
Childhood Acute Lymphoblastic Leukemia : Indian Experience

MANISHA BHUTANI, VINOD KOCHUPILLAI & SAMEER BAKHSHI

INTRODUCTION

Of all cancers in childhood (by WHO definition: 0-14 year age group), leukemias constitute one of the most important groups of tumors. Our understanding of the biologic features of the childhood leukemias has increased greatly over the past decade. The ability to discern cytogenetic and molecular differences among morphologically and immunologically similar populations of leukemic cells has helped to establish the basis for a revised classification of the leukemias. This advance, in turn, has led to new approaches to clinical management.

Acute lymphoblastic leukemia (ALL) is diagnosed in approximately 2000 children in the United States each year, whereas acute myeloid leukemia (AML) is diagnosed in only about 500 children and chronic myeloid leukemia (CML) in fewer than 100.¹ Chronic lymphocytic leukemia (CLL), one of the most common leukemias in adults seldom occurs in children. Leukemias and lymphomas followed closely by tumors of central nervous system constitute the vast majority of childhood cancers in India. In different population based cancer registries, leukemias constitute 27% to 52% of childhood cancers in males and 19% to 52% in female@. It was estimated that within a population of 882 million, six thousand children would develop acute lymphoblastic leukemia each year in India.³ With current population rates, this number is likely to increase.

RISK FACTORS

Numerous factors have been linked to an increased risk of leukemia in children. The higher frequency of acute leukemia in children with constitutional genetic defects (e.g., trisomy 21, Fanconi's anemia, and germ-line p53 mutations) is evidence of a hereditary influence.⁴ The megakaryoblastic subtype of AML predominates in children with

Down's syndrome who are three years of age or younger, whereas ALL is the characteristic leukemia in older children with Down's syndrome.^{5,6}

The high rate of concordance for leukemia in monozygous twins, especially during the first year of life, may reflect a common prezygotic or intrauterine genetic event or perhaps metastasis through shared placental circulation. The latter mechanism was recently confirmed in three pairs of monozygous twins, each pair having unique (clonal) genetic rearrangements in their blast cells?. That the leukemic cells in these twins had 11q23 chromosomal rearrangements — a common feature of secondary AML induced by epipodophyllotoxin therapy* and the most common clonal abnormality in infants with leukemia⁹, suggests that intrauterine exposure to carcinogens is responsible for at least some cases of leukemia in very young children.

Even when other potential risk factors are considered (e.g., exposure to chemicals in children with AML and ionizing radiation in those with leukemias other than CLL), we lack a plausible etiologic explanation for, more than 90 percent of cases of childhood leukemia. It has been proposed that most cases of childhood ALL are the consequence of an abnormal immunologic response to a common infection, perhaps preceded by an initiating mutational event in utero.⁴

MOLECULAR AND CYTOGENETIC FEATURES

ALL is an acquired genetic disease. Blasts from over two thirds of childhood ALL cases demonstrate numerical gains or losses of chromosomes and/or translocations. The presence of certain genetic features correlates highly with the ultimate response to treatment. Classifying cases based on standard karyotype lead to following distribution: 30% normal, 6% hypodiploid, 28% pseudodiploid, 11% low hyperdiploid (47 to 50), and 25% high hyperdiploid (> 50 chromosomes).¹⁰

Correspondence to : **Prof. Vinod Kochupillai, Chief, IRCH**
Department of Medical Oncology, Institute Rotary Cancer Hospital
All India Institute of Medical Sciences, New Delhi 110029

A number of studies have shown that children whose blasts retain fewer than 46 chromosomes fare poorly. The majority (80%) of these cases have 45 chromosomes. Recent data from contemporary treatment protocols suggests a progressively worse outcome with decreasing chromosome numbers, with six year EFS of $65\% \pm 8\%$, $40\% \pm 18\%$, and $25\% \pm 22\%$ for patients whose blasts contain 45, 33 to 44 and <28 chromosomes respectively." Hyperdiploidy, on the other hand, has been correlated with favourable outcome. Presence of >50 chromosomes or a DNA index of 1.16 or more defines a subgroup of patients with a high chance of cure (four year EFS 75% to 90%) using less intense therapy.^{12,13} Patients with 54 to 58 chromosomes do better than those with 51 to 53 or 59 to 68 chromosomes.¹⁰ A better prognosis with hyperdiploidy is probably because of tendency of hyperdiploid blasts to accumulate increased amounts of methotrexate and its polyglutamates,^{14,15} as well as the marked propensity of these cells for apoptosis.¹⁶

Four major translocations have been identified that have prognostic significance in B precursor ALL. The t (9;22) is noted in 3% to 5% of children compared with 20% of adults with ALL. Ph+ ALL has been uniformly associated with poor survival, and these patients have a slower reduction in tumor burden, as evidenced by a higher proportion of peripheral blasts after prednisone prophase, an elevated proportion of day 7 M3 marrow after a four drug induction, and a lower remission induction rate.^{17,18} Overall 5-yr EFS for these patients is 20% to 25%. The t (1;19) is seen in 25% of pre-B ALL.¹⁹ With more intensified therapy this translocation is no longer associated with an adverse prognosis.¹⁷ The t (4;11) is found in approximately 60% of ALL cases in infants younger than 1 year, and in 2% childhood cases. The 5 year EFS for such infants is 20 to 25 % and in children older than one year the EFS is 45 % .²⁰ The t (12;21) is recognized in only 0.05% of patients using conventional cytogenetic techniques, but molecular screening can detect this translocation in 20% to 25% of precursor B ALL, making it the most common somatically acquired genetic lesion in ALL.²¹ Several studies have documented favorable outcome in TEL/AML 1 positive patients. As a group, patients with TEL/AML 1 translocation tend to be younger (<10 years) and blasts have B-precursor phenotype, and are non-hyperdiploid.

TEL/AML 1 positive blasts have been shown to be uniquely sensitive to L-asparaginase.

Preliminary research on the molecular characteristics of ALL in children and young adolescents in India suggests that chromosomal translocations associated with poorer prognosis in western series are more frequent, and those associated with a good prognosis are less frequent. In a study from Mumbai, a lower frequency of hyperdiploidy (15%) and a higher frequency of hypodiploidy in children (38.4%) were found, in contrast to literature.²² In a study from AIIMS,²³ t (9;22) was seen in 1/35 (2.8%) and t (1; 19) in 2/35 (5.7%) children. None of the children showed t (12; 21) and t (4; 11) translocations. In another study from AIIMS²⁴, Ph chromosome was detected in 4/17 (24%) childhood cases of ALL.

TREATMENT

Since 1970, the rate of cure of acute lymphoblastic leukemia (ALL) in children has increased dramatically, from less than 30 percent to approximately 80 percent. This remarkable improvement has resulted from the culmination of laboratory and clinical science. The identification of effective agents in randomized cooperative-group studies, the application of treatment to the central nervous system before the onset of symptoms, the intensification of treatment, and the use of "risk-adapted therapy" (therapy tailored to the predicted risk of relapse) have led to today's impressive cure rates.

Treatment with a glucocorticoid, vincristine, and L-asparaginase results in a complete remission in 99 percent of children with lower-risk ALL (those with B-lineage ALL, an age of one to nine years, and a leukocyte count $<50,000/\text{mm}^3$).²⁵⁻²⁸ Post-remission therapy with antimetabolite combinations, usually 6-mercaptopurine and methotrexate for two to three years, produces a cure in more than 80% of these patients. The need for an intensification phase of chemotherapy immediately after induction of a remission or later in the clinical course of the disease is controversial, although recent studies show a significant increase in the proportion of long-term survivors with the use of this modification.^{29,30}

Approximately 40 percent of patients with ALL have one or more features predictive of a poor outcome (e.g., a leukocyte count $>50,000$ per cubic

millimeter, an age over nine years, and the T-cell immunophenotype). Most current protocols specify the use of four or more drugs to induce a complete remission in such high risk ALL patients, followed by a brief period of intensified treatment to eradicate residual blast cells. With this approach, the cure rates have reached 65 % .²⁶⁻³¹ The prognostic value of an early response, as determined by a morphologic assessment of blast clearance or by means of sensitive methods to detect minimal residual disease, including flow cytometry and polymerase-chain-reaction techniques, has been used as the basis for risk stratification. Clinical trials have shown that patients with "slow early response" may benefit from early application of intensified therapy, thus helping a subgroup of patients who would otherwise be destined to have a poor outcome.

Patients with very-high-risk ALL include those with Philadelphia chromosome, the t (4;11) chromosomal translocation, or leukocyte count of at least 200,000/mm³, as well as infants with *MLL* gene rearrangement. The cure rates for such patients are about 40%. Patients with B-cell ALL and the t (8;14) translocation have an exceptionally poor prognosis with standard antimetabolite-based therapy. However, with intensive short-term therapy (less than six months) including high-dose cyclophosphamide, cytarabine, and methotrexate, as well as repeated intrathecal chemotherapy to prevent central nervous system leukemia, cure rate of 80% can be achieved.^{32,33}

In a study from AIIMS,³⁴ a total of 250 children up to 15 years age from June 1992 to June 2002 with newly diagnosed ALL were included and were uniformly treated on MCP 841 protocol. There was a male preponderance (male: female-3.8: 1). The fraction of patient in more than 10 years age group, and with WBC count >50,000/mm³ were almost similar to data from western countries. Immunophenotyping was performed in 196 patients of whom 30.6% had T-ALL, which was much higher than western country study groups (about 15%). Similar high incidence of 'T' ALL in India has been found in previous studies.³⁵⁻³⁷ Hepatosplenomegaly (95 %) and lymphadenopathy (87%) was much commoner in our patients as compared to patients in west where the incidence is about 65% and less than 50% respectively.³⁸⁻⁴⁰ There were 27 induction and 35 remission deaths. 218 patients achieved complete remission (87.2%).

Total number of relapses were 38 (17.1%). Overall, event free and disease free survivals were 67.5, 51.6 and 69.1 respectively

LATE EFFECTS

Few complications of leukemia therapy are as devastating as a second cancer. In a retrospective study of 9720 children treated for ALL, 7-fold excess of all cancers and 22-fold excess of central nervous system tumors was detected as compared with prevalence rates in the general population.⁴¹ Children who underwent cranial irradiation at or before the age of five years had the greatest susceptibility to brain tumors. In another report, a sevenfold excess of second cancers, mainly non-Hodgkin's lymphoma, brain tumors, and melanoma was detected among patients who had undergone bone marrow transplantation.⁴² An increase in cases of AML among patients treated intensively for ALL has been attributed to the genotoxic effects of the epipodophyllotoxins, which are inhibitors of the intranuclear enzyme topoisomerase II, but the risk of developing secondary leukemia appears to be dependent on the treatment schedule.⁴³

Treatment with anthracycline has been associated with cardiomyopathy in a substantial proportion of patients, especially when the drug was administered in doses above 200 mg/m² of body-surface area and when it was given to patients under four years of age.⁴⁴ Cranial irradiation has been implicated in neuropsychological deficits and endocrine dysfunction, most often in young children treated for leukemia.⁴⁵⁻⁴⁹ Girls appear to be more susceptible than boys to these sequelae.^{45,47} Short stature and obesity are common in children who have undergone cranial irradiation, particularly those treated at a very young age.^{48,49} In modern day protocols, the reduced doses of radiation and wider use of intrathecal and high-dose systemic chemotherapy for central nervous system disease has lessened the severity of neuropsychological sequelae. In a study in which patients received intensive systemic chemotherapy, however, a small reduction in final height was observed among patients who had not received added cranial irradiation.⁴⁹ There are reports of growth hormone deficiency and gonadal failure in patients receiving high-dose busulfan and cyclophosphamide as preparative therapy for bone marrow transplantation.⁵⁰

FUTURE CONSIDERATIONS

Despite these successes, however, much work remains. Many of the children with ALL who are cured by current therapies are over treated and thus unnecessarily exposed to the risk of short and long-term adverse effects. Even among subgroups with the most favorable prognostic factors, 10-20% will have a relapse and most of these children will ultimately die of their disease. Subgroups of children with ALL, including infants, those with unfavorable genotypes such as Philadelphia positive ALL, and those who do not have a complete remission initially or who relapse after a remission, still have an extremely poor prognosis. Further intensification of existing therapies is unlikely to improve the cure rate substantially in these populations. Therefore, identification of additional prognostic variables that can be used to tailor therapy more precisely and discovery of drugs that can modify pathways involved in transformation and resistance to therapy are top priorities.

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