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Review Article

Recent Research Advances in Childhood Acute Lymphoblastic Leukemia

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Recent progress in risk-adapted treatment for childhood acute lymphoblastic leukemia has secured 5-year event-free survival rates of approximately 80% and 5-year survival rates approaching 90%. With improved systemic and intrathecal chemotherapy, it is now feasible to omit safely in all patients prophylactic cranial irradiation, which was once a standard treatment. As high-resolution, genome-wide analyses of leukemic and normal host cells continue to identify novel subtypes of lymphoblastic leukemia and provide new insights into leukemogenesis, we can look forward to the time when all cases of this disease will be classified according to specific genetic abnormalities, some of which will yield "druggable" targets for more effective and less toxic treatments. Meanwhile, it is sobering to consider that a significant fraction of leukemia survivors will develop serious health problems within 30 years of their initial diagnosis. This underlines the need to introduce early countermeasures to reduce late therapy-related effects. The ultimate challenge is to gain a clear understanding of the factors that give rise to childhood leukemia in the first place, and enable preventive strategies to be devised and implemented.

Key Words: acute lymphoblastic leukemia, genome-wide analysis, hematopoietic stem cell transplantation, treatment resistance

Acute lymphoblastic leukemia (ALL) is the most common pediatric cancer, accounting for a quarter of all malignancies diagnosed among children aged < 15 years. This potentially catastrophic disease was once fatal in four-fifths of patients, but its clinical outcome has improved remarkably over the past 50 years (Figure), with event-free and overall survival rates in contemporary trials ranging from 72.1% to 85.6% and 83.0% to 93.5%, respectively (Table 1).[1–14] As treatment efficacy has reached optimal levels for most patients, the prognostic significance of conventional risk factors such as male sex, black race and hyperleukocytosis has diminished or disappeared.[11,15] We are left with only a few disease subtypes that remain a challenge to therapists [infant ALL with *MLL* (mixed lineage leukemia) rearrangement, hypodiploidy with < 44 chromosomes, and cases resistant to early treatment are good examples]. Major concerns of the leukemia research community include the development of strategies to combat these cases effectively and to target crucial leukemogenic pathways in

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individual patients, and minimizing the risk of acute or late side effects. This article reviews the progress that has been made towards achieving these and other goals.

Diagnosis, Classification and Genetic Alterations

Immunophenotyping by flow cytometry is essential to make a diagnosis of ALL and distinguish subtypes with therapeutic implications, including B-cell precursor ALL, mature (Burkitt) ALL and T-cell ALL. Recently, using a combination of flow cytometry, gene expression profiling and single nucleotide polymorphism (SNP) array analysis, Coustan-Smith et al[16] have identified a unique T-cell ALL subtype termed early T-cell precursor (ETP) leukemia, with an exceptionally poor response to lymphoid-cell-directed therapy. The transformed thymocytes in ETP-ALL appear to arise from stem-cell-like thymic precursors that have recently migrated from the bone marrow to the thymus. Early recognition of these cases, using immunophenotypic criteria, is essential for the development of an effective clinical management strategy for ETP-ALL.

Leukemic lymphoblasts often express myeloid-associated antigens, whose pattern of expression can be correlated with specific genetic subtypes of ALL. For example, *MLL*-rearranged ALL cases express CD15, CD33 and CD65, and those with the *ETV6-RUNX1* (also known as *TEL-AML1*) fusion gene express CD13 and CD33. Expression

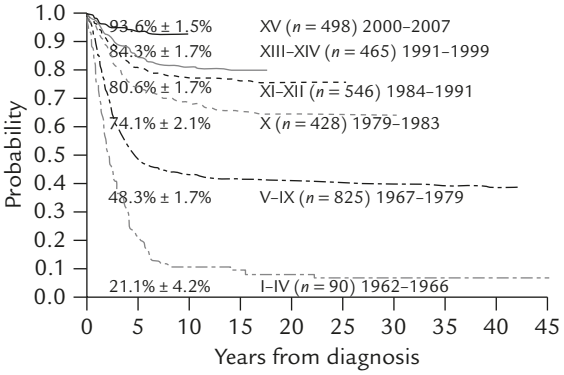

Figure. Kaplan–Meier analysis of survival for 2852 children with newly diagnosed acute lymphoblastic leukemia treated in 15 consecutive studies at St. Jude Children's Research Hospital from 1962 to 2007. Five-year survival estimates are shown. The results demonstrate steady improvement in outcome over the past 40 years.

Table 1. Results of recently completed clinical trials for acute lymphoblastic leukemia

Study	Years of study	No. of patients	Age range (yr)	Event-free survival at 5 yr (% ± SE)	Survival at 5 yr (% ± SE)	Reference
AIEOP-95	1995–2000	1743	0–17	75.9 ± 1.0	85.5 ± 0.8	Conter et al [1]
BFM-95	1995–2000	2169	0–18	79.6 ± 0.9	86.3 ± 0.6	Möricke et al [2]
CCG-1900	1996–2002	4464	0–21	76.0 ± 0.7	86.3 ± 0.6	Gaynon et al [3]
COALL-7	1997–2003	667	0–18	76.7 ± 1.7	85.4 ± 1.4	Escherich et al [4]
CPH-95	1996–2002	380	0–18	72.1 ± 2.3	83.0 ± 1.9	Stary et al [5]
DCOG-9	1997–2004	859	1–18	80.6 ± 1.4	86.4 ± 1.2	Kamps et al [6]
DFCI 00-01	2000–2004	492	0–18	80.0 ± 2.0	91.0 ± 1.0	Vrooman et al [7]
INS 98	1998–2003	315	0–18	78.7 ± 2.3	83.8 ± 2.1	Stark et al [8]
NOPHO-2000	2002–2007	1023	1–15	79.4 ± 1.5	89.1 ± 1.1	Schmiegelow et al [9]
SJCRH-13B	1994–1998	247	0–18	80.1 ± 2.6	85.7 ± 2.2	Pui et al [10]
SJCRH-15	2000–2007	498	1–18	85.6 ± 2.9	93.5 ± 1.9	Pui et al [11]
TCCSG-95-14	1995–1999	597	1–15	76.8 ± 1.8	84.9 ± 1.5	Tscuhida et al [12]
TPOG-2002	2002–2007	788	0–18	77.4 ± 1.7	83.5 ± 1.6	Liang et al [13]
UKALL-97/99	1999–2002	938	1–18	80.0 ± 1.2	88.0 ± 1.1	Mitchell et al [14]

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. SE = Standard error.

of myeloid-associated antigens can be useful in immunological monitoring of patients for minimal residual leukemia, although it lacks prognostic significance in ALL.[17] By contrast, a subset of cases co-express lymphoid- and myeloid-associated markers but do not cluster with T-cell, B-cell precursor or acute myeloid leukemia in gene expression profiling. It is important to recognize these cases at diagnosis because they might respond poorly to myeloid-directed therapy, which requires a switch to ALL-directed induction treatment.[18]

ALL arises from lymphoid progenitor cells that carry specific genetic and epigenetic alterations. Therefore, analysis of these changes yields more relevant biological information than does any other approach. Using standard molecular methods, one can detect primary genetic abnormalities in approximately 75% of ALL cases but cannot identify the full repertoire of genetic alterations.[17,19] With the availability of high-resolution, genome-wide analysis of gene expression, DNA copy number alterations (CNAs) and epigenetic changes, the potential to fully characterize a patient's genetic makeup fully has increased enormously. Currently, virtually all patients with ALL can be classified according to specific genetic abnormalities.[20]

Experimental models have established that cooperative mutations are necessary to induce leukemia and contribute to the development of drug resistance. Using SNP arrays, Mullighan et al[21] identified an average of six CNAs per case of childhood ALL. These lesions target genes that regulate lymphoid differentiation, tumor suppression, the cell cycle, apoptosis, signaling pathways, MicroRNAs, and drug responsiveness. There are substantial differences in the frequency of CNAs among various leukemia subtypes. Although cases with *ETV6-RUNX1* or *BCR-ABL1* have over six lesions per case, *MLL*-rearranged ALL has fewer than one CNA per case, which suggests that *MLL* is a potent oncogene that requires very few cooperating mutations to induce leukemic transformation. Indeed, *MLL*-rearranged leukemia often presents during infancy and has a concordance rate close to 100% in identical twins, which indicates *in utero* development and transplacental metastasis from one fetus to the other.[17]

In Philadelphia chromosome-positive (Ph^+) ALL with *BCR-ABL1* fusion, *IKZF1* is deleted in approximately 80% of the cases.[22] One high-risk subtype of *BCR-ABL1*-negative ALL is characterized by *IKZF1* deletion, and has a genetic profile similar to that of cases with *BCR-ABL1* fusion.[23,24] In studies to detect activated tyrosine kinase signaling in this leukemia subtype, Mullighan et al[25] identified activating *JAK* mutations in approximately 10% of high-risk *BCR-ABL1*-negative cases. Further analyses have revealed *CRLF2* overexpression in 6–7% of B-cell precursor ALL cases, and notably, in 50–60% of patients with Down-syndrome-associated ALL.[26–29] *CRLF2* alteration is also associated with activating *JAK* mutations; indeed, a combination of these two genetic lesions results in the growth of cytokine-dependent mouse B-progenitor cell lines in the absence of exogenous cytokines, which indicates that they are cooperative mutations in leukemogenesis.[26,29]

The most daunting challenge in the molecular diagnosis of all subtypes of ALL is to distinguish events that drive the continued growth or survival of the leukemic clone from those that simply reflect genetic epiphenomena. Otherwise, it will be difficult to translate the insights provided by emerging DNA and RNA technologies into improved patient care.

Mechanisms of Treatment Resistance and Relapse

Genome-wide studies using matched diagnosis and relapse samples from the same patients have shown that both sets of samples are clonally related, and that the relapse clones are often present as minor populations at diagnosis, which suggests that they are selected during treatment. Indeed, many of the genetic alterations that emerge in the dominant clone at relapse involve genes that have been implicated in treatment resistance (e.g. *CDKN2A/B* or *IKZF1*),[30,31] and gene expression studies have identified a proliferative gene

signature that emerges at relapse with consistent upregulation of genes, such as *survivin*, that could provide useful targets for novel therapeutic intervention.[32]

Inherited Susceptibility to ALL

Inherited genetic syndromes, such as Down or Bloom syndrome, account for only a small fraction of ALL cases (< 5%). A more promising research avenue is the notion that relatively frequent genetic polymorphisms can interact with environmental, dietary and other external factors to increase the likelihood of leukemia induction.

Candidate gene approaches have implicated inherited polymorphisms of several genes in leukemogenesis but the findings have not been consistent. Recent genome-wide studies on patients of European ancestry have failed to confirm these previously reported gene associations, but independently they have identified that germline polymorphisms of the *IKZF1* and *ARID5B* genes are associated with an increased risk of childhood ALL.[33,34] The risk alleles of *ARID5B* are specifically enriched in patients with hyperdiploid ALL, and are also associated with greater methotrexate polyglutamate accumulation.[33,34] Thus, the same genetic variation of *ARID5B* that predisposes to the development of hyperdiploid ALL also underlies the superior response of this subtype of ALL to methotrexate treatment. A subsequent study in patients of African ancestry has shown that *ARID5B* germline polymorphisms are also associated with the risk of developing hyperdiploid ALL in black patients.[35] The lower frequency of this risk allele in the control populations of African ancestry compared to those of European ancestry could also partly explain the lower incidence of hyperdiploid ALL in black patients.

Factors Influencing Risk Classification

Despite the promise of ALL management based on specific genetic lesions, current approaches to risk assessment still rely on a number of key clinical and laboratory findings, such as the initial leukocyte count, age at diagnosis and early treatment response.[36] Children aged 1–9 years have a better outcome than infants and adolescents. Leukocyte count is a continuous variable, with decreasing counts conferring a better outcome. A presenting age between 1–9 years and a leukocyte count $< 50 \times 10^9$/L are minimal criteria for low-risk B-cell precursor ALL, but carry little prognostic value in T-cell ALL. The prognostic impact of age and leukocyte count can be partly explained by their association with specific genetic abnormalities. For example, there is a preponderance of cases with favorable genetic abnormalities of hyperdiploidy > 50 chromosomes or *ETV6-RUNX1* in patients aged 1–9 years.[36] It should be stressed that even so-called low-risk ALL cases need a certain degree of treatment intensification to avoid unacceptable rates of relapse. Table 2 lists the factors commonly used for risk and therapeutic stratification in current clinical trials.

Although many genetic abnormalities, including some identified recently, are associated with

Table 2. Factors commonly used for risk stratification

Factors	Favorable	Adverse
Age (yr)	1–9	< 1 or ≥ 10
Leukocyte count ($\times 10^9$/L)	< 50	> 50
Immunophenotype	B-cell precursor	T-cell
Genotype	Hyperdiploidy > 50 chromosomes	Hypodiploidy < 44 chromosomes
	ETV6-RUNX1	*BCR-ABL1*
		MLL-AF4
Minimal residual disease after induction	< 0.01%	≥ 1%

clinical outcome, only a few are routinely used for treatment stratification (Table 2), largely because too few cases of these lesions have been studied to validate any apparent effects on prognosis. Adverse genetic abnormalities include *MLL* rearrangements and hypodiploidy < 44 chromosomes.[17,36] Ph^+ ALL was once considered to be a very high-risk form of leukemia, even when treatment included matched-related hematopoietic stem cell transplantation.[37] The prospects for a favorable therapeutic outcome in patients with Ph^+ ALL have improved markedly, as demonstrated in a recent study that has combined intensive chemotherapy with a tyrosine kinase inhibitor (imatinib mesylate).[38] It should be stressed that each specific genetic subtype identified to date might show considerable clinical heterogeneity. For example, even among patients with Ph^+ ALL, patients aged 1–9 years fare significantly better than older patients,[37] and among patients with *MLL*-rearranged ALL, young infants have the worst outcome.[39] The basis of these differences might be related to secondary genetic events, the developmental stage of the target cell undergoing malignant transformation, and the pharmacogenetics or pharmacokinetic features of the patient.

The most useful prognostic factor is the response to early treatment, as determined by measurements of the rate of clearance of leukemic cells from the blood or bone marrow. This estimate of minimal residual disease accounts for the drug sensitivity or resistance of leukemic cells and the pharmacodynamics of the drugs, which is affected by the pharmacogenetics of the host.[40] Flow cytometric profiling of aberrant immunophenotypes and polymerase chain reaction amplification of fusion transcripts or antigen-receptor genes, which are at least 100-fold more sensitive than conventional morphological determinants, have allowed minimal residual disease to be detected at very low levels (< 0.01%). This provides a useful means to identify patients at very low or high risk of relapse. Patients with ≥ 1% leukemic cells after remission induction fare almost as poorly as those who fail to achieve clinical remission by the conventional morphological standard (≥ 5% leukemic cells), whereas those who achieve molecular or immunologic remission (< 0.01%) have an excellent outcome.[40,41] Minimal residual disease can be measured by the current techniques in nearly all patients, and has become a crucial factor for risk stratification in childhood ALL.

Advances in Treatment

Supportive care

Optimal management of patients with ALL requires careful attention to supportive care. Hyperuricemia and hyperphosphatemia with secondary hypocalcemia are frequently encountered, even before chemotherapy is initiated, especially in patients with a high leukemic cell burden and those with T-cell or mature B-cell ALL. Rasburicase (recombinant urate oxidase), a potent uricolytic agent, rapidly decreases serum uric acid level, improves renal function and facilitates the excretion of phosphorus.[42] Even in patients with massive tumor lysis, the combined use of rasburicase (followed by allopurinol), adequate hydration and a phosphate binder can prevent acute renal failure and avoid the need for hemodialysis in the vast majority of patients.

Remission induction

Rates of complete remission range from 97% to 99% with the use of contemporary chemotherapy.[1–14] Induction regimens typically include a glucocorticoid (prednisone, prednisolone or dexamethasone), vincristine, and asparaginase. Children with high- or very-high-risk ALL receive one or more additional drugs including an anthracyline and cyclophosphamide; however, intensification of induction therapy can lead to increased morbidity and mortality. In one study, the use of high-dose dexamethasone (10 mg/m^2/day) instead of prednisone (60 mg/m^2/day) improved leukemia control in patients with T-cell ALL but resulted in a high mortality rate, especially in adolescent patients.[43] Although in most randomized trials, patients treated with dexamethasone have had a better outcome than those treated with prednisone,

it is debatable whether dexamethasone is more effective than prednisone, and one could argue that the dose of prednisone might have been too low in these studies.[44] Whether intensification of remission induction is even necessary for children with standard-risk ALL, particularly if they receive intensive post-induction therapy,[3] is also debatable. As a result of its lower immunogenicity, less frequent dosing, and feasibility of intravenous administration, pegaspargase (a polyethylene glycol form of *Escherichia coli* asparaginase) has replaced the native product as the first-line treatment for children in the United States, and it is increasingly used in clinical trials worldwide.[45] Antibodies to *E. coli* asparaginase cross-react with pegaspargase; therefore, patients with allergic reactions to either form of the enzyme should be treated with a product derived from *Erwinia chrysanthemi*.[45] A final caveat is that antibodies can develop against polyethylene glycol and adversely affect drug efficacy.[46]

Intensification (consolidation) therapy

Post-remission intensification (consolidation) therapy improves outcomes, even in patients with low-risk ALL.[3] Commonly used regimens include high-dose methotrexate with daily mercaptopurine, and a combination of high-dose asparaginase given for an extended period together with vincristine, dexamethasone or lower-dose methotrexate.[2,3,7,11,36] Patients with ALL and *ETV6-RUNX1* fusion had an especially good outcome in clinical trials that featured intensive post-remission treatment with glucocorticoids, vincristine and asparaginase.[11,47] Although high-dose methotrexate ($5\ g/m^2$) is associated with improved outcome in T-cell ALL, lower doses appear to be sufficient for low-risk B-cell precursor ALL.[3,11]

Delayed intensification (or re-induction), which consists of repetition of the initial remission-induction therapy approximately 3 months after the end of remission induction, has been an essential treatment component. Although extended and stronger intensification therapy with asparaginase, methotrexate and vincristine has improved outcomes for children and adolescents with high-risk ALL and slow responses to initial induction therapy, recent studies have demonstrated that early intensive (rather than extended) post-induction treatment benefits most patients.[11,48,49]

Continuation therapy

Weekly methotrexate and daily mercaptopurine for 2–2.5 years constitute the usual continuation regimen for ALL. Administration of this combination to the limits of tolerance (i.e. leukocyte counts consistently $< 3.5 \times 10^9/L$) and compliance has been associated with improved clinical outcomes.[50]

Approximately 10% of the patients have an inherited heterozygous deficiency of thiopurine S-methyltransferase; the enzyme that catalyzes the S-methylation (inactivation) of mercaptopurine. Almost half of these patients require moderate reductions in mercaptopurine dosage to prevent severe myelosuppression. Patients with this enzyme deficiency are also at risk for therapy-related leukemia.[51] A reduction of mercaptopurine dose might reduce the risk of therapy-related leukemia in these patients.

Intermittent pulses of vincristine and a glucocorticoid have been widely adopted in the treatment of childhood ALL. In an intergroup trial of initial intensive chemotherapy, the addition of six pulses of vincristine and dexamethasone during early continuation treatment failed to improve clinical outcomes in children with intermediate-risk ALL.[52] However, with a longer follow-up, one of the groups showed that the pulses of vincristine and corticosteroids improved disease-free survival, without an accompanying gain in overall survival.[53] Thus, whether this pulse therapy is necessary in contemporary regimens that feature early intensification of therapy remains to be determined.

CNS-directed treatment

Systemic treatment including high-dose methotrexate, intensive asparaginase, and dexamethasone, as well as optimal intrathecal therapy, are important in the control of CNS leukemia.[54] Thus, triple intrathecal therapy with methotrexate, cytarabine and hydrocortisone is more effective than intrathecal methotrexate in preventing CNS relapse.[55]

Two recent studies have shown that, with effective intrathecal and systemic chemotherapy, prophylactic cranial irradiation, once a standard CNS-directed treatment, can be safely omitted from first-line protocols, even in patients with T-cell ALL, hyperleukocytosis, or overt CNS leukemia at diagnosis, all high-risk features for CNS relapse.[11,56] The reported 5-year event-free survival rates were 85.6% and 81%, and the isolated CNS relapse rates were only 2.7% and 2.6%, respectively. Importantly, all 11 patients with isolated CNS relapse in the first study remained in second remission for 0.4–5.5 years after salvage therapy. This innovative treatment approach promises to improve the quality of life of survivors of childhood ALL.

Stem cell transplantation

The indications for hematopoietic stem cell transplantation during first remission must be continuously reviewed as treatment improves and new agents become available. Currently, failure to respond, or a poor early response to initial remission induction treatment (e.g. ≥ 1% blasts), is the most frequent indication for transplantation. Although transplantation does not appear to improve outcome in hypodiploid ALL[57] or *MLL*-rearranged ALL in infants,[39,58,59] many leukemia therapists still recommend transplantation for patients with poor early responses to treatment. In view of the markedly improved early treatment results with combined use of intensive chemotherapy and a tyrosine kinase inhibitor (imatinib),[38] many investigators do not recommend transplantation in first remission for children with *BCR-ABL1*-positive ALL, unless they have poor response to remission induction treatment. Whether transplantation benefits patients with ETP-ALL remains to be determined.

Targeted therapeutics

Targeted cancer therapy is best defined as a treatment that is designed to modulate a single molecular target, usually through inhibition but sometimes through activation. Use of the tyrosine kinase inhibitor imatinib in *BCR-ABL1*-positive ALL offers an excellent example of this approach. More potent second generation tyrosine kinase inhibitors (dasatinib and nilotinib) have been developed to address the problem of resistance to imatinib.[60] Other novel agents with potential roles in ALL include FLT3 (FMS-like tyrosine kinase receptor-3) inhibitors, farnesyltransferase inhibitors, proteasome inhibitors, demethylating agents and histone deacetylase inhibitors.[60] Immunotherapeutic options are also emerging. Rituximab (anti-CD20), alemtuzumab (anti-CD52), inotuzumab (anti-CD22) and epratuzumab (anti-CD22) have already been incorporated into some clinical trials,[20] and recombinant immunotoxins and bispecific antibodies (blinatumomab) are being tested.[61,62] The chief difficulty with targeted therapeutics for any cancer is that the molecules or signaling pathways selected for manipulation might not be crucial drivers of the malignancy process. This means that their inhibition or activation might produce only transient effects on the cancer, while introducing excessive toxicity in normal tissues. Also, the curative potential of cytotoxic chemotherapy in most cases of childhood ALL is high, which makes the selection of pediatric patients for trials of targeted therapies more challenging, and raises the required level of activity necessary for success.

Late Complications of Therapy

Cranial irradiation causes many serious late sequelae and occasional fatal complications, such as second cancers, neurocognitive deficits, and endocrine abnormalities that can lead to obesity, short stature, precocious puberty, and osteoporosis.[63–66] In general, these complications are seen in girls more often than in boys, and in young children more often than in older children. Survivors of childhood ALL who were treated 20–40 years ago face a considerable mortality risk during adulthood; by one estimate they have an average loss in life expectancy of 10 years, which is most probably due to the use of cranial irradiation.[67]

Contemporary treatment programs have largely abandoned the use of cranial irradiation and

replaced it with intensive systemic and intrathecal treatment with methotrexate and glucocorticoids, which leads to a different set of complications. Short-term complications of glucocorticoid use include myopathy, myalgia, infection, behavioral problems, hyperglycemia, and adrenal axis suppression.[68] Although these complications are transient, osteonecrosis induced by glucocorticoids can be a severely debilitating toxicity that results in joint collapse that requires total joint replacement.[69,70] The pathogenesis of glucocorticoid-induced osteonecrosis is still being investigated, but has been variously attributed to intravascular thrombotic occlusion, adipocyte hypertrophy and marrow ischemia, as well as apoptosis of endothelial cells, osteoblasts, and osteoclasts.[68] Risk factors for osteonecrosis include age 10–20 years, high body mass index, female sex, and white race.[69–71] Early identification of bone and joint lesions for therapeutic intervention is important for minimizing toxicity. To this end, intermittent use of dexamethasone (i.e. days 1–7 and 15–21 of re-induction treatment), even at higher total doses, appears to have reduced the risk of osteonecrosis compared with continuous administration of the drug.[49] Additional studies are needed to determine if such intermittent administration might compromise leukemia control.

Treatment with anthracyclines can produce severe cardiomyopathy, especially when these agents are given in high cumulative and peak doses to young girls. Cardiac abnormalities are persistent and progressive for years following anthracycline therapy.[72] Although dexrazoxane can reduce anthracycline-induced cardiotoxicity without interfering with antileukemic activity[73] or causing secondary malignant neoplasms,[74] the use of anthracyclines in current clinical trials is limited, even for high-risk cases.

Summary

Cure rates for childhood ALL have improved remarkably over the past 40 years; largely through intensive use of conventional chemotherapy in the context of rigorous clinical trials. Clinical factors, genetic features of the leukemia, initial response to therapy, and in some clinical trials, pharmacogenetics are now used in concert to select treatment plans for increasingly smaller subsets of patients. However, the side effects of cytotoxic chemotherapy remain significant, and a useful mechanistic understanding of non-responding and drug-resistant cases is often lacking. Rapid advances in functional and chemical genomics have made it possible to identify ever-larger numbers of genetic lesions in leukemic cells. This, in turn, will soon enable precise discrimination between patients who are likely to be cured with antimetabolite-based therapies, and those who will require more intensive treatment. It will also provide an expanding repertoire of therapeutic targets for clinical evaluation. Finally, the recognition of host factors associated with the risk of leukemic transformation and the response to therapy will probably lead to more sophisticated treatment strategies in the near future.

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