Clinical and Laboratory Biology of Childhood Acute Lymphoblastic Leukemia

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Acute lymphoblastic leukemia (ALL) is the most common malignancy of childhood, accounting for 25% of cancers diagnosed in children and adolescents aged 1–19 years, and translating to approximately 3000 new cases diagnosed in the US yearly. Progress in therapy for childhood ALL has been dramatic, with event-free survival (EFS, meaning that patients do not relapse or succumb to side effects) improving from 10%-15% in the 1960s to as high as 80% in published studies from early 2000 in developed countries (Table 1). Present cure rates are estimated to approach 90%. The primary factors that led to advances in ALL survival are: (1) the development of multiagent chemotherapy regimens based on the results of successive cooperative group protocols; (2) the use of preventive or prophylactic central nervous system (CNS) therapy to prevent relapse in this sanctuary site; (3) intensification of conventional chemotherapy by increasing the number of agents, dose, and/or schedule; and (4) allocation of therapy based on the predicted risk of relapse using clinical- and laboratory-based outcome variables (“risk-adapted therapy”). The fact that childhood cancer is relatively rare and that no single institution accrues a sufficient number of cases to allow for randomized trials of interventions led to an early history of international collaboration and the development of highly disciplined cooperative group protocols, which have been critical to the success in improving outcomes.

Despite these advances, significant challenges remain. First, even with the most contemporary therapy, up to 1 in 5 children may suffer disease recurrence, and their prognosis is poor. Death due to relapsed ALL remains one of the leading causes of cancer mortality in children. Second, even though current therapy is associated with gratifying outcomes, treatment is associated with short- and long-term side effects.

**Biology of Childhood ALL**

Although the exact causes of ALL remain elusive, laboratory advances in the analysis of chromosome structure and, more recently, high-throughput genomic approaches have clearly demonstrated 2 important findings: (1) childhood leukemia results from a multistep process associated with the acquisition of genetic alterations in the leukemic blast cells (eg, somatic changes); and (2) childhood ALL is a heterogeneous disease composed of multiple biological subgroups often classified by sentinel genetic lesions. In 85% of cases, the target cell is the immature B lymphocyte (B precursor ALL), whereas in the remaining 15% of cases, thymic progenitor cells are involved (T cell ALL).

**Natural History of ALL**

Most cases of ALL are thought to result from somatic mutations that occur postconception in developing lymphoid cells. A familial tendency has been established only in rare cases. There is strong evidence that initial steps in some leukemias occur in utero. This evidence comes from studies in identical twins where there is a high concordance of leukemia with identical genetic rearrangements and from “backtracking” studies using neonatal blood spots (Guthrie cards), which have demonstrated the presence of specific leukemic translocations years before the clinical diagnosis of ALL.

**Predisposition to Childhood ALL**

Childhood ALL generally is considered a sporadic disease, but an underlying predisposition exists in <5% of cases. Down syndrome is by far the most common syndrome with a clearly documented relationship with ALL. Children with Down syndrome have a 20-fold increased incidence of ALL (and a 500-fold higher incidence of acute megakaryocytic leukemia) compared with the general population. These children are prone to a unique biological subtype of ALL characterized by the absence of a T cell phenotype, lack of association with the favorable genetic subtypes (hyperdiploid ALL and the ETV6/RUNX1 translocation), a particularly high incidence (up to 28%) of Janus kinase (JAK2) mutations, and increased expression of the cytokine receptor gene CRLF2 in >55% of patients, most commonly as a fusion with P2RY8, but occasionally as a translocation with the immunoglobulin heavy chain (IgH). The overwhelming majority of ALL cases have no known genetic predisposition, and the primary trigger of most cases of ALL also remains unknown. Various environmental exposures...
have been linked with ALL, but these associations have been difficult to replicate in validation studies, suggesting that the role of the environment may be minimal or absent in childhood ALL. Two recent genome-wide association studies that examined background genetic variation (eg, differences in normal cells, so-called “germline variation”) between controls and patients with ALL showed linkages with ARID5B and IKZF1, 2 genes involved in B cell differentiation. Moreover, inherited variation in ARID5B may explain differences in the incidence of ALL in different racial/ethnic populations.

**Genetics of Childhood ALL**

Genetic studies have been used to classify childhood ALL into many unique subtypes. Using a combination of technologies, genetic alterations now can be detected in virtually all cases of ALL. The most common chromosomal defects seen in ALL blasts are numerical gains or losses of whole chromosomes and translocations. Excess chromosomes, or hyperdiploidy, is seen in up to one-third of B-precursor cases, and high hyperdiploidy (51–65 chromosomes) is associated with a good outcome. In contrast, hypodiploidy (fewer than 44 chromosomes in leukemic blasts) is linked to very poor survival.

The Philadelphia chromosome, or t(9;22) (q34;q11), is the prototypical example of a leukemia-associated translocation, first described in chronic myelogenous leukemia in the 1960s. The t(9;22) leads to a “fusion” transcript that encodes the BCR/ABL tyrosine kinase. Philadelphia chromosome-positive (Ph+) ALL occurs in 2%-3% of childhood ALL cases; however, approximately 25% of adult cases carry this translocation. Historically, Ph+ ALL has been associated with a poor prognosis, with <40% of children surviving despite aggressive therapy. The BCR/ABL fusion protein has unique biological properties compared with the normal ABL protein. Other chromosomal abnormalities are routinely tested for in B-precursor ALL because of their prognostic relevance. The t(12;21) is a cryptic translocation observed in approximately 25% of children with B-precursor ALL. This translocation results in a fusion transcript between ETV6 and RUNX1. Importantly, the t(12;21) is associated with a good prognosis and is now used to assign specific therapy. Infants aged <1 year do poorly, and 80% of these B-precursor cases harbor a translocation involving the MLL (mixed-lineage leukemia) gene located at 11q23. MLL is involved with numerous other fusion partners, but t(4;11) (MLL/AF4) is most common in infant ALL. The t(1;19) E2A/PBX1 translocation is seen in 4%-5% of pediatric ALL cases and no longer carries prognostic significance with recent intensification of therapy.

In contrast to B-precursor ALL, T cell ALL (T-ALL) lacks well-defined translocations in the majority of cases. Detailed molecular analyses have now revealed more widespread events shared by subtypes of T-ALL. These include inactivation of the tumor-suppressor genes CDKN2A/2B in up to 90% of cases and mutations that activate the NOTCH1 pathway in 70% of cases. NOTCH1 is a cell surface receptor whose activation promotes T cell development. Under normal circumstances, NOTCH activation results from successive proteolytic cleavages of the receptor, leading to release of intracellular NOTCH that travels to the nucleus and activates key target genes.

### Table I. Outcome of childhood ALL on selected contemporary treatment protocols

<table>
<thead>
<tr>
<th>Group</th>
<th>Patient ID</th>
<th>Years</th>
<th>10-year EFS, % (SE)</th>
<th>10-year survival, % (SE)</th>
<th>10-year EFS in B-lineage ALL, % (SE)</th>
<th>10-year EFS in T-ALL, % (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIEOP 95</td>
<td>1743</td>
<td>1995-2000</td>
<td>71.7 (1.3)</td>
<td>82.4 (1)</td>
<td>72.7 (1.3)</td>
<td>64.1 (3.6)</td>
</tr>
<tr>
<td>BFM 95</td>
<td>2169</td>
<td>1995-2000</td>
<td>78.0 (1.0)</td>
<td>85.0 (1.0)</td>
<td>79.0 (1.0)</td>
<td>73.9 (2.7)</td>
</tr>
<tr>
<td>CCG 1900</td>
<td>4464</td>
<td>1996-2002</td>
<td>72.6 (2.9)</td>
<td>82.1 (2.5)</td>
<td>72.3 (3.7)</td>
<td>70.7 (8.4)</td>
</tr>
<tr>
<td>DFCI 95-01</td>
<td>491</td>
<td>1996-2000</td>
<td>79.0 (2.1)</td>
<td>88.9 (1.5)</td>
<td>78.4 (2.2)</td>
<td>84.6 (5.0)</td>
</tr>
<tr>
<td>SJCRH 138</td>
<td>247</td>
<td>1994-1998</td>
<td>77.6 (2.9)</td>
<td>83.7 (2.5)</td>
<td>80.3 (3.0)</td>
<td>64.7 (7.8)</td>
</tr>
</tbody>
</table>

AIEOP, Italian Association of Pediatric Hematology and Oncology; BFM, Berlin-Frankfurt-Munster; CCG, Children’s Cancer Group; DFCI, Dana-Farber Cancer Institute; SJCRH, St Jude Children’s Research Hospital.
in B cell differentiation (eg, PAX5, IKZF1, EBF-1). This suggests that an arrest in differentiation is a crucial step in the transformative process. Combining data from gene expression studies and copy number analyses has uncovered some interesting correlations; for example, gene expression studies have defined a unique group associated with an inferior outcome that shares many pathways with Ph⁺ ALL but lack the BCR/ABL fusion.66,67 Samples from this group of patients often demonstrate small deletions at a pseudoautosomal region at Xp22.3/Yp11.3 that leads to up-regulation of cytokine receptor-like factor 2 (CRLF2).30,68 Interestingly, this somatic rearrangement is seen frequently in Down syndrome-associated ALL, as described earlier. CRLF2 also may be dysregulated due to translocations involving IgH.30

The latest advances in cancer biology have come through developments in massively paralleled gene sequencing, and indeed the genetic sequences of many cancers have been reported. Investigators from the Children’s Oncology Group (COG) and the National Cancer Institute recently sequenced 125 genes in a large cohort of patients with high-risk ALL (COG–National Cancer Institute TARGET Project). Activating somatic mutations in the RAS signaling pathway (eg, NRAS, KRAS, PTPN11) were seen in 39% of patients, and inactivating mutations in B cell development genes (eg, PAX5, IKZF1) and the TP53/RB1 DNA damage checkpoint pathway were seen in 14% and 10% of cases, respectively. Interestingly, activating mutations of the JAK family of tyrosine kinases were observed in the aforementioned Ph⁺-like subgroup that also contained CRLF2 overexpression.69 This is particularly important because JAK inhibitors already have been evaluated in adults with hematologic malignancies, and a clinical trial is now ongoing in children.

**Epigenetics and ALL**

In addition to alterations in the primary genetic sequence, it is now clear that genetic programs can be altered through “epigenetic” regulation as well.70,71 In this circumstance, the primary genetic sequence is normal, but other factors affect gene expression. The helical DNA strand is insulated with complex protein packaging, chromatin, and wound-around nucleosomes whose histone tails extend outward. These histones can be acetylated to an “open” chromatin structure and provide accessibility to transcription factors that increase gene expression. In addition, DNA methylation of cytosine residues in promoter regions generally leads to more tightly packed chromatin and decreased DNA transcription.72 This mechanism has been shown to prevent the expression of tumor-suppressor genes in cancer. Methylation profiles have been correlated with biological subtypes of ALL (eg, T-ALL is less methylated than B-precursor ALL, infant MLL rearranged ALL is frequently hypermethylated).73 The translational impact of these observations is substantial, given that hypomethylating agents and histone deacetylase inhibitors have shown promise in clinical trials in adults with hematologic malignancies, and phase I clinical trials have been completed in children.74

<table>
<thead>
<tr>
<th>Early response</th>
<th>Favorable</th>
<th>Unfavorable</th>
</tr>
</thead>
<tbody>
<tr>
<td>M2 (5%-25%)/M3 (≥25%) marrow on days 8 and 15</td>
<td>≥0.01% marrow MRD on day 29</td>
<td>Positive MRD at second time point</td>
</tr>
<tr>
<td>M1 (&lt;5% blasts)/M3 (≥25%) on day 8</td>
<td>&lt;0.01% marrow MRD on day 29</td>
<td>Positive MRD at second time point</td>
</tr>
<tr>
<td>&lt;1000 blasts/µL during week 1</td>
<td>≤0.01% peripheral blood MRD on day 8</td>
<td>Positive MRD at second time point</td>
</tr>
<tr>
<td>&lt;1 year or &gt;10 years</td>
<td>≥50 000/µL</td>
<td>Patients with t(9;22) now have much better outcome with tyrosine kinase inhibitors combined with chemotherapy.</td>
</tr>
</tbody>
</table>

Another area of intense interest is the role of altered microRNA expression in leukemia.75 Micro-RNAs are small (19-22 nucleotides) RNAs that inhibit translation of mRNAs and/or lead to premature degradation. It is estimated that 1% of the genome and 30% of genes may be regulated by micro-RNAs.76 Data suggest that micro-RNA expression patterns correlate with the biological subtype of ALL, and that aberrant expression may be responsible for drug resistance.

**Leukemia Stem Cells**

Numerous studies in a wide variety of cancers have indicated that only a small subset of cells, known as cancer stem cells, are responsible for propagating the bulk population of the tumor.77 Cancer stem cells share important properties with normal stem cells, but they are clearly distinct. Leukemia stem cells have been most clearly defined in acute myelogenous leukemia, but numerous studies also have suggested the existence of ALL stem cells whose characteristics may differ depending on the biological subtype and/or experimental conditions used for analysis. The presence of leukemia stem cells has important therapeutic implications. Therapy that eradicates the bulk tumor but fails to eradicate the stem cell reservoir is likely to fail. For example, studies in ALL have shown that ALL stem cells are more resistant to glucocorticoids than bulk leukemia cells.78

**Modern Therapy for Childhood ALL**

**Risk Stratification**

Risk stratification, in which the intensity of therapy is tailored to the predicted risk of relapse, is an essential element of contemporary ALL treatment. Well-validated prognostic variables include age at diagnosis and initial white blood cell count (both National Cancer Institute risk criteria), cytogenetic characteristics within the leukemic blast population, and the rapidity of early treatment response (Table II).
Historically, early response has been assessed by morphologic detection of blasts in the peripheral blood or bone marrow blasts during the first month of therapy, and the widespread adaptation of minimal residual disease (MRD) testing now has added a more precise measurement, with >100-fold greater sensitivity. MRD is typically detected using flow cytometry–based techniques or polymerase chain reaction amplification of clonotypic immunoglobulin or T cell receptor gene rearrangements and can detect residual leukemic cells with a sensitivity of at least 0.01%. End-induction bone marrow MRD recently was shown to be the most important prognostic variable in multivariate analysis for B-precursor ALL, and peripheral blood MRD at 1 week after initiation of therapy is now replacing bone marrow aspirates for early response determination in the newest COG ALL protocols. In that study, the combination of favorable early MRD responses and favorable blast cytogenetics (ETV6-RUNX1 or trisomies 4 and 10) defined a subgroup of children with >95% 5-year EFS. Conversely, children with high levels of MRD at the end of induction and/or at a second time point further along in the course of therapy are candidates for therapy intensification on most protocols.

Emerging data for comprehensive genomic studies in childhood ALL offer promise for future refinements in existing risk algorithms and the prognostic significance of such findings as JAK2 mutations, CRLF2 overexpression, IKZF deletions, and gene expression signatures associated with poor response will be validated in upcoming prospective therapeutic trials.

**Therapy for Newly Diagnosed Patients**

Standard treatment for the majority of children with ALL involves multiagent chemotherapy for a period of 2-3 years. Although there are variations in treatment structure among the major cooperative groups that guide therapy for childhood ALL, treatment is traditionally divided into 3 phases: remission induction (usually 4-6 weeks), consolidation (intensification), and continuation/maintenance. CNS preventive therapy with intrathecal chemotherapy, and less commonly cranial irradiation, is also an essential component of therapeutic protocols. The goal of induction is to eliminate >99% of the tumor burden and restore normal hematopoiesis. Approximately 98% of children achieve remission at the end of induction. Intensification is designed to eradicate any residual disease by alternating non–cross-resistant drugs, and continuation or maintenance is aimed at sustaining remission. Why prolonged continuation is required is not clear; however, previous attempts to shorten the duration of treatment to 18 months or less have been unsuccessful.

Many recent advances in curative therapies have come from intensifying therapy using traditional agents, such as methotrexate, asparaginase, and vincristine. With recent advances in the delivery and schedule of systemic and intrathecal chemotherapy, far fewer children now receive cranial radiation therapy (CRT), and in some groups CRT has now been eliminated. A long-standing component of maintenance or continuation therapy for ALL has been pulses of vincristine and corticosteroids, often delivered on a monthly basis, along with weekly methotrexate and daily 6-mercaptopurine. Given concerns about bone toxicity, obesity, and mood disturbances associated with corticosteroid administration, several groups have studied reduced pulse frequency and have reported that excellent outcomes can be preserved, perhaps due to optimization of the chemotherapy delivered in earlier phases of treatment.

Therapy for newly diagnosed T-ALL is similar to that for B-precursor ALL; however, patients receive a more intensified regimen, given that T-ALL is associated with older age at the time of diagnosis, higher white blood cell count at presentation, and a greater incidence of bulky adenopathy and CNS disease. With this approach, outcomes have paralleled those observed in B-precursor ALL and the majority of patients achieve a cure. However, some subsets of patients with T-ALL have not fared as well, such as those with an end-induction MRD level >0.1%. A recently described immunophenotype in T-ALL is the early thymocyte precursor, in which T cells retain stem cell–like features. The early thymocyte precursor phenotype has been associated with inferior responses to induction therapy and outcomes, and children with this T-ALL phenotype might be candidates for future novel therapies. The COG is currently studying the addition of nelarabine, a produg of Ara-G that is uniquely cytotoxic to T lymphoblasts, in newly diagnosed higher-risk T-ALL based on the promising single-agent responses to this drug in patients with refractory/relapsed disease.

**New Agents in the Treatment of ALL**

As knowledge of the unique biology of ALL accrues, future treatment strategies may include additional drugs that currently in clinical trials, such as gamma secretase inhibitors (especially for T-ALL), the proteasome inhibitor bortezomib, and mammalian target of rapamycin inhibitors, such as sirolimus (rapamycin) and temsirolimus, which target important pathways in this disease: the NOTCH, nuclear factor kappa light-chain enhancer of activated B cells, and mammalian target of rapamycin pathways, respectively.

Certain selected subgroups of children with ALL can benefit from more targeted approaches. Ph+ ALL is a paradigm for this approach. In a recently completed trial, patients with Ph+ ALL received the tyrosine kinase inhibitor imatinib in combination with chemotherapy and attained a 3-year EFS of 80%, more than twice that achieved with historical regimens without a tyrosine kinase inhibitor.

Infants with ALL (aged <1 year at diagnosis) are another population in which the addition of targeted therapy is being investigated. Infant ALL presents unique treatment challenges, given that these infants have historically inferior outcomes, with a 4-year EFS of 47% reported in the largest recent trial. Infants with ALL are susceptible to toxicity, especially those aged <90 days at diagnosis. To address these challenges, many groups have recommended that infants with ALL now receive an induction regimen tailored for age with enhanced and aggressive supportive care measures. The FLT3 tyrosine...
kinase has been shown to be highly expressed in MLL-rearranged infant ALL,\(^91\) and the addition of the FLT3 inhibitor lestaurtinib is also being studied in combination with chemotherapy.\(^92\) The role of allogeneic hematopoietic stem cell transplantation in infants with ALL has been a matter of debate; larger analyses have not demonstrated an overall benefit for this strategy, but recent data indicate that it may prove beneficial for a subgroup.\(^53,93,94\)

### Therapy for Relapsed Disease

Although there have been significant improvements in survival for children and young adults with newly diagnosed ALL, outcomes after relapse remain poor, with less than half of patients surviving long term.\(^95-100\) Several prognostic factors predictive of postrelapse survival have been identified, including timing and site of disease recurrence, disease immunophenotype (T-ALL worse than B-precursor ALL), risk group, and age at initial diagnosis.\(^95-101\) Patients with isolated extramedullary relapse fare better than those with isolated bone marrow relapse (EFS 50%-80% vs 20%-50%). Patients who relapse within the first 18 months of therapy have an EFS of <20%, compared with approximately 50% in those who relapse more than 36 months after the initial diagnosis.\(^98\)

Therapy for relapsed ALL involving the bone marrow traditionally consists of intensive reinduction chemotherapy,\(^102\) often followed by allogeneic hematopoietic stem cell transplantation in those who relapse within 36 months after the initial diagnosis, whereas treatment for isolated extramedullary relapse often consists of intensive chemotherapy and radiation therapy to extramedullary sites of disease. Given the poor outcomes for children with recurrent ALL, various novel targeted agents in combination with traditional cytotoxic chemotherapy are being tested and developed for relapsed disease (Table III). Emerging data from integrated genomic analyses of ALL blasts as they evolve from diagnosis to relapse offers further promise for identifying pathways and drugs for resistant disease.\(^103-105\)

#### Long-Term Side Effects of Treatment and Follow-Up

The long-term outlook for ALL survivors is excellent, with an overall survival of 96.1% at 25 years for children treated without radiation therapy and 87.3% for children who received radiation.\(^106\) Even though 92% of nonirradiated survivors report no severe medical conditions at 25 years, survivors are 3.7 times more likely to report a significant chronic medical condition compared with siblings, indicating that those cured may be left with significant morbidity. The highest risks are for musculoskeletal, cardiac, and neurologic conditions.\(^106\) The risk of cardiotoxicity is associated with the use of anthracyclines (Table IV).

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### Table III. Examples of targeted therapy in childhood ALL\(^87,88\)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Target</th>
<th>ALL subtype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monoclonal antibodies</td>
<td>CD20</td>
<td>B-precursor ALL</td>
</tr>
<tr>
<td>Epratuzumab</td>
<td>CD22</td>
<td></td>
</tr>
<tr>
<td>Blinatumomab</td>
<td>CD19</td>
<td></td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>CD52</td>
<td></td>
</tr>
<tr>
<td>Tyrosine kinase inhibitors</td>
<td>BCR/ABL</td>
<td>Ph(^+) ALL</td>
</tr>
<tr>
<td>Imatinib</td>
<td>Other tyrosine kinases</td>
<td></td>
</tr>
<tr>
<td>Dasatinib</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FLT3 inhibitors</td>
<td>FLT3 receptor</td>
<td>Infant ALL; hyperdiploid ALL</td>
</tr>
<tr>
<td>Nilotinib</td>
<td>tyrosine kinase</td>
<td></td>
</tr>
<tr>
<td>Gamma secretase inhibitors</td>
<td>NOTCH</td>
<td>T-ALL</td>
</tr>
</tbody>
</table>

### Table IV. Screening and prevention of late effects in childhood ALL survivors

<table>
<thead>
<tr>
<th>Late effect</th>
<th>Exposure risk</th>
<th>Screening</th>
<th>Prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurocognitive</td>
<td>CRT</td>
<td>Baseline neuropsychological assessment</td>
<td>Special education services</td>
</tr>
<tr>
<td></td>
<td>Intrathecal methotrexate</td>
<td>Neuropsychological assessment at educational transitions</td>
<td>Education accommodations</td>
</tr>
<tr>
<td></td>
<td>High-dose systemic methotrexate</td>
<td>Yearly evaluation</td>
<td>Cognitive rehabilitation</td>
</tr>
<tr>
<td></td>
<td>Young age at exposure</td>
<td></td>
<td>Stimulant medications (investigational)</td>
</tr>
<tr>
<td>Cardiac</td>
<td>Anthracyline dose &gt;300 mg/m(^2)</td>
<td>Baseline electrocardiogram and echocardiogram</td>
<td>Avoidance of isometric exercise</td>
</tr>
<tr>
<td></td>
<td>Chest irradiation</td>
<td>Echocardiogram at 5 years and/or based on risk</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Steroids</td>
<td>Magnetic resonance imaging</td>
<td>Statins (investigational)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bone mineral density analysis</td>
<td>Weight-bearing exercise</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Adequate calcium and vitamin D</td>
</tr>
<tr>
<td>Second malignancy</td>
<td>Alkylation agents</td>
<td>Yearly complete blood count</td>
<td>Risk-stratified therapy to avoid exposure in lower-risk patients</td>
</tr>
<tr>
<td></td>
<td>Topoisomerase II inhibitors</td>
<td>Yearly physical examination</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Radiation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obesity/metabolic syndrome</td>
<td>Steroids</td>
<td>Yearly evaluation</td>
<td>Exercise</td>
</tr>
<tr>
<td></td>
<td>Inactivity</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Neglia et al.\(^107\)
of anthracyclines, especially in doses exceeding 300 mg/m². Because most protocols have far less cumulative exposure, overt congestive heart failure now is infrequent. Follow-up for these children includes yearly physical examinations and periodic echocardiograms based on exposure (Table IV; also see the COG’s recommendations at www.survivorshipguidelines.org).

Given the improved survival rate and developmental trajectory of children, neurocognitive deficits are particularly distressing. The incidence of these problems is related to CRT but also is associated with the use of intrathecal methotrexate and greater systemic exposure to methotrexate. Fortunately, the use of CRT has diminished greatly, although many long-term follow-up studies include many patients who received CRT, and thus the current incidence of these problems may be overestimated. Chronic neurologic conditions, such as headache, auditory-vestibular dysfunction (eg, hearing loss, tinnitus) and focal problems (eg, coordination, sensation) are 1.6, 1.8, and approximately 5 times more likely, respectively, to be reported in long-term survivors compared with siblings. Cognitive deficits occur in 20%-30% of children and range widely in magnitude, from overt problems in school/vocational performance to milder deficits detected on proactive screening. Children who have received CRT, those aged <5 years at the time of diagnosis, and patients treated for relapse are particularly susceptible. In children treated without CRT, modest deficits in intelligence, attention, reading, arithmetic, and visuomotor skills can occur, yet many children are in the normal range. Baseline and periodic neuropsychological assessment allows for interventions to enhance academic performance.

Osteonecrosis (ON), or avascular necrosis, and decreased bone mineral density are well-known side effects of glucocorticoids in ALL therapy. ON has emerged as one of the most significant causes of treatment-related morbidity in ALL survivors, particularly in adolescents. Symptomatic ON has been reported in up to 20% of children and adolescents with ALL, and its pathogenesis is thought to involve ischemia due to intravascular thrombi and extravascular lipid deposition, as well as compromised intramedullary blood flow due to increased intraosseous lipocyte size. Adolescence (age 10-20 years) and exposure to dexamethasone are 2 of the most significant risk factors for this complication. Emerging evidence is suggesting that ON may be associated with inherited genomic variation. Pain is the most common initial symptom of ON, and the hips and knees are the most commonly affected joints. In severe cases, ON results in joint collapse, requiring total joint replacement. Statins and other classes of drugs are being considered for prevention.

Second malignant neoplasms are the most serious complications of therapy and include therapy-related myelodysplastic syndromes/acute myelogenous leukemia and solid tumors, which are related to the use of topoisomerase II inhibitors (eg, epipodophollotoxins, such as etoposide), alkylating agents, and radiation therapy. The long-term risk for such cancers is <1%. The cumulative incidence of secondary brain cancers is also <1% at 10 years and is clearly linked to CRT, with the risk correlated with both the radiation dose and the patient’s age at the time of exposure (greatest in children aged <5 years).

Survivors are at risk for additional side effects, including obesity and metabolic syndrome, possibly related to corticosteroid exposure and decreased exercise as a result of real or perceived physical limitations during and after treatment. Although preadolescents with ALL fare better when it comes to issues related to physical, emotional, and social functioning, adolescent ALL survivors often report issues related to fatigue, depression, and anxiety. Children and adolescents are best managed in a long-term follow-up clinic staffed by a variety of specialists trained to meet the unique challenges of these patients. Each child is best served by developing a comprehensive plan of follow-up and intervention that takes into account the specific risks associated with the treatment protocol, acquired side effects, family history/ genetic predisposition, and personal lifestyle.

Conclusion

ALL is the most common childhood cancer, and remarkable improvements in outcome have been achieved. Certain subgroups of children with ALL now have a >95% chance for cure. This has afforded an opportunity to maintain excellent outcomes while minimizing the risk for late effects. Exciting new discoveries from high-throughput genomic technologies offer great promise in understanding disease mechanisms and will shape further development of targeted therapies, especially in subgroups with inferior outcomes.

References


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