Childhood Acute Lymphoblastic Leukemia: Currently Applied Prognostic Factors

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Abstract

Several clinical and biologic factors have been found to be significant predictors of outcome in childhood acute lymphoblastic leukemia (ALL), including age, presenting leukocyte count, immunophenotype, recurrent chromosomal abnormalities, and response to initial therapy as assessed by light microscopy as well as more sensitive measures of submicroscopic disease. Over the last several decades, these prognostic factors have been used to stratify therapy; patients with “high risk” features have received more intensive treatments, while those with features associated with a lower risk of relapse receive less aggressive therapy. This article will review those factors that are currently utilized by clinical trials groups world-wide to determine treatment for children and adolescents with ALL.

Introduction

Over the last sixty years, there has been a dramatic improvement in the outcome of children with acute lymphoblastic leukemia (ALL). With current treatment regimens, event-free survival rates now approach or exceed 80%.(1-3) This success was achieved, in part, through the implementation of risk-stratified therapy. Patients presenting with features that are associated with a higher risk of relapse receive more intensive treatment, while those with features associated with a lower risk of relapse receive less aggressive therapy. The goal of risk-stratified therapy is to “treat away” the adverse prognostic significance of various leukemia subtypes, so that even “high-risk” patients achieve favorable rates of cure. Ultimately, the prognostic significance of any factor is treatment-dependent, and the relevance of any particular factor must be evaluated within the context of the administered therapeutic regimen. The prognostic factors that are currently applied by most clinical trials groups in the design and implementation of risk-stratified protocols for children with newly diagnosed ALL are summarized in Table 1. These include:

1. Age

The age of patients with ALL significantly correlates with clinical outcome. In childhood ALL, infants and adolescents have a worse prognosis than patients aged 1-10 years.(5) The superior outcomes of children aged 1-10 years is at least partly explained by the high frequency of more favorable underlying biologic features in the lymphoblasts of patients in this age group, including high hyperdiploidy (51-65 chromosomes) and the TEL/AML1 (also known as ETV6-RUNX1) fusion.(5, 6)

ALL in infancy (< 12 months at diagnosis) is associated with high presenting leukocyte counts, increased frequency of central nervous system leukemia at presentation and a very high incidence (~80%) of rearrangements of the MLL gene on chromosome 11q23.(7, 8) Infants whose lymphoblasts lack MLL gene rearrangements have a significantly better prognosis than those with this chromosomal abnormality.(7, 9) Amongst infants with MLL gene rearrangements, those presenting at a young age (< 6 months) or with extremely high leukocyte counts (≥ 300, 000/mL) appear to...
have the worst prognosis.(7) MLL-rearranged infants are usually treated with more intensive therapies than children aged 1-10 years, often including agents not typically administered to older children with ALL, such as high-dose cytarabine.(7)

Adolescents (ages 10-21 years) with ALL also have a less favorable outcome than children aged 1-10 years, although not as poor as infants. Compared with younger children, adolescents with ALL more frequently present with T-cell immunophenotype, high presenting leukocyte counts, a lower incidence of favorable cytogenetic abnormalities (eg, high hyperdiploidy and the TEL/AML1 gene fusion) and a higher incidence of the Philadelphia chromosome [t(9;22)].(5, 10) Adolescents also appear to be at higher risk for certain treatment-related complications, such as osteonecrosis, pancreatitis and deep vein thromboses, (10, 11) which may also impact prognosis. On most pediatric protocols, adolescents are considered high risk, regardless of other presenting features. A number of retrospective studies published over the last decade suggest that adolescents

Table 1: Prognostic Factors Currently Used to Determine Therapy by a sample of Childhood ALL Clinical Trials Group

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<th></th>
<th>BFM</th>
<th>COG</th>
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<th>FRALLE</th>
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* Except infants; **Duration of therapy only; *t(4;11) only

Group Name:
- **BFM**: Berlin-Frankfurt-Munster Study Group/Italian Association of Pediatric Hematology and Oncology
- **COG**: Children’s Oncology Group
- **DCOG**: Dutch Childhood Oncology Group
- **DFCI**: Dana-Farber Cancer Institute ALL Consortium
- **FRALLE**: French Acute Lymphoblastic Leukemia Group
- **St. Jude**: St. Jude Children’s Research Hospital
- **TPOG**: Taiwan Pediatric Oncology Group

[Personal communication from Martin Schrappe (BFM/AIOEP), Stephen Hunger (COG), Rob Pieters (DCOG), Andre Baruchel (FRALLE), Ching-Hon Pui (St. Jude), Der-Cherng Liang (TPOG)]
achieve better outcome if treated using high-risk pediatric regimens rather than adult ALL protocols.(12, 13)

2. Leukocyte Count
Along with age, the initial peripheral blood leukocyte count was one of the first identified prognostic factors in childhood ALL. Presenting leukocyte count has continued to be an independent predictor of outcome in recent studies, even when controlling for minimal residual disease levels and/or prognostically significant chromosomal abnormalities, (14, 15) and so is still a component of risk group determination on most regimens. Since 1996, based upon guidelines developed by the Cancer Therapy Evaluation Program (CTEP) of the National Cancer Institute (NCI), a leukocyte count of 50,000/mL has typically been used as the cut-off to classify patients as either high risk or low/standard risk.(4)

3. Immunophenotype
Approximately 80-85% of childhood ALL has a B-lymphoblastic (B-precursor) phenotype, while 10-15% has a T-cell immunophenotype. Historically, patients with T-ALL had an inferior outcome, but when treated more intensively, these children appear to fare as well as those with B-precursor phenotype.(16) Thus, patients with T-ALL are excluded from the low-risk arm of many ALL regimens, and are treated more intensively either on high-risk arms or on separate protocols.

In approximately 15-30% of patients with newly diagnosed ALL, flow cytometry reveals co-expression of at least one myeloid antigen on the cell surface of the lymphoblasts. Myeloid antigen co-expression has been associated with several chromosomal abnormalities, both favorable and unfavorable, including the TEL/AML1 fusion [(12;21)], MLL gene rearrangements, and the Philadelphia chromosome [(t(9;22)), but is almost never observed in high hyperdiploid ALL (>50 chromosomes).(17) Myeloid antigen co-expression is no longer considered an independent predictor of outcome in childhood ALL, (17, 18) and it is not currently a factor in the determination of risk group status on most regimens.

4. CNS Status at Diagnosis
Approximately 15-20% of children with ALL present with detectable lymphoblasts in their cerebrospinal fluid (CSF).(19) Some patient subsets, such as infants and those with T-cell ALL, have a higher incidence of CNS leukemia at diagnosis.(5) CNS status at diagnosis has been correlated with outcome, and is used by most clinical trials groups to determine the intensity of both systemic and CNS-directed therapies.

CNS status at presentation is standardly classified as CNS-1 (no blast cells in the CSF), CNS-2 (fewer than five leukocytes per microliter with blast cells), and CNS-3 (more than five leukocytes per microliter with blast cells or cranial nerve palsy). Patients with CNS-3 status at diagnosis appear to have a higher risk of both CNS and marrow relapses, and so are typically treated with more intensive CNS-directed therapies and often more intensive systemic chemotherapy as well.(19, 20)

CNS-2 status at diagnosis has also been associated with an inferior outcome (although not as unfavorable as CNS-3 status). However, the adverse prognostic significance of CNS-2 status appears to be overcome by the administration of more doses of intrathecal therapy, especially early in therapy, without intensification of systemic therapy.(19, 20) Thus, CNS-2 status is, in general, used as a determinant of CNS-directed therapy but usually does not change a patient’s risk group status. A traumatic lumbar punctures with lymphoblasts at diagnosis has also been associated with an increased risk of subsequent CNS relapse; (19, 21) patients with this feature are often treated with intensified CNS-directed treatments, including additional doses of intrathecal chemotherapy, and sometimes with intensified systemic therapy as well.

5. Chromosomal Abnormalities.
Many recurrent chromosomal abnormalities have been reported to have prognostic significance in childhood ALL, and several are utilized in current regimens to risk-stratify patients. Most of the cytogenetic abnormalities used to stratify treatment are much more common in B-precursor ALL than in T-ALL. Thus,
it is predominantly patients with B-precursor ALL who have therapy changed because of a chromosomal abnormality. While multiple chromosomal aberrations with possible prognostic significance have been identified in T-ALL, they are not currently considered by most groups when stratifying therapy.

Two chromosomal abnormalities, high hyperdiploidy (51-65 chromosomes or DNA index greater than or equal to 1.16) and the TEL/AML1 fusion [t(12;21)], have been associated with a more favorable prognosis. (14, 15) Both of these abnormalities are more common in non-adolescent/non-infant children (i.e., those aged 1-10 years) with B-precursor phenotype.(5, 6) The most favorable outcomes in high hyperdiploid ALL have been associated with the presence of trisomies of chromosomes 4, 10 and 17.(22, 23) Up to 80% of children with B-precursor ALL diagnosed between the ages 2-7 years have either high hyperdiploidy or the TEL/AML1 fusion, (6) although never both; these two chromosomal abnormalities appear to be mutually exclusive.(24) Some groups will alter therapy based upon the presence of either high hyperdiploidy (and/or favorable trisomies) or TEL/AML1; patients with one of these abnormalities (often in conjunction with other favorable presenting features, such as age between 1-10 years, low leukocyte count and rapid response to initial therapy as determined by morphology or minimal residual disease levels) are given less intensive, potentially less toxic treatment.(23)

Chromosomal abnormalities associated with an adverse prognosis currently utilized by most groups to classify patients as “higher risk” include hypodiploidy (fewer than 44-45 chromosomes), (25) rearrangements of the MLL gene on chromosome 11q23 (especially t(4;11) translocation), (26) and the Philadelphia chromosome [t(9;22)].(27, 28) Patients with the Philadelphia chromosome are often treated on separate clinical trials which include intensive myelosuppressive chemotherapy, tyrosine kinase inhibitors and/or allogeneic stem cell transplantation in first remission.(28, 33)

6. Early Morphologic Response to Initial Chemotherapy

The rapidity with which a patient responds to initial chemotherapy is a significant predictor of long-term outcome. Treatment stratification for protocols of the Berlin-Frankfurt-Muenster (BFM) and other groups is, in part, based on the absolute peripheral blood blast count measured after a steroid prophase consisting of one dose of intrathecal methotrexate and 7-days of prednisone given immediately prior to the initiation of multiagent induction chemotherapy (2) Patients with an absolute blast count less than 1, 000/µL at the end of the prophase (a good prednisone response) have a more favorable prognosis than do patients whose peripheral blast counts remain above 1, 000/µL (a poor prednisone response). (2) On studies conducted by the BFM and AIEOP groups, prednisone prophase response is an independent predictor of outcome, even when controlling for other prognostic factors such as minimal residual disease levels and chromosomal abnormalities.(14)

Morphological persistence of marrow disease 7 or 14 days following initiation of multiagent induction chemotherapy also correlates with long-term outcome. Patients with fewer than 5% marrow lymphoblasts as detected by light microscopy at these early time points have a more favorable prognosis than those who disease persists at higher levels.(29) Based on trials which demonstrated that intensification of therapy could abrogate the adverse prognostic significance of slow early morphologic marrow response, (30) patients with this feature receive more intensified post-induction treatment on some clinical trials.

Persistence of microscopically visible leukemia at the end of the first month of induction chemotherapy, observed in up to 5% of children with ALL, is associated with a very poor outcome.(31, 32) While the majority of the patients with initial induction failure will ultimately achieve complete remission, the risk of subsequent relapse is very high and such patients are typically treated with more intensive therapies, including allogeneic stem cell transplant in first remission.(33)

7. Minimal Residual Disease (MRD)

MRD evaluation is a more sensitive measure of early treatment response than assessments based on light microscopy. Submicroscopic
levels of disease can be measured using the polymerase chain reaction (targeting lymphoblast-specific immunoglobulin or T-cell receptor gene rearrangements, or chromosomal translocations) or specialized multiparameter flow cytometry. Using these techniques, leukemia cells have been identified at levels as low as 1/1000 to 1/100,000 cells. (14, 34, 35)

Multiple studies have demonstrated that end-induction MRD is an important, independent predictor of outcome in children with ALL. (14, 35, 36) Patients with higher levels of end-induction MRD have a poorer prognosis than those with lower or undetectable levels. MRD at end-induction is used by almost all groups as a factor to determine the intensity of post-induction treatment, with patients found to have higher levels allocated to more intensive therapies regardless of other presenting features. MRD levels at earlier (e.g., Days 8 and 15 of induction) and later time points (e.g., Day 78 of therapy) also predict long-term outcome. (14, 36, 37) For example, the BFM group uses both end-induction (day 33) and Day 78 measurements to risk-stratify patients. (14)

In addition to identifying patients who might benefit from more intensive therapy, MRD assessments, in conjunction with other presenting features, may also be used to identify patient subsets with extremely low risk of relapse. For instance, the Children’s Oncology Group (COG) reported that standard-risk B-precursor patients with favorable cytogenetic abnormalities (such as the TEL-AML1 fusion and trisomies of chromosomes 4 and 10) as well as MRD negativity at both Day 8 and at the end of remission induction had a particularly favorable prognosis. (36)

8. Other Prognostic Factors

The following are other prognostic factors which are not universally applied for risk stratification, but are used by individual clinical trial groups when determining intensity or duration of therapy:

- **Sex**: In some studies, the prognosis for boys with ALL is slightly worse than it is for girls. (29) This difference in outcome cannot be entirely explained by the frequency of testicular relapses, which, on current regimens, is quite low. Because of this outcome difference, on some regimens, such as those of the Children’s Oncology Group, boys receive a longer maintenance phase than girls, resulting in a longer total duration of treatment. However, on many other regimens, boys and girls receive the same duration of treatment.

- **Overt Testicular Involvement at diagnosis**: Overt testicular involvement at the time of diagnosis occurs in approximately 2% of males. Historically, testicular involvement at diagnosis was identified as an adverse prognostic factor, but its prognostic relevance is less clear on more recent studies. (38, 39) Overt testicular involvement at diagnosis is still considered a high-risk feature in some ALL treatment programs.

- **t(1;19) translocation (TCF3-PBX1 or E2A-PBX1)**: The t(1;19) translocation occurs in approximately 5% of childhood ALL cases, and has previously been associated with inferior outcome. (40) More recently, the results of several clinical trials have suggested that the t(1;19) translocation is not an independent predictor of outcome. (15) The presence of this translocation is considered a high-risk feature in some trials, such as those currently being conducted by the St. Jude Children’s Research Hospital, (20) but it is not a determinant of risk group status for most other clinical trials groups.

- **Intrachromosomal amplification of chromosome 21 (iAMP21)**: This abnormality, characterized by multiple extra copies of the AML1 (RUNX1) gene on a single chromosome 21, occurs in fewer than 5% of precursor-B cell ALL. (41) It has been associated with an inferior outcome, (41) and is considered a high-risk feature on some clinical trials.

**Summary and Future Directions**

Several clinical and biologic features have been found to have important prognostic significance in childhood ALL, including age, presenting leukocyte count, immunophenotype, CNS status, recurrent chromosomal abnormalities, and response to initial therapy. The application of risk-stratified therapy utilizing these prognostic
factors has resulted in long-term event-free survival in up to 80-85% of children with ALL. Further improvement in outcome will require, in part, the discovery of novel prognostic factors to identify the 15-20% of patients who are not cured with current therapies. Recent advances in our understanding of underlying leukemia biology, including the identification of prognostically distinct subsets of patients, and of host pharmacogenomics may allow for more precise risk stratification and more targeted, individualized treatment planning.

References


