Leukemia in Infants

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ABSTRACT

Acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) in infants have in common a high incidence of translocations of the *MLL* gene at chromosome band 11q23. Similar translocations occur in leukemias associated with chemotherapies that target DNA topoisomerase II. *MLL* has numerous different partner genes. The role of the many MLL fusion proteins in leukemogenesis is not yet understood. The t(4;11) translocation, the most common translocation in infant ALL, adversely affects the outcome. Additional genetic changes, especially Ikaros alterations, are found in infant ALL. Other forms of myeloid leukemia in infants present as myelodysplastic and myeloproliferative syndromes, which may be associated with constitutional disorders. This review will consider all leukemia in infants, but will focus on leukemias with *MLL* gene translocations. *The Oncologist* 1999;4:225-240

INTRODUCTION

Leukemia in infants has unique epidemiological, biological, and clinical characteristics. The majority of cases of acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) in infants are characterized by high white blood cell count, bulky extramedullary disease, a propensity to express lymphoid and myeloid phenotypic markers, and cytogenetic or molecular translocations of the *MLL* (*ALL-1, HRX, Htrx-1*) gene at chromosome band 11q23 [1-14]. Similar clinical features, morphologies and *MLL* gene translocations characterize leukemias that follow therapy with epipodophyllotoxins and other DNA topoisomerase II inhibitors, although hyperleukocytosis and exramedullary disease are less consistent [15-20]. The translocation process seems central to leukemogenesis, but additional genetic changes also may occur [21-23]. The *MLL* gene translocations are associated with poor outcome, especially in ALL [1, 3-6, 10, 13, 14, 16, 24-32].

EPIDEMIOLOGY AND ETIOLOGY OF LEUKEMIA IN INFANTS

The incidence of acute leukemia in the first year of life in the United States is 30 cases per million live births. The annual incidence of ALL (20 per million) is almost twice the rate of AML (10.6 per million) [33] (Table 1). While 2.5% to 5% of pediatric ALL occurs in infants, AML in infants comprises 6% to 14% of pediatric AML [8, 12, 34]. The peak annual incidence of pediatric AML of 10.6 per million occurs during the first year of life. In contrast, the peak annual incidence of pediatric ALL of 76.6 per million occurs between two and three years of age [33]. Both ALL and AML occur more frequently in female than male infants [33]. The rates of ALL and AML in white infants are higher than the rates for blacks [33].

MLL gene translocations occur in up to 80% of cases of ALL, in up to 50% of cases of AML in infants, and in 80% of monoblastic variants of AML in infants and young children [2, 5, 7-11, 24, 26, 30, 34-40] (Table 1). About 5% to 10% of myeloid leukemias in infants present as myelodysplastic syndromes (MDSs) or myeloproliferative syndromes (MPSs) [41, 42]. The MDSs include the monosomy 7 and del(7q) syndromes. The MPSs include juvenile myelomonocytic leukemia (JMML), formerly called juvenile chronic myeloid leukemia and sometimes seen in patients with neurofibromatosis type 1 (NF1) and the transient

Table 1. Comparison of lymphoid and myeloid leukemia in the first year of life

	Lymphoid	Myeloid
Incidence	$20.0/10^6$	$10.6/10^6$
Sex: M/F	0.63/1	0.67/1
Risk factors	Monozygous twin with ALL	Monozygous twin with AML Down syndrome (TMS) Neuorfibromatosis type 1 (JMML) Noonan syndrome
Leukemia cutis	Rare	Common
Hepatosplenomegaly	Common	Common
CNS disease	14%-41%	52%
WBC $\geq 50 \times 10^9/l$	66%	44%
FAB morphology	L1>L2; L3 absent	M4/M5 most common
t(11q23)	50%-80%	34%-50%
Most common translocation	t(4;11)(q21;q23)	t(9;11)(p22;q23)
Spontaneous regression in the neonate	Single case report associated with t(4;11)(q21;q23)	Expected in neonate with Down syndrome Possible in neonate with Noonan syndrome Rare in constitutionally normal neonate

myeloproliferative syndromes (TMSs) associated with Down syndrome, Noonan syndrome, and ill-defined constitutional disorders [41-48]. Myeloid leukemia and TMS in neonates with Down syndrome are indistinguishable. In contrast, ALL of infancy is not associated with specific constitutional disorders.

Leukemia in infants has been the subject of numerous epidemiological investigations [49]. Because environmental or occupational exposures to ionizing radiation, solvents, petroleum products, and pesticides correlate with an increased risk of AML in adults, the early epidemiological studies on pediatric leukemia focused on these agents [50, 51]. Case control studies conducted between 1980 and 1984 by the Children's Cancer Group (CCG) found that parental perinatal exposures to pesticides and marijuana and maternal use of ethanol during pregnancy were significantly associated with FAB M4 and FAB M5 AML in infants and young children [51-53]. Other studies suggested that similar exposures might be significant, but subsequent case control studies carried out by the CCG did not validate the original associations [54-56]. The CCG also found an association of maternal history of fetal loss with FAB M4/M5 AML and ALL in infants [57].

Since epipodophyllotoxin treatment is specifically associated with *MLL* gene translocations [58], and since epipodophyllotoxins increase DNA topoisomerase II-mediated chromosomal breakage [59], the treatment-related

leukemias have suggested that DNA topoisomerase II plays a role in the translocations. Observed clinical and molecular similarities between leukemia in infants and epipodophyllotoxin-induced cases formed the basis for the epidemiological study in which *Ross et al.* determined that maternal consumption of dietary DNA topoisomerase II inhibitors might be a factor in AML but not ALL in infants [60]. The maternal dietary DNA topoisomerase II inhibitors included caffeine, quercitin in fresh fruits and vegetables, and catechins in cocoa [60]. As already stated, associations between maternal alcohol consumption during pregnancy and infant AML have been suggested; red wine contains quercitin [55, 61]. In addition, alcohol metabolites may interfere with DNA topoisomerase II [61]. Soy-based formulas may expose young infants to high levels of isoflavones, including daidzein and genistein, other DNA topoisomerase II inhibitors [59, 62], raising further questions about the potential role of DNA topoisomerase II in leukemia in infants.

Studies of leukemia in monozygous infant twins have advanced our understanding of both the epidemiology and natural history of leukemia in infants. Since the rate of twin births in the United States is 24.6 per thousand live-born infants [63], the annual incidence of leukemia in infants is 30 per million [33], and estimated concordance rates in monozygous twins are from 5% to 25% [64-66], leukemia in infant twins is rare. Nonetheless, detailed cytogenetic and/or molecular studies have been possible in pairs of monozygous infant twins where both twins were affected [67-70]. Within pairs of infant twins, the ages at diagnosis of leukemia generally have been similar [65, 67-71]. Unique, identical, clonal molecular *MLL* gene rearrangements were first detected in cases of ALL [67-69], and then in AML [71]. The t(4;11)(q21;q23) or t(11;19)(q23;p13) occurred in most cases that were ALL [58, 67, 68, 70], whereas the AML in a pair of infant twins showed the t(11;22)(q23;q11) [71]. The nonconstitutional origin of the unique, identical, clonal *MLL* gene rearrangements has suggested that the translocations occur in utero and that leukemia metastasizes from one twin to the other via the placenta [67-69, 71]. The delineation of *MLL* gene rearrangements in twins as in utero events justifies research on prenatal exposures to environmental toxins, including maternal dietary DNA topoisomerase II inhibitors. Additional evidence for prenatal events in the genesis of leukemia in infants comes from the studies of *Gale et al.* [23]. By polymerase chain reaction (PCR) amplification of genomic DNA from routine Guthrie neonatal bloodspots, these investigators showed that the leukemia-specific t(4;11)
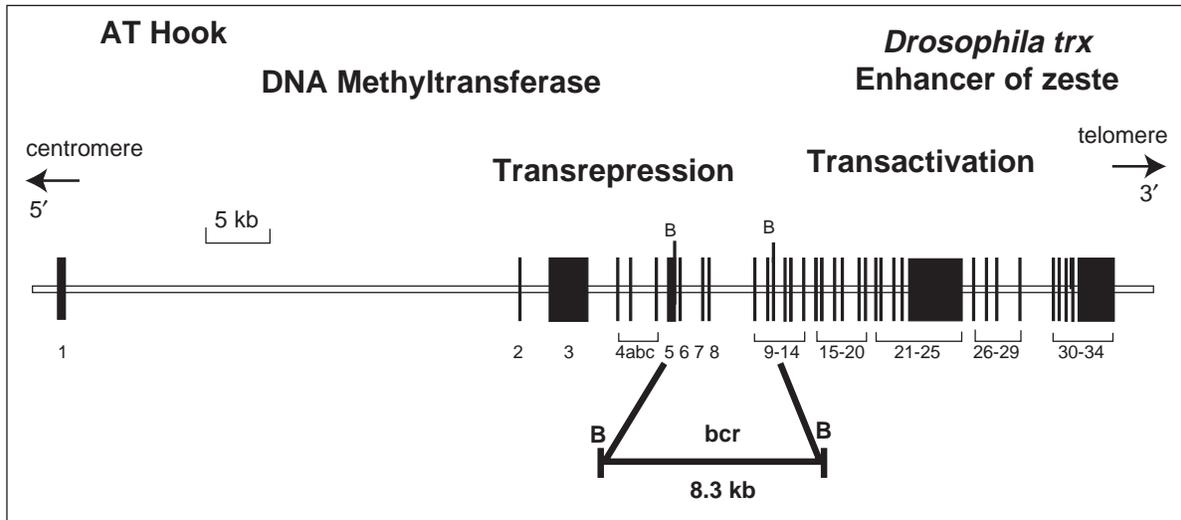
Figure 1. **MLL (ALL-1)** *genomic structure (adapted from [74], with permission). The translocation breakpoints occur within an 8.3 kb breakpoint cluster region (bcr). B (bold) indicates* BamHI *restriction enzyme sites that define the bcr. The* MLL *protein contains several structural motifs that suggest a function in the regulation of transcription of other genes [75-79]. The regions of the gene that encode these motifs are shown. Included are the AT hook motifs for binding to the minor groove of DNA and the DNA methyltransferase domains in the more 5′ region in exons 3 and 4b-5, respectively [74]. A transrepression domain spans exons 3-7, and a zinc finger domain spans exons 8-13; translocation breakpoints in the bcr may affect these regions [74]. Exons 18-20 of* MLL *encode additional zinc fingers, exon 25 encodes a transactivation region, and exons 30-34 are regions of homology to* Drosophila Trithorax *and* Drosophila Enhancer of zeste *[74]; these regions would be absent from the protein product of the der(11) chromosome with a translocation breakpoint within the bcr.*

translocations were already present at the time of birth in patients diagnosed with ALL from five months to two years of age [23].

PATHOGENESIS OF LEUKEMIAS WITH TRANSLOCATIONS OF THE *MLL* GENE AT CHROMOSOME BAND 11Q23

Two different murine models have suggested that the *MLL* gene plays an important role in both normal and malignant hematopoiesis. *Hess et al.* generated an *Mll* knock-out mouse and found defective yolk sac hematopoiesis in the *Mll*-null murine embryos [72]. A block in hematopoietic differentiation in *Mll*-null embryonic stem cells has also been observed [73]. These observations support a major role of *MLL* in the regulation of hematopoietic differentiation. The introduction of the t(9;11) translocation in the knock-in mouse resulted in leukemia after a latency of about one year, indicating that the *MLL* gene plays a pivotal role in leukemogenesis as well [21].

The *MLL* gene is 90 kb long, contains 36 exons, and encodes a 3969 amino acid protein [74]. The gene alternatively was called *HRX* and *Htrx-1* for its homology in the 3′ region to the *Trithorax* gene that controls Drosophila thoracic body segmentation [75, 76]. Figure 1 shows the *MLL* genomic structure and the breakpoint cluster region (bcr) disrupted by the translocations. The MLL protein contains structural motifs that suggest a function in the regulation of transcription of other genes [75-79]. *Yu et al.* determined that *MLL* is a positive regulator of *Hox* gene expression [80].

Figure 2 shows the chromosomal breakpoints in a common translocation and the two derivative chromosomes produced in the translocation process. Approximately two-thirds of *MLL* gene translocations are identified by standard cytogenetic techniques; the remainder are detected only by molecular analysis or by fluorescence in situ hybridization (FISH) analysis using *MLL*-specific probes [11]. The translocation breakpoints in leukemia in infants and in DNA topoisomerase II inhibitor-related cases are distributed throughout the same 8.3 kb bcr between *MLL* exons 5-11 [10, 79, 81-86]. At the molecular level, the breakpoints are in introns. Several of the translocation breakpoints, both in *MLL* and in the partner DNAs, are either within or near sequences in the introns called *Alu* repeats, suggesting that these sequences may be of importance in joining *MLL* with its translocation partners [84, 87].

MLL gene translocations involve about thirty different partner genes [69]. Translocations of *MLL* with sixteen partner genes have been characterized so far [71, 88-104] (Table 2). The partner genes encode protein products of several different types. The *AF-4* gene at chromosome band 4q21, which is a member of a transcriptional transactivating gene family, is the most common partner gene of *MLL* in ALL [40, 89, 105-107]. The *AF-9* gene at chromosome band 9p22 and the *ENL* gene at chromosome band 19p13 are also common partner genes. *AF-9* and *ENL* also encode transcription factors [89, 90].
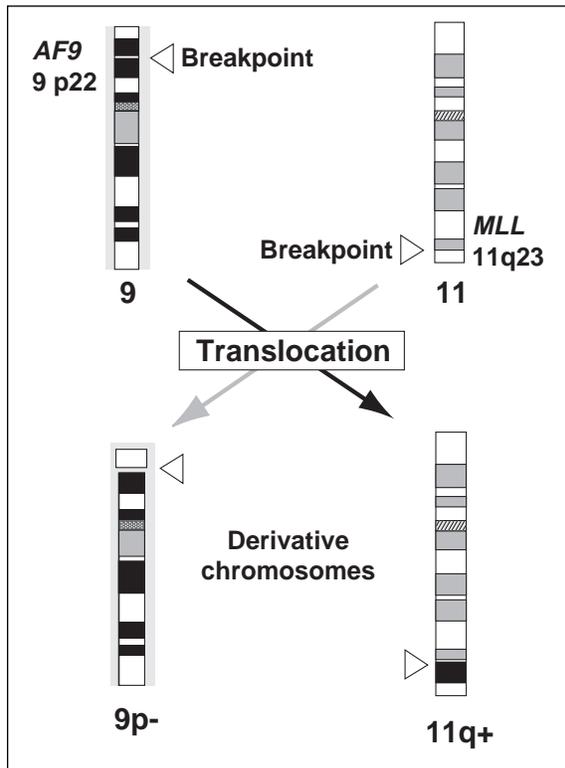
Figure 2. Cytogenetic ideograms showing chromosomal break-points in a t(9;11) translocation and the two derivative chromsomes produced in the translocation process.

Table 2. Partner genes of *MLL*		
Gene	**Location**	**Function**
AF4	4q21	Transcription factor
AF6q21	6q21	Forkhead transcription factor
AF9	9p22	Transcription factor
AF10	10p12	Transcription factor
ENL	19p13	Transcription factor
AFX1	Xq13	Forkhead transcription factor
AF17	17q21	Transcription factor
ELL	19p13	Poly (ADP-ribose) polymerase DNA binding domain
EEN	19p13	SH3 domain-containing protein
AF1p	1p32	Cytoplasmic phosphoprotein
AF6	6q27	Cell-cell junction protein
AF5α	5q12	Nuclear localization motif, leucine zipper motif, alpha-helical coiled-coil domain
AF1q	1q21	Cytokine motif
CBP	16p13	Histone acetyltransferase
ABI-1	10p11.2	Abl binding protein
hCDC*rel*	22q11.2	GTP binding protein
MLL	11q23	Transcription factor

The involvement of myriad partner genes has made PCR-based cloning of the translocation breakpoints difficult because many involve either partner genes that have not yet been cloned or uncharacterized intronic regions of known partner genes. Panhandle PCR and a variant of that method, both of which attach known *MLL* sequence to the unknown 3′ partner gene and amplify a stem-loop template schematically shaped like a pan with a handle, offer new strategies to clone the breakpoints [71, 87, 108, 109]. Figure 3 shows an example of an *MLL* translocation breakpoint characterized in this manner [108].

Similar partner genes appear to be involved in leukemias in infants and in the treatment-related cases, but several less commonly occurring partner genes such as the CREB-binding protein (*CBP*) gene at chromosome band 16p13.3, the *p300* gene at chromosome band 22q11, and *AF6q21* were discovered in treatment-related cases and have not yet been reported as translocation partners in leukemia of infants [98, 99, 101, 103, 110]. The hCDC*rel* partner gene at chromosome band 22q11.2 found in AML of infant twins is in the genomic region of deletion of the DiGeorge and velocardio-facial syndromes, which are constitutional disorders [71]. The translocations can be three-way, complex translocations that fuse *MLL* with two different partner genes such as *AF-6* and *AF-5α*, as was found in the FAB M5a leukemia of one infant [97]. In addition to the numerous translocations, partial duplication of several exons of the *MLL* gene causes *MLL* gene rearrangement within the bcr [87, 111-114].

In general, chromosomal translocations lead to leukemia either by gene activation or gene fusion. Gene activation occurs when the translocation results in the placement of a gene in proximity to the regulatory elements of another gene, causing transcriptional activation. In contrast, gene fusion occurs when the translocation results in the formation of a chimeric messenger RNA (mRNA) and a chimeric onco-protein [115]. *MLL* gene translocations are believed to be leukemogenic by the mechanism of gene fusion rather than by gene activation [115]. The der(11) chromosome uniformly yields a fusion transcript which encodes a fusion protein consisting of the amino terminus of MLL and the carboxy terminus of the translocation partner [115-118]. However, in contrast to the der(11) chromosome, the fusion gene on the other derivative chromosome resulting from the translocation may or may not be expressed. For example, in one study of 23 cases of pediatric ALL with t(4;11), a der(11) transcript was detectable by reverse transcriptase PCR (RT-PCR) in all cases and a der(4) transcript was detectable in 84% [116]. In a combined adult and pediatric study, the der(4) transcript was present in 65% of cases with *MLL-AF-4* mRNAs [119]. Fusion genes involving the 5′ region of *AF1p, AFX1, CBP* or p300 and the 3′ region of
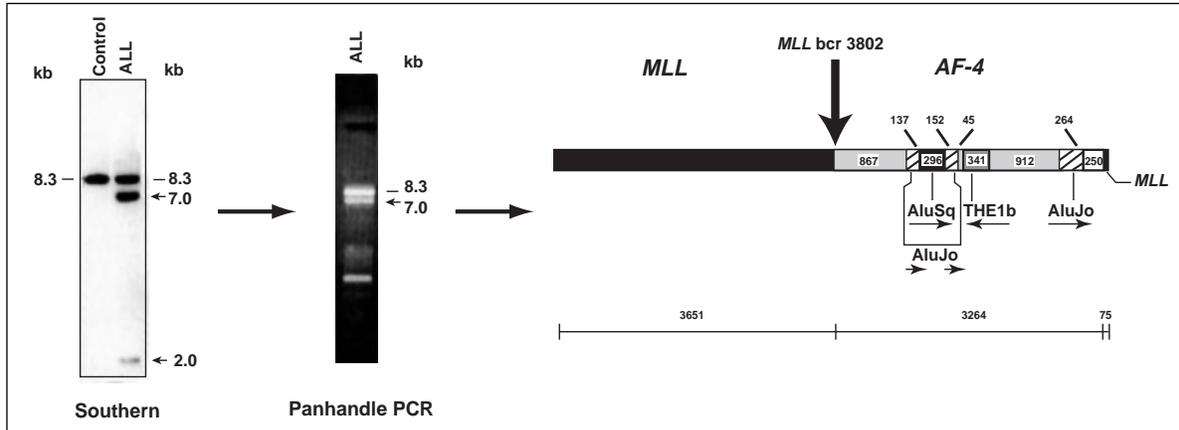
Figure 3. Characterization of MLL *genomic translocation breakpoint by panhandle PCR in a case of ALL in a three month-old girl where karyotype was unsuccessful (adapted from [85, 108], with permission). Southern blot analysis of* Bam*HI-digested genomic DNA with B859 probe from the* MLL *bcr detected the normal allele, which appears as the 8.3 kb fragment (dash), and the two rearranged fragments (arrows) representing both derivative chromosomes that resulted from the translocation (left) [85]. Panhandle PCR was performed to isolate the translocation breakpoint on the der(11) chromosome (middle); two products were obtained, an 8.3 kb product from the normal allele (dash), and a 7.0 kb product from the der(11) chromosome (arrows). The 7.0 kb product containing the translocation breakpoint on the der(11) chromosome was subcloned and sequenced. The sequence findings are summarized at right. Panhandle PCR attaches known* MLL *sequence to the unknown 3′ partner gene and, therefore, there was* MLL *sequence at both ends. The* MLL *breakpoint was found at position 3802 in intron 8 of the bcr (bold arrow) [108]. Further evaluation of the sequence of the partner DNA at the breakpoint junction and RT-PCR analysis of RNA from the leukemia (not shown) indicated that the partner DNA was a previously uncharacterized intronic region of the* AF-4 *gene [108]. The* AF-4 *intronic region was rich in various repetitive DNA sequences, including Alu and THE1b elements, in the vicinity of the* AF-4 *translocation breakpoint [108]. Numbers indicate sizes of regions in the sequence in base pairs.*

MLL on der(other) chromosomes also are expressed [88, 98, 99, 102, 103]. More often, however, only der(11) transcripts have been examined [9, 79, 87, 108].

Even in cases where there is partial duplication of several exons of the *MLL* gene, fusion transcripts are produced [87, 111-114]. Thus, in considering *MLL* partial duplications as a special kind of translocations, *Schichman et al.* proposed that *MLL* gene translocations are leukemogenic by a dominant negative mechanism in which the amino terminus of MLL is uncoupled from the remainder of the protein, leading to the formation of inactive MLL protein complexes [115]. Additional studies are required to fully understand the role of the many MLL fusion proteins in leukemogenesis.

INTERFERENCE WITH DNA TOPOISOMERASE II IN THE GENESIS OF TRANSLOCATIONS

DNA topoisomerase II catalyzes the relaxation of supercoiled DNA through a mechanism of transient cleavage and religation of both strands of the double helix [59, 120, 121]. Epipodophyllotoxins are called DNA topoisomerase II inhibitors because they decrease the rate of religation, causing chromosomal breakage [121-127]. Previously, we observed a correspondence between in vitro DNA topoisomerase II cleavage sites and the *MLL* genomic translocation breakpoint in the AML of an infant male as well as the leukemia-associated translocation breakpoints in two additional de novo cases [128].

This correspondence suggests that the repair of DNA topoisomerase II-mediated chromosomal breakage occasionally may result in translocations [128]. Genomic sequence analysis also has suggested potential DNA topoisomerase II recognition sites in the vicinity of *MLL* genomic breakpoints [84].

Maternal exposure to dietary DNA topoisomerase II inhibitors has been implicated as a risk factor for leukemia in infants, as described above [60]. Abasic sites, the most common form of spontaneous damage to the chemical structure of DNA, are characterized by the loss of a base [129]. Apurinic and apyrimidinic sites are the two kinds of abasic sites [129]. Abasic sites also increase DNA topoisomerase II cleavage [130-132]. This led *Kingma et al.* to propose that abasic sites may disrupt DNA topoisomerase II and lead to translocations [133]. Interference with DNA topoisomerase II, whether by DNA topoisomerase II-targeted anti-cancer drugs, dietary substances, or spontaneous abasic sites, may be the shared feature in treatment-related leukemia and leukemia in infants.

While demonstration of a correspondence of some *MLL* genomic translocation breakpoints with functional DNA topoisomerase II cleavage sites may support a role of DNA topoisomerase II as mediator of the chromosomal breakage that results in translocations, DNA duplications and DNA insertions have been observed at *MLL* translocation breakpoint junctions [82, 128, 134, and *Felix et al.*, unpublished]. These findings suggest a complicated translocation mechanism that

involves chromosomal breakage—possibly by DNA topoisomerase II, further processing, and ligation of the broken ends by DNA repair [128, 134, and *Felix et al.*, unpublished].

It has also been suggested that the VDJ recombinase system, which mediates immunoglobulin (Ig) and T-cell antigen receptor (TCR) gene rearrangements, might mediate *MLL* gene translocations [81]. However, the DNA sequence specificity for VDJ recombinase recognition is stringent [135] and, to date, no perfect signal sequences for the VDJ recombinase have been identified at the *MLL* genomic breakpoints. In addition, imperfect homologies with enzyme recognition sites or the presence of repetitive DNA sequences have suggested potential involvement of TRANSLIN and χ-like elements, respectively [79, 136]. Nonetheless, there is general agreement that it is not possible to ascertain the translocation mechanism from genomic sequences alone.

Site-specific DNA cleavage within the 3′ *MLL* genomic bcr also occurs as part of higher-order chromatin fragmentation during the initial stages of apoptosis [137]. It was shown more recently that this 3′ site of cleavage is not DNA topoisomerase II-induced [138]. Since the translocation breakpoints are heterogeneously distributed throughout the bcr and are not necessarily in proximity to this 3′ site, its significance with respect to translocations remains controversial [138].

ADDITIONAL GENETIC CHANGES IN LEUKEMIAS WITH *MLL* GENE TRANSLOCATIONS

Whether the protein products from the translocations are sufficient for leukemic transformation has been unresolved. The latency to onset of leukemia in the murine knock-in model of the t(9;11) translocation corroborates observations in the human that latency occurs [21]. One interpretation of the latency in both the mouse and human has been that full leukemogenesis requires additional genetic changes besides the translocations [21, 23, 67]. Detection of *MLL* partial duplications in the peripheral blood and marrow of normal adult subjects and *MLL-AF-4* fusions in normal fetal liver and normal infants' marrow also may suggest that the leukemia-associated translocations alone are insufficient [22, 139]. p53 mutations, *Ras* mutations, and p16 mutations are present in some cases, but none are consistent alterations [140-144]. Thus, the necessity for additional genetic changes and the determination of which changes are important are as yet uncertain.

Ikaros is a DNA-binding protein required for normal lymphoid development. Knock-in mice carrying abnormal isoforms of Ikaros that lack the DNA-binding portion of the protein develop leukemia three to six months after birth [145]. Similar abnormal Ikaros isoforms were recently identified in seven cases of infant ALL with t(4;11) or t(11;19) [145]. Thus, disruption of the Ikaros gene is an additional alteration in ALL in infants [145].

PRESENTATION AND NATURAL HISTORY OF ALL IN INFANTS

At initial diagnosis, ALL in infants is characterized by a median white blood cell count of $>50 \times 10^9/l$, frequent hepatosplenomegaly, and involvement of the central nervous system (CNS) [2, 4, 10, 12-14, 24]. Fourteen percent to 41% of infants have CNS disease at diagnosis, compared with approximately 5% of children [12, 14, 34, 146]. Leukemia cutis and chloromas, which usually are associated with AML, may occur in ALL in infants. These archetypal clinical features of ALL in infants occur with *MLL* gene translocations [10, 34, 146].

The FAB morphology is L1 more often than L2 [12]. Occasionally, the lineage is ambiguous, mixed, or morphologically and immunophenotypically biclonal, with lymphoid and myeloid populations present side by side [2, 13, 147-149]. The characteristic TdT+, CD19+, HLA-DR+, CD10− immunophenotype is that of a minimally differentiated, early B-cell precursor [4, 13, 34, 35, 37, 146]. The myeloid-associated antigens CD33 and CD15 are sometimes expressed [13, 34, 148]. Twenty percent of cases of ALL in infants without *MLL* gene translocation are characterized by a clinical presentation and TdT+, CD19+, CD24+, HLA-DR+, CD10+ immunophenotype more typical of B-lineage ALL in children [14]. T-cell ALL is exceptional in infants compared with that in children, where T-cell ALL accounts for up to 20% of ALL [150]. Expression of NG2, a chondroitin sulfate proteoglycan expressed on human melanoma cells and on human leukemic blasts, correlates with poor outcome and with translocations of chromosome band 11q23 in ALL in infants [151, 152].

Ig heavy chain (Ig-H) genes, which are rearranged in nearly all cases of B-lineage ALL in children, are rearranged in about two-thirds of cases of ALL in infants, suggesting that the target cell for transformation may be less mature [153, 154]. TCR genes are most often germline, but occasionally they are rearranged [13, 153]. The t(4;11) translocation is the most common translocation in ALL in infants [9, 10, 24, 26, 28, 155], followed by the t(11;19) [1, 156-158]. In cases with t(4;11), Ig-H and Ig light chain (Ig-L) genes can be rearranged or germline and Ig gene rearrangements can occur during subclone evolution [13, 148, 159, 160]. The t(5;15)(p15;q11-q13) is also a recurring chromosomal abnormality in infant ALL [26].

ALL in infancy is clinically aggressive, and spontaneous remission is uncommon. There is a single case report of spontaneous remission after marrow relapse in one twin of a pair of monozygous twins, both with congenital ALL associated with t(4;11), but the spontaneous remission was followed by a second relapse five months later [70].

PROGNOSTIC VARIABLES IN ALL IN INFANTS

High white blood cell count, younger age, bulky extramedullary disease, CNS disease at diagnosis, and *MLL*
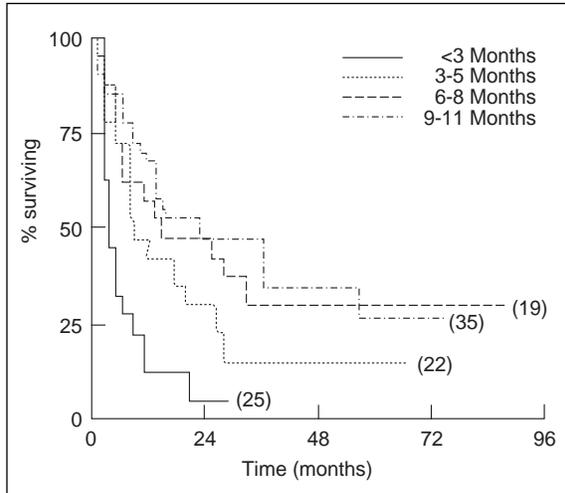
Figure 4. Relapse-free survival of infants with ALL by age at diagnosis (used with permission from [12]).

Figure 5. EFS curves for ALL in infants by karyotype (used with permission from [14]).

gene translocations are significant unfavorable characteristics [3, 6, 10, 12, 14, 34, 146]. Figure 4 shows the effect of age on outcome. Lack of CD10 expression, but not expression of myeloid-associated antigens, is associated with poor outcome [4, 14, 34, 146, 161, 162]. Treatment outcomes are similar in cases with and without CD13 and/or CD33 myeloid antigen positivity [162]. The adverse effect of CD10 negativity is due to its association with t(4;11) translocations [14]. In contrast, the CD10$^+$, CD19$^+$, CD34$^+$ B progenitor immunophenotype, present in about 20% of cases, identifies a subset of infants with more favorable event-free survival (EFS) [14, 161]. The probability of an *MLL* gene translocation and the probability of poor outcome both are greatest in the younger infants (Figure 4) [12, 14, 34, 146]. As in other age groups, a slow early response to therapy, defined as $\geq$ 25% residual blasts in the marrow on day 7 or day 14 of induction, is associated with inferior EFS [14, 163].

Cytogenetic evidence of the t(4;11) translocation in ALL in infancy confers a poor prognosis [9, 10, 14, 24, 28, 34]. In one large study of 183 cases of acute leukemia with t(4;11), age had an important impact on the outcome; EFS was 73.2% for children two to nine years of age compared with 32.4% for infants [164]. While somewhat controversial, the presence of an RT-PCR-detectable *MLL-AF-4* fusion transcript may not be as unfavorable as cytogenetic evidence of the t(4;11) [22]. Whether all translocations involving *MLL*, and the t(11;19) in particular, confer the same unfavorable prognosis as the t(4;11) is also controversial [1, 9, 14, 26, 28, 146, 156, 165]. In a study of 35 pediatric cases of ALL with t(11;19) and molecular evidence of the *MLL-ENL* translocation, the EFS was worst for infants with B-lineage ALL less than one year old at diagnosis,
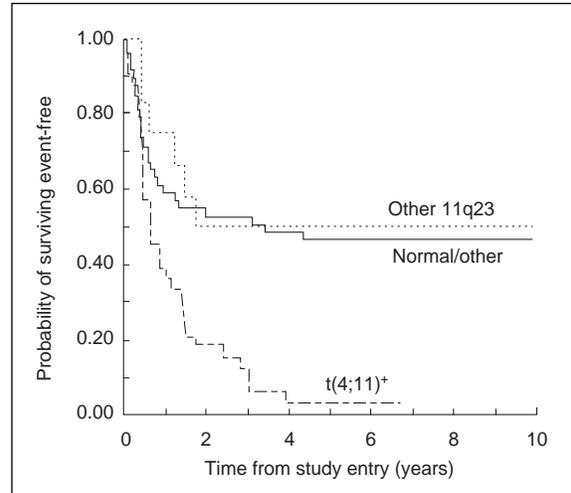
while the T-cell phenotype, which is rare in infants, was favorable [165]. The lack of *MLL* gene translocation was associated with 80% EFS in a previous study conducted by the CCG [9, 10]. In larger studies of ALL in infants, EFS rates in cases without *MLL* gene translocation have been lower [4, 14, 24, 34, 36]. Nonetheless, although the t(4;11) remains unfavorable, in contrast to studies of one or two decades ago, translocations of band 11q23 other than t(4;11) and normal or other karyotypes in infant ALL now are associated with ~50% EFS rates [14]. This has led to the conclusion that the specific translocation t(4;11), but not other translocations of chromosome band 11q23, is associated with poor prognosis in infant ALL [14, 26]. Figure 5 shows the impact of the t(4;11) translocation and other translocations of chromosome band 11q23 on treatment outcome for infants with ALL treated by the CCG.

TREATMENT AND TREATMENT OUTCOME IN ALL OF INFANTS

In the mid 1970s, the five-year EFS in infants less than one year old who were diagnosed with ALL was about 20%, while the cure rate for childhood ALL approached 50% [12]. The few infants who survived sustained substantial neurologic damage from the cranial irradiation used to prevent or treat CNS disease [6, 12]. Today, infants continue to have the worst prognosis of all pediatric patients diagnosed with ALL. Although marrow relapse is the most common first event, extramedullary relapses, combined relapses, and toxic deaths are all more common than in children [4, 14, 34].

Both the poor treatment outcome and the daunting CNS complications of standard ALL regimens led to specialized approaches. The CCG-107 regimen eliminated the therapeutic

and prophylactic cranial irradiation, and infused very high-dose methotrexate at $33g/m^2$ for systemic therapy and to treat the extramedullary sites [14]. Anthracyclines were added in induction [14]. This strategy increased the remission induction rate from 75% to >95% and increased the four-year EFS to 33% [14]. The successor protocol, CCG-1883, further intensified post-induction chemotherapy with the addition of systemic cytarabine, L-asparaginase, and cyclophosphamide and intrathecal cytarabine to consolidation, resulting in a four-year EFS of 39% [14]. The marrow, nonetheless, remained the primary site of relapse, with low isolated CNS relapse rates without CNS irradiation [14]. Twenty-eight survivors of this cohort underwent extensive neurodevelopmental testing at a mean of five years after ending treatment. The results were in the average range for all parameters, indicating that the goal of reducing the morbidity of therapy had been achieved, with some improvement in survival [166].

The modestly improved outcome with high-dose chemotherapy led to the current strategy of bone marrow transplantation in first remission for infants with evidence of *MLL* gene translocation in their leukemic cells, whether by cytogenetic, FISH, RT-PCR, or Southern blot analysis. The Medical Research Council of the United Kingdom concluded that there was excessive treatment-related mortality and a high rate of relapse among 14 infants prospectively treated with an HLA-matched transplant while in first remission [4]. In contrast, *Hilden et al.* reported three survivors among seven infants treated in this manner while in either first or second remission and concluded that bone marrow transplantation may be the treatment of choice, or at least the treatment most worthy of consideration [9].

Bone marrow transplantation in first remission for this disease has theoretical and real problems. First is the practical limitation that few infants have HLA-matched related donors, necessitating the use of alternative donor transplants, which have greater risks [167-176]. Second, there is reluctance to use total-body irradiation (TBI) in patients less than one year old, while efficacy of cytoreductive regimens that do not contain TBI has not been established in the management of ALL [177]. Available data from infants treated with TBI suggest that short stature is a consistent late effect, while infants who have had neither CNS disease nor prior cranial irradiation do not experience the same degree of neurodevelopmental effects as infants treated with prior cranial irradiation [178-180]. In general, bone marrow transplantation is more successful in AML than in ALL, where an advantage over chemotherapy has been shown for early relapse only [181].

Both bone marrow transplantation and aggressive chemotherapy offer alternatives for current and future trials on the treatment of ALL in infants. The CCG and Pediatric Oncology Group together reported on a pilot study of induction intensification for ALL in 18 infants in which the use of continuous, intensive, multiagent chemotherapy without interim maintenance in the first year achieved a 60% EFS at two years [182]. The current practice of allogeneic bone marrow transplantation after reinduction if there is molecular evidence of an abnormality at chromosome band 11q23 further builds upon the intensification strategy. The molecular assays used include Southern blot analysis for rearrangement of the *MLL* genomic bcr and RT-PCR analyses using gene-specific primers to detect the fusion transcripts involving *MLL* and its more common partner genes. A relevant caution regarding interpretation of the diagnostic tests is that cells undergoing apoptosis may exhibit site-specific chromosomal fragmentation within *MLL*, as described above; this appears as pseudo-rearrangements on the Southern blot [183]. This phenomenon is sometimes seen in cells left at room temperature for prolonged periods before processing and may confound the genotype results [183]. In *Bam*HI-digested DNA, the pseudo-rearrangements are 6.8 kb and 1.5 kb in size [183].

PRESENTATION AND NATURAL HISTORY OF AML IN INFANTS

AML in infants is also characterized by hepatosplenomegaly, leukemia cutis, CNS disease, and high white blood cell count at diagnosis (Table 1) [8, 34, 184-186]. Despite the high tumor burden, infants are less likely than children to develop cerebrovascular accidents and pulmonary leukostasis (*Lange*, unpublished). About half of AML in infants is of FAB M4 or FAB M5 morphology, and there is translocation of the *MLL* gene at chromosome band 11q23 and CD14 reactivity in most FAB M4 and M5 cases [5, 34, 187-190]. The t(9;11) translocation is the most common translocation in AML in infants, followed by the t(11;19) [35, 39, 191, 192]. The FAB M4 or M5 cases without *MLL* gene translocation include leukemias with inv(16), which are FAB M4 with eosinophilia (FAB M4eo), and leukemias with monosomy 7, random cytogenetic abnormalities, or normal karyotypes [35, 41, 191-193].

Although the time from diagnosis to death in AML of childhood was about one to two months prior to the use of combination chemotherapy [194], rare neonates experienced spontaneous regression [195-197]. Most were affected with Down syndrome or had mosaicism for trisomy 21. A TMS, which is a self-limited form of AML, occurs in 20% of neonates with Down syndrome or mosaicism for trisomy 21 [45]. Similarly, a TMS may occur in neonates with Noonan syndrome [48]. There also are reports of spontaneous remission of a disease that is indistinguishable from AML in normal neonates [196, 198, 199]. We have observed transient regression of AML with translocation of chromosome band

11q23 in two infants (*Lange et al.*, unpublished). In most cases where there has been spontaneous remission, AML will recur, usually within months or, less often, years.

Older infants and young children with Down syndrome may develop MDS or overt AML, which usually is the FAB M7 acute megakaryoblastic type [45]. Infants with NF1 and other constitutional disorders are predisposed to JMML [41, 46, 200, 201] and to monosomy 7 syndrome [41, 202]. These disorders are clinically aggressive and are not characterized by spontaneous regression [42].

PROGNOSTIC VARIABLES IN AML IN INFANTS

A white blood cell count of $>50 \times 10^9$/l in AML is unfavorable at all ages [184]. FAB M4 and FAB M5 AML in infants previously were considered unfavorable morphologic subtypes [186], but in more recent studies they are not [34, 203, 204]. While *Pui et al.* found male gender unfavorable, with EFS rates of 61% ± 16% for 13 infant girls and 8% ± 6% for 12 infant boys [34], gender has not been a significant prognostic variable in other studies [12, 14]. In contrast to ALL, NG2 expression is not as well correlated with *MLL* gene translocations in AML in infants and is not associated with poor outcome [152, 205].

Some groups have reported that the presence of the t(9;11) translocation has a favorable effect, while others find that this specific translocation does not affect the outcome [206-208]. The outcome for patients with AML with t(9;11) may depend on both age and WBC, since a large study on this translocation found the best outcome for patients one to nine years old with low WBC [209]. There is agreement that *MLL* gene translocations involving certain partner genes confer an unfavorable prognosis, [157, 210, 211], while for other translocation partners the response to treatment varies [212]. In contrast to ALL, infancy itself is not prognostically unfavorable in AML [34, 184, 204, 213-215]. This difference may be due to the high incidence of *MLL* gene translocations and FAB M4/M5 morphologies in children up to four years old, the combination of more and less favorable *MLL* gene translocations in AML, and the relatively poor outcome for most of AML outside the infant population. The differences in prognostic factors among treatment regimens further indicate that therapy has a major impact on prognosis [214-219].

THERAPY OF AML IN INFANTS

Odom et al. reported unusual success in four of five infants with monoblastic leukemia treated with epipodophyllotoxin-based chemotherapy [220]. Although *Kalwinsky et al.* suggested that AML with the t(9;11) was particularly responsive to epipodophyllotoxin treatment, subsequent trials conducted by the St. Jude Children's Research Hospital did not reproduce the same results [191]. In the CCG-213

study in which 17 infants with monoblastic leukemia received epipodophyllotoxin during induction, the induction rate was satisfactory, but there was no impact on the long-term EFS (*Lampkin et al.*, personal communication).

In studies on AML conducted by the CCG, FAB M4 and FAB M5 morphologies and translocations of chromosome band 11q23 did not affect prognosis, but treatment with intensively-timed induction chemotherapy and HLA-matched related marrow transplantation was associated with a trend toward improved EFS [204]. In a study of 40 infants less than two years old who underwent bone marrow transplantation for AML or MDS, neurologic development in survivors was appropriate for age whether the preparative regimen included cyclophosphamide and busulfan or cyclophosphamide and TBI, but TBI had adverse effects on growth [221]. However, because of the possible favorable effect on outcome of the t(9;11), whether marrow transplant in first remission is necessary for the management of AML with t(9;11) remains to be determined. It seems reasonable to continue to enroll infants on experimental protocols for AML in children, since the results for infants and children have been the same. Because of the high probability of spontaneous regression in neonates with Down syndrome and TMS [45], supportive care alone is recommended.

FUTURE DIRECTIONS

Leukemia in infants is unique. Through studies of exposures to DNA topoisomerase II inhibitors, studies of leukemias in infant twins and molecular analyses of *MLL*, the etiology and pathogenesis should become clearer. While the clinical and molecular similarities between ALL and AML with *MLL* gene translocations have suggested that the optimal therapy for both diseases might be the same, such a combined approach for leukemia in infants has not yet been tested. The NG2 antigen or the fusion proteins from the translocations may serve as potential targets for less conventional, albeit more challenging, future trials. In cases without *MLL* gene translocations, the associations of specific constitutional disorders with AML and MDS may provide the clues to additional regions of the genome that are important in leukemic transformation.

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