Biological and therapeutic aspects of infant leukemia

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Leukemias diagnosed in the first 12 months of life are characterized by an equal distribution of lymphoid and myeloid subtypes and account for 2.5% to 5% of acute lymphoblastic leukemias (ALLs) and 6% to 14% of acute myeloid leukemias (AMLs) of childhood.[1,2] In contrast to an excess of boys among older children with leukemia, there is a slight female predominance among infants with this disease.[3-5] Infant leukemias display unique biological and clinical features that have provided important insights into the mechanisms governing normal and aberrant hemopoiesis in the fetus and young children, as well as reasons for the increased rates of treatment failure in infants as compared with older children. This review summarizes recent progress in understanding the biology of infant leukemias and the prospects for better treatment.

Epidemiology

The risk of leukemia in children, as in cancer patients in general, reflects a complex interplay between inherited predisposition, exogenous exposures to agents with leukemogenic potential, and chance events. Infant leukemias afford unique investigative models for the study of leukemogenesis. Despite the fact that such leukemias arise very early in life, the leukemogenic contribution of abnormal alleles (transmission of parental mutations) is generally assumed to be small. Familial clustering is not seen in the infant leukemias, and constitutional predisposing alleles have not been identified. However, new germinal mutations in 1 parent could affect a single predisposed offspring if the alterations occur downstream in the spermatogenetic/oogenic pathway; reciprocal translocations that target cells of the developing hemopoietic system could also play a role.[6] Infant leukemias have been associated with Down syndrome,[7] with Turner syndrome, and with trisomy 9.[8] In contrast to other cases, some infant leukemias associated with Down syndrome undergo spontaneous remission.[7] These proliferations have distinguishing morphologic, immunophenotypic, and cytogenetic features.[9] Infants with acute lymphoblastic leukemia (ALL) or acute myeloid leukemia (AML) usually have acquired *ALL1/MLL/HRX* gene fusions as the major consistent genetic abnormality (see "*ALL1/MLL/HRX* cloning, structure, and function: clues to pathogenesis?").

Epidemiological and molecular genetic studies demonstrate that most, if not all, cases of infant leukemia arise in utero. First, infant leukemias exhibit fetal-type *DJH* joining sequences in the immunoglobulin gene.[10] Second, the very early onset of some cases with 11q23 chromosomal rearrangements strongly suggests a prenatal leukemogenic event.[11] In fact, a report of fetal death due to AML with an *ALL1/MLL/HRX* rearrangement provided direct evidence of oncogenesis in utero.[12] Third, molecular studies of identical twins with leukemias harboring *ALL1/MLL/HRX*–rearranged genes have corroborated suggestions that *ALL1/MLL/HRX* rearrangement is acquired in utero. Indeed, the detection of an identical clonal, nonconstitutional rearrangement of the *ALL1/MLL/HRX* gene in the leukemic cells of both twins provided evidence for a single clonal event in utero in 1 twin, generating leukemic clonogenic progeny that metastasized to the other twin through placental anastomoses or by crossing the maternal circulation and reaching the second twin.[13-17] Finally, the same clonotypic *ALL1/MLL/HRX-AF4* genomic fusion sequences have recently been backtracked to neonatal blood spots from individuals who were diagnosed with ALL at ages 51 months to 2 years.[18] The fetal origin of leukemia has also been established in older children (up to 14 years old) with T-cell ALL or B-precursor cell ALL with *TEL-AML1* fusion by studies of monozygotic twin pairs[19-21] or neonatal blood spots (Guthrie cards).[22] One interpretation of this finding is that many childhood leukemias are initiated by a mutagenic event in utero. The presence of *ALL1/MLL/HRX* fusion in a susceptible cell type appears sufficient to induce leukemia, whereas with other genetic alterations, additional postnatal mutations are required. It is also likely that *ALL1/MLL/HRX* fusion occurs more frequently during fetal development, accounting for the high incidence of this genetic abnormality in infants with leukemia.

The types of exposures that give rise to leukemogenic somatic genetic changes in utero can be assessed with greater precision in infants than in older children. Thus, maternal alcohol consumption, but not smoking, during pregnancy has been correlated with an increased risk of infant leukemia, especially AML.[23,24] It was postulated that ethanol induces microsomal enzymes, such as cytochrome P450, which in turn activate precarcinogens.[25] Most studies have shown that an increased incidence of high birth weights and a low incidence of low birth weights correlate with higher rates of infant ALL and AML.[26-31] It was suggested that high levels of insulinlike growth factor–1 might produce large babies and contribute to leukemogenesis, an interesting theory that remains to be proved.[26] An increased maternal consumption of DNA topoisomerase-II-inhibitor–containing foods, such as specific

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fruits and vegetables that contain quercetin; soybeans (genistein); tea, cocoa, and wine (catechins); and caffeine have all been related to an increased risk of infant AML.[32-34]

ALL1/MLL/HRX gene rearrangements are common in secondary acute leukemia (usually with monoblastic or myelomonoblastic morphology) arising after exposure to an epipodophyllotoxin or an anthyacycline, both of which inhibit topoisomerase-II.[35,36] This observation supports the theory that exposure of pregnant women to substances that inhibit topoisomerase-II might be a critical event in the development of leukemia in infancy. Anticancer drugs, quinolone antibiotics, flavonoids, catechins, podophylline resin, benzene metabolites, and estrogens can all inhibit topoisomerase-II in vivo or in vitro and may be considered potential mutagens in the induction of acute leukemias with rearranged *ALL1/MLL/HRX* genes.[37] Exposures of the pregnant mother and fetus to dietary, medical, and environmental chemicals that interact with topoisomerase-II may be order-of-magnitude lower in functional doses than in exposures to drugs used in cancer chemotherapy, even though the first class of agents are as biologically active as the latter class.[38] It has been proposed that interindividual pharmacogenetic-based differences in metabolism between these types of chemicals might play an important role in dose-response relationships that modulate the risk of pediatric leukemia. Thus, *ALL1/MLL/HRX* rearrangement has been correlated with low NAD(P)H quinone oxidoreductase (NQO1) activity,[39] the quinone moiety being shared by many topoisomerase-II-inhibiting drugs and other chemicals.[40-42] Some of the different maternal exposures during pregnancy that have been implicated in the genesis of infant leukemia could therefore operate via the quinone metabolic pathway.

The possible role of parental genetic susceptibility factors in modulating the effects of parental carcinogen exposure was recently suggested by studies of glutathione-S-transferase (GST) genes polymorphisms in parents of diseased infants. Among the parents of infants with leukemias lacking *ALL1/MLL/HRX* gene rearrangements, the frequencies of single and double GST genes (class M-GSTM; class T-GSTT) deletions were significantly higher than expected. The deletion of both *GSST1* and *GSTM1* genes in either parent may therefore affect the risk of infant leukemia through a pathway independent of the *ALL1/MLL/HRX* gene.[43] Whether parental preconceptional or in utero exposure to radiation increases the risk of infant leukemia remains controversial. One report suggests that there might have been a transient increase in infant leukemia in northern Greece in association with radioactive fallout from the Chernobyl accident.[44] However, the European Childhood Leukemia-Lymphoma Incidence Study failed to show any increase in the incidence of childhood leukemia as a consequence of this event.[45] Likewise, in a subsequent study, German investigations were not able to correlate an increased incidence of infant leukemia with ionizing radiation from the accident.[46]

ALL1/MLL/HRX cloning, structure, and function: clues to pathogenesis?

The *ALL1/MLL/HRX* gene, located at cytogenetic band 11q23, is consistently altered in infant acute leukemia, being rearranged in more than 60% to 70% of cases.[1,2] This gene was identified in 1991 and completely cloned and characterized in 1992. Somatic cell-hybrids or fluorescent in situ hybridization (FISH) was used to map the chromosomal 11q23 breakpoints into a region between the *CD3*γ and the porhobilinogen deaminase genes. Subsequently, a yeast artificial chromosome (YAC), containing the *CD3*δ gene was cloned and shown by FISH analysis to span the t(4;11), t(6;11), t(9;11), and t(11;19) chromosomal translocation breakpoints.[47] When a similar YAC was used, a DNA insert was obtained in which Southern blot analysis detected rearranged bands in leukemic cells from patients with t(1;11), t(4;11), t(6;11), t(9;11), t(10;11), and del(11q23) abnormalities. Breakpoints were clustered in a small region of ≈8 kilobases (kb) within a gene named *ALL1* by Cimino et al[48] because rearrangements were first identified in a patient with ALL. Other investigators completed characterization of the gene and added the designation *MLL* because the gene could be altered in myeloid or lymphoid leukemias, and the designations *HRX* or *Hrtx1* to indicate homology with the *trithorax (trx)* gene of *Drosophila*.[47,49-51] *ALL1/MLL/HRX* spans approximately 90 kb of DNA, encodes a major transcript of ≈15 kb, and consists of 36 exons, ranging in size from 65 to 4249 base pairs. The protein product consists of more than 3910 amino acids containing 3 regions homologous to sequences of the *Drosophila trx* gene, including cysteine-rich regions that can fold into 6 zinc-finger–like domains and a highly conserved 200–amino acid SET domain located at the carboxyl-terminal end.[49-56]

In *Drosophila*, the *trx* gene acts to spatially maintain restricted expression pattern of the *Antennapoedia* and *Bithorax* complexes during fruit fly development. *trx* activates transcription of multiple genes of the 2 complexes and, thus, counteracts the activity of Polycomb group (*PcG*) genes, which repress the transcription of the same genes. Gene-targeting studies demonstrated that *ALL1/MLL/HRX* is also a positive regulator of *Hox* genes in mice.[57] *Hox* expression is shifted posteriorly in *ALL1/MLL/HRX* heterozygous (+/−) embryos and completely abolished in *ALL1/MLL/HRX* homozygous null (−/−) embryos. Shifts in *Hox* expression are also observed in mice with targeted mutations in *PcG*.[58,59] More recently, Yu et al[60] showed that mice with deletions of the *ALL1/MLL/HRX* gene had altered maintenance rather than activation of the *Hox* gene.

The *ALL1/MLL/HRX* gene product possesses 2 other regions that could be directly or indirectly involved in the control of gene transcription. These are (1) a region that is similar to the AT hook of high-mobility–group-I proteins and that binds to AT-rich regions of the minor groove of the DNA and (2) a cysteine-rich region homologous to the mammalian DNA methyltransferase double helix, which by favoring conformational DNA changes, facilitates the action of other regulatory genes.[49-51]

To date, at least 16 different fusion partner genes involved in chromosomal translocations with *ALL1/MLL/HRX* have been characterized (Table 1).[61-77] Additionally, internal duplications within the amino-terminal part of *ALL1/MLL/HRX* and specific deletions of exon 8 have been detected in leukemic blast cells of some leukemia patients [78-80]

The impressive heterogeneity of *ALL1/MLL/HRX* recombination raises difficult questions as to how fusion proteins cause leukemia and the role of partner genes in activating the *ALL1/MLL/HRX* gene and determining the leukemic phenotype. Thus, several investigators have searched for structural similarities among the different *ALL1/MLL/HRX* partner genes. With the exception of the homology shown by *AF9* with *ENL*, by *AF10* with *AF17*, by *AFX* with *AF6q21*, and by *MSF* with *hCDCrel*, sequence analysis did not reveal structural or functional similarities. Thus, it is unlikely that these fusion partners could play a role in the function of the hybrid gene by simply providing transcriptional modulation (activation or repression) domains. By contrast, the active functional contribution of partner genes in determining the oncogenic capacity

Table 1. Structural characteristics, location, and putative functions of *ALL1/MLL/HRX* partner genes

Partner gene	Chromosomal location	Transcript size (kb)	Protein size (aa)	Putative function	Shared homology	References
AF4 or *FEL*	4q21	12 and 15	1200	Transcription factor	None	61, 62
AF9	9p22	5	578	Transcription factor	*ENL*	61
ENL	19p13	4.7	559	Transcription factor	*AF9*	61, 64
AF6	6q27	8	1612	Cytoplasmic protein	None	63
AF1p	1p32	4.4	896	Cytoplasmic protein	None	70
AF10	10p12	5.5	1027	Cytoplasmic protein	*AF17*	72
AF17	17q21	7.5 and 5	1093	Dimerization protein	*AF10*	66
ELL	19p13.1	4.4	621	Transcription factor	None	65
AF1q	1q21	1.7	90	Growth factor	None	69
AFX1	Xq13	Not determined	Not determined	Transcription factor	*AF6q21*	68
CBP	16p13	9	2491	Transcriptional coactivator	None	71
AF6q21	6q21	6	403	Transcription factor	*AFX*	77
ENN	19p13	2.6	368	Cytoplasmic protein	None	72
ABI-1	10p11.2	2.9	387	Cytoplasmic protein	None	75
HCDCrel	22q11.2	2.5 and 3.5	369	Cytoplasmic protein	*MSF*	74
MSF	17q25	2.8	568	Cytoplasmic protein	*HCDCrel*	76

of the resulting hybrid gene is strongly suggested by several observations. All partner genes are fused in frame to *ALL1/MLL/HRX*, generating a full-length fusion protein, whereas terminal deletions of *ALL1/MLL/HRX* have not been identified in leukemic cells. In addition, by testing a series of *ALL1/MLL/HRX-ENL* mutants to investigate the participation of several conserved sequence motifs in the oncogenic activity of the fusion product, Slany et al[81] recently demonstrated that the DNA binding motifs of *ALL1/MLL/HRX*, as well as the transcriptional transactivation activity of *ENL*, are required for in vitro immortalization of murine myeloid cells. Finally, knock-in mice expressing an *ALL1/MLL/HRX-AF9* fusion gene under the control of the natural *ALL1/MLL/HRX* promoter developed AML, while mice expressing an *ALL1/MLL/HRX/Myc* tag fusion gene remained free of leukemia.[82]

Despite extensive studies, it is still unclear as to how fusion products participate in leukemogenesis. One possibility is that they might supply a dimerization domain, which could activate the *ALL1/MLL/HRX* chimeric genes. This hypothesis is supported, first, by the observation that several *ALL1/MLL/HRX* partner genes possess structures involved in the protein-protein interactions and, second, by the finding that the novel self-fusion genetic mechanism mentioned above leads to internal duplication of the amino-terminal part of the *ALL1/MLL/HRX* gene, which functionally could be equivalent to a dimer of the NH2 portion of the *ALL1/MLL/HRX*. Since the RNA polymerase elongation factor *ELL* and the transcriptional coactivator *CBP* (gene for CREB binding protein) are 2 *ALL1/MLL/HRX* fusion partners involved in transcriptional regulation, an interaction of the *ALL1/MLL/HRX* fusion genes with the RNA polymerase-II transcription machinery has been proposed.

Of all the *ALL1/MLL/HRX* motifs present in all the fusion proteins, the AT hook region is the best characterized, and several lines of evidence suggest that this region has an important role in targeting and regulating transcriptional units for normal hematopoietic growth and differentiation. In this respect, it has been suggested that the Trx protein maintains target genes in a transcriptionally active state by an epigenetic mechanism that probably involves chromatin remodeling. Although *ALL1/MLL/HRX* has not been shown to remodel chromatin, the carboxy-terminal SET domain of *ALL1/MLL/HRX* interacts with hSNT5/INI1, a component of the SNF/SWI complex, a chromatin-remodeling system.[83,84] Importantly, the SET domain is lost when the aminoterminus of the ALL1/MLL/HRX and the carboxyl-terminal partner residues fuse to form ALL1/MLL/HRX fusion protein. The loss of this domain may explain the down-regulation of the *ARP1* gene in embryonic stem cells from *ALL1/MLL/HRX* double-knockout mice, as *ARP1* was recently identified and characterized as a target of ALL1/MLL/HRX.[85]

Finally, Adler et al[86] have shown that the *GADD34* gene, which encodes a DNA damage–inducible factor, is another target of ALL1/MLL/HRX. These authors also showed that, while ALL1/MLL/HRX protein interacts directly with *GADD34*, resulting in a significant increase in apoptosis after treatment with ionizing radiation, the coexpression of 3 different ALL1/MLL/HRX fusion proteins (ie, ALL1/MLL/HRX-ENL, ALL1/MLL/HRX-AF9, and ALL1/MLL/HRX-ELL) had an antiapoptotic effect, abrogating *GADD34*-induced apoptosis. The authors also observed a difference between wild-type and leukemic ALL1/MLL/HRX fusion proteins, leading them to postulate a gain of function for ALL1/MLL/HRX compared with the wild-type protein, suggesting that the inhibition of apoptosis may be relevant to leukemogenesis.[86]

With regard to the precise function of the wild-type ALL1/MLL/HRX protein, Hess et al,[87] after examining the effects of the haploinsufficiency or absence of *ALL1/MLL/HRX* on the in vitro differentiation of yolk sac progenitor cells, concluded that ALL1/MLL/HRX is required for the generation of normal numbers of hematopoietic progenitors and their proper differentiation, especially along the granulocytic and monocytic lineages.

Possible mechanisms of aberrant *ALL1/MLL/HRX1* recombination

Chromosomal translocations leading to oncogene activation are common events in the pathogenesis of leukemia, but the molecular basis for this process is still incompletely understood. *ALL1/MLL/HRX1* offers a useful model for elucidating such mechanisms. First, the gene is altered by promiscuous chromosomal recombination with a variety of partner genes in various subsets of acute leukemias, including some childhood and adult acute lymphoid or myeloid leukemias, secondary leukemias associated with prior exposure to drugs that target topoisomerase-II (etoposide, tenoposide, and anthracyclines), and, especially, infant leukemias.[88-92] Second, several DNA motifs implicated in DNA-recombination mechanisms have been recently identified and localized within the

ALL1/MLL/HRX1 breakpoint cluster region (bcr). These include (1) recombinase signal sequences (heptamers and nonamers); (2) scaffold attachment regions (SARs); (3) high-affinity topoisomerase-II–binding sites, including a strong site in exon 9; and (4) Alu sequences.[93-95] By comparing *ALL1/MLL/HRX* rearrangements in de novo versus therapy-related acute leukemias, Broeker et al[93] identified statistically significant differences in the breakpoint distribution between the 2 groups. In particular, they found that in therapy-related acute leukemias, the breakpoints clustered in the telomeric portion of the *ALL1* bcr, which is characterized by the presence of SARs and high-affinity topoisomerase-II binding sites, in contrast to cases of de novo leukemias, whose breakpoints in most instances clustered in the centromeric or 5′ bcr. On the basis of these observations, the authors suggested that the mechanisms of translocation in de novo and treatment-related leukemias secondary to treatment with topoisomerase-II inhibitors might be different.[93] This conclusion has important implications for attempts to understand the etiology and pathogenesis of infant leukemias. Molecular analyses of *ALL1/MLL/HRX* rearrangements in infant twins showed that these genetic aberrations arise during fetal hemopoiesis in utero.[13] Epidemiologic evidence has also indicated that certain conditions during pregnancy, such as exposure to drugs, alcohol, and pesticides, are associated with an increased risk of infant leukemia.[96,97]

Therefore, one mechanism leading to *ALL1/MLL/HRX* translocations might be chromosomal breakage induced by topoisomerase-II inhibitors within the *ALL1/MLL/HRX* gene, while another could be represented by mistakes in DNA-repair mechanisms. This hypothesis is supported by recent observations by Aplan et al[98] showing that topoisomerase-II–inhibiting drugs cleave double-stranded DNA at a site in *ALL1/MLL/HRX* exon 9 both in vivo and in vitro. More recently, Gillert et al[99] implicated ''error-prone repair'' as the DNA-repair process leading to *ALL1/MLL/HRX* translocations.

From these considerations and from analogy with the involvement of the *ALL1/MLL/HRX* gene in treatment-related leukemia, it was suggested that the critical leukemogenic event(s) occurring in utero might similarly involve prenatal exposure to topoisomerase-II inhibitors as represented by several natural and medicinal substances. That infant leukemias and topoisomerase-II–related secondary leukemias show the same biased distribution of *ALL1/MLL/HRX* breaks[100] lends credence to this hypothesis. A substantial list of candidate leukemogenic agents are under investigation in international case-control epidemiological studies.

Why are infant leukemias so different?

Clinical and biological features

ALL of infancy is associated with a high leukocyte count at presentation, hepatosplenomegaly, and central nervous system (CNS) involvement.[1,101,102] The immunophenotype is usually that of immature B-lineage precursors and is characterized by a lack of CD10 expression and the coexpression of myeloid-associated antigens. A high frequency of myeloperoxidase-gene expression typifies infant ALL.[103] These findings suggest that the classic form of infant ALL originates in a stem cell that has not fully committed to lymphoid differentiation. This hypothesis is supported by the observation that multipotential stem and progenitor cells prime the commitment and differentiation of several different hematopoietic lineages.[104] The frequency of *ALL1/MLL/HRX* gene rearrangements is very high, possibly as high as 75% when studied with molecular techniques,[1,2] as would be predicted from the frequency of the t(4;11), the translocation most often involved in the generation of this fusion gene.

These 3 characteristics—lack of CD10 expression, expression of myeloid-associated markers, and *ALL1/MLL/HRX* gene rearrangements—are correlated with one another, and their presence is inversely related to the age of the infant.[2,102,105-111] For example, *ALL1/MLL/HRX* rearrangement is associated with 90% of the $CD10^-$ cases, contrasted with only 20% of the $CD10^+$ cases.[109,110,112] Among infants, a lack of CD10 expression, coexpression of myeloid-associated markers, *ALL1/MLL/HRX* rearrangement, and age of less than 6 months are associated with a poor prognosis.[2,101,102,105-107,109-115] The event-free survival of infants with $CD10^-$ B–precursor-cell ALL is only about 25%, as compared with 50% to 55% for those with the $CD10^+$ phenotype.[102,106,113] Similar estimates apply to cases with an *ALL1/MLL/HRX* rearrangement: 10% to 20% as compared with 50% in cases with *ALL1/MLL/HRX* in a germ-line configuration.[102,107,109-111,115] Two studies[105,111] have analyzed the relation between myeloid-associated antigen expression and outcome in infant ALL: the event-free survival in cases expressing the antigens was 0% to 10%, compared with about 60% in the other cases. Finally, age itself can be used as a prognostic factor in infant ALL. Infants younger than 6 months of age have a worse outcome (10% to 20% event-free survival) than do infants between 6 and 12 months of age at diagnosis (40% to 45% event-free survival).[102,106,107,111]

The above-mentioned high-risk factors are closely interrelated. In several analyses, the *ALL1/MLL/HRX* rearrangement emerged as an important adverse prognostic factor.[109,114-117] In one large multivariate analysis, it was shown that *ALL1/MLL/HRX* rearrangement, age, CD10, and white blood cell count were all independent prognostic factors.[115] Two other small studies showed that the *ALL1/MLL/HRX* rearrangement was of prognostic relevance independent of the white blood cell count.[109,114] Recent studies by the Childrens Cancer Group (CCG) suggested that the t(4;11) is the only *ALL1/MLL/HRX*-related translocation associated with a dismal outcome.[107,112,118] In a combined Pediatric Oncology Group (POG)–St. Jude study, infant ALL cases with *ALL1/MLL/HRX-ENL* fusion due to the t(11;19) had an extremely poor prognosis.[119] However, the adverse outcome cannot be attributed solely to the t(4;11) or the t(11;19), as children 1 to 9 years old with this abnormality have a reasonably favorable prognosis.[119-121] Thus, other factors must contribute to the generally poor treatment results obtained in infants. In a recent study by the Berlin-Frankfurt-Münster (BFM) group, a poor early-treatment response to prednisone was found to be the strongest predictor of outcome in infant ALL, even in the subgroup with the t(4;11).[122] Hence, a poor early-prednisone response is being used as the sole criterion for allogenic, hematopoietic stem cell transplantation in the Interfant ’99 study of infant ALL, conducted by a consortium of European and US investigators.

In AML, age and the presence of 11q23 abnormalities have no clear adverse prognostic impact.[1,111,123,124] Infant AML is characterized by myelomonoblastic or monoblastic morphology, a high percentage of CNS involvement, and a high leukocyte count. *ALL1/MLL/HRX* rearrangements are found in about 60% of infant AML cases.[111,125] The prognostic factors that define infant AML are not clearly defined. In a St. Jude study, high presenting leukocyte counts and male sex were the only 2 independent adverse prognostic factors.[111] The association of high leukocyte counts with a poor outcome is not unexpected; however, the basis for the predictive strength of male sex is uncertain. Lie et al[126] have also

found male gender to be a predictor of a poor outcome. The prognostic impact of M4 and M5 morphology is controversial, probably owing to the use of different treatment regimens.[111,127] In a recent St. Jude study, the presence of the t(9;11)(p22;q22) conferred a favorable prognosis.[128] Clearly, additional studies are needed to ascertain the prognostic factors in infant AML.

Drug-resistance profile

Age, immunophenotype, and *ALL1/MLL/HRX* rearrangement reflect or cause differences in drug-resistance factors. These can be pharmacokinetic factors that determine the amount of drugs to which the leukemic cells are exposed or differences in cellular pharmacodynamics that determine the sensitivity of the cells to the drugs. There are no data suggesting that pharmacokinetic resistance might explain the poorer outcome of infant ALL; infants simply do not show increased clearance of antileukemic drugs.

Nonetheless, some studies suggest differences at the cellular level. Kumagai et al[129] showed that leukemic cells from infants with 11q23 rearrangements grow better on stromal layers in vitro than do cells from other cases. Uckun et al[130] similarly showed that cells from infants with *ALL1/MLL/HRX*-rearranged ALL are more readily recovered from severe combined immunodeficiency (SCID) mice than are cells from children with other types of ALL. In related studies, Kersey at al[131] found that leukemic cells with the t(4;11) are more resistant to stress-induced death than are other B-lineage blast cells, while Pieters et al[132] showed that cells from infants with ALL are significantly more resistant in vitro to prednisolone and L-asparaginase than are cells from older children. In vitro resistance to these drugs is a strong adverse prognostic factor.[133-135] Of considerable therapeutic interest, the leukemic cells of infants with ALL are significantly more sensitive to cytarabine than are cells from older children.[132] In addition, B-cell precursors that lacked CD10 expression were resistant to prednisone and L-asparaginase but showed significant sensitivity to cytarabine, in contrast to cases with CD10 expression. A study by the Dana-Farber Cancer Institute Consortium showed that high-dose cytarabine given immediately after remission induction is a feasible strategy and might benefit infants with ALL.[136] Recent data from a German study of adult ALL patients showed that the long-term survival of adults with pro-B ALL with the t(4;11) has increased to about 40% with the introduction of high-dose cytarabine/mitoxantrone consolidation therapy.[137] Finally, Reiter et al[108] reported that infants with ALL more frequently show a poor in vivo response to prednisone than do older children. In their study, age lost its prognostic value in a multivariate analysis because of its association with a poor prednisone response in vivo. A recent update of the BFM 1986 and 1990 studies confirmed the prognostic significance of the steroid response: the 6-year event-free survival for infants with a good prednisone response was 58% versus only 16% for infants with a poor prednisone response.[122]

Differences between infants and older children

Rapid changes in physiologic processes govern drug disposition in infants, especially neonates. First, the total body water content as a percentage of total body weight decreases from 75% in the newborn period to 60% at 1 year and 55% by adulthood; extracellular water as a percentage of total body water decreases from 45% in the neonate to 20% in the adult.[138] Second, many drugs bind less avidly to serum proteins in the neonate than in the adult, leading to an increase in the unbound fraction (presumably the active drugs) and potentially enhanced pharmacologic responses in the former age group.[139] Third, the activity of many P-450 enzymes is low during infancy.[140,141] This decreased metabolic activity could result in reduced cytotoxic effects of antineoplastic drugs that require bioactivation (eg, cyclophosphamide) or in enhanced cytotoxicity of those that undergo inactivation (eg, vincristine and daunorubicin). Fourth, renal tubular function and the glomerular filtration rate reach adult levels by 7 months and 5 months of age, respectively[142,143]; hence, any drugs that depend on renal function for clearance will have increased systemic exposure and pharmacologic effects in infants.

There are, in addition, many important anatomical differences by age. For example, the volume of the CNS relative to body surface area or body weight is much larger in young children than in adults. While the CNS volume in infants approaches 80% to 90% of the adult value by age 4 to 6 years, body surface area does not reach adult values until approximately 16 to 18 years of age.[144] Indeed, Bleyer[144] demonstrated that the dosage of intrathecal chemotherapy should be based on age rather than body surface area to avoid undertreatment in young children. Another major age difference is the ratio of body weight (kg) to body surface area (m^2); for example, the ratio for neonates is 18, which is lower than the ratio of 25 in 5-year-olds, which in turn is a lower value than the value of 40 in adults.[145] Thus, if drug dosage were based solely on body weight for all age groups, infants would receive a substantially lower dosage by body surface area than would other children. Whether the dosage of any given drug in infants should be based on body surface area or body weight remains in question. This uncertainty is well illustrated by the empirical approach to drug dosing in different clinical trials of infant leukemias, some based entirely on body weight, others on body surface area, and still others on body surface area adjusted by age (ie, proportionally lower in young infants).

There are only limited pharmacokinetic and pharmacodynamic data on individual antileukemic drugs and on the tolerance to these agents in infants. An early report suggested that infants with leukemia are more susceptible to severe vincristine neurotoxicity than are children.[146] In a subsequent study of remission-induction therapy with vincristine (1.5 mg/m^2), prednisone, L-asparaginase, and intrathecal methotrexate, 7 of the 9 patients with a body surface area less than 0.5 m^2 developed vincristine neurotoxicity, which was severe in 4.[147] It was uncertain whether L-asparaginase or methotrexate contributed to increased toxicity by altering hepatic function or whether the infant nervous system is more sensitive to vincristine. Because infants have a large body surface area relative to body weight, the authors proposed that the drug doses in infants should be calculated on the basis of body weight (in kilograms), with dosages normalized from those of body surface area (dividing by 30). This conversion effectively lowers the final dosage and has proved adequate for vincristine treatment in infants. Limited data suggest that dosing of teniposide, etoposide, and cytarabine based on body surface area would yield similar systemic exposure in infants and adults.[145] By contrast, normalized dosing of doxorubicin by body weight was more likely to achieve similar systemic exposure in these 2 age groups. The study also showed that methotrexate clearance tended to be lower in infants, but there was no need to reduce dosage, as methotrexate was better tolerated in these patients. Thus, uniform rules for dosage adjustment of all antileukemic agents used in infants is inappropriate; additional

pharmacokinetic and pharmacodynamic studies are needed in infants younger than 2 months of age.

Have treatment results for infant leukemias improved?

Acute lymphoblastic leukemia

Contemporary treatment for childhood ALL has cured approximately 80% of patients in some clinical trials,[148] but results for infant ALL are still suboptimal. A variety of treatment regimens have been tested in infants, generally yielding event-free survival rates of 20% to 35% (Table 2).[101,102,106,122,132,136,149-154] (See also A. Biondi, unpublished data, 1999.) In several recent clinical trials, high-dose methotrexate, high-dose cytarabine, and intensive consolidation/reinduction therapy appear to have improved clinical outcome,[106,112,122,136,153] but these results should be viewed as preliminary because of the small numbers of patients enrolled, the lack of randomization, and the disproportionate numbers of cases with high-risk disease (ie, *ALL1/MLL/HRX-AF4* fusion). Moreover, the efficacy of any treatment component is affected by the overall therapeutic strategy. Hence, while clinical trials incorporating high-dose methotrexate with or without cytarabine have generally yielded improved results, 1 study with a similar therapeutic strategy resulted in an inferior outcome, partly because of an increase in remission deaths from infection or gastrointestinal complications due to combination treatment with etoposide and high-dose cytarabine.[102] Likewise, excessive toxicities and treatment-related deaths, presumably due to high-dose daunorubicin in very young infants, were encountered in a POG study, despite encouraging overall results.[153] Both studies underscore the need for pharmacokinetic and pharmacodynamic studies to ensure optimal dosing in infants.

Neuropsychological abnormalities are well-recognized complications of cranial irradiation, especially in very young children. Severe neurological deficits and learning disabilities were observed in 4 of 8, in 9 of 11, and in 2 of 4 long-term survivors of infant ALL who had received cranial irradiation in 3 separate studies.[101,106,136] By contrast, in another study, infants who did not receive cranial irradiation showed normal neuropsychological development when tested at 5 years of age.[155] In virtually all studies, attempts have been made to reduce neuropsychological complications by reducing the dosage of cranial irradiations, delaying the radiotherapy until the child was more than 1 year old, or avoiding irradiation altogether (Table 2). To date, most investigators favor eliminating irradiation in all infants with ALL, even in those with CNS

Table 2. Treatment regimens and results for infants with ALL

			Treatment				
Study (year)	No. of patients	Event-free survival	Cranial irradiation	High-dose methotrexate	High-dose cytarabine	Consolidation/ reinduction therapy	Reference
AIEOP 88-91 (1988-1995)	61	5-y = 40%	12-18 Gy if >1 y (6 mo from diagnosis)	5 g/m^2 × 4 doses	—	+	*
ATRG (1984-1988)	24	2-y DFS = 20%	all patients	—	—	−	137
BFM 83 (1983-1086)	13	6-y = 23% ± 12% SE	±†	—	—	−	113
BFM 86 (1986-1990)	34	6-y = 37% ± 8% SE	±†	5 g/m^2 × 4 doses	—	+	113
BFM 90 (1990-1995)	59	6-y = 51% ± 7% SE	±†	5 g/m^2 × 4 doses	—	+	113
CCG 101, 143, 141, 141 A, 162, 163 (1972-1982)	115	4-y = 23%	12-15 Gy (n = 8); 18-20 Gy (n = 49); 24 Gy (n = 21)	—	—	−	93
CCG 192P (1982-84)	27	4-y = 36%	18 Gy after 1 y old	—	—	−	138
CCG 107 (1984-1987)	99	4-y = 33% ± 5% SE	—	7.2 g/m^2 × 3 doses	—	+	103
CCG 1883 (1987-1993)	135	4-y = 39% ± 4% SE	—	7.2 g/m^2 × 4 doses	1.5 to 3 g/m^2 q 12 h × 4 doses × 2 courses	+	103
DFCI 73-01, 77-01 81-01 (1973-1985)	11	4-y = 9% ± 9% SE	22 Gy after 1 y of age	—	—	−	124
DFCI 85-01, 87-01 91-01 (1985-1995)	23	4-y = 54% ± 11% SE	18-22 Gy	130 mg/kg × 2-3 doses	100 mg/kg q 12 h × 6 doses × 1 course	−	124
EORTC 58831, 58832 (1982-1989)	28	4-y = 43%	12-20 Gy at the end of therapy (first 9 points)	2.5 g/m^2 × 4 doses	—	+	97
MRC UKALL VIII, X (1980-1987)	48	4-y = 30%	18 Gy after 2 y of age	—	—	−	94
MRC UK Pilot (1987-90)	40	4-y = 20%	—	8 g/m^2 × 3 doses	0.5 g/m^2 q 12 h × 10 doses 1 g/m^2 q 12 h × 6 doses	+	94
POG 8398 (1984-1990)	37	5-y = 17% ± 7.7% SE	—	—	—	−	140
POG 8493 (1984-1990)	82	4-y = 28% ± 5% SE	—	—	—	−	141
POG 9407 Pilot (1994-1998)	21	2-y = 50%	—	4 g/m^2 × 4 doses	3 g/m^2 q 12 h × 4 doses	+	142
SJCRH Study XI (1984-1988)	11	5-y = 36% ± 1% SE	18 Gy after 1 y of age	1 g/m^2 × 2 doses	—	−	143

AIEOP indicates Associazione Italiana Ematologia Oncologia Pediatrica; ATRG, Aggressive Treatment Research Group; BFM (Berlin-Frankfurt-Münster group); CCG, Children's Cancer Group; DFCI, Dana-Farber Cancer Institute/Children's Hospital ALL Consortium; EORTC, European Organization for Research and Treatment of Cancer; MRC UK, Medical Research Council, United Kingdom; POG, Pediatric Oncology Group; SJCRH, St. Jude Children's Research Hospital; DFS, disease-free survival; EFS, event-free survival.

*Biondi A, unpublished, 1999.

†Infants <12 months of age at the intended time of cranial irradiation (24 to 26 weeks from diagnosis) were not given preventive (12 Gy) or therapeutic (20/18 Gy) irradiation.

leukemia at diagnosis, relying instead on intensive systemic and intrathecal treatments. Several observations support this approach. First, in the early studies of the CCG, cranial irradiation had no impact on treatment outcome.[101] Second, in the recent CCG-1883 trial, which did not include cranial irradiation, the cumulative risk of isolated CNS relapse was only 3% ± 2%,[112] despite a 14.2% prevalence of CNS leukemia at diagnosis. Third, in a POG study that employed only intrathecal treatment of the CNS for all patients, failure rates were similar in infant cases with and without CNS leukemia at diagnosis.[152] In fact, none of the 21 patients with CNS leukemia at diagnosis had CNS involvement at the time of relapse.

There is a paucity of data on allogeneic hematopoietic stem-cell transplantation in infants with ALL. Two limited collaborative group studies have yielded dismal results: only 2 of 11 and none of 3 patients survived.[102,112] The experience of the Fred Hutchinson Cancer Research Center is more encouraging, with 7 of 9 infants alive in first remission for 2 to 11 years after allogeneic transplantation.[156] Additional studies are clearly needed to determine the role of hematopoietic stem-cell transplantation in high-risk infant cases.

Acute myeloid leukemia

While infants with ALL are treated on separate protocols in most clinical trials, those with AML receive essentially the same therapy as older children in virtually all studies.[1,126,157-166] Infants with acute monoblastic leukemia are sometimes treated with epipodophyllotoxin-containing regimens,[167] apparently because of the increased sensitivity of their leukemic cells to this class of agents.[168,169] In most clinical trials of AML therapy, event-free survival rates are similar for infants and older children.[126,157-160,164,165] In the BFM 1983 and 1987 trials, children younger than 2 years had an inferior treatment outcome, as compared with older children.[166] However, in multivariate analyses, age lacked independent significance after adjustment for the FAB M5 or M7 subtypes, hyperleukocytosis, and an unfavorable karyotype. In the POG 8498 study, children younger than 2 years had a more favorable outcome than did older children.[161] The inclusion of children 1 to 2 years of age made it difficult to determine the prognosis for infants younger than 12 months.

Since treatment outcome generally does not differ by age group in childhood AML, there is no compelling reason to develop separate trials for infant AML, with the following exception. Infants with megakaryoblastic leukemia and the t(1;22) (p13;q13) appear to have a particularly poor prognosis[170,171] and may be candidates for innovative experimental therapy or perhaps allogeneic hematopoietic stem-cell transplantation. Although the latter procedure has yielded long-term survival in some infant cases,[3,172,173] its relative efficacy compared with contemporary intensive chemotherapy is unknown owing to the lack of randomized studies.

Ongoing clinical trials

Currently, 2 large international prospective studies for the treatment of infant ALL are under way. One is a collaborative US study conducted by the POG and CCG. The other is a large international effort, Interfant ’99, by European and US study groups. The POG/CCG trial tests the feasibility and efficacy of intensive therapy. Infants with an *ALL1/MLL/HRX* rearrangement are eligible for allogeneic hematopoietic stem-cell transplantation. The Interfant ’99 protocol is based on a so-called hybrid form of therapy, consisting of elements from both ALL and AML treatments administered on an ALL-like schedule and combining both low-dose and high-dose cytarabine. Only patients with a poor initial response to prednisone are eligible for hematopoietic stem-cell transplantation. No CNS or total-body irradiation is used, and anthracyclines, epipodophyllotoxins, and alkylating agents are either avoided or used only sparingly. Both studies will prospectively analyze whether age, immunophenotype, leukocyte count, initial response to therapy, and *ALL1/MLL/HRX* rearrangement have independent prognostic value.

Conclusion

In most cases of infant ALL and AML, the discovery of *ALL1/MLL/HRX* gene involvement opened new opportunities for molecular diagnosis and monitoring, molecular epidemiology, and studies to unravel basic biologic mechanisms. Continued molecular investigations are needed to gain further insight into the basic differences between leukemias in infants and older children. Current therapy for infant ALL and AML is inadequate. Although intensification of chemotherapy and wider use of allogeneic hematopoietic stem-cell transplantation could improve this situation, there remains an urgent need to develop novel therapies by exploiting the unusual biologic properties of leukemic progenitor cells expressing the abnormal *ALL1/MLL/HRX* gene product.

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