Leukemia

Clonal proliferation of leukocytes (lymphoid or myeloid) associated with bone marrow involvement and frequent appearance of abnormal cells in the peripheral blood.
LEUKEMIA

**ACUTE**
- AML
  - Older age group
  - Transcriptional dysregulation
  - Characteristic translocations

- ALL
  - Younger age group
  - High remission rates
  - Worse in adults

**CHRONIC**
- CML
  - Myeloproliferative disease
  - Chronic phase: normal maturation
  - Acute phase: AML

- CLL
  - Defect in apoptosis
  - Normal-appearing lymphs
  - Indolent course
  - Inexorable progression
Age-Related Leukemia Incidence

- ALL
- AML
- CML
- CLL
Leukemia Transformation

*Like all cancer, dependent on “multiple hits”*

Defect in proliferation

Not increased proliferative rate (most leukemic cells grow more slowly than normal cells), but a failure of normal controls of proliferation and/or apoptosis.

Defect in differentiation

Neutrophils and lymphocytes arise by differentiation from pluripotent stem cells. The stage of differentiation at which arrest occurs determines the natural history and clinical response of resultant leukemia.
MYELOID DIFFERENTIATION

Failed differentiation
MYELODYSPLASIA

Hyperproliferation
MYELOPROLIFERATIVE DISEASE

ACUTE MYELOGENOUS LEUKEMIA
Myelopoiesis

Target of transforming event

HSC → CML
AML

PMN

myeloblast promyelocyte myelocyte metamyelocyte band
segmented neutrophil
Acute Myelogenous Leukemia (AML)

Malignancy of the hematopoietic stem cell.
Aggressive leukemia

Diagnosis:
- Peripheral blood, bone marrow
- Cytogenetics: major predictor of prognosis
- Flow cytometry

Treatment:
- Aggressive chemotherapy
- Transplantation

Prognosis:
- Improving, but still <50% survival
Induction therapy

Obtained by using high doses of chemotherapy
Severe bone marrow hypoplasia
Allowing regrowth of normal residual stem cells to regrow faster than leukemic cells.

Goal is “Remission”:

- Normal neutrophil count
- Normal platelet count
- Normal hemoglobin level

Remission defined as < 5% blast in the bone marrow
<table>
<thead>
<tr>
<th>Acute Leukaemia: Morphological Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Myeloid (AML)</strong></td>
</tr>
<tr>
<td>( M_0 ): minimally differentiated</td>
</tr>
<tr>
<td>( M_1 ): without maturation</td>
</tr>
<tr>
<td>( M_2 ): with maturation</td>
</tr>
<tr>
<td>( M_3 ): hypergranular promyelocytic</td>
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<tr>
<td>( M_4 ): myelomonocytic</td>
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<tr>
<td>( M_5 ): a) monoblastic b) monocytic</td>
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<tr>
<td>( M_6 ): erythroleukaemia</td>
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<tr>
<td>( M_7 ): megakaryoblastic</td>
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<tr>
<td>Rare types, e.g. eosinophilic</td>
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<tr>
<td><strong>Lymphoblastic (ALL)</strong></td>
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<tr>
<td>( L_1 ): small, monomorphic</td>
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<tr>
<td>( L_2 ): large, heterogeneous</td>
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<tr>
<td>( L_3 ): Burkitt cell-type</td>
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</tbody>
</table>
Acute Promyelocytic (t 15:17) or “M3” Leukemia - a special case

Aspirate showing hypergranular morphology with multiple Auer rods (“faggot cells”) having very high content of toxic proteases, lipases, oxidases, etc.

These enzymes are released when blasts are killed by cytotoxic drugs, causing DIC and tumor lysis syndrome.

This caused major morbidity and mortality during induction therapy and poor prognosis.

A key discovery that t 15:17 translocation creates differentiation blockade due to retinoic acid dys-metabolism development of all trans-retinoic acid (ATRA) as differentiation therapy, causing cells to mature and die on their own.

Now one of the better prognosis forms of AML, due also in part to surprising efficacy of arsenicals, first noted in Chinese folk medicine.
Acute Myeloid Leukaemia (AML)

Prognostic factors in AML

**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
CML
Malignancy of the hematopoietic stem cell
Chronic phase: myeloproliferation
Diagnosis:
  • Peripheral blood, bone marrow
  • Cytogenetics: t(9;22)
Treatment:
  • Transformed by TKIs over last 2 decades
  • Transplantation
Prognosis:
  • Changing/improving with new therapies
Chronic Myelogenous Leukemia (CML)

A myeloproliferative disorder

- Caused by failure of control of cellular proliferation.
- Chronic phase: a proliferation of a partially transformed hematopoietic stem cell, resulting in increased numbers of cells that function essentially normally.
- Acute phase: Acute myelogenous leukemia

*Constant proliferative drive promotes 2^0 genetic events that contribute to the development of acute phase (Blast Crisis)*
Acute Lymphoblastic Leukemia (ALL)

Malignancy of the lymphoid stem cell. Aggressive leukemia

Diagnosis:
• Peripheral blood, bone marrow
• Cytogenetics
• Flow cytometry

Treatment:
• Aggressive chemotherapy
• Long duration (2 years)

Prognosis:
• Children: CR 98%; CCR 75%
• Adults: CR 65-85%; CCR 25-35%
Acute Lymphoblastic Leukaemia (ALL)
Prognostic factors in ALL

Poor Prognostic Factors
Age < 2 yrs and > 10 yrs
Male sex
High WBC count (> 50 x10⁹/L)
Presence of CNS disease

Cytogenetics
Good risk
Hyperdiploid (>50 ch)

Poor risk
Hypodiploid, t(9:22), t(4:11)

Bone Marrow: Blasts present on day 14
Day 28: No complete response
Treatment of acute leukemias

1. Specific therapy (chemotherapy)
2. Supportive treatment

3. Stages of Therapy
   a. Induction
   b. Consolidation
   c. Maintenance
Consolidation Therapy

Different or same drugs to those used during induction

Higher doses of chemotherapy

Advantage: Delays relapse and improved survival
CLL
Chronic Lymphocytic Leukemia (CLL)

- CLL is characterized by a failure of apoptosis.
- Associated primarily with cellular *accumulation* rather than proliferation.
- CLL cells actually proliferative very slowly, but do not undergo programmed cell death.
- Rarely transforms to an acute leukemia.
- Disease of the elderly; patients and frequently die of other causes before succumbing to CLL.
- Associated with inexorable progression, concomitant immune deficiency
CLINICAL STAGING-CLL

Stage

(0-1) - lymphocytosis ± LNS.

(II) - above + hepatosplenomagely.

(III-IV) - Anaemia. Hb< 10 g/l
  Thrombocytopenia.
  Platelet count : <100x10⁹/L.
Flow Cytometry in CLL

Aberrant expression of CD5
  • pan-T cell marker
  • Seen on B cells during fetal development
  • Found on very small subset of normal B cells in the adult.

Also usually express potential targets of therapeutic antibodies
  • CD20, target of rituxan
  • CD52, target of CAMPATH
TREATMENT OF CLL

Observation

Chemotherapy. Oral chlorambucil
Fludarabine, cyclo

Immunotherapy Anti-CD 20 (rituximab),
Anti-CD 52 (Alemtuzumab)

FC-R is the current standard

Indications for starting chemotherapy

Progressive Symptoms
Progressive Anemia or Thrombocytopenia
Bulky LN, large spleen
Recurrent Infections
How do we classify hematopoietic tumors?

Predominant site of disease
- Leukemia vs. Lymphoma

Lineage of the malignant cell
- Lymphoid vs. Myeloid

Stage of development
- Immature vs. Mature

Clinical behavior
- Acute vs. Chronic (leukemia)
- Indolent vs. Aggressive vs. Highly Aggressive (lymphoma)

Molecular genetic features

“malignant counterpart” of a normal cell
Acute Myeloid Leukaemia (AML)

Prognostic factors in AML

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
**Maintenance Therapy**

Smaller doses for longer period

Produce low neutrophil counts & platelet counts

Objective is to eradicate progressively any remaining leukemic cells.
Supportive Care

Vascular access (Central line)
Prevention of vomiting
Blood products (Platelets, RBC’s)
Prevention & treatment of infections (antibiotics)
Management of metabolic complications
Bone marrow or PBSC transplantation in leukemias

**Process of transplantation:**
- MHC + HLA matching of donor and host
- Marrow Ablative Chemotherapy
- Total body irradiation
- GVHD prophylaxis

**Complications of transplantation:**
- Prolonged BM suppression (graft failure)
- Serious infections
- Mucositis
- Graft versus host disease (GVHD)
Bone marrow or PBSC transplantation in leukemias

Types of transplant
Autologous transplant
Allogeneic Transplant

Purpose of transplant

**Autologous**
- To deliver a high dose of chemo to kill any residual cancer
  (lymphoma, multiple myeloma)

**Allogeneic**
- To eradicate residual leukemia cells
- Graft vs leukemia effect
Acute Myeloid Leukaemia (AML)

Treatment and prognosis of AML

Intensive chemotherapy
- Patients < 55 years old: 80% remissions
- Patients > 55 years old: progressive reduction in remission rate

Bone marrow (stem cell) transplantation
- 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
Chronic Lymphocytic Leukemia (CLL)

Pathogenesis:
- Defective apoptosis leading to accumulation of cells rather than aggressive proliferation.
- Associated with more global defect in immune regulation from which the CLL clone emerges.

Diagnosis:
- Cytogenetics
- Flow cytometry

Treatment: Very responsive, but always relapses

Prognosis: Indolent disease with inexorable progression; main problem: immune deficiency