Although seemingly rare, leukemia is the second most common cancer in children less than 1 year of age. This represents 5 to 10% of childhood leukemias, with an incidence of 44 per million “infants” or approximately 200 infants diagnosed with leukemia in the United States each year. For unclear reasons, this incidence appears to be rising over the past 20 years. Infant leukemias include subsets of both acute lymphoblastic and acute myeloblastic leukemias (ALL and AML) with unique clinical and biologic features, including mixed lineage leukemia (MLL) rearrangements. The historical definition of “infant” leukemia is based on the observation that children less than 1 year of age respond poorly to standard therapies for older children with leukemia. In recent years, we have gained an appreciation for the unique biologic nature of infant leukemias and struggled with the poor outcome of our youngest patients with ALL, as well as with the public health implications of emerging environmental and dietary risk factors. In the past 2 years, four major trials have reported improved outcomes in infant ALL, bringing new hope and greater understanding. These studies will encourage new research opportunities and intense discussion. In this review, we hope to introduce you to the current knowledge and discussions in this field.

Leukemia can present at anytime, beginning in utero. Fetal leukemia has been detected by umbilical blood sampling as early as 33 weeks of gestation when ultrasound may detect polyhydramnios, hydrops, and/or fetal hepatosplenomegaly. Such congenital leukemias are a significant cause of stillbirth and are often related to genetic predispositions, such as Down and Noonan syndromes. These syndromes, as well as infants with neurofibromatosis 1 mutations, may have physical findings consistent with their disorder including facial, cardiac, and skin lesions. Interestingly, 50% of infants with leukemia in the neonatal period present with leukemia cutis (“blueberry muffin” baby), which appear as blue, purple, brown, or red nodules, and/or hepatosplenomegaly. Such subcutaneous nodules can also represent disseminated neuroblastoma or, quite rarely, extramedullary hematopoiesis related to severe hemolytic disease of the newborn. Similarly, hepatosplenomegaly is quite common in infant leukemia but is also a manifestation of disseminated neuroblastoma. Often pancytopenia resulting in pallor, petechia, or ecchymoses is present; however, these are not universal presenting signs. Rarely a “bulging” fontanelle can represent central nervous system (CNS) leukemia and/or intracranial bleeding due to thrombocytopenia.

As infants leave the neonatal period, the manifestations of their leukemia become more vague and more closely resemble leukemia in older children. However, CNS leukemia, hepatosplenomegaly, and cutaneous leukemia remain more common in children with leukemia throughout the first year of life. In addition, failure to thrive, fever, pallor, and petechiae are nonspecific symptoms of leukemia at any age.

Since many cases of infant leukemia do not present with overwhelming signs and symptoms, it is useful to remember that a complete blood count (CBC) is quite sensitive for leukemia. That said, leukemoid reactions related to infections, hemolytic disease, and hypoxia in the neonatal period can be difficult to distinguish based solely on a single CBC. Review by a pediatric hematologist may be helpful to determine if bone marrow aspiration is warranted. Immunohistochemical and cytogenetic assays can often be informative in these cases. Similarly, multilineage cytopenias with or without blasts warrant referral for further evaluation.
Infant ALL: Highest Risk in Our Smallest Patients

Infants represent 2 to 5% of pediatric ALL cases.\(^4,5\) The incidence of ALL rises sharply after the first year of life, peaking between ages 2 and 4 years (Fig 1).\(^1\) Infants often present with high white blood cell (WBC) counts at diagnosis (>300,000 per \(\mu\)L), and more frequently hepatosplenomegaly and CNS involvement compared with children >1 year old with ALL.\(^6,7\) Phenotypically, infant ALL is often early B-cell precursor (CD34\(^+\), CD19\(^+\)), lacking the CD10 antigen,\(^8,9\) while often expressing myeloid precursor antigens (CD15/CD65s)\(^10,11\) and myeloperoxidase RNA\(^12,13\) (Table 1). This suggests that these leukemias originate from very early B-cell progenitors with both lymphoid and myeloid features.\(^12\) This assertion is consistent with the relatively immature immunoglobulin rearrangements seen in infant ALL blasts.\(^14-16\)

In reports of infant ALL, CD10 negativity and age <3 to 6 months have been two of the strongest adverse prognostic factors.\(^10,17-21\) As noted above, CD10 negativity is associated with early B-cell precursors with myeloid features and this may indicate why these leukemias are resistant to standard ALL-based therapy.\(^22\) The incidence of infant leukemia is equally distributed across the first year of life.\(^9\) Infants less than 6 months of age at diagnosis have had poor event-free survival (EFS) from 8 to 40%, while those 6 to 12 months old at diagnosis have had better EFS from 40 to 71%.\(^18\) Although there is a slight excess of females in several case series, gender does not appear to influence outcome.\(^9,23\) Interestingly, WBC >50,000/\(\mu\)L at diagnosis, which is a strong predictor in older children with ALL in most reports, is only marginally predictive in infants with ALL.\(^9,17,18\) Even very high WBC (>300,000/\(\mu\)L), although predictive of poor outcome in some studies (26 versus 52% 4-year EFS),\(^9\) is not in others.\(^21\)

Infant AML: The Highest Incidence in Infants

Infants with AML comprise 6 to 20% of pediatric AML cases.\(^4,24\) Indeed the peak yearly incidence for childhood AML is in the first year of life.\(^7,25\) Although ALL is at least four times as common as AML in older children, AML has a slightly higher incidence than ALL in this age group, 25 versus 19 per million (Fig 1).\(^1,126\) As in infant ALL, infant AML presents with relatively high WBC counts, hepatosplenomegaly, CNS involvement, but distinct from ALL, frequent chloromas (granulocytic sarcomas) (Table 2).\(^5,27-29\)

Phenotypically, French-American-British types M4/M5 (myelomonocytic/malignant) and M7 (megakaryocytic) are more common in infants.\(^27,30\) A subset of infants with AML have preleukemia or constitutional syndromes that suggest heterogeneous etiologies for these cases. Indeed, approximately 10% of infants with AML have myelodysplastic syndrome with monosomy 7 or del(7q), or have Down or Noonan syndrome, or carry neurofibromatosis type 1 mutations, which all predispose to early AML.\(^5\) Infants with Down and Noonan syndromes may present from 30 weeks gestation to 6 months of life with transiently circulating blasts that are indistinguishable from megakaryocytic leukemia. This transient myeloproliferative disease (TMD) or transient leukemia is associated with specific mutations in the GATA1 gene.\(^31\) These infants may present with hydrocephalus, pleural effusions, and/or heart failure contributing to a 15 to 27% mortality rate.\(^32\) In addition, these circulating blasts may induce hepatic fibrosis, leading to addition morbidity and mortality.\(^32,33\) Over the course of 1 to 4 months, these blasts typically resolve spontaneously, while low-dose cytarabine has been shown to be effective in hastening the resolution of TMD. Unfortunately, as many as 33% will develop a nontransient leukemia in the first 3 years of life, requiring close follow-up.\(^32\) Similar to the transient myeloproliferative diseases of Down/Noonan syndromes, nonsyndromic congenital AMLs can spontaneously regress in up to 10% of cases, often following acute infection.\(^5,34,35\)

Once an infant develops leukemia, the only reproducible prognostic factor for infant AML is high WBC (>50,000 per \(\mu\)L) at diagnosis, a measure of tumor growth.
burden.\textsuperscript{17} In contrast to infant ALL, age does not appear to contribute to outcome in infant AML,\textsuperscript{17,27} and male gender may or may not predict worse outcome.\textsuperscript{17,25}

The dual lineage (B-myeloid) nature of infant ALL and the similar clinical and phenotypic characteristics of infant AML suggest a common etiology for infant leukemias.

**MLL Gene Rearrangement Defines the Majority of Infant Leukemias**

Although pediatric oncologists did not know it at the time, their observations in the \(<1\) year age group had identified a subset of leukemias in which the majority of children carry alterations in one specific gene. The MLL (also known as HRX or ALL1) gene was identified at the common translocation breakpoint in rearrangements involving chromosome 11q23.\textsuperscript{36-39} Since then, the MLL gene has been shown to be translocated and/or rearranged in \(~80\)% of infants with ALL and \(~50\)% with AML.\textsuperscript{5} In contrast, MLL rearrangements are only found in 2 to 8% and 10 to 20% of older children with ALL and AML, respectively.\textsuperscript{40-43} Interestingly, other translocations seen in older ALL patients are rare in infants with ALL, eg, t(12;21), t(1;19), t(9;22). It is important to note here that as many as 16 to 40% of MLL rearrangements are not detected by conventional cytogenetics, making interpretation of prognosis of individual translocation partners difficult to discern in studies based solely on cytogenetics. Since over 55 translocation partners exist, fluorescence in situ hybridization (FISH) is currently the standard method for detection of MLL rearrangements.\textsuperscript{23,44-46} However, Southern blot has higher sensitivity and can resolve unclear FISH results and therefore may be warranted if stratification is based on MLL status.\textsuperscript{47-49} Newer technology, such as the MLL FusionChip, may allow for accurate identification of MLL rearrangements and may facilitate the evaluation of prognostic significance in rare translocation partners.\textsuperscript{50} Of the translocation partners, MLL-AF4 is seen most commonly in ALL, and MLL-AF9 in AML (Table 3).\textsuperscript{23,51,52}

<table>
<thead>
<tr>
<th>TABLE 1. ALL in infants</th>
<th>Frequency</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender F:M</td>
<td>1.14:1 (1- to 2-fold)</td>
<td>9,43,87</td>
</tr>
<tr>
<td>WBC at diagnosis</td>
<td>Median: 93-102,000/µL</td>
<td>21,133</td>
</tr>
<tr>
<td>&gt;50,000/µL</td>
<td>63% (52-78%)</td>
<td>18,43</td>
</tr>
<tr>
<td>&gt;100,000/µL</td>
<td>48% (39-69%)</td>
<td>9,23,43</td>
</tr>
<tr>
<td>&gt;300,000/µL</td>
<td>28% (27-29%)</td>
<td>9,23</td>
</tr>
<tr>
<td>Hepatosplenomegaly</td>
<td>73-81%</td>
<td>18,177</td>
</tr>
<tr>
<td>CNS involvement at diagnosis</td>
<td>17% (9-50%)</td>
<td>9,18,23,43,168,177</td>
</tr>
<tr>
<td>CD10 negative</td>
<td>61% (43-76%)</td>
<td>9,18,43,53,168,178</td>
</tr>
<tr>
<td>CD34+ (stem cell)</td>
<td>60%</td>
<td>11</td>
</tr>
<tr>
<td>CD15+ (myeloid)</td>
<td>35-48%</td>
<td>11,53</td>
</tr>
<tr>
<td>CD65s+ (myeloid)</td>
<td>34%</td>
<td>11</td>
</tr>
<tr>
<td>Myeloperoxidase (RNA+/protein)</td>
<td>56-65%</td>
<td>12,13</td>
</tr>
<tr>
<td>CD33+ (myeloid)</td>
<td>11%</td>
<td>11</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TABLE 2. AML in infants</th>
<th>Frequency</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC at diagnosis &gt;100,000/µL</td>
<td>24-40%</td>
<td>27,132,133,179</td>
</tr>
<tr>
<td>CNS involvement at diagnosis</td>
<td>12-36%</td>
<td>27,29,56,61,179</td>
</tr>
<tr>
<td>Chloroma/granulocytic sarcoma</td>
<td>4-50%</td>
<td>179,180</td>
</tr>
<tr>
<td>FAB M4/M5, monocytoid</td>
<td>58-95%</td>
<td>27,43,179</td>
</tr>
<tr>
<td>FAB M7 t(1;22) (non-Downs)</td>
<td>6-28%</td>
<td>29,43</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TABLE 3. MLL rearrangements found in infant leukemias</th>
<th>ALL</th>
<th>AML</th>
</tr>
</thead>
<tbody>
<tr>
<td>MLL rearrangement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any MLL 11q23 rearrangement</td>
<td>80% (63-90%)</td>
<td>50% (35-66%)</td>
</tr>
<tr>
<td>t(4;11) MLL-AF4</td>
<td>44-70%</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>t(11;19) MLL-ENL</td>
<td>12-25%</td>
<td>15%</td>
</tr>
<tr>
<td>t(9;11) MLL-AF9</td>
<td>4-12%</td>
<td>50%</td>
</tr>
<tr>
<td>Other 11q23</td>
<td>8-19%</td>
<td>35%</td>
</tr>
</tbody>
</table>

It is clear that MLL rearrangements are associated with poor prognosis in infant ALL.\textsuperscript{9,11,18,23,39,40,45,52,53} Two prior studies reported that t(4;11) translocations predicted a worse outcome than the other 11q23 groups.\textsuperscript{45,52} In Children’s Cancer Group (CCG)-1953, infant ALL samples were evaluated by cytogenetics, Southern blot, and reverse transcription–polymerase chain reaction to identify the most common translocation partners, AF4, ENL, and AF9.\textsuperscript{18} The 5-year EFS for all three ranged from 22
to 30% \((P = 0.77)\), while the less common “other 11q23” rearrangements had a 5-year EFS of 53% \((P = 0.03)\).\(^{18}\) Interfant-99 also found no difference between the common translocations (33-36%), while “other 11q23” led to a nonsignificant increase to 45% 4-year EFS.\(^{9}\) In contrast, a recent review of 212 cases of infant ALL with MLL rearrangements found no difference in outcome between various MLL subgroups, including the “other 11q23” group.\(^{19}\) Of note, “other 11q23” leukemias tend to have additional cytogenetic abnormalities that may imply a different role for MLL in these leukemias.\(^{54}\)

In contrast, MLL translocations in infants with AML have not predicted worse outcome.\(^{4,55}\) Interestingly, the t(9;11) translocation may even predict better outcome,\(^{56}\) while t(9;11),\(^{57}\) t(4;11), or t(11;19) may predict a favorable prognosis in older children with AML.\(^{58,59}\)

The name, Mixed Lineage Leukemia, describes the coexistence of both lymphoid and myeloid features including morphology and phenotype in infant ALL. It is the presence of MLL rearrangements that is associated with the CD10-negative B precursor phenotype, which often expresses the myeloid precursor antigens.\(^{11}\) Infants with MLL gene rearrangements (MLL-R) and the associated B-myeloid phenotype in infant ALL are associated with poor outcome (34-39% 4/5-year EFS), as noted above.\(^{9,18,23,45,53}\) In contrast, infant ALL cases without an MLL rearrangement (MLL germline or MLL-G) are 80 to 96% CD10 positive, without myeloid antigens,\(^{60}\) and resemble common precursor B-cell leukemia seen in older children. These MLL-G infants have a median age of 9 months (versus 4 months for MLL-R), present with a lower WBC counts (21,000 versus 168,000 per \(\mu L\)),\(^{23}\) and these infants have a significantly better 5-year EFS of 60 to 74%.\(^{9,18}\) Two trials from Japan have reported extremely high 89% 3-year\(^{40}\) and 95% 5-year\(^{60}\) EFS in small series of MLL-G infants, although the later cohort was atypical with a 10:1 male:female ratio.\(^{60}\) Nevertheless, it is evident that infants without an MLL-R have much better outcomes on intensified infant ALL protocols.

MLL rearrangements in infants with AML also define a particular phenotype including high levels of CD15 expression, as seen infant ALLs with MLL rearrangement.\(^{61}\) These cases tend to have French-American-British M4/M5 morphology (>90%) as well as high WBC at diagnosis.\(^{43}\) This suggests that MLL rearranged leukemias, either ALL or AML, may reflect a common biology and may have a common mechanism of leukemogenesis.

### How Does MLL Lead to Leukemia?

The MLL protein is a widely expressed transcription factor that is critical for normal hematopoietic differentiation.\(^{52,63}\) MLL fusion proteins have been shown to play a direct role in the induction of leukemia in mice.\(^{64}\) However, it is not known how the MLL fusion proteins contribute to leukemogenesis.\(^{55}\) The search for this mechanism has led to the discovery of three important pathways.

First, gene expression analysis of leukemia samples demonstrated that MLL-R ALLs define a unique subset that have consistently high expression of the fms-related tyrosine kinase-3 (FLT3) gene.\(^{66}\) Activating mutations of FLT3 are common in both pediatric and adult AML (20 and 30%, respectively) but are rare in pediatric ALL (1-3%).\(^{67-69}\) Surprisingly, 15 to 20% of MLL-R ALLs contain activating mutations in FLT3 and the majority have overexpression of this gene.\(^{70-72}\) It appears that FLT3 expression levels correlate with poor outcome in infants with MLL-R ALL.\(^{73}\) Importantly, FLT3 small molecule inhibitors, PKC412 and CEP-701, have been shown to induce apoptosis in the majority of MLL-R ALL patient samples.\(^{74,75}\) Furthermore, lestaurtinib (CEP-701) demonstrates synergy with several chemotherapeutics in infant ALL samples, making FLT3 inhibition a biologically rational therapeutic approach in infant MLL-R ALL.\(^{76}\)

Second, the HOXa9 and Meis1 genes are also overexpressed in MLL-R ALLs and AMLs.\(^{66,77-79}\) The Drosophila homologue of MLL, Trithorax, regulates Hox genes, and MLL is necessary for Hox gene expression in mice, suggesting a critical connection between MLL and the Hox family of genes.\(^{80}\) Meis1 is a frequently upregulated gene in leukemias and cooperates with Hox genes to activate the c-Myb oncogene, suggesting a mechanism for leukemogenesis.\(^{81,82}\)

A third observation is the frequent partial deletion of the Ikaros gene in infants with MLL-R ALL, leading to the expression of dominant-negative Ikaros isoforms.\(^{83}\) The dominant negative Ikaros isoform 6 has been correlated with t(4;11) MLL translocations and M4/M5 AML. Ikaros isoform 6 appears to provide a survival advantage in leukemia cells through upregulation of the anti-apoptotic Bcl-2 pathway.\(^{84,85}\) Importantly, these dominant negative Ikaros isoforms lead to
ALL in mice, suggesting that they play an important role in leukemogenesis.  

Understanding how these three pathways contribute to MLL-R leukemias may provide important therapeutic targets in infant leukemias.

Etiology: Risk Factors for Infant Leukemia

Infants are at increased risk of developing leukemia likely from a range of genetic circumstances and environmental factors. As in ALL in older children, white ethnicity has been associated with higher incidence of ALL in infants. In contrast, females may be at increased risk of ALL and equal risk in AML in non-infants. Inherited genetic alleles, such as those conferring reduced function of NAD(P)H:quinone oxidoreductase (NQO1), are more frequently seen in infants with leukemia, whereas one study reported a higher frequency of deletion of glutathione-S-transferase (GSTT1 and GSTM1) genes in the parents of infants with leukemia. The NQO1 and GST proteins detoxify many carcinogens and their absent or reduced function may lead to the accumulation of these toxins. Similarly, methylenetetrahydrofolate reductase (MTHFR) alleles with reduced function may be protective against translocations and leukemia. One study found that MLL-R infant leukemias rarely have these protective alleles. Additionally genetic syndromes such as Down, Noonan, and Turner syndromes, as well as trisomy 9, predispose to infant leukemia. These predisposing factors are primarily genetically determined and not easily amenable to intervention.

Interestingly, high birth weight (>4 kg) has also been associated with a 26% overall increased risk of childhood leukemia. While it is not clear why high birth weight is associated with an increased risk, it is notable that high birth weight is positively correlated with insulin-like growth factor-1 (IGF-1) levels. It is possible that these increased IGF1 levels may be particularly etiologically relevant for children who already have one genetic mutation present before birth. Of note, one recent study suggested a correlation between high birth weight (>4 kg) and MLL rearrangements. Further studies are needed to investigate the role of IGF1 in leukemia.

Importantly, the incidence of infant leukemia has risen ~2% each year over the past 20 years, suggesting an increasing environmental exposure(s). Evidence suggests that MLL translocations occur in utero and are present at birth in many cases. Therefore preconception and prenatal exposures have been suspected.

Through epidemiologic studies, many factors have been correlated with increased incidence of infant leukemias, including prior miscarriage, higher birth order, birth weight over 4 kg, maternal behaviors (lack of prenatal folate supplementation, anti-histamine use, metronidazole antibiotic use, estrogen use, dipyrone analgesic use, herbal medicine use, alcohol consumption, marijuana use, mind-altering drug use, propoxur insecticide exposure), paternal behaviors (smoking, pesticide exposure, mind-altering drug use), exposure to mold, and medical or environmental radiation. The evidence in support of these correlations must be carefully examined and confirmed, and the contribution of these factors to leukemogenesis must be explored.

One epidemiological clue into etiology was that MLL translocations are found in 71 to 88% of secondary leukemias and are highly associated with a class of chemotherapeutics known as epipodophyllotoxins, eg, etoposide and teniposide. These agents function as DNA topoisomerase II inhibitors and induce the accumulation of double strand breaks through stabilizing enzyme/DNA complexes. Although this is an effective approach in the treatment of cancer, double-strand breaks in normal cells can lead to chromosomal aberrations and malignant transformation. The MLL gene locus appears to be particularly sensitive to these double-strand breaks. Indeed, etoposide exposure has been shown to directly contribute to MLL rearrangements in human hematopoietic cells grown in vitro, establishing a potential causative role for DNA topoisomerase II inhibitors in MLL rearrangements. However, neither the infants nor their parents are likely exposed to chemotherapy. Therefore environmental and dietary compounds with DNA topoisomerase inhibitor activity have been investigated. Surprisingly, there are many DNA topoisomerase II inhibitors in everyday use, including caffeine, catechins (tea, wine, and chocolate), flavonoids (quercetin (fruits and vegetables) and genistein (soy)), quinolone antibiotics, thiram (fungicide), permethrin (insecticide), benzene (solvent), and some Chinese herbal medicines (reviewed by Ross). Several of these compounds have been shown to be capable of inducing DNA damage and/or...
specifically lead to MLL rearrangements in human hematopoietic stem cells, including natural flavonoids (quercetin/fisetin), genistein, and common chemicals such as the insecticide, permethrin. In a retrospective diet survey of 84 families of infants with leukemia and 97 controls, an increased risk of infant AML was observed for mothers whose diet contain larger quantities of these DNA topoisomerase II inhibitors (odds ratio = 10.2, P = 0.04). Further, a recent Children’s Oncology Group case-control study of infant leukemia (240 cases, 255 controls) found about a threefold increased risk of infant AML with MLL rearrangements among mothers who reported consuming the highest amounts of dietary DNA topoisomerase II inhibitors during pregnancy. Importantly, this observation was not seen in any of the other three leukemia groups (AML-MLL negative, ALL-MLL positive, ALL-MLL negative). This study has been expanded to include more than 200 additional cases to confirm these findings.

How Do We Treat Infant Leukemias?

Due to the limited number of patients diagnosed with infant leukemias, these diseases can only be adequately studied in the context of cooperative groups and international collaborations. The current Children’s Oncology Group represents over 240 hospitals and is the merged product of the Children’s Cancer Group (CCG) and the Pediatric Oncology Group (POG). Other important groups studying infant leukemias are the Japan Infant Leukemia Study Group (JILSG) and the international collaboration supporting the INTERFANT trials. The majority of protocols/trials described hereafter have come from these groups, although others are included as well.

Infants with AML are currently treated on standard childhood AML protocols as they generally have a prognosis similar to that of older children with AML. Some studies have reported that infants have better outcome than older children. In contrast, other studies have found that infant AML has a poorer prognosis and infants may have higher toxicity on standard AML protocols. For example, induction mortality on MRC AML10/12 was four times higher for infants than children overall (12% versus 3%) despite an arbitrary 25% reduction in chemotherapy dosing for infants on these protocols. Historically, outcomes for infants with AML were poor with 5-year EFS of 31 to 42%. More recent trials from POG, CCG, and MRC have all shown improved EFS of up to 58% in this group of patients, similar to older patients. Most strikingly, the JILSG reported 35 infants with AML having a 3-year EFS of 72%. There is evidence that cytarabine, doxorubicin, and etoposide are effective for infant AML. Current AML protocols typically include anthracycline (daunorubicin/doxorubicin/mitoxantrone), high-dose cytarabine, etoposide, and 6-thioguanine.

In contrast to infant AML, infant ALL does not respond adequately to standard ALL therapies. MLL-R ALL blasts appear to be resistant to steroid and asparaginase treatment, whereas they are more sensitive to cytarabine, similar to myeloid leukemias. Given the poor prognosis of infants when treated with conventional ALL therapies, hybrid infant ALL protocols have been developed that intensify therapy and combine elements of both ALL and AML protocols, particularly utilizing high-dose cytarabine (Table 4). This approach has improved outcome for adults with t(4;11) ALL.

Intensive combinations have led to increased long-term survival, sometimes at the cost of increased short-term toxicity and increased late effects. CCG-107 intensified methotrexate to 33 g/m² with modest toxicities, but only modest efficacy. The intensified DFCI trials led to bacteremia in 52% of infants with an average of two episodes per patient and no deaths. In contrast, CCG-1953 had serious infections in 95% of patients with an average of four to five infections per patient and no deaths. In contrast, CCG-1953/POG-9407 initially had an infection-related induction mortality rate of 25% (10/40). Modification of the steroid and anthracycline dosing reduced that to 13%. However death as a first event was still twice as frequent as relapse, particularly in the MLL-R group. CCG-1953/POG-9407 also identified infants <90 days of age at diagnosis as the most susceptible to toxicity. Twenty-nine percent of infants <90 days old at diagnosis died during induction/intensification from infection-related complications, mostly bacteremia, and almost two-thirds of all induction deaths occurred in this very young age group. POG-9407 found age <3 months to be the strongest prognostic factor, more so than MLL rearrangement or initial WBC.
related toxicity seen in younger patients may have
been due to poor methotrexate clearance and increased
renal toxicity.\textsuperscript{146} Indeed, the very young patients, $<$3
months, have lower total body water content, lower
P450 enzyme activity, lower serum protein binding,
and decreased renal function. McLeod and coworkers
provide evidence which suggests that etoposide and
cytarabine should be dosed based on body surface
area, whereas daunorubicin should be dosed based on
weight in infants.\textsuperscript{147} Due primarily to relapse, infants
$<$3 months old had a dismal 5-year EFS of 5\% on a
large review of infant ALL cases.\textsuperscript{20} More recently,
although induction mortality in the JILSG MLL96/98
protocols was only 1\%, the 5-year EFS in the $<$3
month old group was only 26\%.\textsuperscript{23} In contrast, the
CCG-1953 trial dramatically improved outcome for
these very young patients, with a 42\% 5-year EFS at
diagnosis and a 56\% 5-year EFS if alive at the end of
induction.\textsuperscript{18} These results suggest that the younger
patients are at risk for both increased toxicity and
higher relapse rates but changes in treatment regimens
can profoundly impact survival.

Most recently Interfant-99 confirmed that response
to a 7-day prednisone prophase is highly predictive of
outcome in infant ALL, with good responders (75\% of
patients) having a 4-year EFS of 56\% versus 30\% in
poor responders ($P = 0.001$).\textsuperscript{9} Although the outcome
for prednisone good responders on Interfant-99 is
similar to prior BFM studies (EFS 56\% versus 53\%),
the outcome for prednisone poor responders is signif-
ically improved (EFS 30\% versus 15\%).\textsuperscript{148} Inter-
fant-99 also found that addition of a late intensification
phase did not provide a survival benefit, 4-year OS
66\% versus 65\% ($P = 0.98$) but did add significant
grade 3 + 4 toxicity.\textsuperscript{9} This is of concern, as there may
be limited gains to be made by further intensification
of chemotherapy.

### To Transplant or Not to Transplant

The role for hematopoietic stem cell transplant
(HSCT) in infant leukemias is controversial. For
AML, a potential benefit of transplant is often extrap-
olated to infants, although large series of infants have
not been examined.\textsuperscript{149-152} In one promising study,
infants with AML had a 5-year EFS of 71\% (n = 15)
after non-TBI HSCT.\textsuperscript{153} However, the JILSG reported
a 72\% 5-year EFS, with 83\% (29/35) receiving only
chemotherapy without transplant.\textsuperscript{138} Therefore it is
not clear that HSCT provides a survival benefit over
chemotherapy alone in infants with AML. The role of
HSCT in future AML studies has yet to be determined.

The benefit of HSCT in infant ALL is also contro-
versial. Early data suggested an advantage to trans-
plant in infant ALL.\textsuperscript{48} However, early review of the
largest prospective clinical trial evaluating HSCT in
infants with ALL, POG-9407/CCG-1953 suggested a
disadvantage to unrelated donor transplant, 67\% (4/6)
with a matched-related donor versus 33\% (4/12) with
unrelated donors (Dinndorf P. Unpublished data,
2007). Ultimately combined analysis of POG-9407/
CCG-1953 data demonstrated 5-year EFS of 51 and
49\% with and without transplant, finding no survival
benefit for transplant.\textsuperscript{154} Moreover, a multi-institu-
tional review of 131 infants with t(4;11) transplanted
between 1983 and 1995 revealed a worse outcome for
transplanted patients compared with chemotherapy
alone (HR, 1.8; $P = 0.015$).\textsuperscript{20} However, some small
cases series have suggested a benefit to transplant. The

### TABLE 4. Infant ALL outcomes

<table>
<thead>
<tr>
<th>Protocol name</th>
<th>Years enrolling</th>
<th>EFS All pts. (n)</th>
<th>EFS MLL-R (n)</th>
<th>EFS MLL-G (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCG-107\textsuperscript{145}</td>
<td>1984-1988</td>
<td>33% (99)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EORTC 58831/58832\textsuperscript{185}</td>
<td>1983-1989</td>
<td>43% (28)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>POG-8398\textsuperscript{177}</td>
<td>1984-1990</td>
<td>17% (33)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>POG-8493\textsuperscript{186}</td>
<td>1984-1990</td>
<td>28% (82)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interfant 87\textsuperscript{187}</td>
<td>1987-1992</td>
<td>23% (40)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCG-1883\textsuperscript{145}</td>
<td>1988-1993</td>
<td>39% (135)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DFCI experience\textsuperscript{41}</td>
<td>1985-1995</td>
<td>54% (23)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BFM-83/86/90\textsuperscript{148}</td>
<td>1983-1995</td>
<td>43% (105)</td>
<td>28% (29)</td>
<td>56% (18)*</td>
</tr>
<tr>
<td>Interfant-92/UKALL-92\textsuperscript{187}</td>
<td>1992-1999</td>
<td>33% (86)</td>
<td>~30% (54)</td>
<td>48% (21)*</td>
</tr>
<tr>
<td>AIEOP ALL-95\textsuperscript{168}</td>
<td>1995-2000</td>
<td>54% (31)</td>
<td>38% (8)</td>
<td>68% (22)</td>
</tr>
<tr>
<td>CCG-1953\textsuperscript{18}</td>
<td>1996-2000</td>
<td>42% (115)</td>
<td>34% (79)</td>
<td>60% (36)</td>
</tr>
<tr>
<td>POG-9407\textsuperscript{21}</td>
<td>1998-2000</td>
<td>46% (71)</td>
<td>40% (50)</td>
<td>65% (17)</td>
</tr>
<tr>
<td>JILSG MLL96/98\textsuperscript{23}</td>
<td>1995-2001</td>
<td>51% (102)</td>
<td>39% (80)</td>
<td>96% (22)</td>
</tr>
<tr>
<td>Interfant-99\textsuperscript{9}</td>
<td>1999-2006</td>
<td>47% (482)</td>
<td>37% (308)</td>
<td>74% (82)</td>
</tr>
</tbody>
</table>

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TABLE 5. Transplant outcomes for infant ALL

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen</th>
<th>EFS HSCT (n)</th>
<th>EFS chemo</th>
<th>P value</th>
<th>HSCT mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMH156</td>
<td>TBI, VP16, CY</td>
<td>75% (12/16)</td>
<td>4-yr 30%</td>
<td>MLL unknown</td>
<td>—</td>
</tr>
<tr>
<td>FHRC157</td>
<td>TBI+CY+/-ARAC</td>
<td>73% (3-yr MLL CR1</td>
<td>—</td>
<td>—</td>
<td>14%</td>
</tr>
<tr>
<td>Multi-institution20</td>
<td>various</td>
<td>25% (7/28) t(4;11)</td>
<td>—</td>
<td>—</td>
<td>21%</td>
</tr>
<tr>
<td>POG-9407/CCG-1953154</td>
<td>ARAC, CY, TBI + various</td>
<td>51% (53) 5-yr CR1</td>
<td>—</td>
<td>—</td>
<td>21%</td>
</tr>
<tr>
<td>JILSG23</td>
<td>TBI or BU, VP16, CY</td>
<td>55% (27/49) MLL CR1</td>
<td>—</td>
<td>—</td>
<td>16%</td>
</tr>
<tr>
<td>Interfant-999</td>
<td>BU, VP16, CY</td>
<td>50% 4-yr</td>
<td>37% 4-yr</td>
<td>0.19</td>
<td>7%</td>
</tr>
</tbody>
</table>

*Non-HSCT patients alive at median time to transplant (143 days).

Children’s Memorial Hospital reported very promising outcomes with HSCT for 16 infants with ALL resulting in a 75% 4-year EFS. However, 30% of these patients have unknown MLL status and 33% of the survivors came from this unknown MLL group. The most notable series is the Fred Hutchinson Cancer Research Center experience where 11 of 14 MLL-R infant ALLs, transplanted in first complete remission, have survived with 3-year EFS of 73%. Recently, Interfant-99 reported a 4-year disease-free survival (DFS) of 50% for HSCT, compared with 37% DFS with chemotherapy alone, although this difference was not significant due to limited numbers of patients (P = 0.19). Similarly, posttransplant EFS on JILSG MLL98 was 55%; however, this outcome is similar to the POG-9407/CCG-1953 experience where non-HSCT patients had a 49% 5-year EFS.

It is important to note that several of these studies included varied conditioning regimens and a variety of donor sources. This makes it difficult to evaluate the true benefit of a particular transplant approach. For example, in the POG-9407/CCG-1953 studies, 53% of transplant patients received nonprotocol conditioning regimens. Furthermore, the median time to transplant in many of these trials is over 4 months, and >25% of relapses occur before the patient receives a transplant. This suggests that the dose and schedule intensity of induction chemotherapy needs to be altered to allow patients to remain in complete remission until transplant. Although the POG-9407/CCG-1953 and Interfant-99 studies did not reveal any benefit of transplant for infant ALL as a whole, the ongoing Interfant-06 trial is testing the benefit of HSCT in selected high-risk patients.

Late Effects: What Happens to Those We Cure?

As more children are cured of infant leukemia, we have an increasing population of older children and adults who have received intensified chemotherapy and often transplant. High-dose chemotherapy, intrathecal chemotherapy, cranial radiation, and total body irradiation have all been associated with significant late effects, particularly when used in young children. Transplant regimens, particularly with total body irradiation (TBI), are associated with significant long-term toxicity and late effects. Overall at least three of four survivors of infant leukemia have at least one late effect (Table 6).

Many of these toxicities are related to cranial irradiation and/or TBI. Indeed, growth and thyroid hormone deficiencies, neurocognitive difficulties, as well as skeletal, dental, ophthalmic, and metabolic abnormalities are common in young children who have received cranial irradiation and/or TBI. Unfortunately, inconsistent outcome measures and inadequate long-term follow-up make it difficult to assess the true impact of these therapies. Of note, two reports have found a high 12 to 13% incidence of second malignancies in children treated for infant leukemias with TBI. Therefore, alternate non-TBI conditioning regimens should be explored to reduce these toxicities, such as the busulfan-based regimens used in JILSG-MLL98 and Interfant-99. New transplant protocols, including fludarabine-based conditioning and KIR-mismatched NK cell-directed transplants may increase efficacy while decreasing toxicity.

Where Do We Go from Here?

Prevention of Infant Leukemia

Given the emerging data regarding the potential role of many environmental, dietary, and medicinal exposures in the etiology of infant leukemias, definitive trials that establish clear associations will be necessary before public health education can begin. Although public campaigns against smoking, alcohol, and illicit drug use are commonplace, new regulation of insecti-
icides, fungicides, solvents, and warnings against commonly used medicines such as antihistamines, metronidazole/quinolone antibiotics, and analgesics may be warranted. Even more concerning is the association of dietary compounds found in coffee, tea, chocolate, and soy products with MLL translocations and infant leukemia. It is critical that these correlations be precisely defined and confirmed before recommendations can be made to prospective parents and environmental/governmental agencies.

To provide these definitive associations, large epidemiologic trials will need to be performed with extensive collaboration and rigorous methodology. One such trial is underway with over 450 cases already identified (Ross J. Personal communication, 2007).

**Define Risk Groups**

Perhaps the tradeoff between toxicity and outcome can be balanced if risk groups can be defined. Risk stratification has been used successfully in ALL to target high-risk populations with intensified chemotherapy, while sparing low-risk patients. MLL rearrangements have been shown to strongly predict outcome and have been used to stratify infants with ALL. In addition, Infant-99 confirmed that response to prednisone prophase was strongly predictive of outcome, with good responders (75% of patients) having a 4-year EFS of 56% versus 30% in poor responders ($P = 0.001$). However, the importance of early bone marrow response appears to be less clear. Early CCG studies showed that infants not in morphologic remission by day 14 had an increased risk of relapse. On CCG-1953, there was no difference between rapid and intermediate responders (EFS 43% versus 44%), although the rare slow responders had poor outcome. Similarly, although bone marrow blast percentage >25% on day 15 of treatment predicted poor outcome, no significant increase in survival was seen at 5 to 25% versus <5%. Given these data, risk stratification based on MLL status/CD10 expression, age <3 or 6 months, and early prednisone response seems warranted.

**Rethinking Infant Leukemia**

Perhaps it is time to focus on the differences between MLL-R and MLL-G infant leukemias. Just as ALL which carries a BCR-ABL translocation is recognized as having a distinct biology, MLL-R define a distinct biology of leukemia present in the majority of infants with either ALL or AML. Indeed, patients <1 year of age with MLL-G have a type of ALL that more closely resembles typical precursor-B ALL, expressing CD10, and have far better response rates and long-term survival than those with MLL rearrangements. Perhaps this group of infants, historically combined with the MLL-R patients, would benefit from therapy similar to noninfant high-risk ALL, receiving four-drug induction/intensification followed by extended antimetabolite mainte-

### TABLE 6. Late effects in survivors of infant leukemia

<table>
<thead>
<tr>
<th>Late effect</th>
<th>Frequency</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Developmental delay/learning disabilities</td>
<td>11-82%</td>
<td>23,41,157,160,185</td>
</tr>
<tr>
<td>Ophthalmologic (corneal opacity, retinal vasculitis)</td>
<td>6-67%</td>
<td>23,41,150,157,160,161</td>
</tr>
<tr>
<td>Short stature (growth hormone deficiency)</td>
<td>18-86%</td>
<td>23,41,158,160,160</td>
</tr>
<tr>
<td>Primary gonadal failure</td>
<td>12-50%</td>
<td>150,161</td>
</tr>
<tr>
<td>Chronic GVHD</td>
<td>14-40%</td>
<td>23,150</td>
</tr>
<tr>
<td>Skin abnormalities (alopecia, scleroderma, pigmentation)</td>
<td>33%</td>
<td>23</td>
</tr>
<tr>
<td>Cardiac dysfunction/ECHO abnormalities</td>
<td>6-30%</td>
<td>41,150</td>
</tr>
<tr>
<td>Obesity</td>
<td>27%</td>
<td>41</td>
</tr>
<tr>
<td>Dental abnormalities</td>
<td>17-88%</td>
<td>23,157,161</td>
</tr>
<tr>
<td>Pulmonary (bronchiolitis obliterans, interstitial pneumonitis)</td>
<td>17%</td>
<td>23</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>14-35%</td>
<td>23,150,157,160,161</td>
</tr>
<tr>
<td>Dyslipidemias</td>
<td>59%</td>
<td>161</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>6%</td>
<td>23</td>
</tr>
</tbody>
</table>

In contrast, MLL-R ALL has evidence of a common lymphoid/myeloid precursor and appears to respond better to “hybrid” protocols combining high-risk ALL and AML regimens. Based on these recent successes, the current Interfant-06 trial incorporates two typical AML blocks into Interfant-99 therapy. As these hybrid protocols incorporate more and more AML-type regimens, the question arises whether these hybrid therapies would be effective for both MLL-R ALL and AML. Although the MLL biology may be shared between infant ALL and AML, the risk is that infant AML will not respond as well to hybrid protocols as standard AML therapy. This concern will likely prevent a combined “infant MLL” leukemia protocol; however, MLL-based targeted therapies should be explored in parallel.

**Develop Targeted Therapies**

The next generation of infant leukemia trials will attempt to limit toxicity while improving outcome through the use of targeted therapies. Recent efforts at intensification of chemotherapy have not improved outcome. If significant gains are to be had, novel therapies are needed. FLT3 inhibition, as mentioned above, is a promising therapeutic approach. Given the association of MLL and activation of FLT3, the availability of a FLT3 inhibitor, eg, lestaurinib (CEP-701), and its synergy with chemotherapy, this class of compounds will be used in upcoming trials. The next COG Infant ALL trial tests the benefit of adding the FLT3 inhibitor lestaurinib to POG-9407 treatment in MLL-R infants (AALL0631). Alternatively novel chemotherapy regimens may be used, such as all-trans retinoic acid and 5-azacytidine, which can induce differentiation of MLL leukemia cells, decitabine, which demethylates tumor suppressor genes and induces apoptosis, or the Hsp90 inhibitor 17-allylamino-17-demethoxygeldanamycin, which depletes FLT3 and synergizes with etoposide to induce cell death in FLT3+ MLL leukemias. Future strategies in infant leukemia may include inhibition of the HOX, Menin, or Ephrin/Epha7/ERK pathways, or stimulation of the TRAIL or Fas death receptors, or the putative MLL-fusion tumor suppressors ARPI or FHIT. Clearly there are many opportunities. However, with limited patient numbers and long trial accrual windows, rigorous preclinical testing will be required to determine the best candidates for intervention.

In summary, the majority of infant leukemias are defined by MLL gene rearrangement. The biology and mechanisms of MLL leukemogenesis are still not clear 15 years after its discovery. Many questions remain to be answered, including the public health concerns over dietary exposures, appropriate risk stratification, and the use of transplant in both ALL and AML. However, we have made steady improvements in the outcome of infants with ALL over the past 25 years (Fig 2). Recent trials using hybrid AML/ALL therapies have proven successful in infant ALL, raising long-term survival to >50%. Novel therapies must be evaluated rapidly through innovative trial design and international cooperation. Above all, there is great hope for the future.

**Acknowledgments**

We thank our patients, families, and colleagues for supporting our work and providing the motivation and expertise to continue the struggle against infant leukemias. We thank Drs. Patrick Brown, Julie Ross, and ZoAnn Dreyer for helpful insights.

**References**


33. Al-Kasim F, Doyle JJ, Massey GV, Weinstein HJ, Zipursky


61. Sorensen PH, Chen CS, Smith FO, Arthur DC, Domer PH, Bernstein ID, et al. Molecular rearrangements of the MLL gene are present in most cases of infant acute myeloid leukemia.
may contribute to infant leukemia. Proc Natl Acad Sci USA 2000;97:4790-5.


