Advancing Diagnostics and Therapy to Reach Universal Cure in Childhood ALL

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ABSTRACT

Systemic combination chemotherapy and intrathecal chemotherapy markedly increased the survival rate of children with ALL. In the past two decades, the use of minimal (measurable) residual disease (MRD) measurements early in therapy improved risk group stratification with subsequent treatment intensifications for patients at high risk of relapse, and enabled a reduction of treatment for low-risk patients. The recent development of more sensitive MRD technologies may further affect risk stratification. Molecular genetic profiling has led to the discovery of many new subtypes and their driver genetic alterations. This increased our understanding of the biological basis of ALL, improved risk classification, and enabled implementation of precision medicine. In the past decade, immunotherapies, including bispecific antibodies, antibody-drug conjugates, and cellular therapies directed against surface proteins, led to more effective and less toxic therapies, replacing intensive chemotherapy courses and allogeneic stem-cell transplantation in patients with relapsed and refractory ALL, and are now being tested in newly diagnosed patients. It has taken 50-60 years to increase the cure rate in childhood ALL from 0% to 90% by stepwise improvements in chemotherapy. This review provides an overview of how the developments over the past 10-15 years mentioned above have significantly changed the diagnostic and treatment approach in ALL, and discusses how the integrated use of molecular and immunotherapeutic insights will very likely direct efforts to cure those children with ALL who are not cured today, and improve the quality of life for survivors who should have decades of life ahead. Future efforts must focus on making effective, yet very expensive, new technologies and therapies available to children with ALL worldwide.

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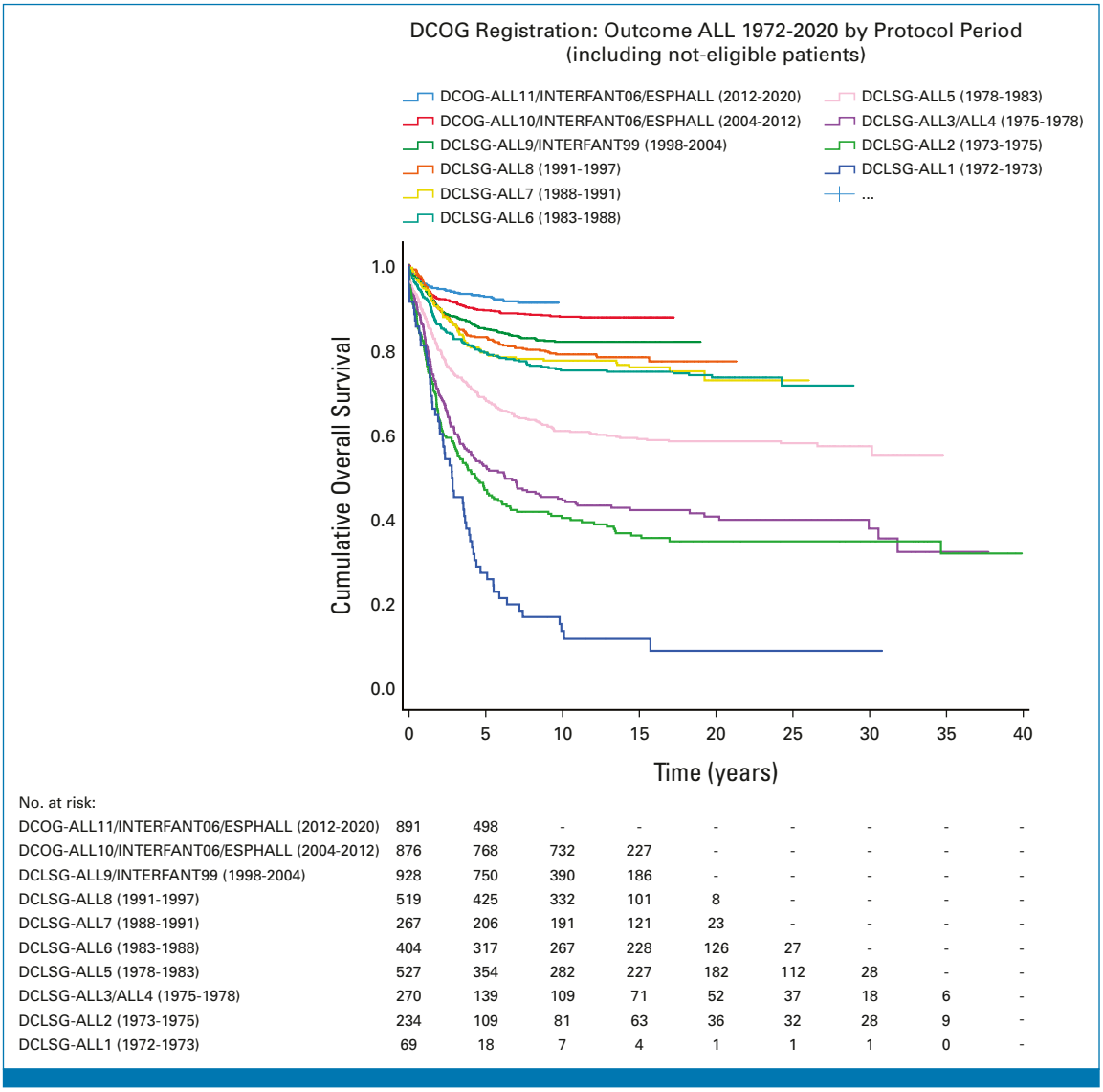
INTRODUCTION

Approximately one of 1,500 newborns develop ALL before their 18th birthday. Long-term survival rates increased from zero in the 1950s to over 90% in the past decade in high-income countries (Fig 1).[1-3] This is attributable to stepwise refinement and intensification of chemotherapy regimens to improve both systemic and CNS control, by more sophisticated use of allogenic hematopoietic stem-cell transplantation (HSCT), improved supportive care, and more recently, improved risk stratification incorporating genomic features and early treatment response quantified by minimal (measurable) residual disease (MRD). In the past decade, genomic analyses have identified many new genetic subclasses of ALL, refining classification of ALL and increased understanding of disease biology.[4] For some subtypes, precision medicine strategies have been or will soon be introduced. The very recent introduction of immunotherapies, including bispecific antibodies, antibody-drug conjugates (ADC), and cellular therapies, has changed treatment for refractory/relapsed (r/r) ALL and is now entering frontline trials.

We review how these developments have and will continue to lead to significant changes in treatment of childhood ALL. We anticipate that this will change ALL from an incurable disease in 1960 to a curable disease for (nearly) all patients and will also significantly reduce the incidence of major toxicities and thereby improve quality of life for survivors.

CURRENT THERAPY

Treatment of childhood ALL involves multiagent chemotherapy, administered in rotating combinations combined with CNS prophylaxis, administered over approximately 2-2.5 years. Regimens typically include induction, followed by one or two consolidation courses, (delayed) intensification and maintenance. Five drugs form the backbone: glucocorticoids (prednisone and dexamethasone), vincristine, asparaginase, methotrexate, and 6-mercaptopurine. Additional drugs include anthracyclines (daunorubicin and doxorubicin), cytosine arabinoside (araC), and cyclophosphamide. Table 1 summarizes the most recent outcome data of the major study groups worldwide.[2,3,5-9]



No. at risk:

DCOG-ALL11/INTERFANT06/ESPHALL (2012-2020)	891	498	-	-	-	-	-	-	-
DCOG-ALL10/INTERFANT06/ESPHALL (2004-2012)	876	768	732	227	-	-	-	-	-
DCLSG-ALL9/INTERFANT99 (1998-2004)	928	750	390	186	-	-	-	-	-
DCLSG-ALL8 (1991-1997)	519	425	332	101	8	-	-	-	-
DCLSG-ALL7 (1988-1991)	267	206	191	121	23	-	-	-	-
DCLSG-ALL6 (1983-1988)	404	317	267	228	126	27	-	-	-
DCLSG-ALL5 (1978-1983)	527	354	282	227	182	112	28	-	-
DCLSG-ALL3/ALL4 (1975-1978)	270	139	109	71	52	37	18	6	-
DCLSG-ALL2 (1973-1975)	234	109	81	63	36	32	28	9	-
DCLSG-ALL1 (1972-1973)	69	18	7	4	1	1	1	0	-

FIG 1. Outcome of Dutch children with ALL from 1972 to 2020. DCLSG, Dutch Childhood Leukemia Study Group; DCOG, Dutch Childhood Oncology Group.

Dexamethasone has greater antileukemic efficacy, but more side effects, than prednisone.[10] Regular 5- to 7-day pulses of corticosteroids and vincristine are widely used during maintenance, but their value is debatable and likely depends on the other components of therapy and the patient subset.[11] The benefit of high-dose versus intermediate-dose methotrexate also depends on the type of ALL.[12,13] Truncation of the asparaginase schedule because of intolerance or silent inactivation of the drug increases the relapse risk.[14-16] Therapeutic drug monitoring is used to detect silent inactivation of asparaginase and facilitates the timely switch to alternative asparaginases.[17,18] How much asparaginase is needed for each subtype defined by MRD or genetics remains to be elucidated.[19] The optimal length of ALL therapy is about 2-2.5 years for both boys and girls.[20] Although 1-year total therapy worsens the overall outcome, half of the patients are long-term survivors with this shorter therapy and limited maintenance duration,[21] but it is unclear how to recognize who will be cured with shorter therapy in advance.[21] Genotyping of the host to adapt chemotherapy is currently limited to the detection of *TPMT* and *NUDT15* polymorphisms that influence 6-mercaptopurine metabolism, with clinical consequences.[22]

Intrathecal therapy is essential to prevent CNS relapses.[23] The benefit of triple intrathecal therapy (methotrexate, hydrocortisone, and cytarabine) versus intrathecal methotrexate is debatable; the intensity of intrathecal versus systemic therapy may influence the site of relapse.[24,25] Cranial radiotherapy reduces the CNS relapse rate only in children with CNS3 disease, but does not influence survival even in this group.[26] A recent report from the Children's Oncology Group shows that outcome in T-cell (T)-ALL is worse with CNS3 status, even with cranial irradiation.[27]

TABLE 1. Outcome Data of the Major Childhood ALL Trials Reporting on Representative Cohorts of Patients With ALL Published After 2015

Protocol	Enrollment Period	Patients, No.	Age, Years	5-Year CIR, %	5-Year EFS, %	5-Year Survival, %	Reference	Remark
AIEOP-BFM 2000 dexamethasone arm	2000-2006	1,853	1-17	11	84	90	Moricke 2016[151]	
AIEOP-BFM 2000 prednisone arm	2000-2006	1,867	1-17	16	81	91	Moricke 2016[151]	
SJCRH total 16	2000-2017	598	0-18	7	88	94	Jeha et al[2]	
COALL-07-03	2003-2010	773	1-18	13	84	91	Schramm 2019[9]	10-year outcome data
UKALL 2003	2003-2011	3,126	1-24	11	85	90	Moorman et al[3]	10-year outcome data
DFCI-05-001	2005-2011	678	1-18	—	87	93	Vrooman et al[5]	
COG	2006-2010	8,090	0-29.9	—	—	91.5	Raetz et al[6]	
NOPHO-2008	2008-2014	1,509	1-45	10	85	91	Toft et al[7]	
Máxima/DCOG-11	2012-2020	778	1-18	8	89	94	Pieters et al[8]	

Abbreviations: CIR, cumulative incidence of relapse; EFS, event-free survival.

Flow cytometric detection of CNS leukemia is more reliable than morphology and positivity is associated with inferior outcome,[28] which is being tested in the ongoing ALLTogether01 protocol. HSCT indications have been reduced by improvements in chemotherapy and are currently T-ALL with induction failure,[29] *BCR::ABL1*-positive ALL with a poor MRD response, and subgroups of *KMT2A*-rearranged (*KMT2A*-R) infant ALL.[30] For high-risk ALL subtypes, including *KMT2A*-R,[31] hypodiploidy <44 chromosomes,[32,33] and *TCF3::HLF*, its value is unproven.

MRD

Monitoring early responses to chemotherapy by MRD significantly improved the prediction of relapse and thereby risk group stratification. MRD is measured by flow cytometry using the leukemic immunophenotype or by PCR of clonotypic *Ig/TCR* rearrangements or fusion genes and genomic deletions.[34] Next-generation sequencing–based MRD[35,36] is more sensitive and more specific. It has not yet been widely implemented in clinical trials but may replace other technologies in the future. MRD-based stratification allows for a reduction of treatment intensity, thereby improving the quality of life for low-risk patients, while not jeopardizing their high survival rate. Persistent MRD identifies a small high-risk group who should be allocated to intensive chemotherapy and HSCT[37] or new precision medicine or immunotherapeutic options to increase survival. The latter may have dual advantages since they also cause fewer side effects.[38]

Successful examples of therapy reduction exist. In some trials, MRD-based low-risk patients do not receive corticosteroid/vincristine pulses, whereas medium-risk patients do. MRD-guided reductions are possible such as reduction of the intensification course and reduction of cumulative anthracycline dose.[8,39-42] The possibility of therapy reductions confronts clinicians and patients/parents with the dilemma of treating all low-risk patients with intensive therapy leading to the lowest relapse risk but increased risk of side effects, versus deintensified therapy for the majority of low-risk patients with better quality of life but possibly a slightly higher relapse rate for a few patients highly likely to be salvaged with rescue therapy. Therapy reductions are mainly applied in good-risk genetic subtypes, for example, *ETV6::RUNX1*, high hyperdiploidy (51-67 chromosomes), and/or those with negative end-of-induction MRD.[43]

SIDE EFFECTS

The most important acute side effects of chemotherapy influencing quality of life are bacterial and fungal infections caused by myelosuppression and the immunosuppressive effect of glucocorticoids, vincristine-induced neuropathy, methotrexate encephalopathy, pancreatitis,[44] and intracerebral venous thrombosis caused by asparaginase, and osteonecrosis, myopathy, and behavioral problems caused by glucocorticoids. Many side effects are reversible, but a small percentage of patients with pancreatitis[44] and about 60% of patients with symptomatic osteonecrosis[45] experience long-term consequences. In patients receiving HSCT, infertility and chronic graft-versus-host disease cause additional serious toxicity. With current survival rates of >90%, quality of life is receiving more attention, leading to outcome indicators cocreated by professionals and survivors focused on toxicity-free survival.[46,47]

MOLECULAR GENETIC PROFILING

Genomic analyses have identified multiple subtypes of B-progenitor (Fig 2) and T-lineage ALL, their drivers, and cooperating genomic alterations, and showed that many children have germline genomic variations that influence leukemia susceptibility and treatment response. Constitutional syndromes such as Down syndrome and ataxia telangiectasia are associated with an increased risk of ALL.[48] Genome-wide association studies identified multiple noncoding polymorphisms influencing the risk of developing ALL, commonly at loci encoding tumor suppressors or hematopoietic transcription factors (*ARID5B*, *BAK1*, *CDKN2A/CDKN2B*, *BMI1-PIP4K2A*, *CEBPE*, *ELK3*, *ERG*, *GATA3*, *IGF2BP1*, *IKZF1 IKZF3*, *USP7*, and *LHPP*). The risk associated with each is subtle but combinatorial.[49] Several may influence acquisition of somatic driver alterations, such as germline *GATA3* alterations and *CRLF2* rearrangement in Ph-like ALL.[50] Pathogenic germline coding variants have been described in multiple genes in ALL, including *TP53*, *PAX5*, *IKZF1*, and *ETV6*.[51-53] These variants have been identified in both familial ALL, which is rare, and sporadic cases with no known family history, at a relatively high frequency (1%-2% of cases). Several germline pathogenic variants show associations with ALL subtypes, such as *TP53* and low hypodiploidy (30-39 chromosomes), and *ETV6* with high-hyperdiploid ALL. Germline *IKZF1* variants also influence drug responsiveness in ALL.[54]

Over 20 subtypes of B-ALL are now recognized, most of which were unknown before genomic profiling as they are not detectable by conventional cytogenetics[55] (Figs 2 and 3). Aneuploid B-ALL subtypes are high-hyperdiploid ALL characterized by gains of at least five chromosomes, most commonly 4, 10, 14, 17, 18, 21, and X, and favorable outcome.[56] Hypodiploid ALL, with multiple chromosomal losses, has two subtypes associated with poor outcome: near-haploid ALL with 25-29 chromosomes, and low-hypodiploid ALL with 30-39 chromosomes.[32,57] Low-hypodiploid ALL is almost always associated with biallelic *TP53* alteration, including a germline variant in about half of the pediatric cases; near-haploid ALL has a similar gene expression profile and mutational spectrum (Ras pathway, *CREBBP*) to hyperdiploid ALL, suggesting a common origin.[4,51,55] B-ALL with intrachromosomal amplification of chromosome 21 (iAMP21) arises from breakage-fusion-bridge cycles and chromothripsis of chromosome 21, and rarely, constitutional alterations of chromosomes 15 or 21.[58]

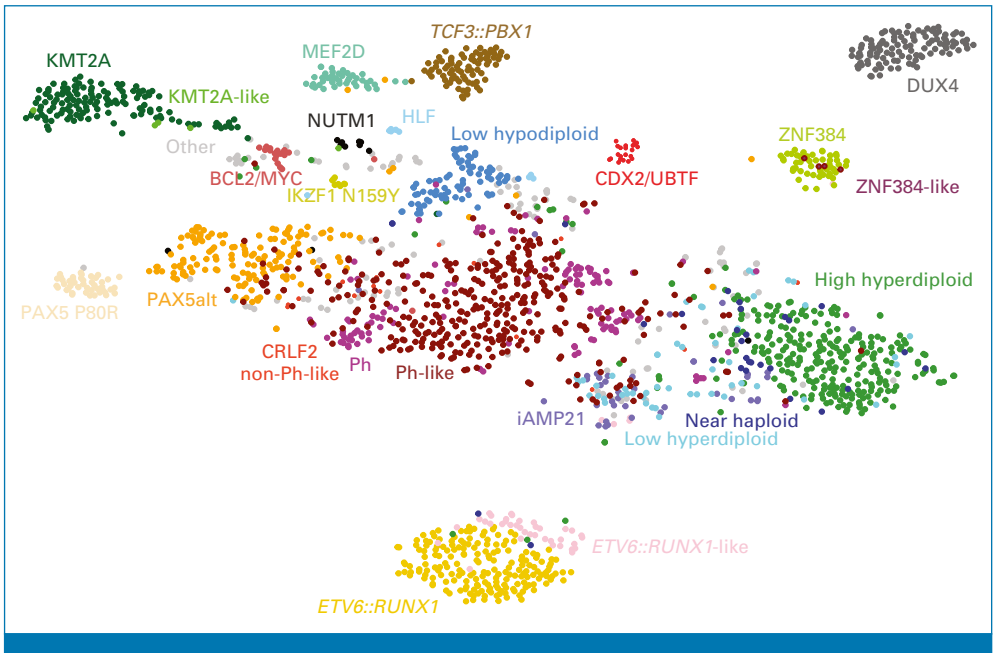


FIG 2. Subtyping of B-ALL using whole-transcriptome sequencing. t-SNE depiction of childhood and adult B-ALL adapted from Kimura et al.[70] Subtypes are color-coded and labeled accordingly. t-SNE, t-weighted stochastic neighbor embedding.

This subtype has been associated with poor prognosis, ameliorated with more intensive treatment regimens.[59]

Chimeric fusion oncoproteins are a hallmark of B-ALL, and commonly arise in utero, years before clinically manifest leukemia, consistent with the requirement for additional genomic alterations to promote leukemogenesis. Several subtypes are defined by a single rearrangement, such as *ETV6::RUNX1*, *TCF3::PBX1*, *BCR::ABL1*, and translocations involving *KMT2A*.[60] By contrast, several recently described subtypes have multiple fusion partners converging on a single gene: *MEF2D*-rearranged,[61,62] *NUTM1*-rearranged,[63] and *ZNF384*-rearranged ALL.[64] *NUTM1*-rearranged ALL is observed in infants without *KMT2A*-R.[63] *ZNF384* rearrangement is characterized by the expression of myeloid antigens diagnosed as ALL or mixed-phenotype acute leukemia that are otherwise biologically indistinguishable, and prone to shift in immunophenotype during disease progression[64,65] or exposure to CD19-directed immunotherapy. Additional subtypes are defined by characteristic alterations in specific genes (*PAX5* P80R, *PAX5*alt with heterogeneous *PAX5* alterations, and *IKZF1* N159Y).[55,66] Rearrangement of *DUX4* to immunoglobulin or other enhancers defines a subtype of favorable-risk ALL,[67-69] albeit with elevated levels of MRD early in therapy. Rare, but high-risk cases have dual alterations that deregulate *CDX2* and encode *UBTF::ATXN7L3*[70]. Ph-like (*BCR::ABL1*-like) ALL[71,72] exhibits a transcriptomic signature similar to *BCR::ABL1* ALL, and is the most genomically diverse form of ALL, with rearrangements and mutations of at least 16 cytokine receptors and tyrosine kinases, most commonly deregulating *JAK-STAT* and *ABL1*-class signaling pathways[73] (Fig 4); this subtype increases in incidence with age and is associated with poor outcome.

Genomic subtypes are associated with relapse risk and chemotherapy response,[74] providing a rationale for comprehensive genomic analysis at diagnosis. Although integrated whole-genome sequencing and transcriptome sequencing provide the most detailed molecular portrait of ALL, transcriptome sequencing provides an analysis of gene expression, mutations, and chromosomal rearrangements, and enables the identification of most risk-stratifying genomic alterations in ALL. Transcriptome sequencing also identifies cases that phenocopy canonical subtypes with similar gene expression but alternative genomic drivers (eg, *ETV6::RUNX1*-like ALL).[67,69,75] Notably, the time for patients to be considered cured is 6 years after diagnosis, irrespective of the prognosis of each genetic subtype.[3] In combination with MRD and cytogenetic abnormalities, copy-number alterations (eg, the UKALL-CNA profile in the ALLTogether01 protocol)[38] are being incorporated into risk-stratification algorithms.

Genomic alterations are less established in the management of T-ALL, as this entity is less common, and more frequently driven by noncoding, enhancer alterations that deregulate T-lineage transcription factors and oncogenes that require genome sequencing for identification.[76] However, this landscape is changing, with recent studies comprehensively defining the taxonomy of T-ALL and showing associations between subtype, outcome, and treatment failure.[77] Similarly,

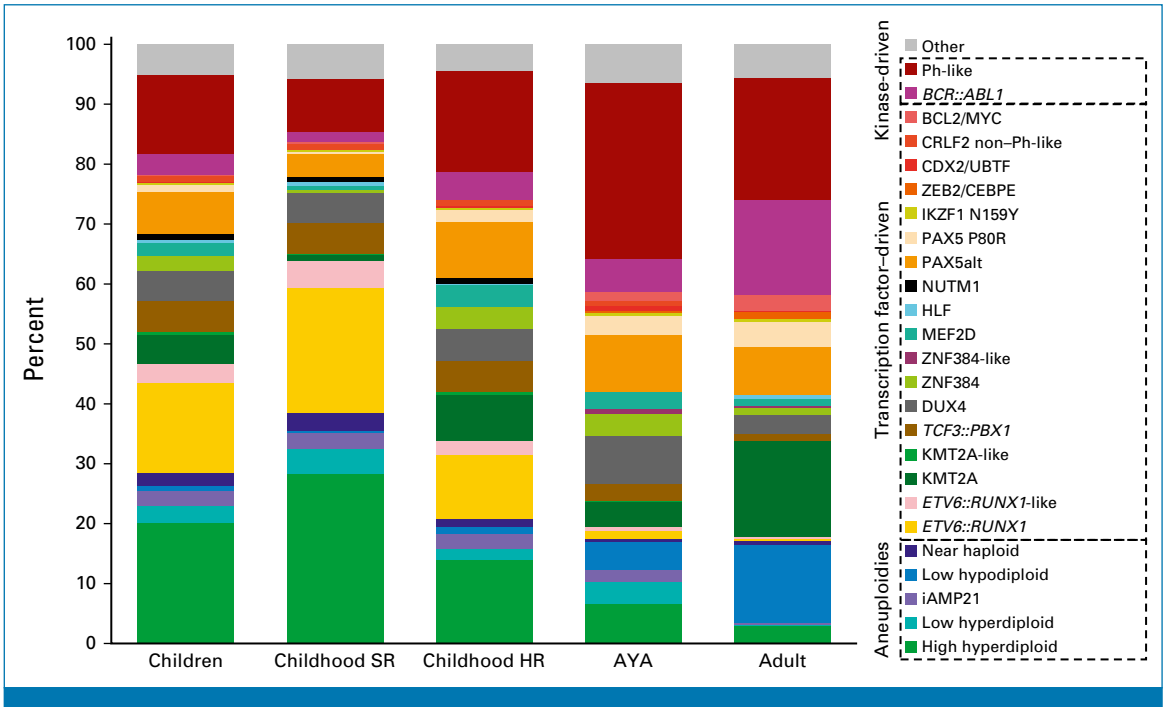


FIG 3. Frequency of B-ALL subtypes. Histogram of prevalence of B-ALL subtypes according to age. Childhood <15 years; AYA 15-39 years; adult >39 years. AYA, adolescent young adult; HR, high risk; SR, standard risk.

acute leukemias of ambiguous lineage that exhibit either minimal differentiation or immunophenotypic features of multiple hematopoietic lineages (most commonly B and myeloid, or T and myeloid) have been poorly characterized from a genomic perspective. In addition to known associations with *KMT2A* and *BCR::ABL1*, several new entities have recently been identified that transcend immunophenotypic criteria, including *ZNF384*-rearranged (either B-ALL or B/myeloid) leukemia[78] and *BCL11B*-rearranged (early T-cell precursor [ETP] or T/myeloid) leukemia.[79,80]

PRECISION MEDICINE IN B-ALL

BCR::ABL1-rearranged (Philadelphia chromosome–positive, Ph+) ALL was the first genetic subtype for which targeted therapy became available. Several large collaborative studies have shown that the addition of ABL tyrosine kinase inhibitors (TKI) to chemotherapy has improved outcome.[81-83] Also, the need for HSCT in these patients has significantly been reduced.[83-85] Before the advent of TKI therapy, most children with *BCR::ABL1*-positive ALL received HSCT; currently, only those with high MRD after two courses of chemotherapy and TKI (5%-10%) are transplanted in first remission. Imatinib and dasatinib are used because of more safety data in pediatrics,[86,87] whereas third-/fourth-generation TKIs such as ponatinib are commonly used in adults because of the much higher prevalence of *BCR::ABL1* and ABL1-class Ph-like ALL in adults, and more data on TKI safety. A randomized trial[88] showed that dasatinib led to better outcome than imatinib in children with *BCR::ABL1* ALL, but because of limited follow-up and the poor outcome of imatinib-treated patients, this has not yet led to the routine implementation of dasatinib.[88] Very recently, highly promising results were obtained with chemotherapy-free treatment regimens in adult *BCR::ABL1*-rearranged ALL. These protocols, consisting of a TKI (usually ponatinib) plus several courses of blinatumomab and inotuzumab,[89] showed low toxicity and excellent early relapse-free survival rates, raising the potential that adult *BCR::ABL1*-rearranged ALL could be a favorable subtype, and that similarly favorable results may be observed in childhood *BCR::ABL1*-ALL (Table 2).

Ph-like ALL is more common than *BCR::ABL1* ALL in children (approximately 10%-15% *v* approximately 2%-3%) but has a similarly poor outcome without the use of TKIs.[90] Both have a very high incidence of *IKZF1* deletions, which further worsens their poor outcome.[84,91] Rexinoids[92] and FAK inhibitors[93] ameliorate the biologic effects of *IKZF1* alterations, but have not been tested clinically. The Máxima/DCOG group observed improved outcomes by prolonging therapy with a third year.[8] Only one of eight *BCR::ABL1*-like cases carry an ABL-class fusion (*ABL1*, *ABL2*, *PDGFRB*, *CSF1R*, and very rare others) that can be targeted by the ABL TKIs.[94] This led to the addition of TKIs to chemotherapy in small cohorts with encouraging results,[95] as well as for larotrectinib for *NTRK3*-rearranged Ph-like ALL[96] (Fig 3). The efficacy of TKIs in ABL1-class Ph-like ALL is being tested in the COG/EsPhALL Ph+ ALL, ALLtogether1, and St Jude Total Therapy 17 protocols.

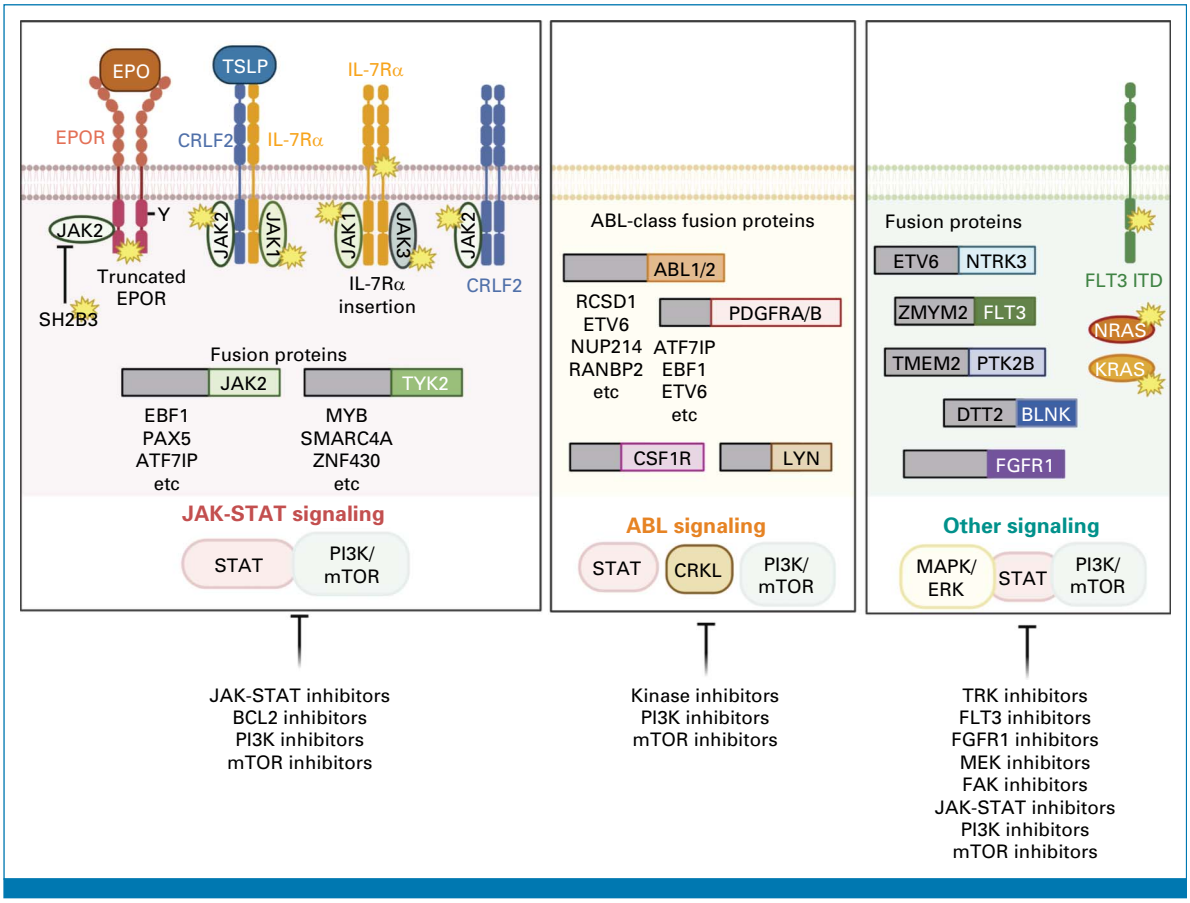


FIG 4. Pathways and therapeutic targets in *BCR::ABL*-like B-ALL. Schematic of genomic subtypes of *BCR::ABL*-like B-ALL, and potential therapeutic targeting opportunities, grouped according to kinase driver (*JAK-STAT* pathway, *ABL1*-class, and other). JAK-STAT, Janus kinase–signal transducers and activators of transcription; mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol 3-kinase.

In *BCR::ABL1*-like cases with mutations activating *JAK-STAT* signaling, approved *JAK* inhibitors such as ruxolitinib are less consistently effective than *ABL1* inhibitors in *ABL1*-class cases.[97] Ruxolitinib is being evaluated by the COG (ClinicalTrials.gov identifier: NCT02723994), but outcome data are not yet available.

Specific therapy protocols have been developed for *KMT2A*-R ALL.[98-100] Infants with low MRD at the end of induction have a better outcome when treated with ALL-like consolidation (course 1B), and those with high MRD benefit from AML-like consolidation therapy (ADE-MAE courses).[101] *KMT2A*-R ALL carries a specific gene expression profile including overexpression of wild-type *FLT3*. Limited efficacy was observed of a *FLT3* inhibitor (*FLT3*i) as a single agent in infant *KMT2A*-R ALL.[102] A randomized study adding *FLT3*i to chemotherapy showed no overall benefit, but suggested a benefit in a small subset identified by inhibition of phosphorylated *FLT3* or by ex vivo sensitivity to the compound.[103] *KMT2A*-R ALL is mainly characterized by epigenetic abnormalities caused by the *KMT2A* fusion protein[104] and shows high sensitivity to demethylating agents and HDAC inhibitors ex vivo.[105] However, a clinical trial with azacytidine in infant *KMT2A*-R ALL did not show promising results.[106] Recently, precision medicine therapies have focused on components of the KMT2A protein complex such as DOT1L and menin. The clinical effect of DOT1L inhibitors was disappointing, but recent phase I/II trials with menin inhibitors showed promising early results,[107] leading to development of multiple upcoming trials. Because of high *BCL2* expression, venetoclax has also been studied in *KMT2A*-R ALL.[108] Venetoclax also showed promising preclinical activity in *TCF3::HLF* rearranged ALL[108,109] and T-ALL (see below). Finally, because of the association of low-hypodiploid ALL and *TP53* mutations, *TP53* is an attractive therapeutic target, but this has not yet led to clinical trials.

PRECISION MEDICINE IN T-ALL

Precision medicine is more difficult in T-ALL.[110] Nelarabine is a DNA-terminating nucleoside prodrug that is metabolized into arabinosylguanine nucleotide triphosphate and preferentially accumulates in T lymphoblasts.[111] It was highly active in early-phase trials for r/r T-ALL but was also associated with significant and often severe neurotoxicity.[112] COG ALL0434 demonstrated that it could be added safely in

TABLE 2. Precision Medicine and Immunotherapy

Target	Subtype of ALL	Precision Medicine/Immunotherapy
BCR::ABL1	Mainly B-lineage ALL	ABL TKI such as imatinib, dasatinib, and ponatinib
ABL-class abnormalities: *ABL1*, *ABL2*, *PDGFRB*, *CSF1R*	Ph-like ALL with *ABL*-class abnormalities	ABL TKI such as imatinib, dasatinib, and ponatinib
NTRK3 rearrangement	Ph-like ALL	Larotrectinib
JAK-STAT signaling	Ph-like ALL	*JAK* inhibitors such as ruxolitinib
FLT3	*KMT2A*-rearranged ALL	*FLT3* inhibitors such as lestaurtinib and midostaurin
Epigenetic abnormalities	*KMT2A*-rearranged ALL	Demethylating agents such as azacytidine; HDAC inhibitors such as panobinostat
Components of the aberrant *KMT2A* complex such as menin and DOT1L	*KMT2A*-rearranged ALL	Menin inhibitors, DOT1L inhibitors
BCL2	*KMT2A*-rearranged ALL, *TCF3::HLF*-rearranged ALL, immature T-ALL	Venetoclax
BCL-XL	T-ALL	Navitoclax
Purine nucleoside pathway	*KMT2A* rearranged ALL, T-ALL	Clofarabine in *KMT2A*-rearranged ALL, nelarabine in T-ALL
Proteasome	T-ALL	Proteasome inhibitor such as bortezomib
LCK	Mature T-ALL	Dasatinib
CD19	B-lineage ALL	Blinatumomab
CD19	B-lineage ALL	CD19-directed CAR T cells
CD22	B-lineage ALL	Inotuzumab
CD22	B-lineage ALL	CD22-directed CAR T cells
CD7	T-ALL	CD7-directed CAR T cells
CD38	T-ALL	Daratumumab

Abbreviations: CAR, chimeric antigen receptor; TKI, tyrosine kinase inhibitors.

newly diagnosed T-ALL/lymphoma (T-LLy) and improved outcome modestly, with a notable impact on CNS relapses.[13,113] The COG also tested the proteasome inhibitor bortezomib in T-ALL/T-LLy with complicated results but a suggestion that bortezomib improved outcome in T-lymphoblastic lymphoma.[114] Preclinical data have shown alterations in BCL2 signaling pathways in T-ALL, with the ETP subset showing BCL2 dependence and remaining non-ETP cases dependent on BCL-XL.[115] These observations prompted efforts to target these pathways with navitoclax (BCL-XL) and/or venetoclax (BCL2). Promising results of an early-phase clinical trial resulted in a trial of low-dose navitoclax plus venetoclax in r/r pediatric B- and T-ALL (ClinicalTrials.gov identifier: NCT05192889).[116] Ex vivo drug sensitivity studies showed that subsets of T-ALLs are very sensitive to dasatinib, with LCK activation driving dasatinib sensitivity associated with high BCL-XL and low BCL2 expression.[108,117] These results raise the possibility of testing subtype-specific targeted therapies in T-ALL (Table 2).

IMMUNOTHERAPY

Immunotherapy has revolutionized the landscape of B-ALL therapy, showing very high remission rates in highly refractory patients[118] and significantly less acute toxicity than intensive chemotherapy. Three approaches have become mainstays of treatment for r/r ALL and are now being tested in newly diagnosed patients (Table 2).

Blinatumomab is a bispecific T-cell engager genetically engineered monoclonal antibody recognizing CD19, expressed on the surface of essentially all B-ALLs, and CD3, expressed on the surface of essentially all T cells. Dual binding by blinatumomab brings cytotoxic T cells to CD19+ B cells, enabling cell killing. Because blinatumomab has a short half-life, it is administered by continuous infusion, typically for 28 days. The side-effect profile of blinatumomab is very different from that of chemotherapy with little neutropenia or mucositis, but some unique CNS toxicities, including seizures and hallucinations, and occasional development of cytokine release syndrome (CRS), usually in patients with high disease burden. Blinatumomab was demonstrated to be highly active in r/r adult and then pediatric B-ALL,[119] leading to testing in randomized trials for the first relapse of ALL in North America and Europe. These showed that replacing one to two cycles of intensive chemotherapy with blinatumomab in children with high- and intermediate-risk relapsed ALL, followed by HSCT, significantly improved outcomes with this approach now considered to be standard of care.[120,121] The COG also showed that replacement of one cycle of intensive chemotherapy with blinatumomab and addition of two cycles later in therapy improved outcome for children with lower-risk first relapse of B-ALL, but this benefit was limited to those with bone marrow relapse, whereas those with isolated CNS relapse fared poorly.[122] A very recent pilot study in *KMT2A*-R infant ALL showed that addition of blinatumomab to the Interfant-06 backbone

significantly improved outcome.[123] Multiple cooperative groups are now testing blinatumomab in newly diagnosed ALL, with some adding the agent to backbone therapy and others using it to replace components of chemotherapy.

Inotuzumab is an ADC composed of a monoclonal antibody recognizing CD22, expressed on most B-ALLs, and the chemotherapy agent calicheamicin. After binding to surface CD22, inotuzumab is internalized and then calicheamicin is released into the cell by the lysozyme. The landmark INO-VATE trial showed that inotuzumab was superior to intensive chemotherapy for adult r/r ALL.[124] Phase I and II trials conducted by the COG and European groups showed excellent activity in pediatric r/r ALL, with remission rates over 50%, allowing many patients to proceed to HSCT.[125-127] Inotuzumab is administered with once a week intravenous 1-hour infusions for 3 weeks, and is well tolerated in heavily pretreated patients. One challenge is the potential for hepatic toxicity if given relatively close to previous HSCT or proximate to subsequent HSCT. Most pediatric trials have used inotuzumab as a single agent, whereas current trials are combining it with chemotherapy generally to replace other components such as anthracyclines. Several groups (COG and ALLtogether) are now testing inotuzumab in patients with newly diagnosed ALL.

The progress with antibody-based therapy is less in T-ALL. The anti-CD38 monoclonal antibody daratumumab has shown good efficacy in preclinical models of T-ALL and in small clinical series of relapsed T-ALL.[128,129] Except for infusion reactions, no significant side effects have been reported. Studies on newly diagnosed T-ALL are planned.

Chimeric antigen receptor (CAR) T-cell therapy has recently entered the mainstream. Development of highly active (third-generation) CAR T cells required genetically engineered constructs with an extracellular ScFv antibody fragment that recognizes a cellular target such as CD19 with intracellular CD3zeta and costimulatory domains (41BB or CD137) or CD28 that mediate cell expansion, persistence and engagement, and cytotoxicity.[130] CD19-directed CAR T cells were shown to be highly active in pediatric r/r ALL, with complete remission (CR) rates over 90% in heavily pretreated patients, most of whom failed three or more lines of therapy and had relapsed after HSCT.[131-134] When treated with high disease burden, there is a high risk of CRS, including severe fluid overload, hypoxemia, and hypotension. Patients with severe CRS had very high interleukin-6 levels, and tocilizumab, a monoclonal antibody that inhibits binding of IL-6 to the IL-6 receptor, was highly effective in treating CRS,[135] which was critical to the clinical development of CAR T cells.[131] The CD19 CAR T-cell agent tisagenlecleucel was US Food and Drug Administration approved in 2017 for children and young adults with r/r ALL on the basis of the worldwide ELIANA trial.[132] Subsequent real-world experience with tisagenlecleucel in r/r pediatric ALL showed very similar results to this pivotal trial with CR rates about 85% (almost all MRD-negative), event-free survival of 50%-55% at 12 months, and overall survival of about 75% at 12 months, all dramatically better than any other therapy.[136] CAR T-cell therapy is also effective in CNS leukemia[137,138] and other extramedullary sites,[139] and its efficacy was shown in high-risk leukemias including infant *KMT2A*-R ALL,[140,141] although perhaps less in ALL with *TP53* aberrations. CAR T-cell therapy appears curative by itself in some cases, with the longest-responding patient now 11 years post-infusion without subsequent therapy and dozens of patients in CR 5+ years. However, about 50% of patients relapse with either CD19+ disease (loss of CAR T-cell persistence or activity) or CD19-negative disease (antigen escape).[134] Several factors predict the lack of response and/or relapse[142-144]: high disease burden, loss of MRD response, early (within approximately 6 months) loss of B-cell depletion, and low plasma levels of fludarabine as part of the preinfusion lymphodepletion schedule.[142-145] Loss of B-cell aplasia is a surrogate marker of CAR activity since CD19 CAR T cells also kill normal B cells. A critical question is whether CAR T cells should be used as a definitive therapy or as a bridge to HSCT.[146] The nature of the CAR costimulatory domain (41BB *v* CD28) influences persistence, and this may influence the decision for definitive versus bridge therapy.

CAR T cells directed against CD22 have also been tested,[147] generally showing high activity but less persistence than CD19-CARs, and there is great interest in testing dual targeting of CD19 and CD22, either with bicistronic CAR constructs allowing CAR T cells to recognize both proteins, or with mixtures of individual CD19- and CD22-targeted CARs.[148]

As there are no cell surface markers distinguishing normal and malignant T cells, the development of CAR T cells against T-ALL has the risk of CAR T-cell fratricide. However, several strategies to overcome this risk have been developed, and the first successful small studies with CAR T cells directed against CD7 have been reported.[149,150]

Given the impressive activity in r/r ALL, there is great interest in testing CAR T-cell therapy in earlier phases of disease such as high-risk first relapse or very high-risk newly diagnosed ALL.

In conclusion, in the past two decades, the use of MRD significantly improved stratification with subsequent treatment reductions or intensifications that improved outcome. More recently, molecular genetic profiling led to the discovery of many new genetic subclasses, which has increased our understanding of the biological basis of ALL, improved risk classification, and enabled refinement of precision medicine regimens. Very recently, immunotherapeutic approaches, including bispecific antibodies, ADC, and cellular therapies, led to more effective and less-toxic therapies replacing intensive chemotherapy courses and

HSCT in relapsed ALL and are now being tested in newly diagnosed patients.

It has taken 50-60 years to increase the cure rate in childhood ALL from 0% to 90% by stepwise improvements in chemotherapy. The developments described herein have been developed over the past 10-15 years and will very likely direct efforts to cure those children with ALL who are not cured today, and improve the quality of life for survivors who should have decades of life ahead. The results discussed here are limited to countries that have next-generation sequencing assays and targeted treatment options at their disposal. Achieving cure that is truly universal will require development of cost-effective mechanisms to make these new technologies and therapies available to children with ALL worldwide.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Advancing Diagnostics and Therapy to Reach Universal Cure in Childhood ALL

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Patents, Royalties, Other Intellectual Property: Inventor on a pending patent application related to gene-expression signatures for detection of underlying Philadelphia chromosome-like events and therapeutic targeting in leukemia (PCT/US2012/069228), WO 2021/022076 A1. This patent highlight shows representative PROTAC compounds bound to JAK2, where ruxolitinib and baricitinib bind to the human JAK2 JH1. Furthermore, representative data illustrate protein degradation, cytotoxicity, and effect of the JAKSTAT signaling pathway of the PROTAC compounds in MHHCALL-4 cells, Marcus Fisher, Fatemeh Keramatnia, Kevin Mcgowan, Jaeki Min, Gisele A. Nishiguchi, Jeanine Price, Zoran Rankovic, Das Sourav, Charles G. Mullighan, Yunchao Chang 2021 Substituted N-(2-(2,6-DIOXOPIPERIDIN-3-YL)-1,3-DIOXOISOINDOLIN-5-YL)Arylsulfonamide Analogs as Modulators of Cereblon Protein, Application No: PCT/US2021/051648 Filed: September 23, 2021. Patent pending (Inst)
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