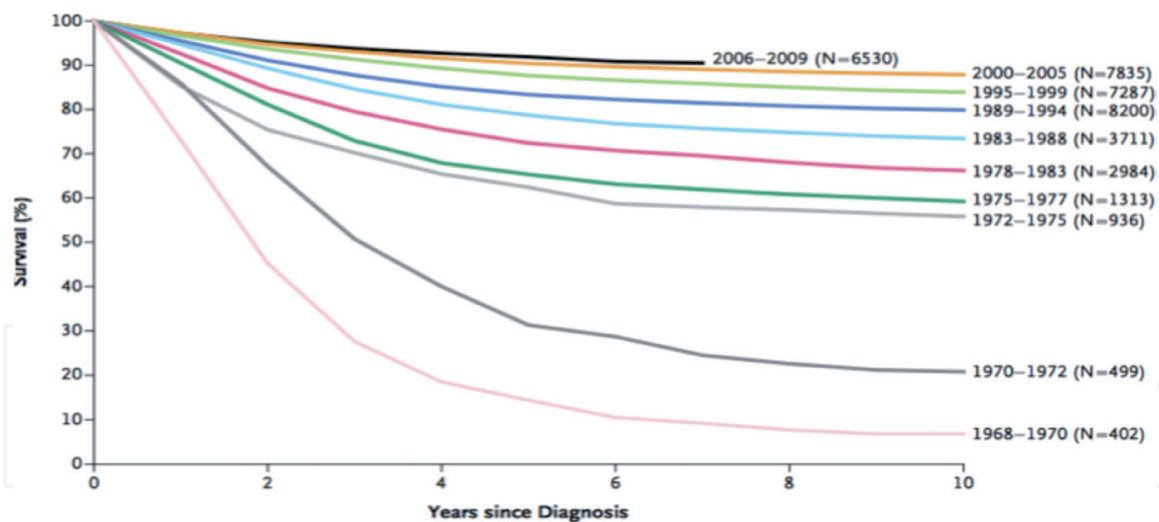


Figure 3. Overall survival of children with acute lymphoblastic leukemia who were treated in the Children’s Cancer Group and Children’s Oncology Group trials between 1968 and 2009 (reprinted from Ref. [6], Copyright (2015) with permission from Massachusetts Medical Society).

[13]. The increased treatment related toxicity in adults could also be due to the increased use of stem cell transplant (SCT) in first remission, unlike the pediatric population where it is reserved only for high risk, poor responding or relapsed subgroups. Additionally, the use of pediatric-type protocols for the treatment of adolescent and young adults has resulted in significant improvements in their long-term survival [14, 15].

2. Minimal residual disease (MRD)-guided therapy

Minimal residual disease measured post-induction has been shown to be most predictive of long-term outcomes across various studies [16–18]. It is an amalgam of leukemia biology, patient factors as well as therapy. With the current protocol-based, risk-directed therapy complemented by MRD based risk stratification, approximately 90% of the children aged 1–18 years are expected to be long-term survivors [19–22]. Various sensitive techniques have been utilized for evaluation of MRD including multi-color flow-cytometry (MFC), RT-PCR and next generation sequencing, which can detect 1 leukemic cell in 10,000–100,000 normal cells [16]. Analysis and tracking of Ig/TCR gene rearrangements by PCR is feasible in 90% of B and T-ALL and detection of fusion gene transcripts in approximately 30–40%. Other new techniques of MRD analysis include high-throughput sequencing (HTS) of Ig/TCR with a sensitivity of 1 in 1 million cells (10^{-6}) [23]. In a recent study by Wood et al., HTS and MFC were comparable and HTS produced similar results as regards the prognostic significance of MRD [23]. Therapy modification based on MRD in the UKALL2003 and the Dutch ALL10 trial was associated with improved outcomes in childhood ALL [22, 24]. The AIEOP-BFM-ALL 2000 trial showed improved outcomes in both pediatric B and T ALL with MRD based therapy [25]. With the use of clinical and biological factors to stratify children with ALL into various risk groups, risk-directed therapy has led to the delivery of less intense as well as less toxic therapy to the low risk groups and more intensive therapy to those with a higher probability of relapse and poorer outcomes.

Despite high cure rates for pediatric ALL, up to 20% of the children will relapse. Re-induction for this group of patients yields remission in 79–90% of patients,

however long-term survival is only 40–50% [26, 27]. Moreover, the outcomes are worse in patients with primary refractory or relapse and refractory disease (r/r) as well as relapse post SCT; hence the unmet need for durable therapies for such children. The incorporation of newer therapies including monoclonal antibodies and Chimeric Antigen Receptor (CAR) T-cell therapy offer an alternative approach to the management of relapsed/refractory pediatric B ALL. The increasing use of upfront genome-based characterization of disease, and incorporation of drugs against identified actionable targets, will ultimately lead to improved clinical outcomes and decreased toxicity of therapy. This chapter will focus on the recent diagnostic and therapeutic advances which are changing the way children with ALL are treated.

3. Novel diagnostics in ALL

The recent WHO 2016 classification has incorporated morphological, immunophenotypic and the existing cytogenetic features with the new molecular features associated with the various subgroups of ALL [28]. Cytogenetic/molecular abnormalities have been identified in 60–80% of patients with ALL using traditional methods [29]; however, with the advent of genome-wide analysis, this number is expected to increase. Evolution of the diagnostics from morphology, immunohistochemistry, and banding techniques to genome-wide analysis and epigenomics has led to an increased appreciation of the biology of leukemia. Genome-wide studies have also provided insight into the variation in the response to chemotherapy drugs among patients, explaining both the differences in toxicities and response to therapy [30]. In the near future, it can be envisioned that ALL will be molecularly characterized and defined, thus enabling us to deliver tailored therapy.

4. Existing and novel genomics of ALL

Cytogenetic aberrations in ALL have emerged as one of the most important prognostic factors driving the biology of the disease and patient outcomes [29]. Existing and recently identified novel prognostic markers are illustrated in **Figure 4** [31]. Children carrying either high hyperdiploidy (51–65 chromosomes) or ETV6-RUNX1 as their cytogenetic drivers have an excellent prognosis with survival of >90% at 5 years. Adverse prognostic factors include t(9; 22), MLL translocation, t(17; 19), complex karyotype, low hypodiploidy (31–39 chromosomes), near haploidy (24–30 chromosomes), and near triploidy (60–78 chromosomes) [13]. Germline TP53 mutations are seen in children with ALL and low hypodiploidy (chromosomes 31–39) and confer a poor prognosis [32]. New additions to the list of adverse prognostic factors include BCR-ABL-1 like mutations, iAMP21, CRFL2 overexpression, JAK mutations, and translocations involving immunoglobulin heavy chain (IGH), TCF-PBX1, IKZF1, PAX5, ERG and EBF1 mutations [31, 33–37]. Association of CDKN2A/2B deletions with Ph + ALL have emerged as a poor prognostic factor with guarded prognosis even with SCT [33]. FLT3 mutations have been found in KMT2A rearranged infant ALL and confer a poor prognosis [38–40]. Growing understanding of the biology of the disease allows better risk stratification and in some cases alterations to therapy to improve outcomes. For example, therapy intensification has resulted in improved outcomes in children harboring the iAMP21 mutation [41, 42].

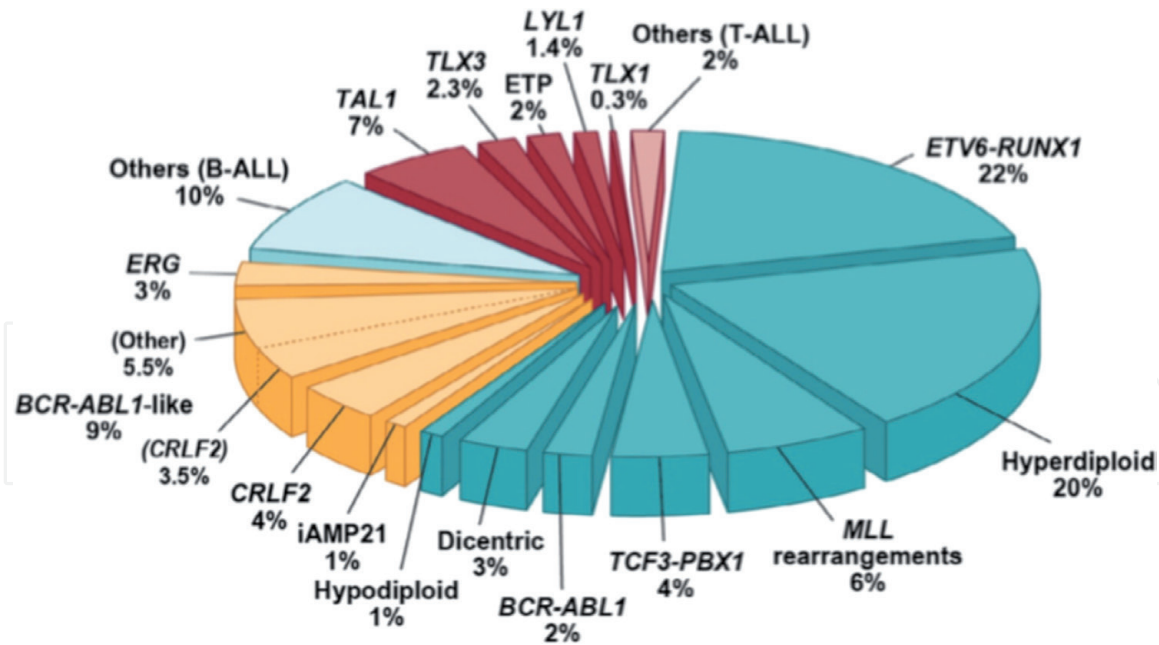


Figure 4. Sub-classification of childhood ALL. Blue wedges refer to B-progenitor ALL, yellow to recently identified subtypes of B-ALL, and red wedges to T-lineage ALL (reprinted from Ref. [31], copyright (2013) with permission from Elsevier).

In T-cell ALL, mutations commonly found are those involved in T-cell development. Mutations of the NOTCH-1 activating gene are seen in approximately 50–60% of all the T-ALL cases, while mutations involving the tumor suppressor gene FBXW7 are found in approximately 15% of cases [43]. The French group (FRALLE) has demonstrated favorable outcomes in those with NOTCH/FBXW7 mutations along with wild-type PTEN/RAS [44]. However, the prognostic significance of these in T-ALL is not well defined [45, 46]. Genome-wide association studies have recently identified a number of inherited genetic polymorphisms that are associated with an increased predisposition to develop ALL. These novel genes include ARID5B, GATA3, IKZF1, CDKN2A, CDKN2B, PIP4K2A and TP63 [47–53].

4.1 Novel genomics

Salient features of the novel prognostic factors are described below:

4.1.1 Ph-like ALL

BCR-ABL1-like ALL has recently been recognized by sequencing studies by the COG-St Jude consortium (TARGET) and the DCOG, and disease shows a similar gene expression profile to that of Ph + ALL in the absence of the BCR-ABL-1 gene translocation [54–56]. This accounts for 10% of pediatric and 15–20% of AYA ALL and confers an extremely poor prognosis with 5-year disease free survival (DFS) of 25% in AYA patients [34, 54]. The AALL0331 study showed decrease prevalence of Ph-like ALL in children with NCI standard risk (SR) compared to high risk (HR) ALL [57]. Ph-like ALL harbors two types of genomic alterations namely *kinase activating* and *cytokine receptor alterations* [58]. The kinase alterations which can be inhibited by ABL inhibitors include *ABL1*, *ABL2*, colony stimulating factor 1 receptor (*CSF1R*), platelet-derived growth factor receptor alpha and beta (*PDGFRA*, *PDGFRB*) [34]. Cytokine receptor alterations include alterations that act via the *JAK/STAT* pathway. This includes membrane-bound thymic stromal

lymphopoietin receptor (*TSLRP*)/*CRLF2*. Other pathways involving *CRLF2* include *PI3K* and the *mTOR* pathways [58]. *CRLF2* gene rearrangements have been associated with 50% of the cases of Ph-like ALL, of which another 50% also show positivity for *JAK* mutations [33, 56]. Additionally, *IKZF1* deletions (28%), *EPOR*, *RAS* pathway (10%) are also seen in this group. Patients harboring the *CRLF2* alterations fare poorly with high risk of relapse [59]. Similarly, increased expression of *IKZF1* possibly translates into high post induction MRD as well as higher risk of relapse [60, 61].

4.1.2 *IKZF1* deletions

The *IKZF1* deletion has recently emerged as a novel genomic marker in childhood ALL. This subtype is commonly seen in older children, those with higher WBC counts, Down syndrome (DS), BCR-ABL and Ph-like ALL [55, 59, 62, 63]. Increased association is also seen with *CRLF2* mutations [62]. *IKZF1* deletion is an independent poor prognostic genomic feature in multivariate analysis [64–68]. The AIEOP-BFM group showed *IKZF1* deletions confer a poor prognosis only in the high end-induction MRD group with co-existent *CDKN2A*, *CDKN2B*, *PAX5*, or *PAR1* mutations [69].

4.1.3 *JAK*-pathway mutations.

JAK mutations are commonly found in Ph-like ALL (20%) and are also associated with *CRLF2* mutations [33]. These are also seen in approximately 15% of children with DS ALL [34, 70, 71]. Identification of this mutation is essential as it has therapeutic implications with responses seen both *in vitro* and *in vivo* to TKIs [72]. The ongoing phase II trial AALL1521 is testing upfront addition of ruxolitinib to chemotherapy for *CRFL2* rearranged or *JAK*-pathway mutant children with ALL [73].

4.1.4 *Immunoglobulin heavy chain gene (IGH) rearrangement, CRLF2 overexpression*

IGH, a novel, adverse prognostic, cytogenetic driver is seen in less than 3% of pediatric and 10% of AYA ALL [74]. This rearrangement is characterized by the juxtaposition of a partner oncogene like *CRLF2* (25%) or *CEBP* (10%) with *IGH* that drives the overexpression. *CRLF2* overexpression is seen in a very high proportion (>50%) of children with DS, but the prognostic significance is still unclear [59].

4.1.5 *iAMP21*

This novel prognostic marker is seen in about 1.5–2% of pediatric ALL and is characterized by ≥ 3 extra copies of *RUNX1* gene on a single abnormal chromosome 21q22 [75, 76]. Increased predisposition to develop *iAMP21* ALL is seen in carriers of the Robertsonian translocation involving chromosomes 15 and 21 [77]. This subtype presents in older children (median 10 years), is more common in females, and presents with WBC count of less than $50 \times 10^9/L$. Presence of this mutation confers a poor prognosis with standard therapy as well as high post remission-induction MRD [41, 78, 79]. However, the outcomes are better with MRD-guided and intensive chemotherapy, as shown in the UKALL2003 and the ALL-BFM 2000 studies, hence precluding the need for SCT in first remission [41, 42].

4.2 Treatment

4.2.1 Adolescents and young adults (AYA) with ALL

AYA constitutes a unique group of ALL with an age range of 15–39 years as defined by the NCI. Based on disease biology, there has always been a debate as to the best regimen to be used in this age group. Historically, ALL in the AYA population has been associated with a poor outcome and higher treatment related morbidity. However, the current focus of treating AYA as per pediatric protocols has resulted in improvement in their outcomes [14, 15] as shown in **Table 1**. Chemotherapy protocols similar to the BFM backbone with corticosteroids, vincristine and asparaginase in induction, post-remission asparaginase, and CNS prophylaxis during induction have shown improved survival in this cohort of patients. Also, SCT is offered only to the very-high risk population in first complete remission (CR1) [80].

To support this further, the excellent results from the large study by the GRAALL group have shown significantly improved survival (66% vs. 44%, $P < 0.001$) for those treated with pediatric-inspired protocols compared to historical controls treated with adult protocols [81]. The largest study which has evaluated this hypothesis is the US intergroup trial C10403, in which 318 AYA patients were treated as per the standard arm of the COG AALL0232 protocol. Encouraging results from this study showed a 2-year event free survival (EFS) of 66% and overall survival (OS) of 78%, with manageable toxicity profile and subsequently the NCI recommended that pediatric-inspired protocols could be used effectively up to the age of 40 years [82].

4.2.2 Philadelphia-chromosome positive ALL (*Ph* + ALL)

This high-risk group of ALL constitutes about 20–30% of the adult ALL and 3% of pediatric ALL [88]. Approximately 90% of the pediatric *Ph* + ALL have the p190 translocation, which results from the translocation within the ‘minor’ breakpoint cluster region (mBCR) [89]. It is also characterized by a high frequency (66%) of deletions in B-cell development genes like IKZF1, PAX5, EBF1 and CDKN2A/B. [33, 88, 90]. Historically, outcomes were extremely poor with 5-year OS of 19%

Serial no.	Study group	Patients numbers (n)	Median age (y)	Survival (%)
1.	CCG [14]	197	16	67, OS 7y
2.	CALGB [15]	124	19	46
3.	FRALLE93 [15]	77	16	67 EFS
4.	AIEOP [83, 84]	150	15	80, OS 2y
5.	DCOG [85]	47	12	71 EFS
6.	NOPHO92 [86]	36	16	74, OS 5y
7.	MRC ALL [87]	61	15–17	71, OS 5y
8.	UKALL2003 [24]	229	16–24	72 EFS

CCG, Children’s Cancer Group; CALGB, Cancer and Leukemia Group; FRALLE, French Acute lymphoblastic Leukemia Study Group; AIEOP, Associazione Italiana di Ematologia e Oncologia Pediatrica; DCOG, Dutch Childhood Oncology Group; NOPHO, Nordic Society for Pediatric Hematology and Oncology; MRC ALL, Medical Research Council (United Kingdom).

Table 1.

Improved outcomes for AYA when treated according to pediatric-based protocols.

without transplant and 35–45% with transplant in CR1. However, survival has drastically improved with the advent of TKIs as seen in the UKALLXII/ECOG2993 study, 4-year OS with imatinib compared to historical cohort, 38% vs. 22% [91]. The AALL0031 reported excellent 5-year EFS of 70% ± 12% in patients treated with continuous imatinib and intensive chemotherapy compared with 31–39% for historical controls [92, 93]. Second generation TKIs are highly potent, demonstrate faster and deeper remissions, as well as increased CNS activity with an acceptable toxicity profile. The COG AALL0622 trial, did not show any survival advantage of dasatinib over imatinib when added to upfront chemotherapy backbone, 5-year OS 81% vs. 86% for AALL0031 and AALL0622 respectively. In the same study, IKZF1 deletions were identified in 57% of cases and were associated with inferior outcomes [94].

Ph + ALL is no longer considered a subgroup for allogeneic SCT in CR1, and is reserved for poor responders or for relapsed disease. The AALL0031 study showed improved 3-year EFS equal to or better than sibling-related SCT (88% vs. 57%) for patients treated with imatinib and intensive systemic chemotherapy. Long-term follow-up data from the same study showed 5-year DFS of 70% in the imatinib plus chemotherapy group compared to SCT (65%-sibling donor, 59%-unrelated donor) [93]. The Korean Society of Adult Hematology working party showed similar 2-year molecular relapse-free survival in those not transplanted versus those transplanted (65% vs. 53%) [95]. In a study by Ravandi et al., achievement of negative MRD status was a significant prognostic factor regulating long-term survival. The 4-year OS rates were 66, 43 and 32% in patients with 3-month CMR, major molecular remission (MMR) and less than MMR, respectively [96]. Hence, adequate molecular response is the deciding factor for no SCT versus SCT.

With regards to the use of TKIs in the post-transplantation period, the consensus statement of the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation, recommends patients with undetectable MRD post allogeneic SCT may be either treated prophylactically or, may be monitored and treated pre-emptively with TKI if they have detectable MRD post-transplant. TKIs may be continued for a period of 12 months of continuous MRD negativity for those undergoing SCT in CR1, and continued indefinitely for those undergoing SCT in ≥2nd CR status [97]. Currently AALL1631, an international collaborative trial between the COG and the EsPhALL groups, is testing combination chemotherapy with imatinib in Ph + ALL. This randomized trial will assess survival and toxicity outcomes with less intensive therapy for those who are MRD negative post induction compared to the current EsPhALL and COG AALL1122 protocols. The role of post-transplant imatinib in the high-risk group of Ph + ALL undergoing SCT is also being evaluated [98].

4.2.3 Philadelphia-like ALL (*Ph-like ALL*)

Ph-like ALL constitutes a high-risk subtype of pediatric B ALL. Most studies demonstrate a poorer prognosis despite augmented traditional chemotherapy [54, 57, 70]. Interestingly, the Total XV study showed MRD directed therapy negated its poor prognosis [99]. Research is currently ongoing for a better understanding of the genomics of this group and we now know that this group harbors certain targetable genetic alterations. Potential targets and agents tested in pre-clinical models include; *CRLF2* inhibition (Givinostat [100], Luminespib [101], Selumetinib [102], TSLPR CART cells [103]), *JAK-2* (CHZ868) [104], *mTOR* pathway (Rapamycin) [105], *PI3K* and *mTOR* pathways (Gedatolisib) [106], and *TNF-α* inhibition (Birinapant) [107]. These targets are now being prospectively studied in clinical trials across various centres. The MDACC trial in children older than 10 years is testing ruxolitinib or dasatinib with chemotherapy [108].

Also, the phase II COG AALL1521 study is testing ruxolitinib with conventional chemotherapy in the age group of 1–21 years [109]. Another phase II trial from the NCI (COG AALL1131) in 1–30-year olds is testing dasatinib in combination with chemotherapy [110].

4.2.4 Hypodiploid ALL

Hypodiploidy (<45 chromosomes) is present in less than 5% of ALL. Survival across various studies ranges between 50 and 60% on currently available therapy [111–113]. Near haploid (24–30 chromosomes) and low-hypodiploidy (chromosome 31–39) fare poorly on current protocols with 5–8-year EFS of 25–40% for near-haploid and 30–50% for low-hypodiploid ALL [111, 112, 114]. Interestingly, MRD has emerged as an important prognostic marker; improved long-term survival is seen in those with MRD negativity post induction compared to MRD positive disease as shown by Mullighan et al. (85.1% vs. 44.4%) [115]. Recent studies show that children carrying pathogenic germline TP53 mutations have a significantly higher incidence of hypodiploidy (65% vs. 1%), inferior EFS, OS and a very high chance of developing second cancers [92]. Also, a significantly large proportion (91.2%) of low hypodiploidy ALL is associated with germline TP53 mutation suggesting a possible association of hypodiploid ALL with Li-Fraumeni syndrome. In a study by Holmfeldt et al., near-haploid ALL was found to be associated with *RAS*-signaling, *CREBBP*, *CDKN2A/B*, *PAG1* and *IKZF3*, and low hypodiploidy with *P53*, *IKZF2*, *RB1*, *histone modifiers* and *CDKN2A/B* [32, 116, 117]. The COG ALL03B1 showed no survival benefit from CR1 SCT. Interestingly, this was also true if children were MRD (>0.01%) positive pre-transplant [113]. Novel therapeutic approaches with emphasis on molecular targets could be the way forward in improving the outcomes of this high-risk subset of pediatric ALL.

4.2.5 Down syndrome ALL

Children with Down syndrome (DS) have an increased predisposition compared to non-DS children to develop ALL with a cumulative risk of approximately 2.1% by age of 5 years and 2.7% by age of 30 [118, 119]. Children with DS constitute a very special group of pediatric ALL characterized by predominantly B immunophenotype and a marked absence of T immunophenotype. This group is neither associated with the favorable nor the unfavorable cytogenetic abnormalities as seen in common pediatric ALL [120]. *IKZF1* gene deletion, seen in approximately 35% of DS ALL portends inferior outcome [121, 122]. About 50–60% of the children with DS ALL harbor *CRLF2* mutation, much higher than in children with ALL without DS (<10%). Approximately, 20% of children with DS ALL also carry *JAK2* mutations, with majority also harboring *CRLF2* mutation. However, their prognostic significance is unknown [121, 123, 124].

4.2.6 Infant ALL

This rare group comprises 2–4% of pediatric ALL and is characterized by high leukocyte count at diagnosis, bulky extramedullary disease, frequent CNS involvement, and a poor prognosis [125, 126]. A relatively large proportion of these infants harbor the *KMT2A* gene on chromosome 11q23 in their malignant clone. [127, 128]. To date, approximately 94 different partner genes of *KMT2A* have been identified, with *AF4* being the commonest [129]. These leukemia may contain *FLT3* mutations (18%) and are characterized by overexpression of homeobox

(HOX) genes [130–133]. Younger age is associated with worse outcome. Despite intensified therapy across various trials groups including COG and Interfant, the 5-year EFS remains poor (34–37%) in the KMT2A-rearranged infants [127, 128, 134]. The role of SCT in CR1 remains controversial. Japanese and COG P9407 studies have not shown any survival benefit with SCT compared to standard chemotherapy alone [134, 135]. The COG study AALL0631 failed to demonstrate any survival benefit with the upfront addition of lestaurtinib to the chemotherapy backbone, despite high levels of FLT3 expression [39, 136]. The COG pilot study AALL15P1, is evaluating the role of upfront addition of azacytidine in combination with standard chemotherapy (Interfant protocol) for epigenetic modification in KMT2A rearranged infant ALL [137].

4.2.7 T ALL

The outcomes for T ALL have been historically very poor, however with current therapeutic approaches, outcomes are now comparable to those of B ALL with 5-year EFS of 85% [138, 139]. MRD has emerged as the most important prognostic factor. Interestingly, kinetics of MRD clearance in T-ALL is slower than B-ALL, with late MRD negativity post-consolidation still translating into improved outcomes (7-year EFS, 80.6% ± 2.3%) [140]. The UKALL2003 and the AIEOP-BFM 2000 trials have shown decreased relapse risk and survival benefit with the use of dexamethasone [138, 140]. Currently, the COG AALL1231 randomized trial is evaluating the role of bortezomib during induction and delayed intensification in patients with newly diagnosed T-cell ALL in the age group of 1–30 years using an augmented BFM-like backbone. Interestingly, this trial is also testing dexamethasone vs. prednisolone during induction and the benefit of the addition of asparaginase during maintenance therapy. Increasingly, cooperative groups are moving away from the use of prophylactic cranial radiation or restricting its use to high risk disease or CNS 3 status in upfront therapy [10, 11, 138, 141, 142]. The COG AALL1231 randomized trial is currently testing the safety of omitting prophylactic cranial irradiation in the non-high risk and non-CNS3 cases. The recent pilot AALL00P2 study tested upfront incorporation of nelarabine in newly diagnosed T ALL and has shown improved 5-year EFS of 73% for all patients and 69% for those with slow early response [143]. The COG AALL0434 randomized study tested nelarabine in frontline therapy and demonstrated safety, however final results are awaited [144]. Allogenic SCT is currently reserved only for those with positive MRD post consolidation [145].

Relapse T-ALL still remains a therapeutic challenge as the salvage rates and OS are less than 25%. In the AALL01P2 study, out of 7 patients with relapsed T-ALL, only 2 achieved CR2 [146]. However, encouraging results from the AALL07P1 trial have shown CR2 of 68% by the addition of bortezomib to a 4-drug re-induction regimen [147]. The focus is on optimizing upfront therapy to prevent relapse in the high-risk patients, with increasing efforts directed at developing effective salvage therapies for relapsed disease. Genomic sequencing studies have identified mutations related to various signaling pathways like *JAK/STAT*, *NOTCH*, *PI3K/Akt/mTOR* and *MAPK* with emerging pre-clinical evidence for targeted therapy [116, 148, 149]. Pre-clinical studies are also underway for the development of CD5 directed CAR T-cell therapy [117] as well as NK cell CARs against the T-ALL (personal communication from DiPersio and Rezvani).

4.2.8 Early T-precursor (ETP) ALL

ETP ALL has emerged as a new entity with increased heterogeneity at the molecular level. This subtype harbors *NOTCH1* mutation at a much lower

frequency than T-ALL. It has a transcriptional profile similar to normal hematopoietic and myeloid stem cells [150]. Comparative genomic hybridization studies have shown absence of biallelic deletion of the TCR gamma locus (ABGD) and inferior outcomes with early treatment failure in this sub-group. [151, 152]. Other pathways implicated are the *JAK/STAT*, *PI3K/Akt/mTOR*, *FLT3*, and *MAPK* [153, 154]. Ruxolitinib, a *JAK1/2* inhibitor has shown single-agent activity in pre-clinical studies [155]. There is emerging evidence that treatment on high risk regimens and MRD guided therapy leads to similar outcomes to those of standard T ALL [156, 157].

4.2.9 Immune-targeting in relapsed/refractory B-ALL

4.2.10 Role of monoclonal antibodies in paediatric ALL

The role of monoclonal antibodies against human differentiation antigens was first demonstrated by Kohler and Milstein using hybridomas with a goal of treatment of hematological malignancies [158]. ALL is an excellent candidate for the incorporation of monoclonal antibody therapy due to a fairly constant lineage-specific antigen expression on the blasts and minimal expression of target antigen on normal tissues. Studies have demonstrated high remission rates with these agents, non-overlapping and manageable toxicity profiles leading to the FDA approval of these treatments for pediatric ALL. Monoclonal antibodies like blinatumomab and inotuzumab ozogamicin (InO) have shown excellent remission rates in pediatric ALL. The COG is currently evaluating antibodies like alemtuzumab, rituximab, blinatumomab, InO, and epratuzumab, both in r/r ALL as well as in newly diagnosed B-ALL in combination with standard chemotherapy, with a potential in future to be either incorporated with upfront therapy or replace certain components of standard of care chemotherapy.

4.2.11 Blinatumomab

Blinatumomab is a bi-specific T-cell engager antibody with binding sites to CD19 on B cells and to CD3 on T cells. Binding activates cytotoxic T cells, which induce cell death in the leukemic cell via the perforin system [159]. This drug is administered as a continuous infusion over 28 days and has shown acceptable activity and safety in various trials and was first FDA approved in December, 2014 for use in r/r Ph negative ALL. Pioneering work by Topp et al. in a phase II, single-arm clinical trial showed that 80 % (16 of 20) of MRD positive patients became MRD negative post first cycle of blinatumomab [160]. Encouraging results from the BLAST trial, wherein 78% of the MRD positive patients became negative post one cycle of blinatumomab led to its FDA approval in MRD positive settings as well [161].

In a phase I/II trial in 70 children <18 years of age with r/r ALL who were treated with single agent blinatumomab, 39% (27) achieved CR and MRD negativity in 52% [162, 163]. The AALL1331 phase III randomized trial is testing whether upfront addition of blinatumomab improves DFS in first relapse of ALL. In this trial all patients receive UK ALL R3 protocol for remission induction. Subsequently, the low risk group gets randomized to either control arm of R3 protocol or to receive three cycles of blinatumomab along with chemotherapy. The intermediate and the high-risk groups are randomized to either chemotherapy or two cycles of blinatumomab along with chemotherapy before proceeding to SCT. This trial is currently accruing patients and the results are awaited [164].

4.2.12 Inotuzumab ozogamicin (InO)

InO is a monoclonal antibody against CD22 and conjugated to calicheamicin, a potent cytotoxic compound which binds to the DNA in the leukemic blasts, resulting in double-stranded DNA breaks and cell death via apoptosis [165]. It was FDA approved in August, 2017 for use in r/r ALL. In a phase II study in r/r ALL in the age group of 6–80 years, Kantarijian et al. demonstrated ORR of 57% with median OS of 6.7 months [166]. In phase III INO-VATE trial in relapsed adult B ALL, single agent InO showed superior outcome compared to standard chemotherapy with CR (81%) and 1-year OS (78%) [167]. However, its use in pediatric population continues in development. A retrospective French study in children <18 years with r/r B-ALL showed promising results (CR 72%), with hepatic and hematologic toxicities [168]. Bhojwani et al. in r/r pediatric ALL showed high CR rate (67%) with MRD negativity, independent of cytogenetic subtype or prior lines of therapy [169]. The AALL1621 phase II randomized trial in the age group 1–21 years is evaluating the role of InO in children and young adults with r/r CD22+ B ALL [170].

4.2.13 CAR T-cell therapy: the new driving force for relapsed ALL

Relapsed or refractory ALL is one of the leading causes of childhood cancer mortality. Refractory ALL in particular has a dismal prognosis with significant chemotherapy resistance in the leukemic clone. The advent of CAR T-cell therapy has brought a paradigm shift in the management of children with highly resistant disease. Rosenberg et al. at the NCI pioneered the CAR T-cell therapy and demonstrated successful treatment of cancer using CAR T-cells. This attractive therapy harnesses the immune system of the host to eradicate the leukemic clone. Adoptive T-cell therapy involves engineering T-cell receptors (TCRs) to bind to specific antigens present on tumor cells. These modified TCRs, known as CARs, allow the immune system to specifically target and destroy tumor cells in an MHC independent manner, bypassing the immune escape mechanisms of downregulation of MHC class I antigens and altered antigen processing by tumor cells [171]. These modified T cells have the capacity to expand and proliferate in the host, produce cytokines to kill tumor cells, as well as cross blood-brain barrier as shown by Maude et al. [172].

Early results from ongoing trials have shown promising and durable responses. Current complete remission rate of 90% have been reported as per the CHP959 phase I study [172]. The ELIANA [173] and ENSIGN [174] trials in r/r B ALL showed high CR rates of 90%, significantly higher than salvage rates of 30% attained with chemotherapy [26, 175]. This led to the FDA approval of CD19 4-1BB CAR T-cell therapy in August 2017 for children and young adults up to the age of 25 years. Maude et al. showed durable remission and survival in children treated with CD19 CAR T cell therapy with EFS (50%) and OS (76%) at 12 months of follow-up [176]. Success from pediatric CAR T-cell therapy trials is driving research programs across ages and disease types worldwide. The advantage of this therapy is that it can be offered to patients who are ineligible for transplant or have relapsed post-transplant, with a potential to ultimately replace SCT.

Tumor lysis syndrome, cytokine release syndrome and neurotoxicity are known complications of this therapy [177]. Another off-target toxicity is the development of B-cell aplasia, a surrogate for CAR T-cell persistence, results in agammaglobulinemia, and requires long-term immunoglobulin replacement [172]. With the use of CD19 directed CART cells, there is a risk of CD19 negative relapse [177]. Trials are underway to study the efficacy of CD22 CART cells as well as the use of dual CARs (CD19 + CD22).

4.2.14 Liposomal drug formulations

The outcomes for pediatric ALL have significantly improved over the past five decades, and the focus is now on minimizing the toxicity and the late effects of chemotherapy. Liposomal doxorubicin has shown remarkably low non-hematological toxicity, although the infection rates may be significant due to severe myelosuppression [178, 179]. In an attempt to decrease the toxicity of therapy, TACL 2012-002 trial is testing the use of liposomal vincristine in children and AYA with relapsed ALL [180]. This study attempts to study the feasibility and safety of liposomal formulation of vincristine sulphate over standard vincristine in first, second or third relapse of B or T ALL.

5. Conclusions and future directions


Treatment of childhood ALL has evolved over the last 50 years with progress made both in the diagnostic and therapeutic arenas. A growing understanding of the biology of the disease has allowed better risk stratification and in some cases alterations to therapy to improve outcomes. Use of pediatric-type protocols in AYA ALL has improved outcomes. Break-through research leading to the development of CAR T-cell therapy, TKIs and monoclonal antibodies have brought a paradigm shift in the management of r/r B ALL. The medical community must now consider the significant cost of these therapies, with questions related to cost-effectiveness and resource allocation ripe for study. Long-term follow-up data for these revolutionary new cancer therapies are required. Outcomes for infant ALL and relapsed T ALL are still dismal and further research is needed to develop newer strategies to combat disease in these group of patients.

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