DEFINITION :

- ✓ Malignancies of immature haematopeotic cells & ↓ ability to differentiate into mature elements.

Or :

- ✓ Clonal malignant disorders characterized: by the proliferation of abnormal (leukemia) Blast cells and impaired production of normal blood cells.
- ✓ > 20% blast cells in the bone marrow

Normally **< 5%**

Myelodysplastic **5-20%**

Acute leukemia **> 20%**

→ **diagnostic**

The most mature cell is the ***Nuetrophil*** [mature nutrophil]

- ➢ Monopotential : one type of cells
- ➢ Poly potential : multiple types of cells

Types :

- ✓ Acute Myeloid Leukaemia (AML)
- ✓ Acute Lymphoblastic leukemia (ALL)

EPIDEMIOLOGY :

- ✓ AML Common in adult (> 15 y) >80%
- ✓ ALL Common in children (<15 y) >80%

ETIOLOGY (or Risk Factors) :

- ➢ Drugs & chemicals
  - ✓ Alkylating agents (Chlorambucil, N mustard, Melphalan)
  - ✓ Topoisomerase inhibitors (Etoposide)
  - ✓ Benzene

- Ionizing radiation
- Viruses
  - ✓ HTLV – 1 [adult T-cell leukemia Lymphoma]
- Genetic disorders
  - ✓ Down's syndrome , Immunodeficiency syndrome
  - ✓ Myelodysplastic syndrome [group of disorders have a tendency to cause bone marrow failure]

Clinical manifestations :

- Usual **1-3 month** [Myelodysplastic syndrome MDS – 1 year] history of signs or symptoms related to:
  - ✓ Pancytopenia:

    - ↓WBC (neutropenia) →infection, fever [sepsis, pneumonia , peri rectal abscess]
    - ↓Hb (severe megaloblastic anemia) → Pallor, fatigue, malaise, dyspnoea..
    - ↓Platelets (thrombocytopenia) →bleeding (esp. after dental procedures), easy bruisability , sever epistaxis, bleeding through

  - ✓ Organ infiltration:

    - Lymphadenopathy.
    - Splenomegally.
    - Hepatomegally.
    - Bone pain.
    - CNS involvement in 5-10% of patient (cranial neuropathies, nausea & vomiting headache)
    - Tumor lysis syndrome.

    Note : this more common with ALL than AML

][Acute Leukemia][

- Leukostasis (when blast count > 50,000 /µl) : occluded microcirculation → local hypoxemia & hemorrhage → headache, blurred vision, TIC/CVA, dyspnea & hypoxia .
- DIC (esp. with M3)
- Leukemic infiltration of skin & gingival
- chloroma : extramedullary tumor of leukemic cells .

Note : this more common with AML than ALL

Investigations :

- CBC:
  - ✓ Variable WBC (60% of pts have a↑ WBC , the rest could be normal or ↓ WBC
  - ✓ Most are anemic
  - ✓ Most are thrombocytopenic
  - ✓ 90% have blast in the peripheral blood film.
- Tumor lysis Syndrome :
  - ✓ Hypo kalemia **↓ Ca**
  - ✓ Hypomagnesaemia **↓ Mg**
  - ✓ Hyperphosphatemia **↑ PO4**
  - ✓ Hyper metabolism **(↑LDH , ↑Uric acid**)

Note : Dry tap can't aspirate bone marrow

- Coagulation Studies (M3-DIC)
- Bone marrow biopsy and aspirate:-
  - ✓ Hypercellular with > 20% or more of all nucleated cells are blasts.
- Radiology:-
  - ✓ CXR: mediastinal mass (T-cell ALL)
  - ✓ Osteopenia or lytic lesion 50% of patients with ALL. (itractable pain).
- CSF analysis:
  - ✓ in all ALL Px & some AML Px.
  - ✓ It is useful in prophylactic chemotherapies.. coz once any malignant cell enter CSF >> rapidly divides ..((ba3deen moshkila coz not all drugs can pass CSF..))
- HLA typing:
  - ✓ For young high risk Px.

Differential diagnosis of acute leukemias :

- ✓ Lymphoma.
- ✓ Myelodysplastic syndrome.
- ✓ Multiple myeloma(malignancy of plasma cells) .
- ✓ Aplastic anemia
- ✓ Sever megaloblastic anemia due to B12 defeciency .
- ✓ Severe lymphocytosis due to infections.
- ✓ Leukemoid reaction (↑ mature leukocyte 30,000)

CLASSIFICATIONS OF ACUTE LEUKEMIA :

- ➢ Three questions must be answered
  - ✓ What is the lineage?
  - ✓ What is the maturational stage?
  - ✓ What is the genotype?
- ➢ Answers to these questions are by
  1. Cytochemistry
  2. Immunophenotyping
  3. Cytogenetics + molecular genetics

Criteria :

- ➢ Morphology : appearance of cell under the microscope.
- ➢ Cytochemistry : chemical activity of the cell [Myloperoxidase , Sudan Black B]
- ➢ Immunophenotyping : antigen present in the cell membrane.
- ➢ Cytogenetics: chromosome of the cell .
- ➢ Molecular biology

Classification :

3 groups of acute leukemias:

- ➢ Acute myeloid leukemias AML (M1 –M6).
- ➢ Acute lymphoblastic leukemias ALL (L1-L3).
- ➢ Biphenotypic leukemias or Acute undifferentiated leukemia .

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Acute Leukaemia: Morphological Classification
Myeloid (AML)
M_0: minimally differentiated M_1: without maturation M_2: with maturation M_3: hypergranular promyelocytic M_4: myelomonocytic M_5: a) monoblastic b) monocytic M_6: erythroleukaemia M_7: megakaryoblastic Rare types, e.g. eosinophilic
Lymphoblastic (ALL)
L_1: small, monomorphic L_2: large, heterogeneous L_3: Burkitt cell-type

Diagnostic methods of importance :

- Romanowsky stain morphology
  - ✓ Enumeration of blasts, maturing cells, recognition of dysplasia

- Cytochemistry
  - ✓ Myeloperoxidase, Sudan Black B, esterases to determine involved lineages

- Metaphase cytogenetics
  - ✓ Detects clonal chromosomal abnormalities, including those of prognostic importance

- Immunophenotyping
- Defines blast cell lineage commitment as myeloid, lymphoid or biphenotypic

- RT-PCR
  - ✓ Detects known translocations by amplifying fusion genes (phyladalphia chromosome 22-9 causes ALL)

- Fluorescence In-Situ Hybridisation (FISH)
  - ✓ Can detect ploidy changes, translocations and deletions in metaphase or interphase nuclei

- Trephine biopsy histology and immunohistochemistry
  - ✓ Useful in the presence of inaspirable marrow

Clinical applications of immunophenotypin :

- Essential for separating morphologically undifferentiated AML from acute lymphoblastic leukaemia
- Essential for identifying acute biphenotypic leukaemias
- Detects aberrant (promiscuous) antigen expression
- Identifies patient specific unique blast cell phenotypes
- Can identify leukaemic contamination of 'remission' marrow harvests
- Can identify early relapse

Acute Myeloid Leukaemia (AML)

- Acute myeloid leukaemia (AML) occurs at all ages, with increasing incidence in the older age groups
- Defined in WHO classification by presence of > 20% blast cells in the marrow
- Thus includes the FAB MDS category of Refractory Anaemia with Excess Blasts in Transformation (RAEB-T)
- AML usually occurs *de novo*
- A minority of cases are secondary to previous chemotherapy or radiotherapy
- It may be a progression from MDS or myeloproliferative disorders

Myelofibrosis = bone marrow empty

AML not otherwise categorised :

This group of cases is classified by morphology and cytochemistry only, and corresponds to the FAB subtypes M0, M1, M2, M4, M5, M6, and M7 with the addition of the new category ,acute basophilic leukaemia.

AML minimally differentiated (FAB M0, defined by immunophenotype)
AML without maturation (FAB M1, cytochemical peroxidase positive blasts)
AML with maturation (FAB M2, showing >10% maturing granulocytes)
Acute myelomonocytic leukaemia (FAB M4, defined by morphology and esterase stains)
Acute monocytic leukaemia (FAB M5, defined by morphology and esterase stains)
Acute erythroid leukaemia (FAB M6, >50% erythroid precursors)
Acute megakaryocytic leukaemia (FAB M7, >30% megakaryoblasts)
Acute basophilic leukaemia. Toluidine Blue helpful in identifying abnormal or agranular basophils

M4,M5,M6 are za most imp.

Prognostic factors in AML1,2

- **Age**
  - ✓ Above the age of 50 years the complete remission rate falls progressively
- **Cytogenetics**
  - ✓ **Three risk groups defined**
    - Good risk: patients with t(8;21), t(15;17) and inv/t(16)
    - Intermediate risk: Normal, +8, +21, +22, 7q-, 9q-, abnormal 11q23, all other
    - Poor risk: patients with -7, -5, 5q-, abnormal 3q and complex karyotypes
- **Treatment response**
  - ✓ Patients with >20% blasts in the marrow after first course of treatment have short remissions (if achieved) and poor overall survival
- **Secondary AML**
  - ✓ Patients with AML following chemotherapy or myelodysplasia respond poorly
- **Trilineage myelodysplasia**
  - ✓ Patients with trilineage myelodysplasia have a lower remission rate

Treatment and prognosis of AML1,2

- **Intensive chemotherapy**
  - ✓ Patients < 55 years old: 80% remissions
  - ✓ Patients > 55 years old: progressive reduction in remission rate
- **Stem cell transplants**
  - ✓ Autologous and allogeneic transplants reduce the relapse rate
- **Importance of cytogenetics for prognosis in children and adults < 55 years old**
- **Good risk cytogenetic group**
  - ✓ 91% remissions, 65% five year survival

Prognosis in AML :

PARAMETERS	*FAVORABLE*	*UNFAVORABLE*
Cytogentics	T (15; 17). T (8; 21). Inv (16).	**Deletion of chromosome5or7.** **11q23** **T(6;9)** **Abn(3q)complex rearrangments**
BM response to remission induction	<5% blasts after first course	**>20% blasts after first course.**
age	<60yrs	**>60yrs**

Acute Lymphoblastic Leukaemia (ALL)

Poor Prognostic Factors :

- **Age** < 2 yrs and > 10 yrs
- **Male** sex
- **High WBC** count (> 50 $x10^9$/L)
- Presence of **CNS disease**
- **Cytogenetics** :
  - ✓ Good [***Hyperdiploid*** (>50 ch)] t(9:22)
  - ✓ Poor [***Hypodiploid***] t(4:11)
- **Bone Marrow**: Blasts present on day 14
- **Day 28**: No complete response

Prognosis in ALL

PARAMETERS	*GOOD*	*POOR*
WBC	*low*	High(>50x10 9 /l)
Gender	FEMALE	MALE
Immunophenotype	C-ALL	B-ALL
Age	Child	Adult or infant.
Cytogenetic	Normal,hyperdiploid	Ph+, 11q23rearrangements.
Time to clear blast from blood	< 1week	>1week
Time to remission	<4weeks	>4weeks
Cns disease at presentation	Absent	Present
Minimal residual disease.	Negative at 1-3 months	Still positive at 3-6 months.

Management of Acute Leukemias :

- **Prognosis improved due to :**
  - ✓ More intensive regimens
  - ✓ Tailored protocols according to prognostic risk factors
  - ✓ Improved supportive care

A-Supportive measure:

- ✓ isolation in positive laminer flux room
- ✓ Vascular access (insertion of central line)
- ✓ family and patient support by permanent social worker
- ✓ Alkaline diuresis to prevent tumor lysis syndrome
- ✓ Prevention of vomiting
- ✓ Oropharynx/GIT decontamination to prevent fungal infection
- ✓ IV antibiotics for infection
- ✓ Blood transfusion if anemia and thrombocytopenia.
- ✓ *Therapeutic option*

B-Curative intent:

- ✓ Only allogenic bone marrow transplant

C- Classical approch (curative/palliative)

Stages of Therapy :

A: Induction, chemotherapy:

- Obtained by using high doses of chemotherapy :

1. Severe bone marrow hypoplasia
2. Allowing regrowth of normal residual stem cells to regrow faster than leukemic cells.
   - ✓ Normal neutrophil count
   - ✓ Normal platelet count
   - ✓ Normal Hemoglobin level

   Remission defined as < 5% blast in the bone marrow

B: Consolidation of remission:

Maintenance of Tx mainly for ALL & M3 type of AML

- Different or same drugs to those used during induction
- Higher Doses of Chemotherapy
- **Advantage**:
  - ✓ Improved clinical & Haematological state of the Px

C: Maintenance of chemotherapy:

- Smaller doses for longer period
- Produce low neutrophil counts & platelet counts
- Object is to eradicate progressively any remaining leukaemic

Special consideration:

- ***CNS***: [by intrathecal chemotherapy,high dose systemic MTX or Aracytine. OR cerebrospinal irradiation]
  - ✓ neuroprophylaxis
  - ✓ meningeal infiltration
- ***Testis***:
  - ✓ Orchidectomy /radiotherapy if testis involvement.
- ***Bone Marrow or PBSC Transplantation in Leukemia***
- ***Allogeneic Transplantation***
  - ✓ To eradicate residual leukemia cells Graft vs leukemia effect
- ***Transplantation between individuals***
  - ✓ MHC + HLA matched
  - ✓ Chemotherapy
  - ✓ Total body Irradiation

AML vs ALL

ALL

- Induction
- Consolidation
- Maintenance
- CNS Prophylaxis all Patients

AML

- Induction
- Consolidation
- No Maintenance
- CNS – Selected group only

Done by : GreEn BloOd Girlz

GBGs

Dr. Aamer Aleem

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