Childhood acute lymphoblastic leukaemia: a short review on the disease biology

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Abstract

Chidhood acute lymphoblastic leukaemia (ALL) is the most frequent childhood cancer constituting ~75% of paediatric malignancies. It is characterized by excessive accumulation of lymphoblasts and their progenitors. The disease is heterogeneous; malignant cells express diverse phenotypes and respond variably to chemotherapy. It originates from various genetic lesions in haematopoietic progenitor cells (HPCs) that are committed to differentiate in the T- or B-cell pathway that lead to precise stage-specific developmental arrest. In some cases, the first mutation along the multistep pathway to overt ALL might arise in a haematopoietic stem cell (HSC) possessing multi-lineage developmental capacity. The leukemic cells have clonal rearrangements in their immunoglobulin (Ig) or T-cell receptor (TCR) genes and express antigen-receptor molecules and other differentiation-linked cell-surface glycoproteins that largely recapitulate those of immature lymphoid progenitor cells within the early developmental stages of normal T- and B-cells. Thus, the leukemic lymphoblasts are the neoplastic counterparts of normal lymphopoietic progenitors, "frozen" at various stages of development. Leukemic clones lose their ability to differentiate but retain their proliferative potential. This review deals with the incidence, epidemiology and cause, symptoms, biologic features, diagnosis, prognosis, risk-assessment, treatment and survival rate of this haematopoietic neoplasticity.

Keywords – Childhood acute lymphoblastic leukaemia; haematopoietic progenitor cells minimal residual disease; 9-O-acetylated sialoglycoproteins

Running title – Biology of childhood ALL

Definition and pathobiology

Acute lymphoblastic leukaemia (ALL) is characterized by excessive accumulation of lymphoblasts and their progenitors. The disease is heterogeneous; malignant cells express diverse phenotypes and respond variably to chemotherapy.[1]

ALL originates from various genetic lesions in haematopoietic progenitor cells (HPCs) that are committed to differentiate in the T- or B-cell pathway, including mutations that impart the capacity for unlimited self-renewal and those that lead to precise stage-specific developmental arrest. In some cases, the first mutation along the multistep pathway to overt ALL might arise in a haematopoietic stem cell (HSC) possessing multi-lineage developmental capacity. The leukemic cells have clonal rearrangements in their immunoglobulin (Ig) or T-cell receptor (TCR) genes and express antigen-receptor molecules and other differentiation-linked cell-surface glycoproteins that largely recapitulate those of immature lymphoid progenitor cells within the early developmental stages of normal T- and B-cells.[2] Thus, the leukemic lymphoblasts are the neoplastic counterparts of normal lymphopoietic progenitors, "frozen" at various stages of development. Leukemic clones lose their ability to differentiate but retain their proliferative potential.[3-4]

The dominant theme of contemporary research in pathobiology of ALL is to understand the outcomes of frequently arising genetic lesions, in terms of their effects on cell proliferation, differentiation, and survival, and then to devise selectively targeted treatments against the altered gene products.[2]

Incidence

ALL is the most frequent childhood cancer constituting ~75% of paediatric malignancies.[1] Its incidence in the United States is approximately 3.4 cases per 1, 00,000 children, younger than 15 years of age, with peak incidence occurring between 2-5 years of age. It is common in males and in whites.[5]

Epidemiology and cause

The precise pathogenetic events leading to the development of childhood ALL are unknown. Only a few cases (<5%) are associated with inherited, predisposing genetic syndromes, such as Down's syndrome, Bloom's syndrome and Nijmegen breakage syndrome, with ionising radiation or exposure to specific chemotherapeutic drugs. Other risk factors include high birth-weight, parental occupation, maternal reproductive history, parental tobacco or alcohol use, maternal diet, prenatal vitamin use, exposure to pesticides or solvents, and exposure to the highest levels (>0.3 or 0.4 ìT) of residential, power-frequency magnetic fields. Retrospective identification of leukaemia-specific fusion genes, hyperdiploidy, or clonotypic rearrangements of Ig or TCR loci in archived neonatal blood spots and studies of leukaemia in monozygotic twins indicate clearly a prenatal origin for some childhood ALL. Genetic variability in xenobiotic metabolism, DNA repair pathways and cell-cycle checkpoint functions that might interact with environmental, dietary, maternal, and other external factors affect the development of ALL. A possible causal role may be polymorphisms in genes encoding cytochrome P450, NAD(P)H quinine oxidoreductase, glutathione S-transferases, methylenetetahydrofolate reductase, thymidylate synthase, serine hyroxymethyltransferase and cell-cycle inhibitors.[2,5]

Symptoms

The clinical manifestations of childhood ALL are protean. Symptoms and signs reflect the effects of dysfunctional haematopoiesis (anaemia, abnormal leukocyte count, fever, thrombocytopenia), clonal proliferation and infiltration of the leukaemia cells (lymphadenopathy, hepatosplenomegaly, and bone pain). Ultimately bone marrow (BM) aspirate establishes a definite diagnosis.

A broad spectrum of peripheral blood (PB) abnormalities is found at diagnosis. Not all patients have elevated blood counts; only half of them have a leukocyte count of >10,000/μL. Thrombocytopenia is often present although rarely as an isolated finding. Idiopathic thrombocytopenic purpura, a fairly common condition affecting young children, is an important differential diagnosis of childhood ALL.[5]

Biologic Features of childhood ALL

I. Morphologic and cyto-chemical classification

The morphologic and cyto-chemical features (Figure 1) of childhood ALL are not pathognomonic. FAB Cooperative Working group subdivided ALL into 3 types. L1 is the most common variety, representing 85% of ALL cases, with small uniform cells. L2, with large varied cells, affect >15%. The L3 designation, being the least common type representing >5%, describes lymphoblasts of mature B-cell stage that require therapy specifically for the Burkitt's type lymphoma. Cytoplasmic vacuoles are a prominent feature but not pathognomonic of L3.[5-6]

II. Immunophenotypic classification

Since ALL is a clonal disease resulting from the transformation of progenitor cells during its process of normal maturation, the phenotypic characteristics of the malignant population reflect the expression of lineage-associated antigens of that stage (i.e., B- or T-cell, Table 1), where transformation occurred.[5-6]

This mode of classification is clinically more relevant as it is based on the expression of certain antigens on the surface of leukemic cells. Approximately 85% of ALL cases belong to the B-cell lineage expressing CD19 and cytoplasmic CD22. Of these, 2-3% is mature B-cell ALL expressing surface Ig (sIg) and CD20. Another 20-30% has a pre-B-cell phenotype having cIg; remaining cases belong to the early pre-B-cell type (B-precursor ALL). They lack Ig expression but can be identified by the presence of common ALL antigen (CD10) and terminal deoxynucleotidyl transferase (TdT). Likewise, the 15% of ALL derived from the T-cell lineage reflects the stages of thymic differentiation. Most cases are from the early thymocyte stage.[6]

These CD antigens are lineage-specific. However, the expression of 9-O-acetylated sialoglycoproteins (Neu5,9Ac2-GPs) is universal in this disease, irrespective of the lineage.[7-9]

The leukemic cells often express markers of different haematopoietic lineages. A large percentage of the cancerous cells are $CD34^+$.[10] $CD34^+$ blast cells more likely co-express CD22, CD9 and CD13 antigens, but less

likely co-express cytoplasmic Ig (cIg). CD34 antigen expression occurs more often in non-T, non-B ALL than in T-cell ALL.[11] The $CD34^+$ cells of ALL lack the expression of CDw90. The dissociation of CDw90 and CD34 expression in the majority of ALL suggests that the development of these leukaemias occurs at a later stage than the HSC.[12] CDw90, expressed in some blasts, is not helpful for lineage determination in ALL immunophenotyping.[13] Once regarded as a specific marker for AML, CD117 is also expressed in a small proportion of ALL which is consistent with its putative role in early stages of B- and T-cell development. A small proportion of T-lineage ALL, mainly consisting of immature pro-T/pre-T-ALL often co-express myeloid antigens and is $CD117^+$. CD117 expression is rare in B-cell precursor ALL.[14] CD133 is an informative marker for the detection and further characterization of pro-B-ALL cells with MLL gene translocations.[13] ALDH is expressed in the progenitor cancer blasts.[15-16]

Ig and TCR gene rearrangements are also clonal markers of childhood ALL. The majority of B-lineage leukemic lymphoblasts have non-productive Ig gene rearrangements, consistent with their inability to develop normally.[3-4,11,17] Although TCR genes are frequently rearranged in B-lineage ALL, such changes is usually non-productive.[11,18]

Several CD antigens not related to a specific cell lineage are expressed on leukemic cells. CDl0, the common ALL antigen (CALLA), was among the first differentiation antigens used to sub-classify ALL. Its presence on leukemic cells was originally taken as a marker of common ALL, whereas its absence in 5-15% of non-T, non-B cases was used to recognize ALL variously termed as null cell, unclassified, or undifferentiated. Recent studies showed CD10 expression on leukemic cells of both B and T lineages and on some non-haematopoietic cells as well, with unknown role in leukemic cell proliferation and differentiation remains uncertain.

CD45 antigen, despite the ubiquitous expression of on normal leukocytes and their precursors, has undetectable to very low on expression on lymphoblasts. The percentage of blast cells expressing CD45 is higher in T-cell than in B-lineage cases. There is an inverse relationship between CD45 expression and that of the CD20 and CD34 antigens. CD38 is expressed by ~20% of normal BM cells, mitogen-activated peripheral T lymphocytes, plasmacytes and blast cells of ALL. CD71 is more common in T-cell than B-cell leukaemias.[6] In many cases, malignant cells express both CD4 and CD8.[11] Myeloid expression is found in 7-25% of ALL cases.[5]

The immunologic classification of ALL correlates with clinical characteristics with certain features associated with specific subtypes, as discussed below.

(i) Early pre-B cell ALL

These patients (~70% of childhood ALL cases, 1-9 years old) have low leukocyte counts and lack expression of cIg or sIg. Nearly half of children (<1 year old) and 10% of older children, lacking CD10, is associated with pseudodiploidy, high leukocyte counts, and poor prognosis. CD10-negative early pre-B ALL represents a more immature early pre-B ALL. More than three fourths of these patients express CD34, a feature often accompanied by hyperdiploidy, low incidence of central nervous system (CNS) involvement at presentation and good prognosis.

(ii) Pre-B cell ALL

This group, defined by the expression of cIg heavy chain, represents ~20% of ALL and often expresses CD10, with a frequency similar to that of early pre-B-cell ALL. It comprises more African-American patients than does the early pre-B-cell subgroup. These patients also have higher haemoglobin levels, leukocyte counts, and lactic dehydrogenase levels. Often pseudodiploid, with frequent association with t(l;l9), are less likely to be hyperdiploid. Poor prognostic characteristics and poor outcome might be correlated with t(1; 19) abnormality. Among patients with t(1; 19), pre-B immunophenotype correlates with a worse prognosis than early pre-B immunophenotype.

(iii) Transitional Pre-B cell ALL

This newly characterized subtype (~1% of ALL cases) expresses μ heavy chains on the surface, but lack light chains. Patients have L1 or L2 morphologic features with low leukocyte counts, are hyperdiploid, and have better outcome than patients with mature B-cell ALL.

(iv) Mature B-cell ALL

It occurs in <5% of patients, representing a leukemic phase of Burkitt's lymphoma. Presented with bulky extramedullary disease, including abdominal lymphadenopathy and frequent CNS involvement, morphologically, this type often represents the L3 subtype. Some cases of them do not show the L3 morphologic type and have lymphoma-like features and particular karyotypic abnormalities, such as 6q—, 14q+, t(l1; 14), or t(14; 18).

(v) T-cell ALL

This subtype, present in nearly 13-15% of cases of childhood ALL, is associated with male sex, older age, high leukocyte counts, CNS involvement, and mediastinal masses, the latter being associated with mature thymocyte phenotype. Patients without CD10 expression have a worse prognosis.[6]

III. Cytogenetics

Cytogenetic abnormalities are common in childhood ALL. A number of non-random genetic abnormalities have been identified, having significance in the pathobiologic condition of the disease. These genetic aberrations cause leukemic cells to differ from their normal lymphoid or myeloid progenitor counterparts.[5,19] A representative metaphase after G-banding in a c-ALL with t(9;22) so called Philadelphia translocation, is shown in Figure 2.

Occasionally, these abnormalities are a consequence of mistakes in the DNA rearrangement of normal lymphoid progenitor cells in the production of functionally diverse Ig and TCR molecules. At the time of DNA rearrangement, a cellular proto-oncogene gene, e.g., MYC on chromosome 8, may form a fusion gene with the Ig gene enhancer (IGH) on chromosome 14 in B- lymphoid progenitors resulting in the t(8;14)(q23;q32.) translocation. The functional outcome of this event is dysregulation of MYC transcription (Table 2).

Childhood ALL arise from recombination that does not involve antigen receptor genes. These rearrangements are the result of breaks and subsequent fusion between portions of the two genes resulting in a chimeric or fusion gene protein product that in turn produces malignant transformation. These oncogenic fusion proteins alter normal cell function.[19]

The most frequent translocations in B-lineage ALL are t(1;19),t(4;11), t(11;14), and t(9;22). ALL with L3 phenotype (mature B-cell leukaemia) typically exhibits abnormalities similar to Burkitt lymphoma, including t(8;14), t(2;8) or t(8;22) with breakpoints near the Ig heavy chain locus on chromosome 14 or light chain loci on chromosomes 2 or 22. In T-cell ALL, translocations frequently occur near the site of the a chain gene of TCR on chromosome 14, including Inv 14, t(14;14) and t(10;14). Inv 14 (q11;q32) can result in juxtaposition of the gene for the TCR joining segment with the Ig heavy chain locus. In other patients with T-cell malignancies, the translocation involves chromosome 7 at the site of the TCR â chain. 6q-, 9p- also occur in T-cell ALL. In addition, t(4;11) is common in hybrid leukaemias with phenotypic features of monocytes and B-lymphoid lineage.[1] Many cases of childhood ALL do not have detectable chromosomal translocations but instead show hyperdiploidy (with 50 chromosomes) or hypodyloidy. Upto 50% of childhood ALL lack defined molecular genetic abnormalities.[19]

For cytogenetics metaphases are analysed after several procedures of banding and staining (Giemsa (G-) or R-banding,). For complex aberrations or marker chromosomes, fluorescence in situ hybridization (FISH) studies are performed, which includes interphase FISH (IP-FISH), whole chromosome painting (WCP-) FISH, 24-color FISH or comparative genomic hybridization (CGH). For molecular methods, PCR, real-time PCR, sequencing and gene expression profiling using microarrays samples are used.[20]

Diagnosis

Several diagnostic techniques are mandatory at diagnosis for classification and individual therapeutic decisions in childhood ALL. Furthermore they are also needed for follow-up studies focussing especially on minimal residual disease (MRD) to guide further treatment decisions based on the response of the disease to given treatment protocols. Only by using a comprehensive diagnostic panel including cyto-morphology, cyto-chemistry, multi-parameter flow cytometry (MFC), cytogenetics, FISH and molecular genetic methods, the correct diagnosis in ALL can be established. The results serve as a mandatory prerequisite for individual treatment strategies and for the evaluation of treatment response using especially newly defined and highly specific MRD markers. However, in spite of so many existing techniques, the most important method for the diagnosis of ALL is MFC.

MFC using three, four or even five colour staining is applied to cases with the suspected diagnosis of ALL. This is absolutely necessary at diagnosis and achieves increasing importance for MRD. It is quicker and in some cases even cheaper in comparison to other MRD techniques, such as real time PCR for fusion genes or patient specific markers, such as FLT3-LM, or IgVH-mutations. These two aspects of MFC lead to a broad spectrum of antibodies to be evaluated at diagnosis. MFC leads to the most important subclasses in ALL - B-lineage versus T-

lineage. Thus, MFC gives important information for diagnosis, leads to treatment decisions and adds important prognostic parameters in ALL.[20]

Prognosis

Prognosis of children with ALL depends on several inter-related factors including age, initial leukocyte level, cytogenetic abnormality, immunophenotype, CNS involvement, sex, race, extent of lymphadenopathy, and response to therapy. Since most patients with ALL achieve remission, these prognostic factors relate primarily to the duration of remission. Impact of prognostic factors depends on the efficacy of therapy; more effective regimens decrease the importance of prognostic variables (Table 3).

Age is an important but complex risk factor. Children aged 1-9 years have the best prognosis. Poorer results occur in infants younger than 12 months of age which is most likely related to a higher incidence of undifferentiated and hybrid leukaemias. Prognosis is inversely related to leukocyte level at diagnosis. Although this is likely a continuous variable, leukocytes >20 or 50 x 10^9/L is often used as a high-risk criterion. Elevated serum levels of lactate dehydrogenase, IL-2 receptor and CD8 antigen correlate with higher leukocyte levels and have also been associated with poor prognosis. Sex is another prognostic factor in ALL. Males have poorer prognosis than females, which is only partly explained by the risk of testicular relapse. CNS leukaemia and extensive lymphadenopathy or hepatosplenomegaly are also adverse risk factors. Race is another risk factor; blacks have a poorer prognosis than whites. The incidence of ALL is however, lower in blacks, but the disease typically occurs at a younger age and is usually associated with other unfavourable prognostic factors.

Morphologic subtype is of limited prognostic import. L1 subtype is associated with better prognosis than L2. Immunologic phenotype of the leukaemia cells is also of prognostic importance. The CALLA positive subgroup has a relatively good prognosis. The early pre-B (cIg-) group is reported to have a better prognosis than the pre-B subset. Mature B-cell ALL has a poor prognosis, but improved results have been reported in recent studies employing therapy similar to that used for Burkitt lymphoma. T-cell ALL is associated with a poor prognosis. However, immune phenotype (CALLA versus T-cell type) is not an independent variable in many studies; its relationship is largely accounted for by other factors, particularly age and leukocyte count. Children whose leukaemia cells express myeloid antigens have a poorer prognosis than those with exclusively lymphoid phenotypes. Cytogenetic abnormalities provide independent prognostic information. In children, hyperdiploidy (>50 chromosomes) is associated with a favourable outcome if translocations are absent. In contrast, pseudodiploidy predicts a poor result. Some specific translocations are associated with a particularly poor prognosis, including t(9;22) and t(8;14).

Combinations of independent prognostic factors have been used to identify low- and high-risk groups. Criteria typically include age and leukocyte count. Other variables include CNS involvement, lymphoma syndrome or mediastinal mass, immunophenotype, and cytogenetics. Response to initial therapy is of major prognostic significance. The rapidity of cytoreduction and time to remission are important determinants of remission duration and survival. Patients achieving complete remission earlier have longer remissions than patients who require more extensive therapy.[1]

Risk-assessment

As the cure rate of ALL in children has reached 80%, stringent risk assessment is an important prerequisite in the selection of therapy, ensuring that patients are neither over-treated nor under-treated. On the basis of prognostic factors, patients are assigned to one of three risk groups (e.g., standard-, high-, or very high–risk groups). Remission induction treatment is same for all risk groups while the intensity of post-remission treatment differs according to the risk groups in all studies. Patients at high risk are typically treated with intensified post-remission chemotherapy, and patients at very high risk are considered as candidates for allogeneic HSC transplantation. A fourth category (low risk) has been advocated for the inclusion of those with a very low risk of relapse to receive treatment at reduced intensity.[2,21]

Treatment

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

Remission-induction phase

The goal of remission-induction treatment is to eradicate >99% of the initial leukemic cell burden and to restore normal haematopoiesis 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 is sufficient for most standard-risk cases provided they receive intensified post-remission treatment. Children with high-risk or very high-risk ALL are treated with four or more drugs for RI-1. MRD is measured after 2 weeks of RI and treatment is intensified in patients with high amounts of residual blasts (>1%). Clinical remission (CR) can thus be induced in 96–99% of children. Addition of cyclophosphamide and intensive treatment with asparaginase are widely considered beneficial to patients with T-cell ALL and imatinib mesilate greatly enhances the RI rate, duration of disease-free survival (DFS), and quality of life of patients with Philadelphia chromosome-positive ALL.[2,21]

Consolidation (intensification) treatment

With the restoration of normal haematopoiesis 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 along with re-induction 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 re-induction treatment and additional doses of vincristine, asparaginase, and intravenous methotrexate during periods of myelosuppression. For patients with high-risk or very high-risk ALL, incorporation of high-dose methotrexate plus mercaptopurine into a regimen based on intensive asparaginase treatment is desirable.[2,21]

Allogeneic haematopoietic stem cell transplantation

Allogeneic HSC transplantation is the most intensive form of treatment for ALL. Comparisons between this modality and intensive chemotherapy have yielded inconsistent results owing to the few patients studied. Nonetheless, allogeneic transplantation clearly benefits several subgroups of patients with high-risk ALL, 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. 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. Autologous transplantation, despite several practical advantages, has failed to enhance outcome in paediatric ALL.[2,21]

Continuation treatment

For reasons that remain elusive, patients with ALL need continuation treatment to prevent or forestall relapse. Although about two-thirds of patients 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 – 2•5 years. Daily mercaptopurine and methotrexate every week constitute the backbone of continuation regimens. Many investigators advocate that drug dosages be adjusted to maintain leukocyte counts below 3 x 109/L and neutrophil counts between 0•5 - 1•5 x 109/L to ensure adequate dose intensity during the continuation phase.[2,21]

CNS-directed treatment

CNS relapse is a major obstacle to cure, accounting for 30–40% of initial relapses in some studies. Factors associated with an increased risk of CNS relapse include a T-cell immunophenotype, hyperleucocytosis, high-risk genetic abnormalities, and presence of leukemic cells in cerebrospinal fluid (CSF). Polymorphisms in genes that code for proteins implicated in the pharmacodynamics of anti-leukemic drugs have also been associated with risk of CNS relapse. Because of its multiple complications, cranial irradiation is administered to only 5–20% of patients at high risk for CNS relapse.[2,21]

Survival rate

Steady progress in development of effective treatments has led to a cure rate of more than 80% in children, creating opportunities for innovative approaches that would preserve past gains in leukaemia-free survival while reducing the toxic side-effects of current intensive regimens.[2,21]

Tables

Table 1 – Immunophenotype in ALL: expression of differentiation markers

B-lineage	HLA-DR	CD19	CD24	CD10	CD20	CD21	CD22	CD23	cIg	sIg	#Neu5,9Ac$_2$-GPs
Early pre-B	+	+	+	+	±	-	Cyt	-	-	-	+
Pre-B	+	+	+	+	+	+	+	-	+	-	+
Transitional B	+	+	+	±	+	+	+	-	+	+μ*	+
Mature B	+	+	+	-	+	+	+	+	-	+	+
											+
T-lineage	**CD7**	**CD2**	**CD5**	**CD1**	**CD4**	**CD8**	**CD3**				+
Early	+	+	+	-	-	-	-				+
Intermediate	+	+	+	+	±	±	-				+
Mature	+	+	+	-	+	+	+				+

*μ heavy chains but no light chains; #9-*O*-acetylated sialoglycoproteins

Table 2 - Cellular genotype defining major forms of childhood ALL

Molecular Genetic Abnormality	Translocation	Biochemical Defect	Associated Features
		B-cell ALL	
TEL-AML1 fusion	t(12;21) cryptic	Transcription	Good prognosis
BCR-ABL fusion	t(9;22)(q34;q11)	Signal transduction	Poor prognosis
E2A-PBX fusion	t(1;19)(q23;p13)	Transcription	Pre-B phenotype, poor response to antimetabolites
MLL-AFX1 fusion	t(x;11)(q13;q23)	Transcription	
MLL-AF4 fusion	t(4;11)(q21;q23)	Transcription	Mixed lineage, infants, poor prognosis
MLL-ENL fusion	t(11;19)(q23;p13)	Transcription	Hyperleukocytosis
IGH-MYC fusion	t(8;14)(q24;q32)	Transcription	FAB L3, extramedullary disease
IGκ-MYC fusion	t(2;8)(p12;q24)	Transcription	FAB L3, extramedullary disease
IGλ-MYC fusion	t(8;22)(q24;q11)	Transcription	FAB L3, extramedullary disease
Hyperdiploidy	None	Unknown	Good prognosis
		T-cell ALL	
TAL1 deletion	None	Transcription	Extramedullary disease, CD2$^+$/, CD10$^-$
TCRδ -TAL1 fusion	t(1;14)(p32;q11)	Transcription	Extramedullary disease, CD2$^+$/, CD10$^-$
TCRβ-TAL1 fusion	t(1;7)(p32;q35)	Transcription	Extramedullary disease, CD2$^+$/, CD10$^-$
TCRα-MYC fusion	t(8;14)(q24;q11)	Transcription	Extramedullary disease
TCRδ-RBTN1 fusion	t(11;14)(p15;q11)	Transcription	Extramedullary disease
TCRδ-RBTN2 fusion	t(11;14)(p13;q11)	Transcription	Extramedullary disease
TCRδ-HOX11 fusion	t(10;14)(q24;q11)	Transcription	Extramedullary disease
TCRβ-LCK fusion	t(1;7)(p34;q34)	Signal transduction	Extramedullary disease

Table 3 - Prognostic factors for childhood ALL

Factors	Favourable	Unfavourable
Age	1-9 yrs	<1, >10 yrs
WBC	<50,000/μL	>50,000/μL
Sex	Female	Male
Race	White	Black, Hispanic
Fulky disease)*	Absent	Present
Extramedullary leukemia*	Absent	Present
Morphology (FAB)"	L1	L2, L 3
Immunophenotype*	B-Precursor	B, T
Cytogenetics	t(12:21), Hyperdiploidy (54-68 chromosomes)	Hypodiploidy (<45 chromosomes), Philadelphia chromosome, 11q23,t(1:19)*
Response to early treatment (Day 7 or 14)	Rapid	Slow*

*Prognostic value modified by treatment

Figure 1

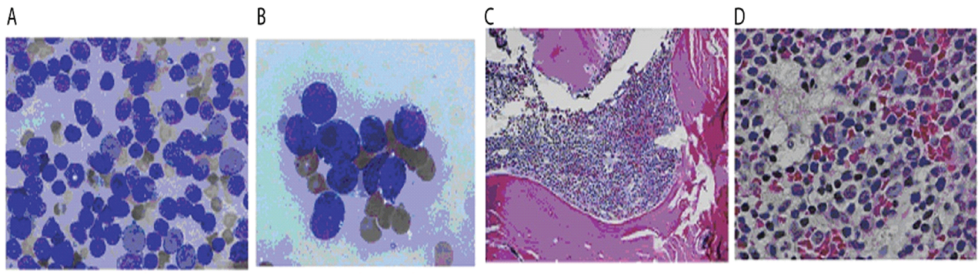

Figure 1. (A) BM aspirate showing sheets of blast cells (Wright). (B) Higher magnification showing blasts with markedly basophilic cytoplasm (Wright). (C) BM biopsy showing hypercellular marrow (haematoxylin–eosin). (D) Higher magnification showing extensive marrow replacement by leukemic blasts. [Reproduced from - Hayne *et al*, 2006].

Figure 2

Figure legends

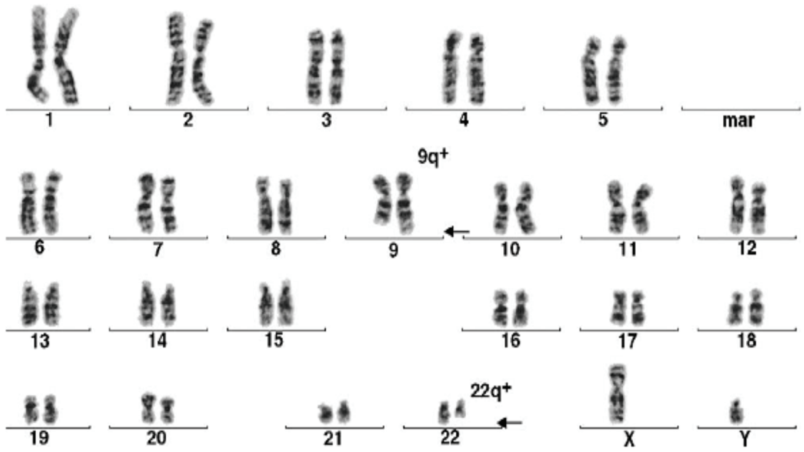

Figure 2. Metaphase after G-banding in a c-ALL with t(9;22) so called Philadelphia translocation. [Reproduced from - Haferlach *et al*, 2005]

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