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REVIEW ARTICLE

# Biology, Risk Stratification, and Therapy of Pediatric Acute Leukemias: An Update

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## ABSTRACT

**Purpose**
We review recent advances in the biologic understanding and treatment of childhood acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML), identify therapeutically challenging subgroups, and suggest future directions of research.

**Methods**
A review of English literature on childhood acute leukemias from the past 5 years was performed.

**Results**
Contemporary treatments have resulted in 5-year event-free survival rates of approximately 80% for childhood ALL and almost 60% for pediatric AML. The advent of high-resolution genome-wide analyses has provided new insights into leukemogenesis and identified many novel subtypes of leukemia. Virtually all ALL and the vast majority of AML cases can be classified according to specific genetic abnormalities. Cooperative mutations involved in cell differentiation, cell cycle regulation, tumor suppression, drug responsiveness, and apoptosis have also been identified in many cases. The development of new formulations of existing drugs, molecularly targeted therapy, and immunotherapies promises to further advance the cure rates and improve quality of life of patients.

**Conclusion**
The application of new high-throughput sequencing techniques to define the complete DNA sequence of leukemia and host normal cells and the development of new agents targeted to leukemogenic pathways promise to further improve outcome in the coming decade.

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## INTRODUCTION

The treatment outcome for children with acute myeloid leukemia (AML) and especially acute lymphoblastic leukemia (ALL) has improved substantially with the use of risk-directed treatment and improved supportive care. The 5-year event-free survival rates for ALL now range between 76% and 86% in children receiving protocol-based therapy in the developed countries (Table 1),[1-14] and those for AML range between 49% and 63% in some of the more successful clinical trials (Table 2).[15-30] The improved treatment has diminished or eliminated the impact of many conventional prognostic factors in ALL, such as male sex and black race.[6,10] Thus current ALL trials have focused on improving not only the outcome of a few subtypes that remain refractory to treatment (eg, infant ALL with *MLL* rearrangement, hypodiploid ALL, and poor early responders), but also the quality of life of the patients. By contrast, with the exception of core-binding factor (CBF) leukemias [t(8;21)(*AML1-ETO*) and inv(16)(*CBFβ-MYH11*)] and AML in Down syndrome, most of the AML cases continue to pose a therapeutic challenge.

Childhood acute leukemias have long been the best characterized malignancies from a genetic viewpoint. Despite remarkable progress in cataloging the molecular lesions, our understanding of how such changes cooperate to produce overt leukemia or to induce drug resistance is still rudimentary. Recent genome-wide studies have begun to enlighten our understanding of leukemogenesis and prognosis and, in some instances, to stimulate the development of target therapy. Because of the space constraints, we review here only some of the most recent advances in the biology and treatment of childhood leukemias.

## MOLECULAR GENETICS OF ALL

Standard genetic analyses can detect primary genetic abnormalities in more than 75% of the ALL cases, but they cannot identify the full repertoire of the genetic alterations.[31] The advent of high-resolution

**Table 1.** Characterizations of the Patients and Treatment Results From Selected Clinical Trials for Childhood ALL

| Study | Years of Study | No. of Patients | Age Range (years) | T Cell (%) | WBC Count ≥ $100 \times 10^9$/L (%) | DNA Index ≥ 1.16 (%) | *ETV6–RUNX1* (%) | Ph+ (%) | Event-Free Survival at 5 Years | | Survival at 5 Years | | Cumulative CNS Relapse at 5 Years | | Cumulative Secondary Neoplasm at 10 Years | | Data Source (first author) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | % | SE | % | SE | % | SE | % | SE | |
| AIEOP-95 | 1995-2000 | 1,743 | 0-17 | 11 | 10.2 | 19.2 | 22.4 | 2.3 | 75.9 | 1.0 | 85.5 | 0.8 | 1.2 | 0.3 | 0.4 | 0.2 | Conter[1] |
| BFM-95 | 1995-2000 | 2,169 | 0-18 | 13.3 | 11.1 | 20.3 | 21.5 | 2.2 | 79.6 | 0.9 | 86.3 | 0.6 | 1.8 | 0.3 | 1.7 | 0.3 | Möricke[2] |
| CCG-1900 | 1996-2002 | 4,464 | 0-21 | 15.9 | 14.1 | 21.5* | NA | 2.9 | 76.0 | 0.7 | 86.3 | 0.6 | 4.6 | 0.3 | 1.0 | 0.2 | Gaynon[3] |
| COALL-97 | 1997-2003 | 667 | 0-18 | 14.1 | 12.0 | NA | 23.9 | 1.9 | 76.7 | 1.7 | 85.4 | 1.4 | 2.1 | 0.6 | 1.1 | 0.4 | Escherich[4] |
| CPH-95 | 1996-2002 | 380 | 0-18 | 14.8 | 12.6 | NA | 22.3 | 2.3 | 72.1 | 2.3 | 83 | 1.9 | 1.2 | 0.6 | 0.6 | 0.4 | Stary[5] |
| DCOG-9 | 1997-2004 | 859 | 1-18 | 11.4 | 12.4 | 21.5 | 15.0 | 1.6 | 80.6 | 1.4 | 86.4 | 1.2 | 2.6 | 0.6 | 0.1 | 0.1 | Kamps[14] |
| DFCI 95-01 | 1996-2000 | 491 | 0-18 | 10.6 | 11.0 | 18.0 | 25.8 | NA | 81.6 | 1.8 | 89.6 | 1.4 | 0.7 | 0.4 | 0.6 | | Silverman[6] |
| INS 98 | 1998-2003 | 315 | 0-18 | 19.4 | 12.1 | 19.9* | 13.7 | 3.3 | 78.7 | 2.3 | 83.8 | 2.1 | 1.9 | 0.8 | 1.0 | 0.5 | Stark[7] |
| NOPHO-2000 | 2002-2007 | 1,023 | 1-15 | 11.3 | 11.5 | NA | 23.2 | 1.1 | 79.4 | 1.5 | 89.1 | 1.1 | 2.7 | 0.6 | NA | | Schmiegelow[8] |
| SJCRH-13B | 1994-1998 | 247 | 0-18 | 17.4 | 15.4 | 18.6 | 15.8 | 4.0 | 80.1 | 2.6 | 85.7 | 2.2 | 1.7 | 0.8 | 3.3 | 1.2 | Pui[9] |
| SJCRH-15 | 2000-2007 | 498 | 1-18 | 15.3 | 12.7 | 24.3 | 19.3 | 2.0 | 85.6 | 2.9 | 93.5 | 1.9 | 2.7 | 0.8 | 0.3 | 0.3 | Pui[10] |
| TCCSG-95-14 | 1995-1999 | 597 | 1-15 | 9.7 | 11.8 | 22.3 | NA | 4.0 | 76.8 | 1.8 | 84.9 | 1.5 | 1.7 | 0.6 | 0.7 | | Tscuhida[11] |
| TPOG-2002 | 2002-2007 | 788 | 0-18 | 9.7 | 14.0 | NA | 13.1 | 2.1 | 77.4 | 1.7 | 83.5 | 1.6 | 3.8 | 0.8 | NA | | Liang[12] |
| UKALL-97/99 | 1999-2002 | 938 | 1-18 | 10.0 | 13.1 | NA | NA | 2.3 | 80 | 1.2 | 88 | 1.1 | 3.0 | 0.5 | NA | | Mitchell[13] |

Abbreviations: ALL, acute lymphoblastic leukemia; Ph+, Philadelphia chromosome positive; AIEOP, Associazione Italiana di Ematologia ed Oncologia Pediatrica; BFM, Berlin-Frankfurt-Münster ALL Study Group; CCG, Children's Cancer Group; COALL, Cooperative ALL Study Group; CPH, Pediatric Hematology in the Czech Republic; DCOG, Dutch Childhood Oncology Group; DFCI, Dana-Farber Cancer Institute ALL Consortium; INS, Israeli National Studies of Childhood ALL; NOPHO, Nordic Society of Pediatric Hematology and Oncology; SJCRH, St Jude Children's Research Hospital; TCCSG, Tokyo Children's Cancer Study Group; TPOG, Taiwan Pediatric Oncology Group; UKALL, UK Medical Research Council Working Party on Childhood Leukaemia; NA, not available.
*Ploidy > 50.

genome-wide analyses of gene expression, DNA copy number alterations (CNA) and loss of heterozygosity, epigenetic changes, and whole-genome sequencing have led to the detection of many novel genetic abnormalities; to date, virtually all patients with ALL can be classified according to specific genetic abnormality (Fig 1A). These studies also provided new insights into the complex interactions of multiple genetic alterations in leukemogenesis and response to therapy.[34]

### Genomic Analysis of ALL

Primary somatic genetic abnormalities have important prognostic and therapeutic implications and play a critical role in leukemogenesis (Table 3).[10,31,34-50] However, experimental models have established that cooperative mutations are necessary to induce leukemia and contribute to the development of drug resistance. Although high-throughput analyses of global gene expression have identified distinct subgroups and may in the future be used to stratify patients, these profiles do not distinguish pathways that are "drivers" of leukemogenesis from "passengers." Using single-nucleotide polymorphism (SNP) array, Mullighan et al[34] identified an average of six CNAs per case of childhood ALL. In general, deletions outnumbered amplifications by a ratio of 2:1. The lesions target genes regulating lymphoid differentiation, tumor suppression, cell cycle, apoptosis, signaling, microRNAs, and drug responsiveness. There were substantial differences in the frequency of CNAs among various subtypes. *MLL*-rearranged cases had less than one CNA per case, suggesting that *MLL* is a potent oncogene that requires very few cooperating lesions to induce leukemia transformation, whereas *ETV6-RUNX1* (formerly known as *TEL-AML1*) and *BCR-ABL1* leukemias demonstrated more than six lesions per case.[34] These findings are compatible with the known behavior of these leukemias. *MLL*-rearranged leukemias often present during infancy and have a concordance rate close to 100% in identical twins, indicating in utero development and transplacental metastasis from one fetus to the other.[31] By contrast, *ETV6-RUNX1* leukemias present after infancy and have a concordance rate of only 10% in identical twins, and this gene fusion can be found in as many as 1% of normal newborn babies, a frequency 100 times higher than the prevalence of this subtype of leukemia, suggesting that additional postnatal mutations are necessary for malignant transformation.[31]

### Genetic Determinants of High-Risk B-Cell Precursor ALL

In Philadelphia chromosome–positive ALL with constitutively active BCR-ABL1 tyrosine kinase, *IKZF1* (encoding the lymphoid transcription factor IKAROS) is deleted in approximately 80% of the cases.[51] Interestingly, there is a high-risk subgroup of *BCR-ABL1*–negative ALL that is characterized by *IKZF1* deletion and has a genetic profile similar to that of cases with *BCR-ABL1* fusion.[46,47] In search of activated tyrosine kinase signaling in this leukemic subtype, Mullighan et al[48] identified activating mutations in the Janus kinases (*JAK1*, *JAK2*, and *JAK3*) in approximately 10% of high-risk *BCR-ABL1*–negative cases. The presence of *JAK* mutations was associated with alteration of *IKZF1* and deletion of *CDKN2A/B*. Recent studies showed *CRLF2* over-expression (predominantly resulting from *P2RY8-CRLF2* fusion or *IGH@-CRLF2* rearrangement) in 6% to 7% of B-cell precursor ALL cases and strikingly in 50% to 60% of patients with Down syndrome–associated ALL, all of whom lacked recurring translocations commonly associated with non–Down syndrome ALL.[40-42,52] *CRLF2* alteration was associated with activating mutations of *JAK1* or *JAK2*; these two genetic lesions together resulted in constitutive Jak-Stat activation and the growth of cytokine-dependent mouse B-progenitor cell lines in the absence of exogenous cytokine, indicating that they are cooperative mutations in leukemogenesis.[40] Importantly, *CRLF2* alteration was associated with Hispanic/Latino ethnicity and a poor treatment outcome.[40,41]

### Genomic Analysis of T-Cell ALL

On the basis of gene expression profiling, T-cell ALL cases can be classified into several distinct genetic subgroups that correspond to specific T-cell development stages: *HOX11L2*, *LYL1* plus *LMO2*, *TAL1*

**Table 2.** Characteristics and Treatment Results From Selected Clinical Trials for Childhood AML

| Study* | Years of Study | No. of Patients†‡ | Early Deaths (%) | CR Rate (%) | Time of CR Evaluation | Anthracyclines (mg/m$^2$)§ | Cytarabine (g/m$^2$) | Etoposide (g/m$^2$) | 5-Year EFS % | 5-Year EFS SE | 5-Year OS % | 5-Year OS SE | Data Source (first author) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| POG 8821 | 1988-1993 | 511 | 3.9 | 77 | 2 courses | 360 | 55.7 | 2.25 | 31 | 2 | 40.4 | 2 | Ravindranath[25] |
| CCG 2891 | 1989-1995 | 750 | 4 | 77 | 2 courses | 350 | 28.3 | 1.9 | 34 | 3 | 45 | 3 | Smith[21] |
| MRC-AML 10 | 1988-1995 | 303 | 4 | 93 | 4 courses | 550 | 10.6 | 0.5-1.5 | 49 | | 58 | | Gibson[27] |
| PINDA-92 | 1992-1998 | 151 | 21 | 74 | Not specified | 350 | 7.64 | 0.45 | 36 | | 37 | | Quintana[29] |
| LAME- 91‖ | 1991-1998 | 247 | 6.4 | 91 | 2 courses | 460 | 9.8-13.4 | 0.4 | 48 | 4 | 62.3 | 4 | Perel[24] |
| TCCSG M91-13/M96-14 | 1991-1998 | 192 | 3.6 | 88 | Not specified | 495 | 69.4-99.4 | 3.75-5.75 | 56 | | 62 | | Tomizawa[17] |
| BFM-93 | 1993-1998 | 427 | 7.4 | 82 | 4 courses | 300-400 | 23-41 | 0.95 | 50 | 2 | 57 | 2 | Creutzig[20] |
| CCG 2961 | 1996-1999 | 901 | 6 | 83 | 2 courses | 360 | 15.2-19.6 | 1.6 | 42 | 3 | 52 | 4 | Lange[15] |
| EORTC-CLG 58,921 | 1993-2000 | 166 | 1 | 84 | 2 courses | 380 | 23-29 | 1.35 | 49 | 4 | 62 | 4 | Entz-Werle[23] |
| GATLA-AML90 | 1993-2000 | 179 | 20 | 70 | Not specified | 300 | 41.1 | 1.45 | 31 | 4 | 41 | 4 | Armendariz[18] |
| AIEOP LAM-92 | 1992-2001 | 160 | 6 | 89 | 2 courses | Not provided | Not provided | Not provided | 54 | 4 | 60 | 4 | Pession[22] |
| NOPHO-AML 93 | 1993-2001 | 223 | 2 | 92 | 3 courses | 300-375 | 49.6-61.3 | 1.6 | 50 | 3 | 66 | 3 | Lie et al[19] |
| MRC-AML 12 | 1994-2002 | 455 | 4 | 92 | 4 courses | 300-610 | 4.6-34.6 | 1.5 | 56 | | 66 | | Burnett[16]/Gibson[27] |
| AML99 | 2000-2002 | 260 | 1.7 | 94 | 2 courses | 300-375 | 59.4-78.4 | 3.15-3.2 | 61 | 3 | 75 | 3 | Tsukimoto[28] |
| BFM-98 | 1998-2003 | 473 | 3 | 88 | 4 courses | 420 | 41-47 | 0.95 | 49 | 3 | 62 | 3 | Creutzig[20] |
| SJCRH AML02¶ | 2002-2008 | 230 | 1 | 94 | 2 courses | 300-550 | 34-48 | 1-1.5 | 63 | 4 | 71 | 4 | Rubnitz[26] |
| COG AAML03P1¶# | 2003-2005 | 350 | 2.6 | 83 | 2 courses | 300-480 | 21.6-45.6 | 1-1.75 | 53 | 6 | 66 | 5 | Cooper[30] |

Abbreviations: AML, acute myeloid leukemia; CR, complete response; EFS, event-free survival; OS, overall survival; POG, Pediatric Oncology Group; CCG, Children's Cancer Group; MRC-AML, United Kingdom's Medical Research Council Acute Myelogenous Leukemia study; PINDA, National Program for Antineoplastic Drugs for Children; LAME, Leucemie Aigue Myeloblastique Enfant; TCCSG, Tokyo Children's Cancer Study Group; BFM, Berlin-Frankfurt-Münster; EORTC-CLG, European Organisation for Research and Treatment of Cancer Children's Leukemia Group; GATLA-AML, Argentine Group for the Treatment of Acute Leukemia; AIEOP LAM, Associazione Italiana di Ematologia ed Oncologia Pediatrica Leucemia Acuta Meiloide; NOPHO-AML, Nordic Society of Pediatric Hematology and Oncology—Acute Myeloid Leukemia; SJCRH, St Jude Children's Research Hospital; COG, Children's Oncology Group.

*Results are reported for only those trials that had ≥ 150 patients and information provided for each of the column headings. The AIEOP LAM-92 did not allow for definitive dose calculations of drugs because consolidation therapy was given based on the treating physician's judgement, but usually included anthracyclines, etoposide, and high-dose cytarabine.

†No. of patients excludes patients with Down syndrome.

‡Ages include patients from 0 up to and including age 15 years: BFM-98 included patients from 0 to less than 17 years of age; CCG-2961 included patients from 0 to < 21 years of age.

§Anthracycline conversions were according to daunorubicin equivalents, including idarubicin 5×, mitoxantrone 5×, doxorubicin 1×. Another conversion factor for idarubicin and mitoxantrone that has been used is 3×.

‖LAME-91 also used 450 mg/m$^2$ of amsacrine; MRC-10 and MRC-12 both also included 500 mg/m$^2$ of amsacrine.

¶SJCRH AML02 and the COG AAML03P1 have EFS and OS at 3-year follow-up.

#COG AAML03P1 enrolled patients ≥ 1 month and ≤ 21 years of age.

plus *LMO1* or *LMO2*, *HOX11*, and *MLL-ENL* (Table 3).[43] Although *HOX11L2* generally confers a poor outcome, *HOX11* and *MLL-ENL* are associated with a favorable outcome.[43,53] Using SNP and other genome-wide platforms, many novel genomic alterations have recently been identified, including focal deletions leading to dysregulated expression of *TAL1* and *LMO2*, deletion and mutation of *PTEN*, mutations of *NOTCH1* and *FBXW7*, deletions of *RB1*, duplications of *MYB*, deletions of *RB1*, and fusion of *SET* or *ABL1* to *NUP214*.[34] Hence T-cell ALL is also a heterogeneous disease. Thus far, mutations of *NOTCH1* and *FBXW7* (observed in 50% of T-ALL) have generally been associated with a favorable prognosis, and *NUP214-ABL1* fusion has been associated with responsiveness to tyrosine kinase inhibition.[43,44,49]

### Genetic Determinants of Relapse in ALL

To explore the genetic basis of relapse, genome-wide studies were conducted using matched diagnosis and relapse samples from the same patients.[54,55] Although 90% of the cases exhibited differential CNAs (gaining or losing genetic lesions) from diagnosis to relapse, most relapse samples are clonally related to diagnosis samples, and backtracking studies showed that the relapse clones were often present as minor populations at diagnosis, suggesting that they were selected during treatment. Notably, many of the genetic alterations that emerge in the predominant clone at relapse involve genes that have been implicated in treatment resistance (eg, *CDKN2A/B*, *IKZF1*).[54,55] Interestingly, some cases had focal deletion of *MSH6*, reduced expression of which was associated with resistance to mercaptopurine and prednisone, providing another plausible mechanism of drug resistance at relapse.[54] Parallel gene expression studies, which have identified a proliferative gene signature that emerges at relapse and consistent upregulation of genes such as *survivin*, provide attractive targets for novel therapeutic intervention.[56]

### Inherited Susceptibility to ALL

Although candidate gene approaches have implicated inherited polymorphisms of several genes in leukemogenesis, the findings have not been consistent. Two recent genome-wide studies on patients of European ancestry failed to confirm these previously reported gene associations but independently identified germline polymorphisms of the *IKZF1* gene and *ARID5B* gene to be associated with an increased risk of childhood ALL.[57,58] The risk alleles of *ARID5B*, a gene that belongs to a family of transcription factors important in embryonic development, cell type–specific gene expression, and cell growth regulation, were specifically enriched in patients with hyperdiploid ALL and were also associated with greater methotrexate polyglutamate accumulation.[57,58] Thus the same genetic variation of *ARID5B* that predisposes to the development of hyperdiploid ALL may also underlie the superior response of this subtype of ALL to chemotherapy. A subsequent study was performed in patients of African ancestry, showing that *ARID5B* germline polymorphisms were also associated with the risk of developing hyperdiploid ALL in black patients.[59] The lower frequency of this risk allele in the control populations of African ancestry compared with that of European ancestry might also partly

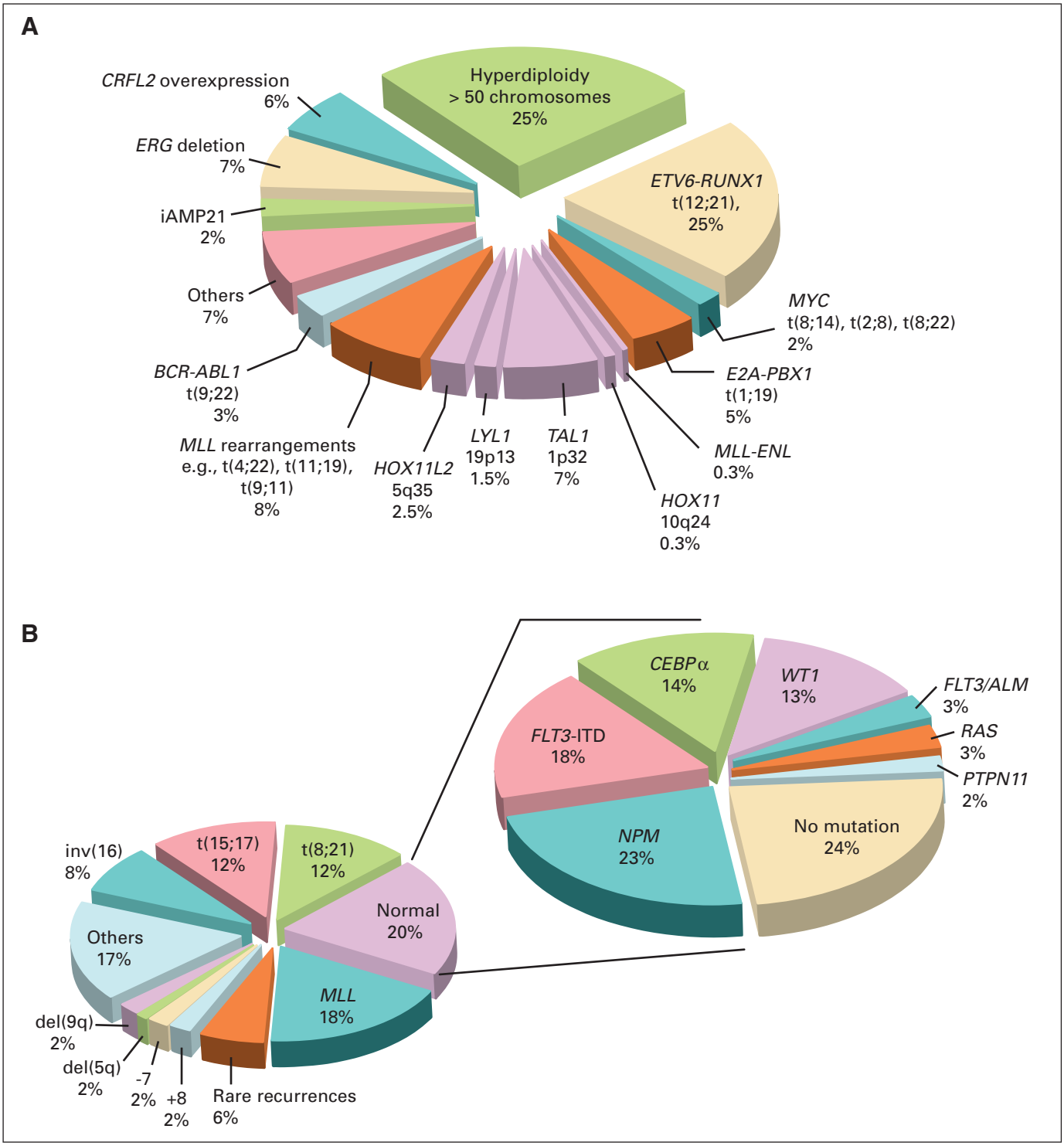


**Fig 1.** Estimated frequency of specific genotypes in childhood leukemias. (A) Genetic abnormalities in acute lymphoblastic leukemia (ALL). Data were modified from Pui et al[32] by including recently identified genotypes. The genetic lesions that are exclusively seen in cases of T-cell ALL are indicated in purple. (B) Genetic abnormalities in acute myeloid leukemia (AML). Panel to the left demonstrates the most common karyotypic alterations. Eighty percent of all children have disease-associated genomic structural alterations. Mutation profile in those without cytogenetic abnormalities (normal karyotype) is shown in the right panel. Seventy-six percent of those in the normal karyotype population have one of the known mutations; thus, more than 95% of all children with AML have at least one known genomic abnormality. (With permission from Reaman and Smith[33]).

  

**Table 3.** Characteristics and Clinical Outcomes of Selected Subtypes of Childhood ALL

| Subtype | Frequency (%) | Clinical Implication | Estimated 5-Year Event-Free Survival (%) | Data Source (first author) |
|---|---|---|---|---|
| B-cell precursor | | | | |
| Hyperdiploidy > 50 | 20-30 | Excellent prognosis with antimetabolite-based therapy | 85-95 | Pui[10,31] |
| t(12;21)(p13;q22) *ETV6-RUNX1* | 15-25 | Expression of myeloid-associated antigens CD13 and CD33; excellent prognosis with intensive asparaginase therapy | 80-95 | Pui[10,31] |
| Trisomies 4 and 10 | 20-25 | Excellent prognosis with antimetabolite therapy | 85-90 | Salzer[35] |
| t(1;19)(q23;p13) *TCF3-PBX1* | 2-6 | Increased incidence in blacks; excellent prognosis with high-dose methotrexate treatment; increased risk of CNS relapse in some studies | 80-85 | Pui[10,31] |
| Intrachromosomal amplification of chromosome 21 | 2-3 | More common in older children and adolescents; poor prognosis; benefit from intensive induction and early re-intensification therapy | 30-40 | Attarbaschi[36] |
| t(4;11)(q21;q23) *MLL-AF4* | 1-2 | Poor prognosis and predominance in infancy, especially those < 6 months of age; overexpression of *FLT3* | 30-40 | Pui[10,31] |
| t(9;22)(q34;q11.2) *BCR-ABL1* | 2-4 | Imatinib plus intensive chemotherapy improve early treatment outcome | 80-90 at 3 years | Schultz[37] |
| t(8;14)(q23;q32.3) | 2 | Favorable prognosis with short-term intensive therapy with high-dose methotrexate, cytarabine, and cyclophosphamide | 75-85 | Pui[38] |
| Hypodiploidy < 44 chromosomes | 1-2 | Poor prognosis | 35-40 | Nachman[39] |
| *CRLF2* overexpression | 6-7 | Poor prognosis; common in patients with Down syndrome (55%) | ? | Mullighan,[40] Cario,[41] Harvey[42] |
| T-cell | | | | |
| *TAL/LMO* rearrangement | 15-30 | Good prognosis in some studies; potentially responsive to histone deacetylase inhibitor | ? | Meijerink[43] |
| *HOX11* rearrangement | 7-8 | Good prognosis | ? | Meijerink[43] |
| *HOX11L2* (*TLX3*) rearrangement | 20-24 | Poor prognosis in some studies | ? | Meijerink[43] |
| *HOXA* rearrangement | 4-5 | Poor prognosis; potentially sensitive to histone H3K79 methyltransferases inhibitor | ? | Meijerink[43] |
| *NUP214-ABL1* | 6 | Sensitive to tyrosine kinase inhibitor | ~50 (survival) | Graux[44] |
| *MLL-ENL* | 2-3 | Favorable prognosis | 80-90 | Pui[31] |
| Early T-cell precursor | 12 | Poor prognosis; expressed myeloid or stem-cell markers | 30-35 | Coustan-Smith[45] |
| Cooperation mutations | | | | |
| B-cell precursor | | | | Mullighan[46] |
| *1KZF1* deletions/mutations | 15-30 | Poor prognosis; resistant to asparaginase and daunorubicin | 50-55 | Den Boer[47] |
| *JAK* mutations | ?2-5 | Predominance in high-risk patients; *JAK2* mutations in 20% of Down syndrome cases; potentially responsive to *JAK2* inhibitors | ~60 | Mullighan[48] |
| T-cell | | | | |
| *NOTCH/FBXW7* mutations | 50 | Favorable prognosis; potentially responsive to *NOTCH* inhibitor | 90 | Breit[49] |
| PTEN-P13K-AKT pathway | ~50 | ? Poor prognosis | ? | Gutierrez[50] |
| *CDKN2A/2B* deletions | ~70 | ? Potentially responsive to DNA methyltransferases inhibitor | ? | Meijerink[43] |

Abbreviation: ALL, acute lymphoblastic leukemia.

explain the lower incidence of hyperdiploid B-cell precursor ALL in the black population.

## CELLULAR AND MOLECULAR ORIGINS OF AML

Despite the extremely heterogeneous nature of AML, the various subtypes seem to share some common pathways leading to leukemogenesis, and the hierarchical nature of the disease is generally well established.[60] Several lines of evidence have led to a model that AML arises from the cooperation between two classes of genetic alterations that regulate self-renewal and differentiation.[61] For example, mutations or epigenetic alterations involving *CBF* or *MLL* genes, termed type II alterations, play key roles in modifying the ability of precursor cells to differentiate, but are usually insufficient by themselves to generate AML. In support of this concept is the finding that the *AML1-ETO* fusion transcript resulting from the t(8;21) translocation can be detected in neonatal blood from teenagers with AML characterized by this translocation.[62] Such fusion transcripts have also been identified to persist in the bone marrow of some patients in long-term morphologic remission.[63] When a cooperative mutation or type I mutation (such as *FLT/ITD* or *c-KIT* point mutations) occurs, a proliferative signal is provided, leading to overt AML. That type II mutations such as *AML-ETO* can be detected far more frequently in neonatal samples than the incidence of leukemia further supports the concept of cooperating mutations in leukemogenesis.[64] Genome-wide studies have identified additional genetic or epigenetic changes that lead to type I and II mutations. Currently, more than 90% of pediatric AML cases are identified to have at least one known genomic alteration (Fig 1B).

### *Altered Transcription and Chromatin-Modifying Factors*

Similar to ALL, many of the chromosomal abnormalities in AML result in alteration of the function of transcription factors critical for normal hematopoiesis and have diagnostic and

therapeutic implications (as discussed in Risk-Adapted Treatment of AML). The t(8;21)(q22;q22) and the inv(16)(p13q22) involving CBF$\alpha$ and $\beta$ subunits respectively account for about a quarter of all cases. These translocations impair CBF transcriptional activation potential. Less common translocations include the t(15;17), 11q23/*MLL* rearrangements and the t(1;22). The t(15;17) generated PML-RARA fusion protein is resistant to physiologic concentrations of retinoic acid but sensitive to pharmacologic levels of all-*trans*-retinoic acid (ATRA), which destabilize the repressor complex, allowing for the expression of genes permissive for differentiation and making this subtype the first successfully treated acute leukemia by molecular targeting. The incidences of chromosomal rearrangements involving the *MLL* gene are age-dependent, being highest in children younger than 2 years and subsequently decreasing to less than 5% in adults.[65] The t(1;22) translocation results in the fusion of the *OTT* gene on chromosome 1 to the Megakaryocytic Acute Leukemia gene on chromosome 22. The translocation is associated closely if not exclusively with acute megakaryoblastic leukemia (AMKL) and has been detected in up to one third of such childhood cases. Monosomy 7, monosomy 5, or 5q deletions are present in only approximately 2% to 4% of cases compared with more than 10% in adults.

Recent genome-wide microarray studies and direct-sequencing approaches have revealed important sub-karyotypic abnormalities. One important finding has been the high percentage of acquired uniparental disomy, resulting in homozygosity of chromosomal regions that occurs after the acquisition of a mutation in one allele.[66,67] Examples of this have included *FLT3-ITD* and *CEBPA* mutations.[68,69]

### Gene Mutations

Biallelic mutations in *CEBPA*, a key leucine zipper containing transcription factor regulating differentiation of several cell types, including myeloid precursors, have been identified in approximately 4% of the cases.[70] The end result of such biallelic mutations is often that of a null phenotype or loss of function.[71]

*WT1*, originally described as a key oncogene in Wilms tumor, functions in non-nephrogenic tissues, including hematopoietic stem cells. Increased expression of *WT1* has been used as a surrogate marker for minimal residual disease (MRD) in AML. Inactivating *WT1* mutations were reported in 8% to 12% of patients with AML, and their prognostic significance remains uncertain and is likely treatment-dependent.

GATA1 is critical in regulating the differentiation of hematopoiesis, particularly for the erythroid and megakaryocyte lineages. Mutations leading to truncated forms of GATA1 are primarily observed in the AMKL or the megakaryoblastic transient myeloproliferative disease that occur in children with Down syndrome.[72] Although not sufficient by themselves in causing leukemia, these *GATA1* mutations have been established as a first genetic hit in these disorders and have even been detected prenatally.

Activating mutations of several cytokine receptors have been shown to result in altered signal transduction and increased leukemia cell proliferation, survival, and chemotherapeutic resistance. *FLT3-ITD*, which involves a duplication of the internal juxtamembrane domain leading to constitutive receptor activation, is rare in infants but is present in 5% to 10% of 5- to 10-year-old patients, 20% of young adult patients, and more than 35% of patients older than 55 years of age with AML.[73] An increased *FLT3-ITD* mutant to wild-type allelic ratio portends a poor prognosis.[74,75] Children's Oncology Group (COG) trials are using a mutant to wild-type allelic ratio of $\geq 0.4$ as a criterion for allogeneic hematopoietic stem-cell transplantation (HSCT) in first remission. Point mutations in the activating loop of the receptor (*FLT3/ALM*) also result in constitutively activated FLT3 but do not confer a poor prognosis.[73] This finding may be in part due to differences in signaling pathway activation by the different forms of FLT3. *FLT3/ALM* occurs in only 6% to 8% of children with AML and is mutually exclusive of *FLT3-ITD*.[73]

Activating mutations of the c-KIT receptor also result in cytokine-independent proliferation, survival, and drug resistance. Such mutations preferentially activate STAT3 signaling and appear to be clustered with CBF abnormalities, occurring in up to 25% of CBF AML cases but in only $\leq$ 5% of overall childhood AML.[74-77] In contrast to initial reports,[74,75] recent studies failed to demonstrate *c-KIT* mutations to have adverse prognostic impact.[78] Mutations involving *FMS* and *PDGFR*, class III type of tyrosine kinases, have been reported in adults but not in children with hematologic malignancies.

*N-RAS* has been reported to be mutated in approximately 10% of children and up to 30% of adults with AML.[79] These activating mutations most frequently involve single-base changes of codons 12, 13, and 61, resulting in inhibition of RAS-GTPase. No clinical significance has been associated with mutations in *RAS* in pediatric AML, and *RAS*-directed therapies have not been successful thus far.[80] However, the recent application of synthetic lethal screening has started to reveal some alternative pathways that could be therapeutically targeted.[81]

*NPM1* mutations are associated with a favorable prognosis. They appear more frequently in AML with normal karyotypes and up to 20% of childhood and 50% of adult cases.[82,83] *NPM1* mutations seem to be present in leukemia-initiating cell populations and are usually maintained at relapse, suggesting they may represent a primary oncogenic event.[84,85]

### Genome-Wide Analysis

The initial whole-genome sequencing of an adult with M1 AML and normal karyotype disclosed 10 somatic mutations and two leukemia-specific SNPs.[86] Two of the mutations involved *FLT3* and *NPM1*, whereas the other eight genes involved nonsense and missense mutations that had not previously been described in AML.[86] These novel mutations were not identified in 200 additional AML samples, raising the question of whether they were merely passenger mutations. Analysis of the second case of cytogenetically normal AML revealed 12 mutations in annotated protein-coding genes or regulatory RNAs and 52 mutations in noncoding regions of the genome.[87] Four genes, *NPM1*, *NRAS*, *IDH1*, and a conserved region on chromosome 10, were found in at least one additional sample of 180 adult AMLs. Although the *IDH1* mutation was observed in 16% of 80 cytogenetically normal adult AML samples,[87] it has not been found in childhood AML.[88] Independent analyses of *IDH1* and *IDH2* mutations showed that they were more frequently associated with AML having a normal karyotype, but had no prognostic or therapeutic impact.[89-92]

Although RNA and microRNA expression signatures can accurately discriminate cases with specific chromosomal translocations and identify novel subsets of AML,[93] two independent pediatric studies failed to identify an expression pattern with consistent prognostic significance.[94,95] Some of the differences observed in gene expression studies are also beginning to be understood in terms of epigenetic regulation of chromatin function. The finding of a similar expression profile between an AML subset with the methylation and silencing of

  

the *CEBPA* promoter and another characterized by *CEBPA* mutations illustrates the critical role that epigenetic changes play in AML.[94] Of further interest, the distinctive myeloid/T-lymphoid characteristics of this subtype have been linked to the finding that decreased *CEBPA* expression leads to increased expression of T-lineage genes in hematopoietic precursors.[94,95] On a genome-wide scale, altered CpG methylation profiles have been associated with distinct subsets of adult AML.[96] A 15-gene methylation classifier has been reported to have prognostic significance.[97]

### Inherited Susceptibility of AML

Several inherited syndromes associated with an increased incidence of AML have been instrumental in demonstrating the importance of key molecular pathways in the development of somatically acquired AML.[98,99] Transient myeloproliferative disease and AMKL in patients with Down syndrome are characterized by specific mutations in the *GATA1* gene, which have been documented even during prenatal development.[72] Fanconi anemia (mutations in DNA repair genes), dyskeratosis congenita (X-linked mutations in dyskerin or autosomal-recessive forms with mutations in genes involved in telomere maintenance and RNA processing), Schwachman-Diamond's syndrome (*SBDS* gene involved in ribosome processing), and Kostmann's syndrome (defects in neutrophil elastase *ELA2*) are all associated with an increased incidence of AML. Mutations in the neurofibromin gene, a *RAS*-inactivating GTPase, are the cause of neurofibromatosis type I, along with its increased incidence of both juvenile myelomonocytic leukemia and AML. Similarly, mutations of the *PTPN11* gene, which encodes the *SHP-2* tyrosine phosphatase, cause Noonan's syndrome, which is also associated with the development of juvenile myelomonocytic leukemia and, less commonly, AML. This group of mutations are all linked to the activation of the RAS pathway. Familial platelet disorder with a propensity to develop AML, as well as congenital amegakaryocytic thrombocytopenia, are associated with an increased incidence of AML and caused by mutations in *CFFA2* and the thrombopoietin receptor, *c-mpl*, respectively. Inherited mutations in the *CEBPA* have also been linked to familial AML.

## RISK-ADAPTED TREATMENT OF ALL

The principal and strategies of contemporary risk-adapted treatment of ALL have been the subject of recent reviews.[31,100] Therefore, only a few selected high-risk subgroups will be discussed here.

### Philadelphia Chromosome–Positive ALL

The Philadelphia chromosome–positive ALL had historically been associated with a dismal outcome, even with allogeneic HSCT, especially in older patients who presented with a high leukocyte count or had a slow early response to initial therapy. In a recent COG study, the addition of continuous exposure of imatinib into an intensive chemotherapy regimen has yielded a 3-year event-free survival of 80%, more than twice that of the historical controls.[37] Patients who were treated with intensive chemotherapy plus imatinib fared as least as well as those historical controls who underwent matched-related or matched-unrelated transplantation. Continuous exposure of imatinib seemed to abrogate the prognostic impact of age, leukocyte count, high level of MRD at the end of induction, and even induction failure. Additional follow-up is needed to determine whether the treatment improved the cure rate rather than merely prolonging the disease-free survival. Meanwhile, many pediatric oncologists have reserved transplantation for therapy after relapse in children with Philadelphia chromosome–positive ALL. Future studies will need to address whether the aggressive backbone therapy that was used in the COG study can be safely omitted or reduced in combination with a tyrosine kinase inhibitor and whether the new generation of tyrosine kinase inhibitors (eg, dasatinib, nilotinib) can further improve outcome. Because of its dual targeting of ABL and SRC, more potent suppression of the BCR-ABL1 signaling, and efficacy to most imatinib-resistant BCR-ABL1 mutants (except for T3151), as well as good tolerability in adult clinical trials,[101] dasatinib is now being tested in children.

### High-Risk T-Cell ALL

With the use of intensive treatment including asparaginase and dexamethasone, T-cell cases fared as well as B-cell precursor cases in some studies.[6,10] Although high-dose methotrexate at 5 g/m$^2$ has been suggested to improve outcome in T-cell ALL, methotrexate was given parenterally at only 30 mg/m$^2$ in the DFCI 95-01 study, which featured intensive asparaginase and doxorubicin for consolidation therapy and has perhaps the best treatment result for this subtype of ALL, with a 5-year event-free survival rate of 85%.[102] In the current COG study for T-cell ALL, the relative efficacy and safety of high-dose methotrexate at 5 g/m$^2$ with leucovorin rescue are being compared with escalating medium doses of methotrexate without leucovorin rescue plus PEG-asparaginase. In the same study, patients are also randomly assigned to receive or not receive nelarabine (a prodrug of 9-$\beta$-D-arabinofuranosylguanine), which has considerable antileukemic effects for T-cell ALL in phase II studies.[103]

Early T-cell precursor ALL, a subset of T-cell ALL characterized by a gene expression profile similar to that of normal early thymic precursor cells with multilineage differentiation potential and a distinct immunophenotype (CD1a-negative, CD8-negative, CD5-weak, and the expression of stem-cell or myeloid markers), was recently identified.[45] These cases have extremely poor outcome, despite the use of transplantation. Because of the significantly improved outcome of patients with T-cell ALL who were treated with high-dose dexamethasone (10 mg/m$^2$ per day) during remission induction in the recently completed Associazione Italiana Ematologia ed Oncologia Pediatrica Berlin-Frankfurt-Muenster AIEOP-BFM-2000 study, albeit with increased toxicity,[104] this dose of dexamethasone is being tested during remission induction for this subset of patients in the current St Jude Total Therapy Study XVI.

### Infant ALL

Even with intensive therapy including high doses of cytarabine and methotrexate, treatment outcome for infants with ALL remains poor, and for those with *MLL* gene rearrangement, the event-free survival rates range between 30% and 40% only.[100,105,106] Although several small studies have suggested that allogeneic HSCT improves outcome, results from large group studies failed to show any benefit of this treatment modality.[105,106] The Interfant-06 Study Group is conducting a randomized trial to test whether the addition of two early intensification courses typically used for AML might improve outcomes for infants with medium-risk or high-risk ALL, including those with *MLL* rearrangement. The role of allogeneic HSCT in first

remission is being investigated in very high-risk cases, as defined by *MLL* rearrangement, age less than 6 months, and WBCs more than 300 $\times 10^9$/L. The current COG trial randomly assigns *MLL*-rearranged infant cases to receive the FLT3 inhibitor lestaurtinib, which has been shown to have schedule-dependent synergistic effects with chemotherapy for *MLL*-rearranged leukemia in preclinical studies.[107] Recent findings suggested that aberrant DNA methylation occurs in the majority of infant ALL case with *MLL* rearrangement,[108,109] raising the possibility of using DNA methyltransferase inhibitors in these patients.

### Adolescent ALL

Older adolescents 15 to 21 years of age have had an inferior outcome as compared with that of children and younger adolescents with ALL, partly due to an increased incidence of Philadelphia chromosome–positive and T-cell ALL, lower incidence of *ETV6-RUNX1* fusion and hyperdiploidy, and poorer compliance.[31,110-112] The relatively poor outcome of older adolescents 16 to 21 years of age with ALL has prompted comparisons of outcome of patients in this age group treated in pediatric versus adult clinical trials in North America and Western Europe. Consistently, pediatric trials have yielded significantly better outcome than adult trials.[112-114] This finding, in all likelihood, reflects differences in the more intensive use of nonmyelosuppressive agents such as dexamethasone, vincristine, and asparaginase; the incorporation of high-dose methotrexate; and early and frequent administration of intrathecal therapy in pediatric regimens.

The importance of these treatment components is supported by several other pediatric trials. In the Children's Cancer Group 1961 trial, which included 262 adolescents 16 to 21 years of age treated from 1996 to 2002,[112] the 5-year event-free survival rate was 71.5%. This randomized trial demonstrated that augmented rather than standard postinduction intensification therapy with additional doses of vincristine and PEG-asparaginase in lieu of mercaptopurine during interim maintenance therapy and increased doses of intravenous methotrexate without leucovorin rescue improved outcome for patients with a rapid early response. The Dana-Farber Cancer Institute (DFCI) protocols (1991 to 2000)[6] and St Jude Total Study XV (2000 to 2007),[115] which yielded excellent results for adolescents, likewise featured early intensification therapy with vincristine and asparaginase. Although some contemporary adult ALL trials have recommended allogeneic transplantation as the best treatment option for good-risk adult ALL patients in first remission,[116] the excellent results obtained in these pediatric trials do not support the routine use of transplantation in older adolescents with ALL.

There are three other important observations from the Children's Cancer Group 1961 study.[112] First, there was no statistical difference in treatment outcome between adolescents with a rapid response who were randomly assigned to receive either one or two courses of postinduction intensification therapy. Second, there was an increased risk of toxic deaths among older adolescents, with 18% of the first events being nonrelapse deaths that occurred during induction or in first remission. Third, there was an increased risk of osteonecrosis. Thus it will be of interest to test whether prednisone pulses, which are commonly given during maintenance therapy, can be omitted in adolescents and young adults with ALL and rapid early response.

The excellent results recently achieved in older adolescents with ALL have prompted many centers and cooperative groups to start treating young adults with pediatric-like regimens. A recent report showed 6-year event-free survival rates of 60% for the 35 adolescents 15 to 18 years old and 63% for the 46 young adults 19 to 30 years old.[117] The DFCI Consortium attained a 2-year rate of 72.5% among 75 adults 18 to 50 years of age.[118] Investigators at Princess Margaret Hospital in Toronto have also adapted the DFCI treatment regimen and achieved a 3-year relapse-free survival rate of 77% among 64 adults with BCR-ABL–negative ALL who did not undergo transplantation.[119] To this end, a US adult intergroup study is testing a pediatric-like regimen in adolescents and young adults up to 39 years of age.

### Other High-Risk Subgroups

Hypodiploidy (< 44 chromosomes), t(17;19)(q22;p13.3) [*TCF3-HLF*], remission induction failure, and the presence of MRD more than 1% at the end of remission induction are also associated with dismal outcome and collectively occur in approximately 5% of children with ALL.[31] Although allogeneic transplantation is frequently used to treat these patients, there is no strong evidence to document the efficacy of this approach. Among many novel therapeutics under investigation (Table 4),[101] killer-cell immunoglobulin-like receptor–mismatch natural cell therapy[120,121] and immunotherapy with a T-cell–engaging CD19-/CD3-bispecific antibody construct (blinatumomab) seem to be particularly promising.[122]

### Cases at High Risk of CNS Relapse

Two recent studies showed that with effective chemotherapy, prophylactic cranial irradiation can be safely omitted altogether in the treatment of childhood ALL,[10,123] showing isolated CNS relapse rates of 2.7% and 2.6%. The complete omission of prophylactic cranial irradiation in these studies allowed the clear identification of risk factors for CNS relapse, which were any CNS involvement at diagnosis, t(1;19)[*TCF3-PBX1*], and T-cell ALL.[10,123] In the current St Jude Total Therapy Study XVI, triple intrathecal therapy is further intensified for these patients with twice weekly administration in the first 2 weeks of remission induction.

## RISK-ADAPTED TREATMENT OF AML

Similar to ALL, risk-adapted therapy has also become an important approach in childhood AML. Many traditional prognostic factors have been replaced by cytogenetic and molecular features, as well as flow cytometric assessment of MRD (Table 5).

### AML Characterized by Chimeric Transcription Factors: "Mostly Low-Risk" AML

With the introduction of intensively dosed and/or timed chemotherapy regimens, AML characterized by alterations of core-binding and transcription factors have emerged as a favorable prognostic group. Both t(8;21) and inv(16) AML have an approximately 80% overall survival rate when treated with three to four courses of intensive chemotherapy.[15-28] Although patients with t(8;21) AML may have a higher relapse rate than those with inv(16), they are still able to be cured with allogeneic transplantation after attaining a second remission.[127]

**Table 4.** Novel Therapeutics Under Investigation in Childhood ALL and AML

| Category and Agent | Properties |
|---|---|
| New formulations | |
| Pegylated asparaginase | Long half-life, reduced immunogenicity (ALL) |
| Sphingosomal vincristine | Decreased neuropathy, higher tissue concentration, non-vesicant (ALL) |
| Liposomal annamycin | Decreased cardiotoxicity (ALL/AML) |
| Liposomal doxorubicin | Decreased cardiotoxicity (ALL/AML) |
| Liposomal cytarabine | Long half-life, potential neurotoxicity when administered intrathecally (ALL/AML) |
| Nucleoside analogues | |
| Clofarabine | Effective for ALL and AML |
| Nelarabine | Selective for T-cell ALL, potential neurotoxicity |
| Forodesine (BCX-1777) | Oral phosphorylase inhibitor (ALL) |
| Monoclonal antibodies | |
| Rituximab (anti-CD20) | Potentiate chemotherapy for $CD20^+$ B-lineage ALL |
| Alemtuzumab (anti-CD52) | Potentiate chemotherapy for $CD52^+$ ALL |
| Epratuzumab (anti-CD22) | May have synergistic effect with anti-CD20 antibody |
| CAT-8015; HA22; inotuzumab ozogamicin (anti-CD22) | Cytotoxic for $CD22^+$ ALL |
| Gemtuzumab ozogamicin (anti-CD33) | Cytotoxic for $CD33^+$ leukemia (AML) |
| Blinatumomab | Bispecific antibodies that direct $CD3^+$ T-cell against $CD19^+$ ALL |
| Molecularly targeted agents | |
| Tyrosine kinase inhibitors (imatinib, nilotinib, dasatinib, MK-O457, bosutinib, AP24534, DCC2036, sorafenib); Aurora kinase inhibitor (danusertib); Src-family kinase inhibitor; VEGF inhibitors (bosutinib); bevacizumab, SU5416, AZD2171 | Potentiate chemotherapy for Ph+ ALL; targeting c-KIT, VEGF in AML |
| Fms-like tyrosine kinase −3 (Lestaurtinib, Midostaurin, Tandutinib) | Phase I studies on *MLL*-rearranged leukemia/*FLT3-ITD* positive AML |
| NOTCH1 inhibitors (γ-secretase inhibitor, antagonists targeting NOTCH transactivation complex, NOTCH1 receptor inhibitors) | Preclinical studies for T-cell ALL |
| mTOR inhibitors (rapamycin, temsirolimus, everolimus) | Testing in post-transplantation use to decrease graft-versus-host disease and to suppress leukemia (ALL); in combination with chemotherapy in AML |
| Demethylating agents (decitabine, azacytidine) | Potentiate chemotherapy by epigenetic modulation of leukemia cells with *MLL* rearrangement and in AML/MDS |
| Histone deacetylase inhibitor (vorinostat, valproic acid, depsipeptide) | Potentiate chemotherapy by epigenetic moderation of leukemia cells in ALL and AML |
| Heat shock protein inhibitor (17-allylaminogeldanamycin) | Potentiate the cytotoxicity of histone deacetylase inhibitor |
| Proteasome inhibitor (bortezomib, carfilzomib, ONX 0912) | Potentiate mTOR inhibitors and anthracyclines; clinical trial in AML |
| Farnesylation (tipifarnib) | Directed at RAS inhibition in AML |
| JAK2 inhibitor (lestaurtinib) | Phase I trial for ALL and AML with *JAK* mutations |
| Microenvironment | |
| Integrin and cell adhesion inhibition (AMD3100, plerixafor) | CXCR4 inhibition; phase I trials in AML planned |
| Immunomodulation | |
| IL-2, IL-6, GM-CSF, WT1, RHAMM-R3 and PR1 peptides, GVAX, dendritic cells | Immunostimulatory approaches to increase T-lymphocyte mediated antileukemic responses in AML |

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; VEGF, vascular endothelial growth factor; Ph+, Philadelphia chromosome positive; mTOR, mammalian target of rapamycin; MDS, myelodysplastic syndrome; IL, interleukin; GM-CSF, granulocyte-macrophage colony-stimulating factor.

Similar to adults, children with acute promyelocytic leukemia (APL) have an excellent overall survival in the 75% to 85% range, with some reports as high as 90%.[124,128] This leukemia is particularly sensitive to ATRA and arsenic trioxide. Children with APL also benefit from maintenance therapy with ATRA and antimetabolites.[129,130] Allogeneic transplantation is not recommended for these children in first remission. Survival after relapse is approximately 70% after reinduction, usually with arsenic trioxide, and then autologous or allogeneic transplantation.[131,132]

*MLL*-rearranged AML represents a diverse group with quite variable outcomes.[65] In an international study, survival was 100%, 63%, 27%, and 22% for patients with the t(1;11), the t(9;11), the t(4;11), and the t(6;11), respectively.[65] In part because of the variability in outcomes, small numbers of patients, and lack of definitive data demonstrating the superiority of HSCT, most cooperative trials do not include patients with *MLL*-rearranged AML in the high-risk group requiring allogeneic HSCT in first remission.[133] Once associated with a poor prognosis,[134] AMKL with the t(1;22) has improved outcome with contemporary treatment, and HSCT may not be indicated in these patients.[26,135]

### *AML Characterized by Mutation Altered Genes: The "Good" and the "Bad"*

FLT3-ITD mutations, particularly when associated with a high mutant to wild-type allelic ratio, are associated with an overall survival rate of usually less than 30%.[136] Although controversial, there are some indications that transplantation might improve outcome of children with this type of AML.[137] Some clinical trials

**Table 5.** Characteristics and Clinical Outcomes of Selected Subtypes of Childhood AML

| Subtype | Affected Genes | Gene Functions | Frequency (%) | Clinical Characteristics | 5-Year EFS (%) | 5-Year OS (%) |
|---|---|---|---|---|---|---|
| Rearrangements | | | | | | |
| t(8;21)(q22;q22) | *ETO-AML1* | Transcription factors | 12 | Associated with chloromas | 55-71 | 75-85 |
| inv(16)(p13;q22) | *MYH11-CBF* | Muscle protein/transcription factor | 8 | Eosinophilia with dysplastic basophilic granules | 72-88 | 75-85 |
| t(8;16) | *MOZ-CBP* | Transcription factors | 1 | High WBCs, chloromas, etoposide-related secondary AML | ID*† | ID |
| t(15;17)(q22;q12) | *PML-RAR* | Transcription factors/retinoid receptor | 12 | Associated with FAB M3, Auer rods common; FAB M3; ATRA-sensitive | 71† | 90† |
| t(11;17)(q23;q12) | *PLZF-RARA* | Transcription factors/retinoid receptor | Rare | Associated with FAB M3, Auer rods common; FAB M3; ATRA-resistant | ID | ID |
| t(1;22) | *RBM15-MKL1* | RNA binding protein, DNA binding protein | 2-3 | Associated with FAB M7 in Down syndrome and non–Down syndrome | ID | ID |
| t(6;9)(p23;q34) | *DEK-NUP214(CAN)* | Transcription factor/nuclear transport | Rare | Basophilia and multilineage dysplasia; associated with *FLT3-ITD* and TdT+ | ID | ID |
| MLL | *MLL* (partner genes) | Histone methyltransferase | 18 | | | |
| t(1;11)(q21;q23) | AF1q (MLLT11) | Function unknown, causes short half-life | 3 | 76% < age 2 years; 20% and 48% FAB M4 and M5, respectively | 92 | 100 |
| t(4;11)(q21;q23) | AF4 (MLLT2) | Associated with EAP[10] | 2 | 61% < age 2 years; 17% and 42% FAB M4 and M5, respectively | 29 | 27 |
| t(6;11)(q27;q23) | AF6 (MLLT4) | Functions as dimerization domain | 5 | 9% < age 2 years; 57% ≥ 10 years; 35% and 41% FAB M4 and M5, respectively | 11 | 22 |
| t(9;11)(p22;q23) | AF9 (MLLT3) | ENL homolog, associated with EAP | 43 | 42% < age 2 years; 81% is FAB M5 | 50 | 63 |
| t(10;11)(p11.2;q23) | AF10 (MLLT10) | Interacts with DOT1L | 2 | 75% < age 2 years; 27% and 55% FAB M4 and M5, respectively | 17 | 27 |
| t(10;11)(p12;q23) | AF10 (MLLT10) | Interacts with DOT1L | 13 | 62% < age 2 years; 72% is FAB M5 | 31 | 45 |
| t(11;19)(q23;p13) | ELL or ENL (MLLT1) | Binds histone H3, Assembles EAP | 4 | 58% < age 2 years; 42% and 45% FAB M4 and M5, respectively | 49 | 49 |
| t(11;19)(q23;p13.1) | ELL or ENL (MLLT1) | Binds histone H3, Assembles EAP | 4 | 41% < age 2 years; 30% and 33% FAB M4 and M5 respectively | 46 | 61 |
| t(11;19)(q23;p13.3) | ELL or ENL (MLLT1) | Binds histone H3, Assembles EAP | 3 | 36% < age 2 years; 44% ≥ age 10 years; 20% and 40% FAB M4 and M5 | 46 | 47 |
| t(11;17)(q23;q21) | AF17 (MLLT6), LASP1 | F-actin rick cytoskeletal activity | 2 | 33% < age 2 years; 42% ≥ age 10 years; 33% and 50% FAB M4 and M5 | 11 | 22 |
| Other | | | 19 | 50% < age 2 years; 29% and 50% FAB M4 and M5, respectively | 39 | 54 |
| Normal karyotype | | | 20 | | | |
| Gene mutations | | | | | | |
| *NPM* | Nucleophosmin | Nuclear transporter RNA processing | 23 | 8%-10% of childhood AML | 65-80 | 75-85 |
| *CEBPα* | CCAAT/enhancer binding protein α | Transcription factor | 14 | 4%-6% of all childhood AML; more common in older patients, FAB M1 or M2 | 70 | 83 |
| *FLT3/ALM* | Fms-like tyrosine kinase 3 activation loop domain | Receptor for FLT3 | 3 | 6%-7% of all childhood AML | 50-60 | 60-70 |
| *FLT3-ITD* | Fms-like tyrosine kinase 3 internal tandem duplication | Receptor for FLT3 | 18 | 10%-15% of all childhood AML | < 35 | < 35 |
| *WT1* | Wilms tumor 1 | Transcription factor | 13 | 8%-10% of all childhood AML | 22-35 | 35-56 |
| *RAS* | Rat sarcoma gene | Signal transduction | 3 | 5% of all childhood AML | ID | ID |
| *PTPN11* | Protein tyrosine phosphatase, non-receptor type 11 | Tyrosine phosphatase | 2 | Most commonly associated with JMML | ID | ID |
| No known mutations | | | 24 | | 40 | 50 |
| Poor-risk cytogenetics | | | < 15 | | < 40 | < 40 |
| Del 5q/E5 | | | 1 | | | |
| −7 | | | 2 | | | |

Abbreviations: AML, acute myeloid leukemia; EFS, event-free survival; ID, insufficient data; FAB, French-American-British; ATRA, all-*trans*-retinoic acid; JMML, juvenile myelomonocytic leukemia.

*Data extracted from Lange et al,[15] Creutzig et al,[20] Smith et al,[21] Ravindranath et al,[25] Rubnitz et al,[26] Gibson et al,[27] and Cooper et al.[30]

†Data extracted from Ho et al,[70] Meshinchi et al,[73] Brown et al,[82] de Botton et al,[124] Hollink et al,[125] and Ho et al.[126]

  

are testing the efficacy of various *FLT3* inhibitors with different degrees of specificity plus allogeneic transplantation in these children. In the next COG trial for newly diagnosed AML, patients with a high *FLT3-ITD* to wild-type allelic ratio will be offered an allogeneic HSCT in first remission. Of note, patients with point mutations of *FLT3* (eg, *FLT3/ALM*) do not have poor outcome and should be treated with chemotherapy only.

The *c-KIT* mutations, most commonly observed in CBF AML, has been reported to portend a poor prognosis in some studies, but not in a recent COG study.[138] Similarly, *RAS* mutations have not been definitively associated with a poor prognosis. Thus patients with these mutations are usually treated with chemotherapy only.

*NPM* mutations convey both increased chemosensitivity and improved outcome.[83] However, whether or not the presence of *NPM* mutations can partially abrogate the adverse affect of coexpressed *FLT3-ITD* is controversial.[82] *CEBPA* mutations are often associated with normal karyotype AML and improved overall survival.[70] Thus HSCT in first remission is not recommended for pediatric patients with isolated *NPM* or *CEBPA* mutations. *WT1* mutations had an independent, poor prognostic impact in one study,[125] but not in another (except in patients with coexpression of *FLT3-ITD*).[126] Most clinical trials do not recommend allogeneic transplantation based on isolated *WT1* mutations.

### The Importance of MRD

Other than a Berlin-Frankfurt-Munster study, the detection of MRD has been associated with adverse prognostic significance.[26,139] COG and St Jude trials are using this factor to stratify patients for risk-directed treatment.

### Combined Approaches to Risk Stratification

In COG, the combination of cytogenetic, molecular, and MRD information is being used to stratify patients into two groups for risk-directed therapy. Low-risk AML includes patients with mutations involving *CBF*, *CEBPA*, and *NPM* and those with no MRD at the end of induction therapy. This group represents approximately 73% of patients, with a predicted survival close to 75%. The high-risk group (the remaining 27% of patients with survival $< 35\%$) includes patients with adverse cytogenetic abnormalities (monosomy 7, del(5q)–, −5), high *FLT3-ITD* to wild-type allelic ratio, or MRD at the end of induction and will be offered HSCT in first remission with the most suitable donor.

Molecularly targeted drugs can be tested in both low- and high-risk groups with the intention of reducing toxic therapy in the former group while improving survival of the latter group (Table 4). For example, the use of bortezomib to augment chemotherapy effects on AML stem cells will be randomized in the next COG phase III trial. In addition, *FLT3-ITD* inhibitors (ie, sorafenib) will be tested in the high-risk group with a high *FLT3-ITD* to wild-type allelic ratio.

### Special Subtypes

*Down syndrome.* In view of superior prognosis of Down syndrome patients with AML,[140] current trials are testing strategies to reduce overall drug exposure, especially cardiotoxic drugs, because of special concerns in this population.[141]

*APL.* Since the demonstration that ATRA significantly improved the outcome of patients with APL, these patients have been treated separately from other patients with AML, resulting in 5-year overall survival rates as high as 87%.[128] A major, adverse prognostic factor is presenting WBC more than $10 \times 10^9$/L, associated with an event-free survival of approximately 60%.[128] Approximately 3% of patients died during induction from hemorrhagic complications, accounting for half of the induction failures. The microgranular variant (M3v), a bcr3 PML breakpoint, and the presence of *FLT3-ITD* had also been associated with a poor prognosis,[142] partly due to increased presenting WBCs. In the current pediatric studies, patients are considered low risk or high risk on the basis of WBCs $\leq$ or more than $10 \times 10^9$/L, respectively.

Although intensive anthracycline treatment (cumulative doses ranging from 400 to 750 mg/m$^2$) has been attributed to improve outcome,[130] one of the key issues for pediatric patients has been to reduce exposure to these cardiotoxic drugs. The efficacy of arsenic in relapsed and newly diagnosed patients has made it an attractive alternative to anthracyclines.[143-145] Thus the current COG trial replaces a course of anthracycline-containing chemotherapy with arsenic, reducing anthracycline exposure to 355 mg/m$^2$ of daunorubicin equivalents for standard-risk patients with negative MRD and to 455 mg/m$^2$ for high-risk patients and standard-risk patients with positive MRD after the third treatment course. This trial also includes high-dose cytarabine based on the survival advantage observed in a European trial.[145] Maintenance therapy with ATRA plus antimetabolites will be given to all patients for approximately 2 years. This trial is similar to the European trial, with one primary difference being the introduction of arsenic during consolidation. Future studies may include other targeted agents, such as anti-CD33 monoclonal antibody therapy.[146,147]

*AML in neonates and infants.* Because spontaneous remissions have been reported more frequently in the neonate age group, it is commonly recommended to initially observe such patients and, if cytoreduction is necessary, to perform an exchange transfusion. However, AML-directed therapy with dosing adjustments is usually required. Outcome in this age group is worse than that in older children, despite similar therapy, as a result of treatment toxicities and resistant disease.[148] Novel approaches to directly target *MLL*[149] and bcl-2[150] are being developed (Table 4). In contrast to neonates, infants more than 1 month old seem to do as well as older children when treated with current, intensive regimens.[15-30] The role of transplantation in infants is controversial because it has not been shown to definitely improve outcome and has significant adverse sequelae.

In conclusion, cure rates for childhood leukemias have improved largely through more intensive use of conventional cytotoxic agents evaluated in the context of large, randomized clinical trials. Clinical factors, genetic features of the leukemia, and initial response to therapy are now used in concert to personalize treatment for all patients. Advances in high-throughput genomics have led to the discovery of additional recurrent somatic lesions in the leukemic cell that offers not only additional prognostic information, but also opportunities for the application of novel targeted treatment. Finally, the recognition of host factors that are associated with the risk of leukemic transformation and the response to therapy will likely lead to more sophisticated treatment strategies in the near future.[151,152]

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

*Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.*

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