

Acute Lymphoblastic Leukemia - An Overview

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Abstract: *Acute lymphoblastic leukemia (ALL) is a malignant disorder resulting from the clonal proliferation of lymphoid precursors with arrested maturation. Specific chromosomal translocations in ALL include mainly, the classical t(8;14) in B-cell ALL, t(4;11) in infant leukemia and t(9;22) translocation (that forms the Philadelphia chromosome). Genome-wide profiling using microarrays, candidate gene, and second generation sequencing have provided a number of key insights into the genetic basis of ALL. Treatment for acute lymphoblastic leukemia typically consists of a remission-induction phase, an intensification (or consolidation) phase, and continuation therapy to eliminate residual disease. Allogeneic haemopoietic stem-cell transplantation is the most intensive form of treatment for acute lymphoblastic leukemia as it clearly benefits several subgroups of patients with high-risk acute lymphoblastic leukemia. Although relatively homogeneous at the morphologic and immunophenotypic level, ALL encompasses a family of extremely heterogeneous disorders when examined at the genetic level. More insights are needed to further improve the treatment outcome of patients with ALL.*

Keywords: Acute lymphoblastic leukemia (ALL), Philadelphia chromosome, translocation, B-cell ALL, T-cell ALL.

1. Introduction

Acute lymphoblastic leukemia (ALL) is a form of leukemia, or cancer of the white blood cells characterized by excess lymphoblasts. It is a malignant disorder resulting from the clonal proliferation of lymphoid precursors with arrested maturation. The disease can originate in lymphoid cells of different lineages, thus giving rise to B-cell or T-cell leukemias or sometimes to mixed lineage leukemia[1]. Technological improvements now make it possible to demonstrate abnormalities in chromosomal number and/or structure in the majority of cases of ALL. The presence of hyperdiploidy (chromosome number >50) is associated with a very good prognosis in contrast to the dramatic poor prognosis in patients with hypodiploidy (chromosome number <45 per cell). Specific chromosomal translocations in ALL include the classical t (8; 14) in B-cell ALL, t (4; 11) in infant leukemia and t (9; 22) trans-location (that forms the Philadelphia chromosome) [4].

Acute lymphoblastic leukemia (ALL) is the single most common pediatric malignancy accounting for one fourths of all childhood cancer and three fourths of all newly diagnosed leukemias. The incidence of childhood ALL is approximately 3-4 cases per 100,000 children under the age of 15 years. Overall, males experience a slightly higher leukemia risk than females. This male preponderance is particularly evident in adolescent boys with T-cell ALL [3]. There is a significant peak in childhood ALL incidences that occur between the ages of 3 and 5 years. This peak is mainly due to pre B-ALL cases (referred to as "common ALL") in this age range [6], [10].

In lymphoblastic or lymphocytic leukemias, the cancerous change takes place in a type of marrow cell that normally goes on to form lymphocytes. Normally, the bone marrow makes blood stem cells (immature cells) that become mature blood cells over time. A blood stem cell may become a myeloid stem cell or a lymphoid stem cell. A myeloid stem cell becomes mature blood cells (red blood cells, white blood cells and platelets). A lymphoid stem cell becomes a lymphoblast cell and then one of three types of lymphocytes (white blood cells):

- B lymphocytes that make antibodies to help fight infection.
- T lymphocytes that help B
- Lymphocytes make the antibodies that help fight infection.
- Natural killer cells that attack cancer cells and viruses.

Initial symptoms are not specific to ALL, but worsen to the point that medical help is sought. They result from the lack of normal and healthy blood cells because they are crowded out by malignant and immature leukocytes (white blood cells). Therefore, people with ALL experience symptoms from malfunctioning of their erythrocytes (red blood cells), leukocytes, and platelets. A bone marrow biopsy gives a conclusive proof of ALL.

Pathological examination, cytogenetics (in particular the presence of Philadelphia chromosome), and immunophenotyping establish whether myeloblastic (neutrophils, eosinophils, or basophils) or lymphoblastic (B lymphocytes or T lymphocytes) cells are the problem. RNA testing can establish how aggressive the disease is. Medical imaging (such as ultrasound or CT scanning) can find invasion of other organs commonly the lung, liver, spleen, lymph nodes, brain, kidneys, and reproductive organs [2], [3]. Few factors associated with an increased risk of ALL have been identified [5]. The primary accepted risk factors for ALL include the following:

- Prenatal exposure to x-rays.
- Postnatal exposure to high doses of radiation (e.g., therapeutic radiation as previously used for conditions such as tinea capitis and thymus enlargement).

Genetic conditions that include the following:

- Down syndrome.
- Neurofibromatosis
- Shwachman syndrome
- Bloom syndrome.
- Ataxia telangiectasia.
- Inherited genetic polymorphisms.

About 25% of cases of B-cell precursor acute lymphoblastic leukemia, the most frequent form of acute leukemia in children, harbor the *TEL-AML1* fusion gene—generated by the t(12;21)(p13;q22) chromosomal translocation [9]. The presence of the *TEL-AML1* fusion protein in B-cell progenitors seems to lead to disordered early B-lineage lymphocyte development, a hallmark of leukemic lymphoblasts. Analysis of *TEL-AML1*-induced cord blood cells suggests that the fusion gene serves as a first-hit mutation by endowing the preleukemic cell with altered self-renewal and survival properties. B-ALL is characterized by the expression of a variety of B-cell-specific antigens, which often include PAX-5 (B-cell-specific activator protein), CD19, CD20, CD22 (surface and cytoplasmic), CD24, and CD79a (cytoplasmic)[8],[9].

In adults, the most frequent chromosomal translocation is t(9; 22), or the Philadelphia chromosome, which causes fusion of the BCR signalling protein to the ABL non-receptor tyrosine kinase, resulting in constitutive tyrosine kinase activity and complex interactions of this fusion protein with many other transforming elements, such as the signalling pathway for RAS (GTP-binding protein that activates target genes involved in cell differentiation, proliferation, and survival).

More than 50% of cases of T-cell acute lymphoblastic leukemia have activating mutations that involve *NOTCH1*, a gene encoding a transmembrane receptor that regulates normal T-cell development [9]. T-ALL is characterized by expression of T-lineage-associated antigens (CD2, CD3, CD4, CD5, CD7, CD8) as well as CD1a, CD10, CD34, CD99, HLA-DR, and Tdt.

2. Cytogenetic Study

Randomized chromosomal changes are encountered in 80% of ALL patients. Cytogenetics is one of the most important prognostic factors for ALL at diagnosis. Cytogenetic abnormalities can be numeric or structural. In children, ploidy is the most important prognostic factor. Patients with hyperdiploid ALL, particularly those with more than 50 chromosomes, have the best prognosis [6], [7]. Hyperdiploidy is present in 25-30% of children with ALL but in only 10-20% of adults.

Hypodiploid cases, most often from loss of chromosome 20, represent 6% of all cases. Although commonly presenting with good prognostic features, such patients have an intermediate prognosis. The prognosis of disease with a normal karyotype is intermediate [7]. Numeric chromosomal abnormalities (hyperdiploid and hypodiploid) are less common in adults and have less of an effect on outcome than they do in children. Patients with near-haploid disease (<1% of all cases) have a very poor prognosis. Eight to ten percent of all patients have a normal diploid karyotype, but the frequency is as high as 30% in those with T-cell ALL. The prognosis of disease with a normal karyotype is intermediate [11]. Pseudodiploid ALL represents a large percentage of patients. Overall, these patients have a poor prognosis.

2.1 Translocation t (9; 22) (q34; q11), or Philadelphia Chromosome

Philadelphia (Ph) chromosome is present in less than 5% of children with ALL but in 15-30% of adults. It involves band 34 of the long arm of chromosome 9, splicing the proto-oncogene *c-abl* to band 11 of the long arm of chromosome 22 in the *bcr* gene [12], [14]. In 50-80% of ALL cases, the breakpoint in 22q11 falls between exons b1 and b2 of the major breakpoint cluster region (*M-bcr*) [19].

2.2 t (4; 11) and Other Abnormalities in Band 23 of the Long Arm of Chromosome 11 (11q23)

Acute lymphoblastic leukemia with 11q23 abnormalities can present de novo and is seen in approximately 5% of all childhood ALL cases and less often in adult ALL cases[11],[12]. Patients with 11q23 abnormalities often are young, are African American, have high leukocyte counts, have CD-10 negative and early pre-B disease and have myeloid features. It is the most common chromosomal abnormality found in infants with ALL and, when analyzed molecularly, is present in more than 70% of cases. Although 11q23 abnormality is associated with a poor prognosis, infants who do not have this chromosomal abnormality may have an outcome comparable to that of children with intermediate risk ALL.

t (1;19) This 5% to 7% translocation in childhood ALL is present in and in less than 5% of adult ALL cases. It is often associated with a pre-B-cell immunophenotype. Patients with this abnormality exhibit other poor prognostic factors (high leukocyte count, high lactic dehydrogenase levels) and in some series have a poor prognosis [4].

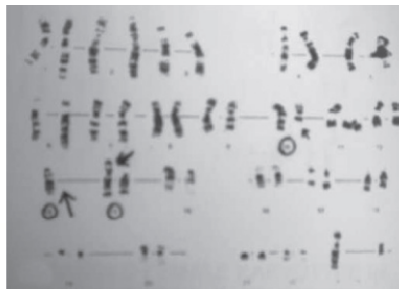
2.3 14q11 and 7q35 Abnormalities

These regions contain the loci for the TCR-alpha/gamma and beta genes respectively. They are rearranged in patients with T-cell ALL. The most common such abnormality is a t(11;14)(p13;q11), present in 7% of cases of T-cell ALL, which fuses the TCR-alpha/gamma to a gene called rhombotin 2, or *Ttg-2*. A less common translocation, t(11;14)(p15;q11), present only in 1% of T-cell ALL, affects rhombotin 1 or *Ttg-1*[3],[4].

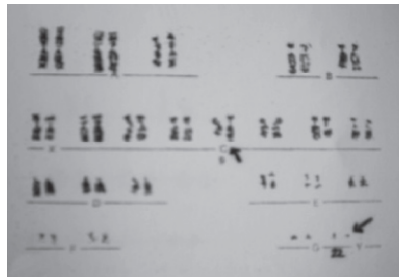
2.4 Other abnormalities

An abnormality in the short arm of chromosome 9, which occurs in 7-12% of cases of childhood and adult ALL, identifies a group of patients with high leukocyte count, older age, T-cell immunophenotype, a high rate of extramedullary relapse and poor outcome[4],[6]. It affects 9p21-22, which contain the IFN-alpha and IFN-beta genes. Abnormalities in 6q occur in 6% of cases, and their clinical and prognostic significance is uncertain. The short arm of chromosome 12 is affected in 10% of cases of childhood ALL, usually of B lineage, but there is great heterogeneity of the specific change.

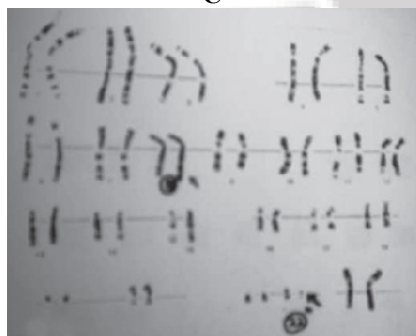
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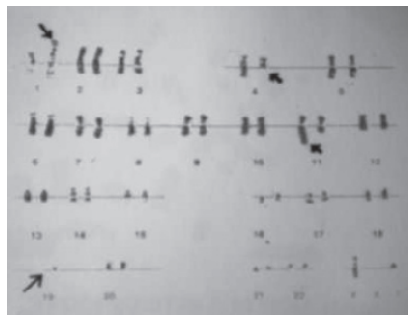
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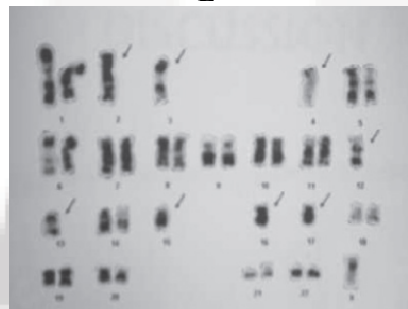
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(A) G-Banded Male karyotype in a patient of acute lymphoblastic leukemia showing translocation t(10;14) and deletion of chromosome 13 (arrow) (40X). (B) G-Banded karyotype in a female child of acute lymphoblastic leukemia showing translocation t(9;22) (arrow) (40X). (C) G-Banded karyotype in a female child of acute lymphoblastic leukemia showing translocation t(8;22) (arrow) (40X). (D) G-Banded karyotype in a male child of acute lymphoblastic leukemia showing translocation t(4;11),

Deletion of chromosome 19(-19), gain of short arm of chromosome 1 (arrow) (40X). (E) G-Banded male karyotype in a patient of acute lymphoblastic leukemia showing deletion of chromosomes 2, 3, 4, 12, 13, 15, 16, 17&Y (arrow) (40X) [ref:3].

Key cytogenetic alterations and genetic subtypes in childhood ALL [ref.19]

Table 1

Subtype	Frequency (%)	Comment
Hyperdiploidy (>50 chromosomes)	20–30	Excellent prognosis with antimetabolite-based therapy
Hypodiploidy (<44 chromosomes)	1–2	Poor prognosis, high frequency of RAS pathway and IKAROS gene family mutation
t(12;21)(p13;q22) <i>ETV6-RUNX1</i>	15–25	Expression of myeloid antigens; excellent outcome
t(1;19)(q23;p13) <i>TCF3-PBX1</i>	2–6	Increased incidence in African Americans; generally excellent prognosis; association with CNS relapse
t(9;22)(q34;q11.2) <i>BCR-ABL1</i>	2–4	Historically dismal outcome, improved with addition of imatinib to intensive chemotherapy
t(4;11)(q21;q23) <i>MLL-AF4</i>	1–2	Common in infant ALL (especially <6 months of age); poor prognosis
ERG deletion	7	Subtype of B-ALL with a distinct gene expression profile; favorable outcome

3. Molecular Study

In the last few years, genome-wide profiling using microarrays, candidate gene, and second generation sequencing have provided a number of key insights into the genetic basis of ALL. These studies have identified new subtypes of ALL and have uncovered recurring submicroscopic genetic alterations in known ALL subtypes. These include loss-of-function mutations involving genes regulating lymphoid development that contribute to the arrest in maturation characteristic of B-ALL, mutations that inactivate tumor suppressor and cell cycle regulatory proteins, and mutations that drive cytokine receptor and/or kinase signaling[20].

4. Clinical Characteristics

The signs and symptoms of ALL reflect the expansion of the leukemic clone in the bone marrow with impairment of normal hematopoiesis and the infiltration of nonhemopoietic tissues by the leukemic cells. Decreased numbers of normal progenitors, deficient production of normal hematopoietic growth factors, and production of inhibitory cytokines by the malignant clone have all been suggested. Patients with ALL have lymphadenopathy in up to 80% and hepatomegaly and/or splenomegaly in up to 75% of the cases [1], [2]. Other organs may also be involved, such as the kidney cortex (in one third of cases), lungs, heart, eyes and gastrointestinal tract. Skin involvement is seldom seen and is almost always associated with pre-B-cell phenotype. Central nervous system (CNS) involvement is observed in 5% of

children and in less than 10% of adults with ALL at diagnosis but is frequently asymptomatic [22]. It is often observed among patients with mature B-cell ALL. However, many patients will eventually develop CNS disease if not adequately treated. Testicular involvement is clinically evident in 1 % of children with ALL at diagnosis, although it may be occult in as many as 25%. Testicular relapse is rare in adults.

4.1 Therapeutic Approach Treatment

With the exception of patients with mature B-cell acute lymphoblastic leukemia, who are treated with short term intensive chemotherapy (including high-dose methotrexate, cytarabine, an cyclophosphamide), treatment for acute lymphoblastic leukemia typically consists of a remission-induction phase, an intensification (or consolidation) phase, and continuation therapy to eliminate residual disease[16]. Treatment is also directed to the CNS (central nervous system) early in the clinical course to prevent relapse attributable to leukemic cells sequestered in this site.

4.2 Remission-Induction Phase

The goal of remission-induction treatment is to eradicate more than 99% of the initial leukemic cell burden and to restore normal haemopoiesis and healthy performance status. This approach typically includes administration of a glucocorticoid (prednisone or dexamethasone), vincristine, and at least a third drug (asparaginase, anthracycline, or both). A three-drug induction regimen seems sufficient for most standard-risk cases provided they receive intensified post-remission treatment [16],[21]. Children with high-risk or very high-risk acute lymphoblastic leukemia, and virtually all adult cases of the disease, are treated with four or more drugs for remission induction. Levels of minimal residual leukemia are measured after 2 weeks and the treatment is intensified accordingly. Although no induction regimen is clearly superior to any others, addition of cyclophosphamide and intensive treatment with asparaginase are widely considered beneficial to patients with T-cell acute lymphoblastic leukemia, and imatinib mesilate has greatly enhanced the remission-induction rate, duration of disease-free survival, and quality of life of patients with Philadelphia chromosome-positive acute lymphoblastic leukemia [22].

4.3 Consolidation (Intensification) Treatment

With the restoration of normal haemopoiesis and body function, intensification treatment is generally used to eradicate drug-resistant residual leukemic cells, thus reducing the risk of relapse. Frequently used strategies include high-dose methotrexate plus mercaptopurine, reinduction treatment with the same agent that was given initially, frequent pulses of vincristine and corticosteroid plus high-dose asparaginase for 20–30 weeks, and an augmented regimen consisting of reinduction treatment and additional doses of vincristine, asparaginase, and intravenous methotrexate during periods of myelosuppression [16]. For patients with high risk or very high risk acute lymphoblastic leukemia, incorporation of high dose methotrexate plus mercaptopurine into a regimen based on intensive asparaginase treatment could be desirable.

4.4 Allogeneic Haemopoietic Stem-Cell Transplantation

Allogeneic haemopoietic stem-cell transplantation is the most intensive form of treatment for acute lymphoblastic leukemia. Allogeneic transplantation clearly benefits several subgroups of patients with high-risk acute lymphoblastic leukemia, such as individuals with Philadelphia chromosome-positive disease (even when treated with a tyrosine kinase inhibitor) and those with a poor initial response to treatment [13], [16], [17], [18]. It also improves the outcome of adults with the t (4; 11) subtype of acute lymphoblastic leukemia, but its benefits in infants with this genotype are controversial. Findings of studies suggest that matched unrelated-donor or cord-blood transplantation could produce results comparable with those obtained with matched related-donor transplantation. In view of the substantial morbidity and mortality associated with this procedure and the growing prospects for effective targeted therapy, the need for allogeneic transplantation should be reassessed continuously.

4.5 Continuation Treatment

Patients with acute lymphoblastic leukemia need continuation treatment to prevent or forestall relapse. Although about two-thirds of childhood cases can be treated successfully with only 12 months of therapy, they cannot be identified prospectively with any degree of certainty. Hence, all patients receive chemotherapy for 2.0–2.5 years. Daily mercaptopurine and methotrexate every week constitute the backbone of continuation regimens.

4.6 CNS-Directed Treatment

The prevention of CNS recurrence has been a well-established concept since late 60's. Since then in fact it became clear that CNS recurrence could represent the first sign of leukaemia resistance and progression. Leukaemia cells, undetected in the CNS at the time of diagnosis, may proliferate because systemically administered antileukemic agents do not penetrate the blood–brain barrier [16], [17]. With modern therapy regimens, which include different modalities of CNS preventive therapy, the incidence of CNS relapse is overall below 5%. Cranial irradiation is generally no longer used for patients with a good prognosis; intrathecal methotrexate alone or triple intrathecal chemotherapy, given periodically throughout maintenance chemotherapy, provide adequate CNS preventive therapy for these patients.

5. Conclusion

Although relatively homogeneous at the morphologic and immunophenotypic level, ALL encompass a family of extremely heterogeneous disorders when examined at the genetic level. This heterogeneity is reflected in the outcome of pediatric and adult patients in the context of contemporary therapies. High-throughput analysis methodologies have begun to characterize this heterogeneity and, although only in their early stages, have begun to uncover new clinically significant disease subsets, previously unidentified markers, mechanisms and predictors of disease relapse, germline polymorphisms important in individualized therapy, and new attractive therapeutic

targets. These insights are likely to further improve the treatment outcome of patients with ALL.

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