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Acute Leukaemia

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Abstract: Acute leukaemia manifests itself into two different types being Acute Lymphocytic Leukaemia (ALL) and Acute Myelogenous Leukaemia (AML) depending on the type of leukocyte being affected. ALL raises a lot of concern since it is the most common type of leukaemia found in children while CML is the most common type of leukaemia in the United States. This study shows the epidemiology, the etiology, such as chromosomal aberrations and gene mutations and the clinical presentations consisting of both signs and symptoms. It also includes how these types of leukaemia are diagnosed as well as their pathophysiology which comprises detailed description of the alterations in various cellular mechanisms. Finally, the treatment involving both chemotherapy and stem cell therapy, amongst others, has also been discussed.

Key words: Chemotherapy, epidemiology, leukocyte, CML, ALL, AML

INTRODUCTION

By definition, leukaemia is 'a progressive, malignant disease of the blood-forming organs, characterised by distorted proliferation and development of leukocytes and their precursors in the blood and bone marrow' (Burgun *et al*., 2005).

The most common types of acute leukaemia are:

- Acute Lymphocytic Leukaemia (Acute Lymphoblastic Leukaemia).
- Acute Myelogenous Leukaemia (Acute Myeloid Leukaemia).

The term acute denotes the progression of the disease where there is a sudden and uncontrolled growth of immature hemapoeitic cells at the expense of normal marrow function. It is fatal if left untreated but it is potentially curable with appropriate therapy (Burgun *et al*., 2005).

The types of leukaemia are also categorised according to the type of leukocyte being affected. In lymphocytic leukaemia, malignant lymphoid cells are observed while abnormalities in myeloid cells are found in myelogenous leukaemia.

ACUTE LYMPHOCYTIC LEUKAEMIA (ALL)

ALL has an overall incidence of 1 to 1.5 per 100,000 persons and is particulary common in children aged 4 to 5 years with the incidence shooting to 4 to 5 per 100,000 persons and in people aged about 50 with an incidence of 2 per 100,000 persons. ALL represents 80% of acute leukaemia in children and 20% of acute leukaemia in adults (Jabbour *et al*., 2005).

In most cases, the cause is unknown. But studies have shown that there is possible genetic predisposition and this was observed among monozygotic and dizygotic twins of patients with ALL which showed higher incidence of ALL. Patients with trisomy 21 and inherited diseases with excessive chromosomal fragility such as Fanconi anaemia have a higher risk of developing ALL.

In pediatric leukaemia most chromosome translocations associated with leukaemia occur in utero during fetal hematopoeisis with secondary genetic events occurring postnatally.

There were also associations of human T-cell lymphotropic virus type 1 with adult T-cell leukaemia, Epstein-Barr virus with mature B-cell ALL and Human Immunodeficiency Virus (HIV) with lymphoproliferative disorders (Jabbour *et al*., 2005).

Symptoms include fatigue, lack of energy, easy bruising or oblivious bleeding, dyspnea, dizziness and infections. Central nervous system involvement was also observed in some subtypes and lypmhadenopathy and hepatosplenomegaly are noted in 20% of the patients with higher incidence in patients with T-cell ALL (Jabbour *et al*., 2005). Elevated LDH and uric acid are also observed (Dale *et al*., 2004).

A blast count of 20% or greater is observed in ALL as well as various chromosomal mutations including hyperdiploidy, hypodiploidy and pseudodiploidy. The latter consists of various chromosomal translocations and deletions. Figure 1 summarises the cytogenetic-molecular abnormalities in ALL (Jabbour *et al*., 2005).

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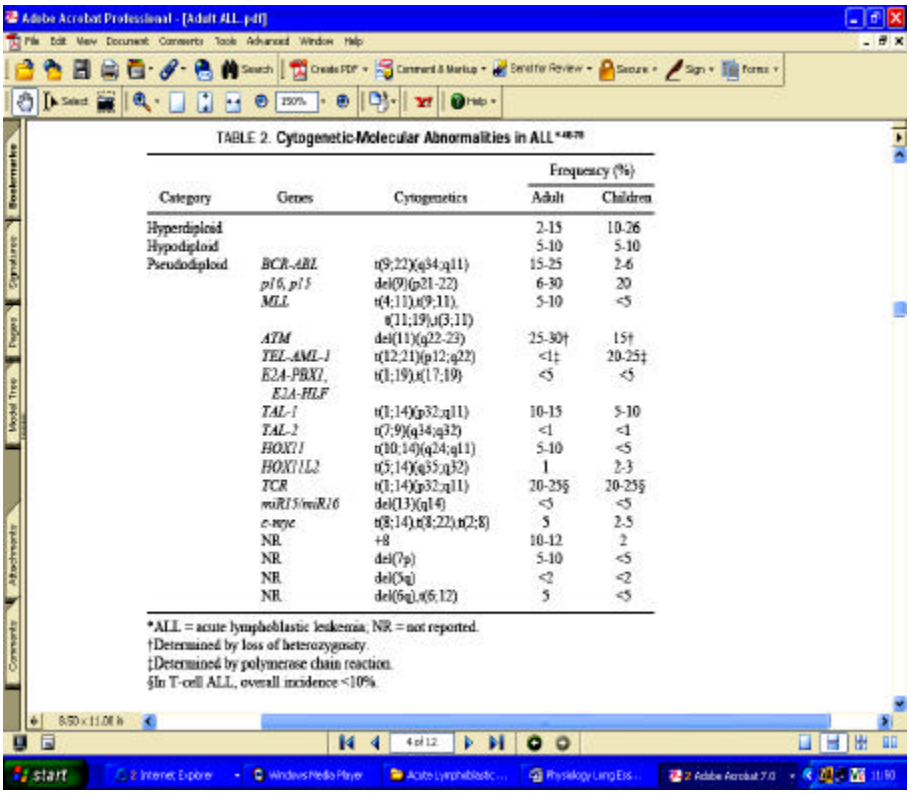

TABLE 2. Cytogenetic-Molecular Abnormalities in ALL

Category	Genes	Cytogenetics	Frequency (%) Adult	Frequency (%) Children
Hyperdiploid			2-15	10-26
Hypodiploid			5-10	5-10
Pseudodiploid	*BCR-ABL*	t(9;22)(q34;q11)	15-25	2-6
	p16, p15	del(9)(p21-22)	6-30	20
	MLL	t(4;11),t(9;11), t(11;19),t(3;11)	5-10	<5
	ATM	del(11)(q22-23)	25-30†	15†
	TEL-AML-1	t(12;21)(p12;q22)	<1‡	20-25‡
	E2A-PBX1, E2A-HLF	t(1;19),t(17;19)	<5	<5
	TAL-1	t(1;14)(p32;q11)	10-15	5-10
	TAL-2	t(7;9)(q34;q32)	<1	<1
	HOX11	t(10;14)(q24;q11)	5-10	<5
	HOX11L2	t(5;14)(q35;q32)	1	2-3
	TCR	t(1;14)(p32;q11)	20-25§	20-25§
	miR15/miR16	del(13)(q14)	<5	<5
	c-myc	t(8;14),t(8;22),t(2;8)	5	2-5
	NR	+8	10-12	2
	NR	del(7p)	5-10	<5
	NR	del(5q)	<2	<2
	NR	del(6q),t(6;12)	5	<5

*ALL = acute lymphoblastic leukemia; NR = not reported.
†Determined by loss of heterozygosity.
‡Determined by polymerase chain reaction.
§In T-cell ALL, overall incidence <10%.

Fig. 1: The cytogenetic-molecular abnormalities in ALL (Jabbour *et al*., 2005)

The World Health Organization proposed an identification method based upon the immunophenotypes as illustrated in Fig. 2. Three broad groups can be distinguished:

- Pre-B-cell ALL (80% approximate frequency).
- Mature B-cell ALL (<5% approximate frequency).
- T-cell ALL (10-15% approximate frequency) (Jabbour *et al*., 2005).

To add to the previous figure, the pre-B-cell ALL is also positive for TdT (Terminal deoxynucleotidyl Transferase) and HLA-dr antigens while the B-cell mature ALL cells are negative for TdT and exhibit surface Ig (Dale *et al*., 2004).

B-cell ALL: The major causes behind B-cell malignancy are a series of chromosomal translocations effecting the c-myc gene overexpression as shown in Fig. 3.

Other causes include mutations in p53, methylation of Death-Associated Protein kinase (DAP-kinase) and down-regulation of p16INK4a or p15INK4b via gene hypermethylation impairing cell apoptosis. Besides this, there are also deletions or mutations or several negative regulatory elements within the c-myc gene. A clear example is the mutation in the threonine 58 residue of c-myc causing its accumulation and therefore, overexpression as a result of impaired proteasome-mediated degradation (Blum *et al*., 2004).

C-Myc overexpression causes both the activation of certain genes involved in cell cycle progression being the cyclins D1 and D2 and the CDKs 4 and 6 genes and the repression of genes involved in cell cycle arrest such as those coding for the CKIs $p21^{cip1}$ and p27. Overall, this leads to the proliferation of B-cells.

Apoptosis is also the target of c-myc overexpression which led to the induction of p19, increased p53, activation of FAS, upregulation of the Bax protein and activation of the apoptosis gene TRAP1 which codes for a Tumour necrosis factor receptor.

Cell adhesion was also effected due to the downregulation of collagen production and decreased fibronectin which is mediated by c-myc over expression as well (Blum *et al*., 2004).

T-cell ALL: A stepwise alteration of at least four specific pathways is required before T-cells become fully malignant associated with four different classes of mutations:

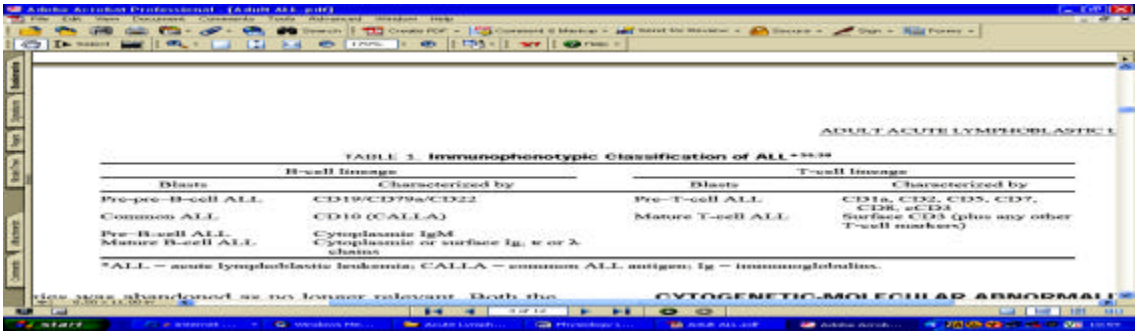

Fig. 2: Immunophenotypic classification of ALL- Different maturation stages have been identified in pre-B-cell ALL being pre-pre B-cell ALL, common ALL and pre B-cell ALL each of which has different markers (Jabbour *et al*., 2005)

Translocation	Gene juxtaposition	Phenotype
T(8;14)*	Combination of c-myc gene with IgH enhancer	Increased *c-myc* mRNA and protein production
T(2;8)(p12;q24)	*c-myc* gene placed adjacent to 8 light chain locus and enhancer elements	*c-myc* transcription uncontrollably enhanced due to high activity of heavy and light chains in B-cells
t(8;22)(q24;q11)	*c-myc* gene juxtaposed to the 8 light chain locus and enhancer elements	*c-myc* transcription uncontrollably enhanced due to high activity of heavy and light chains in B-cells

*Different breakpoints have been identified on chromosome 8 and 14 leading to clinical variants of the disease. In for example Burkitt's Lymphoma (BL) which is considered as a type of B-cell acute lymphocytic leukaemia, different chromosomal breakpoints yield the endemic variant and the sporadic variant

Fig. 3: Chromosomal translocations leading to c-myc overexpression (Blum *et al*., 2004)

- Mutations that affect the cell cycle.
- Mutations that impair differentiation.
- Mutations that provide proliferative and survival advantage.
- Mutations providing self-renewal capacity (De Keersmaecker *et al*., 2005).

The major mutation affecting the cell cycle is the inactivation of CDKN2A and CDKN2B. These are 2 genes located in close proximity on chromosome region 9p21. CDKN2A encodes both p16 and p14 which are potent regulators of the cell cycle since p16 inhibits Rb1 phosphorylation whereas p14 activates p53. In ALL, various deletions are observed in CDKN2A which deletions vary in size and can cover large genomic regions. As a result, nearby genes such as CDKN2B (encoding p15) are therefore co-deleted. Such deletions in CDKN2A and CDKN2B are present in 65 and 23% of T-ALL cases, respectively. Inactivation of CDKN2A and CDKN2B can also be as a result of promoter hypermethylation. RB1, p53, p27 are rarely mutated in T-ALL (De Keersmaecker *et al*., 2005).

Mutations which impair differentiation cause the deregulated expression of normal transcription factor proteins. The mutations include the juxtaposition of promoter and enhancer elements of T-cell receptor genes TRA@ (14q11), TRB@ (7q34-35), TRG@ (7p15) and TRD@ (14q11) to a small number of developmentally important transcription factor genes. This leads to the obvious deregulation of transcription factors which may alter the gene expression programs that regulate hematopoeitic differentiation of a multipotent progenitor. Figure 4 summarises the mutations occurring in T-cell ALL and their effect on the phenotype (De Keersmaecker *et al*., 2005).

Mutations in LCK, ABL1, RAS and PTEN provide proliferative and survival advantage. The latter four genes are all involved in the T-cell receptor signalling pathway which is activated by the antigen binding to the MHC protein on t-cell surface. The final outcome of such TCR signalling pathway is the production of IL-2 involved in T-cell proliferation. The mutations associated with proliferative and survival advantage are summarised in Fig. 5.

Specific treatment: Imatinib mesylate is given to ALL patients with ABL-1 fusions since this drug is a selective inhibitor of the ABL-1 kinase activity (Jabbour *et al*., 2005).

In the case of patients with hyperactive LCK, SRC kinase inhibitors and dual SRC/ABL kinase could be used (De Keersmaecker *et al*., 2005).

Mutations providing self-renewal properties are found in NOTCH1 which is involved in the regulation of stem cell maintenance. Its mutation occurs in a way that it provides the leukemic cells with self-renewal capacity.

Mutation	Gene juxtaposition	Phenotype
t(10;14)(q24;q11)		Overexpression of HOX11-immortalise murine haematopoietic progenitors
t(7;10)(q35;q24)		Same as above
t(5;14) (q35;q32)	Combination of TLX3 to the distal region of BCL11B (a gene highly expressed in T-cell differentiation)	Overexpression of TLX3 which act through oncogenes such as NOTCH 1
inv(7)(p15q34)	TRB@ locus to part of HOXA@ cluster (7p15)	Deregulated expression of HOXA10 and HOXA 11 causing incomplete differentiation of T-cells
t(7;19)(q35;p13)	LYL 1 juxtaposed to the TRB@ locus	Overexpression of LYL 1 gene – its oncogenic potential not yet demonstrated
t(1;14)(p32;q11)	TAL1 combined with regulatory TCR gene elements	Overexpression of TAL1 causes maturation arrest of T-cells in the late cortical stage
T(7;9)(q34;q32)	TAL 2 gene juxtaposed to the TRB@ locus	Same as above
t(11;14)(p15;q11)	Juxtaposition of *LMO1* or *LMO2* to the *TRA*@ or	
t(11;14)(p13;q11)	*TRD*@ loci	Coexpressed with TAL1
t(9;11)	MLL gene rearrangement	Differentiation arrest at an early T-cell differentiation

Fig. 4: Summary of the mutations in T-cell ALL affecting cell differentiation, the gene juxtaposition associated with them and their effect on the phenotype. LYL1, TAL1 and TAL2 are members of the basic Helix Loop Helix (bHLH) family of transcription factors which interact with DNA (De Keersmaecker *et al*., 2005)

Mutation	Phenotype
NUP214-ABL1 fusion	
ETV6-ABL1 fusion	Associated with TLX1 or TLX3 expression and deletion of CDKN2A
EML1-ABL1 fusion	resulting in excessive activation of survival and proliferation pathways
t(1;7)(p34;q34)-Juxtaposition of the LCK and TRB@ loci	Overexpression of LCK leads to cell proliferation
RAS mutation	Associated with proliferation in T-cell ALL
PTEN Inactivation	Inactivation of this tumour suppressor protein leads to high concentrations of PI3K and therefore uncontrolled proliferation

Fig. 5: Mutations providing proliferative and survival advantage (De Keersmaecker *et al*., 2005)

Its hyperactivity occurs due to fusion with the T-cell receptor b gene in t (7; 9) (q 34; q 34.3).

NOTCH1 (ICN) translocates to the nucleus where it associates with other proteins to form a transcription activator complex. ICN normally has a short half-life, being subject to ubiquitination and degradation. In some mutated forms, the heterodimerization domain (the domain joining the extracellular domain (NEC) to the transmembrane domain (NTM) of the NOTCH1 receptor in a covalent manner) is altered and thus destabilizing the NEC and NTM intersubunit association. This leads to increased ICN production rates without ligand stimulation. In other mutated forms PEST domain mutations were observed which extend the half-life of the ICN-containing transcriptional activation complex (De Keersmaecker *et al*., 2005).

GENERAL TREATMENT FOR ALL

Nowadays, 80% of children with ALL are cured showing the success of this anti cancer treatment. It is divided into four phases being:

- Induction.
- Intensified consolidation.
- Maintenance.
- Central Nervous System (CNS) Prophylaxis.

The first phase consists of a combination of corticosteroids, vincristine and anthracylines which results in complete remission rates of 72-92%. Additional drugs are utilised for specific ALL subtypes in order to make the treatment more effective. In mature B-cell ALL, fractionated doses of cyclophosphamide, rituximab and high-dose methotrexate are administered while in T-cell ALL, cytarabine and cyclophosphamide are given. Studies have shown that a faster recovery has been experienced in those patients who received G-CSF (Granulocyte-Colony Stimulating Factor). In fact a remarkable faster recovery of neutrophils and platelets was observed compared with patients who were put on placebo (Jabbour *et al*., 2005).

The second phase consists of a repetition of a modified induction schedule or stem cell transplantation. Treatment is given according to the ALL subtype-high dose methotrexate in standard-risk B-cell lineage ALL, cyclophosphamide and cytaribine in T-cell lineage, high dose methatrexate and high dose cytaribine in high-risk B-cell lineage ALL (Jabbour *et al*., 2005).

The third phase includes daily 6-mercaptopurine, weekly methotrexate and monthly pulses of vincristine and prednisone given for 2 to 3 years. This phase does not include the B-cell ALL subtype since the latter responds well to short-term dose-intense regimens.

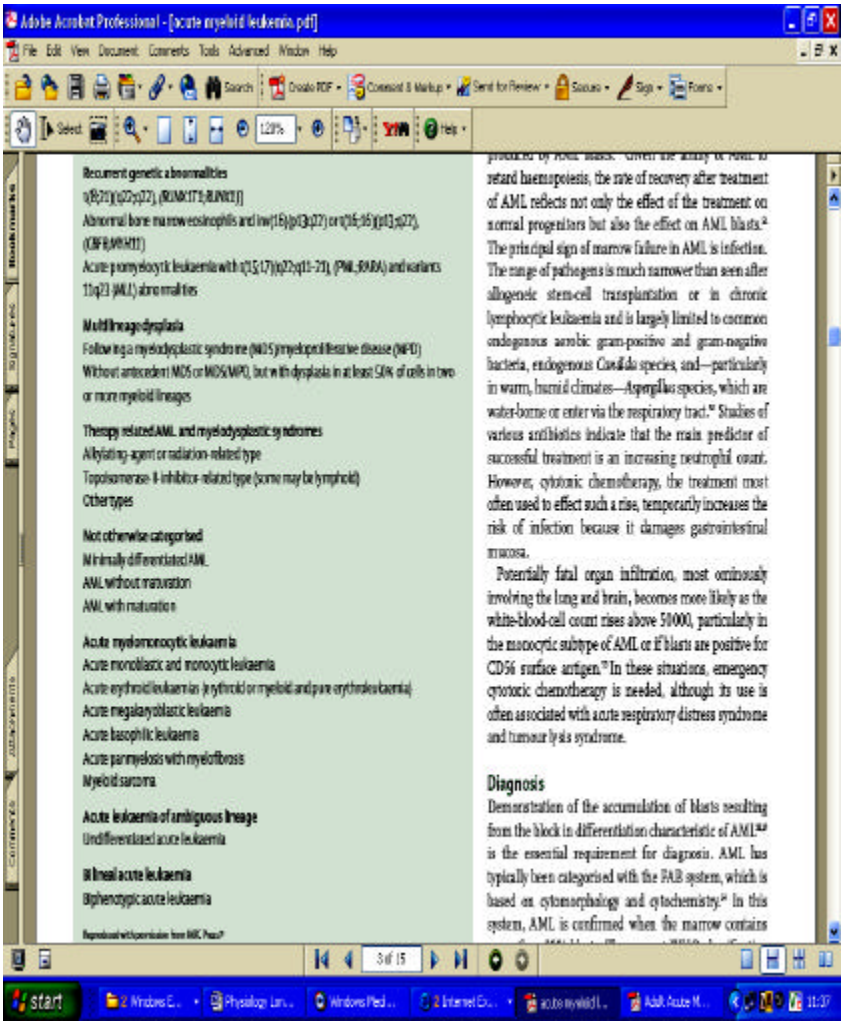

Fig. 6: The classification of Acute Myeloid Leukaemia according to the World Health Organization (Estey *et al*., 2006)

The fourth and last phase targets leukaemia in the CNS. To progress to this treatment phase, there must be more than 5 white blood cells per microlitre in the cerebrospinal fluid and the presence of lymphoblasts. Treatment consists on intrathecal chemotherapy with methotrexate, cytaribine and corticosteroids and the usual high dose systemic chemotherapy (Jabbour *et al*., 2005).

ACUTE MYELOGENOUS LEUKAEMIA

Acute Myelogenous Leukaemia (AML), also known as non-lymphocytic leukaemia, is a heterogeneous clonal disorder of the haematopoietic cells which have lost the ability to differentiate and to respond to normal progenitor regulators. The genetic reprogramming of AML blasts makes them ineffective at generating mature red cells, neutrophils, monocytes and platelets (Jabbour *et al*., 2006). These AML blasts also inhibit the differentiation of the normal blasts into mature progeny by producing various chemokines (Estey *et al*., 2006).

Acute Myelogenous Leukaemia is further subdivided into subtypes. This classification has been proposed by the World Health Organisation as illustrated in Fig. 6.

It is the most common type of leukaemia in the United States with its frequency ranging between 3.8-17.9 cases per 100,000 individuals with a ratio of 3 males: 2 females (Jabbour *et al*., 2006; Estey *et al*., 2006).

AML is associated with exposure to ionising radiation, benzene and to cytotoxic chemotherapy. Benzene exposure is due to cigarette smoking which causes aberrations of chromosomes 5 and 7, trisomy of chromosome 8 and a balanced translocation between

	Genes	Morphological association	Incidence*
Translocations/inversions			
t(8;21)(q22;q22)	*RUNX1;RUNX1T1*	M2 with Auer rods	6%
inv(16)(p13q22) or t(16;16)(p13;q22)	*CBFB;MYH11*	M4Eo	7%
t(15;17)(q22;q11–21)	*PML;RARA*	M3/M3v	7%
t(9;11)(p22;q23)	*MLL;AF9*	M5	2%
t(6;11)(q27;q23)	*MLL;AF6*	M4 and M5	~1%
inv(3)(q21q26) or t(3;3)(q21;q26)	*EVI1;RPN1*	M1, M4, M6, M7?	~1%
t(6;9)(p23;q34)	*DEK;NUP214*	M2, M4	~1%
Chromosomal imbalances			
+8	..	M2, M4 and M5	9%
–7/7q–	..	No FAB preference	7%
–5/5q–	..	No FAB preference	7%
–17/17p–	*TP53*	No FAB preference	5%
–20/20q–	..	No FAB preference	3%
9q–	..	No FAB preference	3%
+22	..	M4, M4Eo	3%
+21	..	No FAB preference	2%
+13	..	M0, M1	2%
+11	*MLL1*†	M1, M2	2%
Complex karyotype‡			10%
Normal karyotype			44%

*Determined among 1311 patients with de-novo AML enrolled onto study 8461 of the Cancer and Leukemia Group B.[48] †Partial tandem duplication of the *MLL* 1. ‡Three or more chromosomal aberrations in the absence of t(8;21), inv(16)/t(16;16), t(15;17), or t(9;11). Reproduced with permission from Elsevier.[29]

Table 1: **Common chromosome aberrations in AML**

Fig. 7: The common chromosomal aberrations in AML (Estey *et al*., 2006)

Result	Diagnosis
>/= 3% stain positive for myeloperoxidase or Sudan Black B	Acute myeloid leukaemia
Peroxidase negative but stain for butyrate	Acute monocytic leukaemia
None of the above	Lineage determination based upon blasts expressing surface antigens associated with myeloid (equivalently monocytic, erythroid, or megakaryocytic) or lymphoid immunophenotype

Fig. 8: Using cytochemical stains to determine the type of AML (Jabbour *et al*., 2006)

chromosomes 8 and 21 while cytotoxic chemotherapy leads to aberrations of chromosomes 5 and 7 (Jabbour *et al*., 2006; Estey *et al*., 2006). Figure 7 depicts the common chromosomal aberrations in AML.

CLINICAL PRESENTATION AND DIAGNOSIS

The patient presents with fatigue, bruising, bleeding, fever and infection which might be fatal (Lancet) and this is due to bone marrow failure (Estey *et al*., 2006). Ten percent of AML patients present with White Blood Cell (WBC) counts greater than 100×10^9/L and these are at a higher risk of tumor lysis syndrome, CNS involvement and leukostasis (Abnormal intravascular leukocyte aggregation and clumping). There can also be organomegaly, lymphadenopathy, retinal hemorrhages and organ infiltration such as the skin, the lung and brain, with the latter two becoming more likely as the white-blood-cell count rises above 50 000 (Jabbour *et al*., 2006).

An increase in the number of myeloblasts in the peripheral blood and in the bone marrow is also observed and there must be the presence of a minimum of 20% blasts in the marrow sample. But the following mutations should immediately be attributed to AML irrespective from the myeloblast percentage results. These mutations are the cytogenetic abnormalities t(8;21)(q22;q22), inversion (16)(pl3q22) or t(16;16)(pl3;q22) and t(15;17)(q22;ql2) (Jabbour *et al*., 2006).

The blast lineage is then determined by means of cytochemical stains as shown in Fig. 8.

Analysis of the Myeloid antigens is also useful. These include CD13, CD33, c-kit, CD14, CD64 (the latter 2 are monocytic markers) glycophorin A (an erythroid marker) and CD41 (a megakaryocytic marker) (Estey *et al*., 2006).

PATHOPHYSIOLOGY

Inversions in chromosome 16 lead to a genetic variation in enzymes that detoxifies benzene and other carcinogens such as the NADPH quinine oxidoreductase 1 (NQO1). A single 609C÷T substitution in NQO1, decreases NQO1 activity and if the two alleles are mutant, the enzyme activity is abolished.

It was found that the AML blasts are derived from normal myeloblasts which have been affected by two types of genetic damage.

Class 1: Activation of cell-surface receptors, such as RAS, or receptor tyrosine kinases, such as FLT3 and c-KIT. This give the myeloblast a survival and proliferative advantage through the activation of various downstream pathways. This thus leads to clonal expansion of the affected haemopoietic progentitors. Studies performed on mice have demonstrated the fact that abnormalities in RAS, FLT3, or c-KIT by themselves produce only a myeloproliferative disorder and not AML (Estey *et al*., 2006).

Class 2: This is caused by the over expression of HOX genes or formation of fusion genes (resulting from the t(8;21) or inv(16) abnormalities) which block the myeloid differentiation. These aberrations alone didn't result in AML in mice. But it has been proved that AML might develop only when both classes of lesion are present (Estey *et al*., 2006).

Various tumour suppressor genes were found to be silenced in AML by permanent hypermethylation.

Studies have shown that the most common somatic gene mutations in AML are in the nucleophosmin gene, NPM1. It causes cytoplasmic and not nuclear localisation of the protein. NRAS or KRAS mutations are less common and occur in about 18% of patients (Estey *et al*., 2006).

Treatment: Usually the treatment consists of two phases.

Phase 1: This step attempts to produce a complete remission i.e., a marrow with <5% blasts, a neutrophil count >1000 and a platelet count > 100,000. This is the only response that leads to a cure thus leading to an increased survival rate.

Phase 2: This step aims to prolong the complete remission that has commenced in Phase 1 (Estey *et al*., 2006).

Several drugs have been developed which target target FLT3 aberrations and the RAS signalling pathway. Besides this, hypomethylating agents, such as decitabine and histone deacetylase inhibitors, such as valproic acid might allow the transcription of genes silenced in AML. Generally AML treatment consists of a combination of an anthracycline line (e.g., daunorubicin and cytarabine). Cytarabine is given by continuous intravenous fusion daily for 7 days together with daunorubicin which is also given daily for 3 days. Fifty to eighty percent of AML patients might achieve complete remission (Estey *et al*., 2006).

Additional chemotherapy must be administered to cure AML in postremission patients. If not, the median disease-free survival will not exceed four months (Jabbour *et al*., 2006; Estey *et al*., 2006). If several courses of induction therapy are given (also known as consolidation therapy), there is a 40-50% chance of survival at 4 years (Estey *et al*., 2006).

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