Acute Lymphoblastic Leukemia in Children

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Approximately 6000 cases of acute lymphoblastic leukemia (ALL) are diagnosed in the United States annually; half the cases occur in children and teenagers. In the United States, ALL is the most common cancer among children and the most frequent cause of death from cancer before 20 years of age. Presenting symptoms of ALL include bruising or bleeding due to thrombocytopenia, pallor and fatigue from anemia, and infection caused by neutropenia. Leukemic infiltration of the liver, spleen, lymph nodes, and mediastinum is common at diagnosis. Extramedullary leukemia in the central nervous system (CNS) or testicles may require specific modifications in therapy.

Since the first description in 1948 of temporary remission of leukemia induced by chemotherapy, pediatric ALL has provided a model for improvement of survival among patients with cancer by progressive improvements in the efficacy of multi-agent chemotherapy regimens and by stratification of treatment intensity according to the clinical features of the patient, the biologic features of the leukemia cells, and the early response to treatment, all of which are predictive of the risk of relapse. Collectively, these advances have increased the survival rate from less than 10% in the 1960s to 90% today (Fig. 1). New discoveries are revealing the promise and challenges of precision-medicine strategies that integrate leukemia genomics into contemporary therapy.

Epidemiology and Risk Factors

In the United States, the incidence of ALL is about 30 cases per million persons younger than 20 years of age, with the peak incidence occurring at 3 to 5 years of age. The incidence varies significantly according to race and ethnic group: 14.8 cases per million blacks, 35.6 cases per million whites, and 40.9 cases per million Hispanics. Childhood ALL develops more frequently in boys than in girls (male:female ratio, 55% to 45%).

Several genetic factors (most prominently Down’s syndrome) are associated with an increased risk of ALL, but most patients have no recognized inherited factors. Genomewide association studies have identified polymorphic variants in several genes (including ARID5B, CEBPE, GATA3, and IKZF1) that are associated with an increased risk of ALL or specific ALL subtypes. Rare germline mutations in PAX5 and ETV6 are linked to familial ALL. Few environmental risk factors are associated with ALL in children. Increased rates of the disease have been linked to exposure to radiation and certain chemicals, but these associations explain only a very small minority of cases.

Genetic Basis of ALL

ALL comprises multiple entities with distinct constellations of somatic genetic alterations (Fig. 2). These genetic alterations include aneuploidy (changes in chromatin properties).
chromosomal rearrangements that deregulate gene expression or result in expression of chimeric fusion proteins, deletions and gains of DNA, and DNA sequence mutations. On average, childhood ALL genomes contain only 10 to 20 nonsilent coding mutations at the time of diagnosis and about twice as many at the time of relapse. Many mutations perturb key cellular processes, including the transcriptional regulation of lymphoid development and differentiation; cell-cycle regulation; the TP53–retinoblastoma protein tumor-suppressor pathway; growth factor receptor, Ras, phosphatidylinositol 3-kinase, and JAK–STAT signaling; nucleoside metabolism; and epigenetic modification. Perturbation of the latter two processes is common at relapse.

ALL may be of B-cell precursor or T-cell lineage. In 25 to 30% of children with B-cell ALL, leukemic cells have high hyperdiploidy (>50 chromosomes) due to nonrandom chromosome gains. This subtype is associated with an excellent prognosis. Hypodiploidy (<44 chromosomes) occurs in 2 to 3% of children with B-cell ALL and is a strong negative prognostic factor. Low hypodiploidy (30 to 39 chromosomes), which is associated with the presence of TP53 mutations that are frequently inherited, is a manifestation of the Li–Fraumeni syndrome.

Chromosomal translocations and intrachromosomal rearrangements are early, possibly initiating events in leukemogenesis. Several can be detected in neonatal blood samples years before there are clinical manifestations of leukemia. These translocations and rearrangements are usually present in all leukemic cells, are retained at relapse, and with additional genetic alterations, induce leukemia in experimental model systems.

There are two functional classes of translocations. The first class relocates oncogenes into regulatory regions of actively transcribed genes, causing dysregulated expression of an intact protein. Examples include translocations that bring C-MYC under control of the immunoglobulin heavy-chain (IGH) or light-chain (IGK and IGL) gene enhancers in Burkitt’s lymphoma and leukemia, rearrangement of the cytokine receptor–like factor 2 (CRLF2) and erythropoietin receptor (EPOR) genes to IGH and IGK in B-cell ALL, and juxtaposition of the transcription factors TLX1 and TLX3 to T-cell receptor (TCR) loci in T-cell ALL.

The second major class of translocations juxtaposes two genes to encode a chimeric protein that has distinct functions from the proteins from which it is derived. An important example is the ETV6-RUNX1 fusion, which fuses two hematopoietic transcription factors; it is observed in one quarter of children with ALL. Other important examples include TCF3-PBX1, the t(9;22)
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(q34;q11.2) translocation that results in formation of the Philadelphia (Ph) chromosome, and chromosomal rearrangements involving the chromosome 11q23 mixed-lineage leukemia (MLL) gene. The Ph chromosome encodes BCR-ABL1, an activated tyrosine kinase. MLL (KMT2A) encodes a histone methyltransferase that is involved in epigenetic regulation of blood-cell development. More than 70 different translocations target MLL, creating fusion proteins that mediate aberrant self-renewal of hematopoietic progenitors.23 MLL translocations are particularly common in ALL that develops before 1 year of age (75% of cases). MLL-rearranged leukemias have very few additional somatic mutations, particularly in infants.24

Genomic profiling and sequencing studies have identified additional subtypes of ALL. These include cases with deregulation of the transcription factor gene ERG25,26 and cases with complex intrachromosomal amplification of chromosome 21.27

In several subtypes of ALL, there is no single defining chromosomal alteration, but these subtypes are defined by other pathological or genomic features. For example, early T-cell precursor ALL is an aggressive stem-cell and progenitor leukemia that has a distinct immunophenotype and genetic alterations targeting transcription factors, signaling pathways, and epigenetic regulation.28,29 Patients with Ph-like ALL have a leukemic-cell gene-expression profile that is similar to that in patients with Ph-positive ALL,
but they do not have BCR-ABL1 and harbor a diverse range of genetic alterations that activate tyrosine kinase signaling. The most common of these alterations are fusions that involve “ABL-class” kinases (ABL1, ABL2, CSF1R, and PDGFRB), which can be targeted with ABL1 inhibitors such as imatinib and dasatinib, and fusions, mutations, or deletions that activate JAK–STAT signaling (including rearrangements of JAK2, CRLF2, EPOR, and mutations of JAK1, JAK2, and JAK3 and the interleukin-7 receptor).

With the exception of MLL-rearranged leukemia in infants, each of these subtypes typically has multiple additional genetic alterations. These alterations commonly target genes encoding proteins involved in cell signaling, tumor-suppressor functions, and lymphoid differentiation. The two most common target genes governing B-lymphoid development are PAX5 (mutated in 35% of cases of ALL in children) and IKZF1 (mutated in 15%).

### Prognostic Factors

Factors that are predictive of an increased or a decreased chance of cure are considered when decisions are made about the intensity of chemotherapy and the selection of patients in first remission for allogeneic hematopoietic-cell transplantation (Table 1). Major prognostic factors include the clinical features that are present at diagnosis, biologic and genetic features of leukemia cells, and early response to treatment.

### Clinical Features

The patient’s age and initial white-cell count are predictive of outcome, with older age or a higher white-cell count portending a worse prognosis. A consensus conference defined “standard risk” (age 1 to 9.99 years and initial white-cell count ≥50,000 per cubic millimeter) and “high risk” (age ≥10 years, initial white-cell count ≥50,000 per cubic millimeter, or both) ALL subgroups comprising, respectively, about two thirds and one third of children with B-cell lineage ALL. Infants younger than 1 year are a special subgroup of patients with worse outcomes.

Age and initial white-cell count have limited prognostic importance in T-cell ALL. Several subtypes of ALL occur more frequently in certain races and ethnic groups, including TCF3-PBX1 ALL in blacks and CRLF2-rearranged ALL in Hispanics. Thus, inherited genetic variations are important in the pathogenesis of ALL.

### Immunophenotype

The cell-surface and cytoplasmic expression of markers of lineage (immunophenotype) classifies childhood ALL into precursor B-cell (85%) or T-cell (15%) subgroups that are reminiscent of normal stages of lymphoid maturation. Patients with Burkitt’s lymphoma or leukemia have a mature B-cell immunophenotype, with expression of cell-surface membrane immunoglobulin, rearrangement of the MYC oncogene, and an aggressive but curable clinical course. Many mutations that are linked to leukemogenesis target genes that regulate normal B-cell or T-cell differentiation, arresting differentiation.

Patients with T-cell ALL are often male, black, older and less likely to be Hispanic than patients with B-cell ALL, have higher initial white-cell counts than patients with B-cell ALL, and have mediastinal lymph node and CNS involvement (Table 2). Historically, survival among children with T-cell ALL was inferior to that among children with B-cell ALL. With the use of more intensive therapy, this difference has narrowed substantially. Some of the preponderance of T-cell ALL among boys and young men may be due to specific mutations that target X-chromosome genes.

### Biologic and Genetic Features

Several genetic alterations are associated with the outcome in children with ALL. High hyperdiploidy and the cryptic t(12;21) encoding ETV6-RUNX1 are associated with a favorable outcome. Hypodiploidy with less than 44 chromosomes, MLL rearrangement, BCR-ABL1, Ph-like ALL, CRLF2 rearrangement, intrachromosomal amplification of chromosome 21, and early T-cell precursor ALL are associated with high-risk clinical features or a poor outcome. Alterations of IKZF1, which encodes the lymphoid transcription factor Ikaros, are common in Ph-positive and Ph-like ALL. These alterations are also associated with a poor outcome.

### Early Response to Treatment

The time required to eliminate the bulk leukemic-cell population to undetectable levels is the single most powerful prognostic factor in ALL in children. Submicroscopic levels of minimal residual disease in ALL (1 leukemia cell per 10⁶ normal cells) can be measured by means of polymerase-chain-reaction amplification of clonotypic IGH or TCR gene rearrangements that are unique to an individual patient’s leukemia or by

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Table 1. Important Prognostic Factors in Acute Lymphoblastic Leukemia (ALL) in Children.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Favorable Factor</th>
<th>Adverse Factor</th>
<th>Use in Risk Stratification</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic and clinical features</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1 to &lt;10 yr</td>
<td>&lt;1 yr or ≥10 yr</td>
<td>This feature is a part of NCI risk group definition</td>
</tr>
<tr>
<td>Sex</td>
<td>Female</td>
<td>Male</td>
<td>No</td>
</tr>
<tr>
<td>Race or ethnic group</td>
<td>White, Asian</td>
<td>Black, Native American, Hispanic</td>
<td>No</td>
</tr>
<tr>
<td>Initial white-cell count</td>
<td>Lower (&lt;50,000/mm³)</td>
<td>Higher (≥50,000/mm³)</td>
<td>Part of NCI risk group definition</td>
</tr>
<tr>
<td><strong>Biologic or genetic features of leukemia cells</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunophenotype</td>
<td>B-cell lineage</td>
<td>T-cell lineage</td>
<td>Often used to select therapy backbone</td>
</tr>
<tr>
<td>Cytogenetic features</td>
<td>ETV6-RUNX1, hyperdiploidy, favorable chromosome trisomies</td>
<td>BCR-ABL1, MLL rearrangements, hypodiploidy</td>
<td>Often used to select treatment intensity, assign the patient to HSCT, or both; some features (e.g., BCR-ABL1) can be used to select targeted therapy</td>
</tr>
<tr>
<td>Genomic features</td>
<td>ERG deletions</td>
<td>IKZF1 deletions or mutations; Philadelphia chromosome–like ALL with kinase gene alterations</td>
<td>Some research groups use IKZF1 deletions to assign patients to more intensive therapy; kinase gene mutations may be used to assign patients to targeted therapy, but this is not yet part of routine care</td>
</tr>
<tr>
<td><strong>Early response to treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response to 1 wk of glucocorticoid therapy</td>
<td>Good response to prednisone (&lt;1000 blasts/mm³)</td>
<td>Poor response to prednisone (≥1000 blasts/mm³)</td>
<td>Easy to measure and used by many groups; may be supplanted by MRD</td>
</tr>
<tr>
<td>Marrow blasts after 1–2 wk of multiagent therapy</td>
<td>M1 marrow (&lt;5% blasts) by day 8 or 15</td>
<td>No M1 marrow (≥5% blasts) by day 8 or 15</td>
<td>Easy to measure and used previously by many groups; now being supplanted by MRD</td>
</tr>
<tr>
<td>MRD quantitation during or at end of induction</td>
<td>Reaching low (&lt;0.01%) or undetectable MRD by specific time points</td>
<td>Persistence of MRD ≥0.01% at specific time points; the higher it is, the worse the prognosis</td>
<td>Most important single prognostic factor for contemporary therapy; critical for modern risk stratification</td>
</tr>
<tr>
<td>MRD at 3–4 mo</td>
<td>Low (&lt;0.01%), preferably undetectable</td>
<td>Persistence of MRD ≥0.01%</td>
<td>May help select patients for HSCT or new therapies in first remission</td>
</tr>
</tbody>
</table>

* HSCT denotes hematopoietic stem-cell transplantation, MRD minimal residual disease, and NCI National Cancer Institute.
The risk of treatment failure and death is 3 to 5 times as high among children with levels of minimal residual disease that are 0.01% or higher at the end of induction therapy and at later time points than among those with levels that are lower than 0.01%. Intensification of therapy for patients with higher levels of minimal residual disease improves their outcome. Emerging next-generation-sequencing techniques for detection of minimal residual disease may be useful by providing sensitive detection of leukemia cells below the level detected reliably by other techniques.

Table 2. Demographic Characteristics of Patients in Children’s Oncology Group (COG) ALL Trials.*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Precursor B-Cell ALL (N=8393)</th>
<th>T-Cell ALL (N=1671)</th>
<th>number (percent)</th>
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<tbody>
<tr>
<td><strong>Race†</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>6375 (76.0)</td>
<td>1219 (73.0)</td>
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</tr>
<tr>
<td>Black</td>
<td>542 (6.5)</td>
<td>230 (13.8)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>374 (4.5)</td>
<td>85 (5.1)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>254 (3.0)</td>
<td>32 (1.9)</td>
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<tr>
<td>Unknown</td>
<td>848 (10.1)</td>
<td>105 (6.3)</td>
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<td><strong>Ethnic group†</strong></td>
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<tr>
<td>Hispanic</td>
<td>1809 (21.6)</td>
<td>238 (14.2)</td>
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<tr>
<td>Not Hispanic</td>
<td>6243 (74.4)</td>
<td>1373 (82.2)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>341 (4.1)</td>
<td>60 (3.6)</td>
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<tr>
<td><strong>Sex</strong></td>
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<tr>
<td>Female</td>
<td>3831 (45.6)</td>
<td>450 (26.9)</td>
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<tr>
<td>Male</td>
<td>4562 (54.4)</td>
<td>1221 (73.1)</td>
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</table>

* Data are from unpublished results of COG ALL trials AALL0232 (ClinicalTrials.gov number, NCT00075725), AALL0331 (NCT00103285), and AALL0434 (NCT00408005). Percentages may not sum to 100 owing to rounding. † Race or ethnic group was reported by parents or guardians.

**CONTEMPORARY THERAPY**

The basic components of various therapies for children with ALL are similar and include several discrete phases. Induction therapy lasts 4 to 6 weeks and includes a glucocorticoid (prednisone or dexamethasone), vincristine, an asparaginase preparation, optional use of an anthracycline, and intrathecal chemotherapy. Almost all patients attain remission, but this is not a cure, since relapse will occur universally without additional therapy.

After remission, treatment includes 6 to 8 months of intensive combination chemotherapy that is designed to consolidate remission and prevent development of overt CNS leukemia. Treatment in an 8-week delayed-intensification (protocol II) phase, based on the 8-week Berlin–Frankfurt–Münster protocol I, is then administered. Repeated courses of methotrexate, administered either through short intravenous infusion or at high doses over 24 hours followed by administration of folinic acid to “rescue” normal tissues from toxic effects, are a critical component of contemporary ALL regimens.

Patients then receive low-intensity “anti-metabolite”-based maintenance therapy for 18 to 30 months. This therapy consists of daily oral mercaptopurine or thioguanine and weekly oral methotrexate. Some regimens also include periodic 5- to 7-day “pulses” of glucocorticoids and vincristine. The exact reasons why maintenance therapy is required and the most effective composi-
<table>
<thead>
<tr>
<th>Research Group</th>
<th>Trial</th>
<th>Reference</th>
<th>Region</th>
<th>Years</th>
<th>Subgroup</th>
<th>No. of Patients</th>
<th>Event-free Survival†</th>
<th>Overall Survival†</th>
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<tr>
<td>COG</td>
<td>Many trials</td>
<td>Hunger et al.37</td>
<td>United States, Canada, Australia, New Zealand</td>
<td>2000–2005</td>
<td>All patients</td>
<td>6994</td>
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<td>B-cell ALL</td>
<td>5845</td>
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<td>N/A</td>
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<td>T-cell ALL</td>
<td>457</td>
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<td>N/A</td>
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<td>SJCRH</td>
<td>Total Therapy Study XV</td>
<td>Pui et al.56</td>
<td>United States</td>
<td>2000–2007</td>
<td>All patients</td>
<td>498</td>
<td>85.6</td>
<td>93.5</td>
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<td>94.6</td>
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<td>T-cell ALL</td>
<td>76</td>
<td>78.4</td>
<td>87.6</td>
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<td>DFCI</td>
<td>DFCI ALL Consortium Protocol 00–01</td>
<td>Vrooman et al.57</td>
<td>United States, Canada</td>
<td>2000–2004</td>
<td>All patients</td>
<td>492</td>
<td>80.0</td>
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<td>AIEOP-BFM</td>
<td>AIEOP-BFM ALL 2000</td>
<td>Conter et al.,49 Schrappe et al.50</td>
<td>Western Europe</td>
<td>2000–2006</td>
<td>All patients</td>
<td>4480</td>
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<td>91.1</td>
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<td>MRC-NCRI</td>
<td>UKALL 2003</td>
<td>Vora et al.38</td>
<td>United Kingdom</td>
<td>2003–2011</td>
<td>All patients</td>
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<td>T-cell ALL</td>
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<td>DCOG</td>
<td>DCOG Protocol ALL-9</td>
<td>Veerman et al.59</td>
<td>The Netherlands</td>
<td>1997–2004</td>
<td>All patients</td>
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<td>86</td>
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<td>B-cell ALL</td>
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<td>T-cell ALL</td>
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<td>EORTC CLG</td>
<td>EORTC CLG 58591</td>
<td>Domenech et al.50</td>
<td>Belgium, France</td>
<td>1998–2008</td>
<td>All patients</td>
<td>1940</td>
<td>82.6</td>
<td>89.7</td>
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<td>NOPHO</td>
<td>ALL-2000</td>
<td>Schmiegelow et al.61</td>
<td>Denmark, Finland, Iceland, Norway, Sweden</td>
<td>2000–2007</td>
<td>All patients</td>
<td>1023</td>
<td>79</td>
<td>89</td>
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<td>T-cell ALL</td>
<td>115</td>
<td>64</td>
<td>72</td>
</tr>
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* Infants younger than 1 year of age were excluded from these studies when possible. AIEOP denotes Italian Association of Pediatric Hematology and Oncology, BFM Berlin–Frankfurt–Münster, DCOG Dutch Childhood Oncology Group, DFCI Dana–Farber Cancer Institute, EORTC CLG European Organization for Research and Treatment of Cancer–Children’s Leukemia Group, MRC-NCRI Medical Research Council–National Cancer Research Institute, N/A not available, NOPHO Nordic Society of Paediatric Haematology and Oncology, SJCRH St. Jude Children’s Research Hospital, and UKALL Medical Research Council Working Party on Leukaemia in Children UK National Acute Lymphoblastic Leukaemia Trial.† Survival percentages shown are the rates at 5 years except for the rates for the AIEOP-BFM trial, which were reported at 7 years.
tion and duration of chemotherapy are unknown. Because maintenance therapy is prolonged and requires daily oral drug administration, adherence can be problematic; 20% of patients are less than 90% adherent, and decreased adherence is associated with a risk of relapse that is 4 times as high as the risk among patients whose rate of adherence is 90% or more.63 Host polymorphisms may influence both the efficacy and toxicity of mercaptopurine, which is the backbone of maintenance therapy.63

CNS-DIRECTED THERAPY
Cranial irradiation dramatically improved cure rates among patients with ALL in the 1960s and 1970s, but it was associated with an increased risk of secondary CNS tumors, delayed growth, endocrinopathies, and neurocognitive effects.64 Consequently, CNS irradiation has been limited to progressively smaller patient subgroups over time.

Several research groups have eliminated CNS irradiation for most or all children with newly diagnosed ALL, and their results are quite similar to those obtained by groups that continue to include irradiation in therapy for children with ALL.56,59 The current role of CNS irradiation is controversial, but all groups now treat at least 80% of children who have newly diagnosed ALL without the use of cranial irradiation.

TREATMENT OF RELAPSED ALL, INCLUDING HEMATOPOIETIC-CELL TRANSPLANTATION
Relapse occurs in 15 to 20% of children with ALL, and cure rates are much lower after relapse.60 Prognostic factors at relapse include the time to relapse (a shorter time is associated with a worse prognosis), immunophenotype (T-cell immunophenotype is associated with a worse prognosis), and the site of relapse (bone marrow disease is associated with a worse prognosis than extramedullary disease).66 Leukemia cells obtained from patients with early relapse frequently harbor mutations that decrease sensitivity to common chemotherapy drugs.67,68 If relapse occurs after the completion of primary treatment, most children will enter a second remission, and the chance for cure is about 50%. If relapse occurs during therapy, the chance of attaining a second remission is only 50 to 70%, and only 20 to 30% of patients are cured.

Allogeneic hematopoietic-cell transplantation is used much more commonly after relapse (in ≥50% of patients) than during primary therapy (in 5 to 10% of patients). Assessment of the minimal residual disease response may be helpful in determining which patients should undergo transplantation during a second remission and which patients should not.69

ALL is frequently a polyclonal disease, and mutations in subclones may be selected by chemotherapy and promote resistance. These include CREBBP mutations that are linked to resistance to glucocorticoids67 and NTSC2 and PRPS1 mutations that are associated with resistance to thiopurines.68,70 In future studies, it will be important to identify emerging mutations that are associated with resistance and explore the potential for modifying therapy to circumvent relapse.

TARGETED THERAPY AND PRECISION MEDICINE
The dramatic improvements in survival among children with ALL over the past 50 years are due to the development of new therapies. Recent discoveries regarding the genetic basis of ALL and the development of therapies that target molecular lesions that drive survival of ALL cells have paved the way for the expanding use of precision-medicine approaches to cancer.72 One notable example is the use of tyrosine kinase inhibitors in patients with chronic myeloid leukemia, a cancer that is driven by the BCR-ABL1 fusion oncoprotein.73 Treatment with tyrosine kinase inhibitors (imatinib and related agents) has converted chronic myeloid leukemia from a disease requiring intensive therapy that often included hematopoietic stem-cell transplantation to a chronic disease that can in most cases be managed successfully for decades with oral tyrosine kinase inhibitors, with the potential for discontinuation of treatment in some patients.74

The BCR-ABL1 fusion protein also occurs in 25% of adults and in 3 to 5% of children with ALL (Ph-positive ALL), and in ALL, as compared with chronic myeloid leukemia, it is associated with secondary genetic alterations, particularly alterations of IKZF1.75 Before the use of tyrosine kinase inhibitors, less than half the children with Ph-positive ALL survived.41 Combining imatinib with cytotoxic chemotherapy has proved to be highly effective in children with Ph-positive ALL and has minimized the need for hematopoietic-cell transplantation in the first remission.76-78

Ph-like ALL is associated with a poor progno-
sis, and it is a logical candidate for individually tailored tyrosine kinase inhibitor therapy.30,43,79 A diverse range of genetic alterations activate kinase signaling in Ph-like ALL; these include a high frequency of rearrangements that converge on a limited number of signaling pathways, including ABL-class and JAK–STAT signaling. Extensive preclinical studies show that the activation of signaling pathways induced by these alterations is sensitive to tyrosine kinase inhibitors; this suggests that precision-medicine approaches should be successful in this ALL subgroup. These findings are supported by anecdotal reports of dramatic responses of chemotherapy-refractory Ph-like ALL to tyrosine kinase inhibitor therapy.30,80 This is particularly important in older children and adults, in whom Ph-like ALL is more common.30

An important challenge in the design of future clinical trials will be to ensure adequate enrollment of patients harboring each class of genetic alteration. To meet this challenge, international clinical trials that involve multiple cooperative groups will have to be developed, as has been done successfully in studies of Ph-positive ALL.

IMMUNOTHERAPY

CD19 is a cell-surface antigen that is present at high density on most B-cell ALL cells. Several groups have developed strategies to transduce autologous T-cells with an anti-CD19 antibody fragment coupled to intracellular signaling domains of the T-cell receptor, thereby redirecting cytotoxic T lymphocytes to recognize and kill B-cell ALL cells. These chimeric antigen receptor–modified T cells provide a major new treatment option.

In one study, 30 children with heavily pretreated ALL that had relapsed multiple times were treated with chimeric antigen receptor–modified T cells; 90% of the children attained remission, with sustained remission in about two thirds. Approximately three quarters of the children were alive 6 months after the infusion.81 Remissions were durable with 1 to 3 years of follow-up. Many patients had a severe cytokine-release syndrome after activation of the cytotoxic T cells in vivo. This syndrome was accompanied by high levels of serum interleukin-6 that could be treated successfully with the anti–interleukin-6 monoclonal antibody tocilizumab. Studies of the durability of chimeric antigen receptor T-cell therapy (ClinicalTrials.gov number, NCT02445222) and its role in patients with ALL who have less advanced disease (NCT02435849) are ongoing.

A different strategy to harness the T-cell immune response against ALL cells is provided by blinatumomab, a genetically modified antibody that contains fragments that recognize both CD19 and CD3 (which is present on all T cells) and therefore brings T cells into direct contact with B-cell ALL cells, allowing the cytotoxic T cells to kill them.82 Blinatumomab is now being tested in children with a first relapse of B-cell ALL (NCT02101853).

SHORT-TERM AND LONG-TERM TOXIC EFFECTS OF TREATMENT

About 1 to 2% of children with ALL die before attaining remission, and an additional 1 to 2% die from toxic effects during remission.83 Patients with Down's syndrome, infants, older teenagers, and those receiving more intensive therapy have an increased risk of death from toxic effects, mostly due to infection. Risks can be mitigated by modifications to therapy and supportive care. As cure rates for childhood ALL improve, treatment-related death accounts for a higher percentage of all deaths.

One of the most vexing problems associated with contemporary therapy for ALL is osteonecrosis, which occurs in 5 to 10% of patients.84 The risk is much higher among teenagers (15 to 20%) than among young children, and girls are affected more commonly than boys. Osteonecrosis most commonly affects major joints, particularly the hips, knees, shoulders, and ankles, and often requires surgical management, including joint replacement. Modifications to glucocorticoid administration schedules can decrease the risk of osteonecrosis.85

Additional treatment-related effects include the metabolic syndrome and obesity, cardiovascular impairment, and CNS and peripheral nervous system toxic effects. Each is caused by highly effective antileukemic agents, and a person's risk of toxic effects is influenced by host genetic factors that influence drug metabolism and activity. Thus, an important goal is the tailoring of drug exposure according to the predicted risk of both relapse and specific toxic effects.

A child who is cured of ALL is expected to have 60 to 80 years of remaining life. Critical questions are whether that expected life span is shortened by the leukemia, its treatment, or both, whether chronic health conditions that affect daily life develop at a higher frequency or increased severity in survivors than in persons who were never
treated for childhood ALL, and whether there are lasting emotional or neurocognitive effects that limit full realization of a survivor’s potential. Unfortunately, many ALL survivors do have chronic toxic effects, and the neurocognitive effects appear to increase as they approach middle age. Continued long-term follow-up of persons who had ALL in childhood is essential to define the risks and to develop strategies to decrease risks, ameliorate toxic effects, or both.

### IMPLICATIONS OF THE SUCCESS OF TREATMENT

Survival rates among teenagers with ALL are inferior to those among young children, and survival is even worse among young adults. The reasons for these differences are multifactorial and include treatment factors, a higher prevalence of unfavorable genetic subtypes among the older patients, the reduced ability of teenagers and young adults to receive intensive therapy without untoward side effects, and social factors such as insurance coverage and lack of parental supervision of therapy. Institutions and cooperative groups treating young adults with ALL have successfully adopted treatment modeled on pediatric regimens. This strategy is feasible for patients up to about 50 years of age, with early results suggesting major improvements in survival.

Since the population of children is higher in low-income and middle-income countries than in high-income countries, the total number of children with a diagnosis of ALL is also higher in these countries; these children have inferior survival as compared with children treated in high-income countries. Because ALL can be diagnosed with simple techniques and treated successfully with relatively inexpensive chemotherapeutic agents, it is feasible to rapidly improve the outcome in children with ALL in low-income and middle-income countries. Partnerships and “twinning” relationships between centers in high-income centers in North America and Western Europe and pediatric cancer centers in Asia, Central and South America, and Eastern Europe have substantially improved survival among children with ALL.

### CONCLUSIONS

In the past few years, we have witnessed tremendous advances in our understanding of the biology of ALL and the remarkable efficacy of targeted chemical and biologic therapeutic approaches in otherwise refractory disease. It is anticipated that in the next several years, the genomic landscape of ALL will be completely described, the biologic causes for treatment failure fully elucidated, and the roles of a range of new chemical and biologic agents defined. As the cure rate for childhood ALL approaches 100%, major challenges will be to identify persons who require less intensive therapy to achieve cure and to refine complex, toxic regimens to incorporate simpler, safer approaches that will result in a high quality of life coupled with long-term survival.

Dr. Hunger reports receiving consulting fees from Jazz Pharmaceuticals, Sigma-Tau Pharmaceuticals, and Spectrum Pharmaceuticals and owning stock in Amgen; Dr. Mullighan, receiving consulting fees from Incyte Pharmaceuticals and speaking fees from Amgen Pharmaceuticals; and Drs. Hunger and Mullighan, being named as inventors 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). No other potential conflict of interest relevant to this article was reported.

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