Leukemia
Leukemia

- Acute
  - Acute Myelogenous Leukemia (AML)
  - Acute Lymphoblastic Leukemia (ALL)

- Chronic
  - Chronic Myelogenous Leukemia (CML)
  - Chronic Lymphocytic Leukemia (CLL)

- Hairy Cell Leukemia
ACUTE MYELOGENOUS LEUKEMIA

(AML)
What is AML?

Clonal, malignant disease of hematopoietic tissue characterized by:

1. Accumulation of abnormal blast cells, principally in the marrow

2. Impaired production of normal cells
Hematopoietic Stem Cell

CLP

T-Lymphocyte

B-Lymphocyte/Plasma Cell

CMP

Erythrocyte

Megakaryocyte/Platelets

Basophil/Mast Cell

Eosinophil

Neutrophil

Monocyte/Macrophage/Kupffer Cell

Langerhans Cell

Dendritic cell
Etiology and Pathogenesis
Predisposing Conditions

• Environmental Factors

• Acquired Diseases

• Inherited or Congenital conditions
Molecular Pathogenesis

- Somatic mutation of hematopoietic multipotent cell or a more differentiated, lineage-restricted progenitor cell

- Somatic mutation occurs from chromosomal translocation in majority of patients
Molecular Pathogenesis

• Translocation occurs at region of proto-oncogene

• Fusion of genes disrupts normal cell pathway and predisposes to a malignant transformation of the cell

• Mutant product often has a
Examples of Mutated Genes

- Core Binding Factor
  - 2 subunits
    - CBF- β
    - RUNX1
- Retinoic Acid receptor – α
- HOX family
- MLL
Frequency of AML cases that involve genes listed previously differ according to age group

- Patient age > 50 yrs → 20%
- Patient age < 50 yrs → 6%
• Core Binding Gene
  – Involved in myeloid or lymphoid differentiation and maturation

• Primary mutation alone not sufficient to cause AML – additional activation mutations required
Additional Proto-oncogene Mutations

- Hematopoietic Tyrosine Kinases FLT3 and Kit
- N–RAS and K–RAS
- FES
- FOS
- GATA–1
- JUN B
- MPL
- WT1
- WNT
- N
- P53
- PU.1
- RB
- PM1
• Interaction of proto-oncogene mutations with loss of function mutations in hematopoietic transcriptions cause acute leukemia phenotype

• Minimum of 2 gene classes proposed:
  – CLASS I (ex: RUNX1 gene)
  – CLASS II (ex: core binding factor)
FLT3

- Encodes tyrosine kinase receptor in normal myeloid and lymphoid progenitors.

- Internal tandem duplications on chromosome 13 occurs in approx. 25–33% of adult AML cases
Deregulated Signaling

• Involves several signal transduction pathways ex: PI3K–AKT, RAS–RAF–MEK–ERK, STAT3

• Small number of downstream signal pathway mediated leukemogenic effect of gene mutations
Mode of Inheritance

• Little evidence seen for influence of inherited factors

• Identical twin of patient with acute leukemia has heightened risk of developing disease
Epidemiology

• AML is predominant form of leukemia during neonatal period.

• 15,000 new cases of AML annually

• 9,000 patients in US die each year
AML Incidence rates

- 2.3 per 100,000 per year

- Higher among men than women (2.9 v. 1.9)

- MC leukemia in adults (80% of cases)

- Majority of patients > 65 yrs of age
Incidence Rates

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Signs and Symptoms

- Pallor
- **Fatigue (50%)**
- Weakness
- Palpitations
- Dyspnea on exertion
- **Bruising (5%)**
- Anorexia (30–40%)
- Weight loss (30–40%)
- Gingival Bleeding
- Conjunctival Hemorrhages
- Pustules and minor pyogenic infections of skin
- Petechiae
- Epistaxis
- Fever
- Splenomegaly and Hepatomegaly (33% of patients)
Signs and Symptoms

- Cough
- Diaphoresis
- Headache
- Bone Pain
- Lymphadenopathy

- Sinusitis, pneumonia, pyelonephritis and meningitis uncommon until chemotherapy
Diagnosis

- CBC with peripheral blood smear
- Bone Marrow aspirate and biopsy
- Chest x-ray
- Histochemical Studies
- Cytogenetics and Immunophenotyping
- Clotting Studies (PT, PTT, D-dimer, fibrinogen)
Hematological Findings

• Anemia

• Thrombocytopenia

• Leukocytosis
Morphology and Cytology

- Blasts in peripheral blood in 90% cases
- More than 20% blasts in bone marrow
- Auer Rods (cytoplasmic granules)
- Positive myeloperoxidase reaction in 3% blasts
AML Histology

Auer rod
AML Histology
AML Histology
• Classification/Subtypes
  – French–American–British Classification
    • 8 major subtypes
    • Based on morphology and cytochemistry

• WHO Classification
  – Based on molecular, morphologic, and clinical features
<table>
<thead>
<tr>
<th>Subtype</th>
<th>FAB Type</th>
<th>Morphology</th>
<th>Cytogenetic Abnl</th>
</tr>
</thead>
<tbody>
<tr>
<td>AML w/o maturation</td>
<td>M0</td>
<td>no azurophil granules</td>
<td>-</td>
</tr>
<tr>
<td>AML</td>
<td>M1</td>
<td>few Auer rods</td>
<td>del(5); del(7); +8</td>
</tr>
<tr>
<td>AML w/ differentiation</td>
<td>M2</td>
<td>maturation beyond promyelocytes; Auer rods</td>
<td>t(8:21) t(6:9)</td>
</tr>
<tr>
<td>Acute Promyelocytic Leukemia</td>
<td>M3</td>
<td>hypergranular promyelocytes; Auer rods</td>
<td>t(15:17)</td>
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<tr>
<td>Acute Myelomonocytic Leukemia</td>
<td>M4</td>
<td>&gt; 20% monocytes; monocyteid cells in blood</td>
<td>inv(16) del(16) t(16:16)</td>
</tr>
<tr>
<td>Acute Monocytic Leukemia</td>
<td>M5</td>
<td>monoblastic; promonocytic</td>
<td>t(9:11) t(10:11)</td>
</tr>
<tr>
<td>Acute Erythroleukemia</td>
<td>M6</td>
<td>predominance of erythroblasts; dyserythropoiesis</td>
<td>-</td>
</tr>
<tr>
<td>Acute Megakaryocytic Leukemia</td>
<td>M7</td>
<td>dry aspirate; biopsy dysplastic with blasts</td>
<td>-</td>
</tr>
</tbody>
</table>
Treatment

- Chemotherapy
- Supportive Care
Chemotherapy

• Current standard induction treatment for AML involves drug regimens with two or more agents that include anthracyclines or an anthraquinone and cytarabine

• Remission rates in the studies cited range from approximately 55 to 90 percent in adult subjects, depending
Prognosis

- Age of diagnosis
- Comorbidities
- Chromosomal Findings
- Symptomatic Interval Preceding Diagnosis
- Presenting Leukocyte count
- Circulating Myeloblast count
- FAB classification
<table>
<thead>
<tr>
<th>Age (years)</th>
<th>AML (expressed as # of cases per 100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;45</td>
<td>50.0</td>
</tr>
<tr>
<td>45–54</td>
<td>28.5</td>
</tr>
<tr>
<td>55–64</td>
<td>17.9</td>
</tr>
<tr>
<td>65–74</td>
<td>7.4</td>
</tr>
<tr>
<td>&gt;75</td>
<td>1.8</td>
</tr>
<tr>
<td>&lt;65</td>
<td>35.8</td>
</tr>
<tr>
<td>&gt;65</td>
<td>4.5</td>
</tr>
</tbody>
</table>
Acute Lymphoblastic Leukemia (ALL)
What is it?

- Acute lymphoblastic leukemia (ALL) is a neoplastic disease that results from multistep somatic mutations in a single lymphoid progenitor cell at one of several discrete stages of development.
Pathogenesis

• Acquired genetic abnormalities are a hallmark of ALL.

• > 75% of all cases have recurring cytogenetic or molecular lesions with prognostic and therapeutic relevance.
Pathogenesis

• Chromosomal changes include:
  1. abnormalities in the number (ploidy)
  2. structure of chromosomes.
     - Translocation (MC abnormality)
     - Inversion
     - Deletion
     - Point Mutations
     - Amplifications
Pathogenesis

• Although the frequency of particular genetic subtypes differs between childhood and adult cases, the general mechanisms underlying the induction are similar.

• Mechanisms include:
  – aberrant expression of oncoproteins
  – chromosomal translocations that generate fusion genes encoding transcription factors
Pathogenesis

Primary genetic rearrangement by itself is insufficient to induce overt leukemia.

Cooperative mutations are necessary for leukemic transformation and include genetic and epigenetic changes in key growth regulatory pathways.
Epigenetic Changes

- Hypermethylation of tumor-suppressor genes

- Hypomethylation of oncogenes and abnormalities in post-transcriptional control mechanisms

- These changes are reversible and do not alter the DNA sequence, yet they can alter gene expression in subtle ways.
Epigenetic Changes

• Analysis of changes applied to developing new biomarkers for risk assignment or disease monitoring, and to the design of alternative treatment in ALL.

• Evidence indicates that the methylation of multiple genes in ALL is associated with a worse outcome.
# Frequencies of Common Genetic Aberrations in Childhood and Adult Acute Lymphoblastic Leukemia

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Children (%)</th>
<th>Adult (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperdiploidy (&gt;50 chromosomes)</td>
<td>23–29</td>
<td>6–7</td>
</tr>
<tr>
<td>Hypodiploidy (&lt;45 chromosomes)</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>t(1;19)(q23;p13.3) [TCF3–PRX11]</td>
<td>4 in white, 12 in black</td>
<td>2–3</td>
</tr>
<tr>
<td>t(9;22)(q34;q11.2) [BCR–ABL1]</td>
<td>2–3</td>
<td>25–30</td>
</tr>
<tr>
<td>t(4;11)(q21;q23) [MLL–AF41]</td>
<td>2</td>
<td>3–7</td>
</tr>
<tr>
<td>t(8;14)(q23;q32.3)</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>t(12;21)(p13;q22) [ETV6–RUNX1]</td>
<td>20–25</td>
<td>0–3</td>
</tr>
<tr>
<td>NOTCH1 mutations*</td>
<td>7</td>
<td>15</td>
</tr>
<tr>
<td>HOX11L2 overexpression*</td>
<td>20</td>
<td>13</td>
</tr>
<tr>
<td>LYL1 overexpression*</td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td>TAL1 overexpression*</td>
<td>15</td>
<td>3</td>
</tr>
<tr>
<td>HOX11 overexpression*</td>
<td>15</td>
<td>3</td>
</tr>
</tbody>
</table>

*Tuesday, February 26, 13*
Etiology

• Uncertain

• Proposed Risk Factors:
  1. Genetic Syndromes (ex: Philadelphia chromosome)
  2. Environmental Factors
  3. Viral infections (ex: EBV and HIV)
  4. Smoking
Incidence Rates

- 5,730 new cases in U.S. in 2011
- 2/3 of ALL cases in children (peak incidence ages 2 – 5)
- Comprises less than 20% of leukemia in young adults
- May be B-cell, T-cell, or null-type (non-B, non-T cell)
Signs and Symptoms

- Pallor
- Fatigue
- Shortness of breath
- Easy bruising
- Petechiae
- Weight loss / failure to thrive
- Fever
- Splenomegaly and/or hepatomegaly
- Lymphadenopathy
- Multiple bruises
- Unexplained infections
Diagnosis

- CBC Chemistry studies to check for organ dysfunction
- Bone marrow aspirate and biopsy
- Genetic/Immunological studies
- Lumbar puncture
Hematological Findings

- Anemia
- WBC < 5,000 (or > 25,000)
- Leukocytosis
- Thrombocytopenia
Histology
Histology
## Classification of ALL

<table>
<thead>
<tr>
<th>Immunologic Subtype</th>
<th>FAB Type</th>
<th>% of Cases</th>
<th>Cytogenetic Abnl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-B cell ALL</td>
<td>L1, L2</td>
<td>75</td>
<td>t(9:22) t(4:11) t(1:19)</td>
</tr>
<tr>
<td>T-cell ALL</td>
<td>L1, L2</td>
<td>20</td>
<td>14q11 or 7q34</td>
</tr>
<tr>
<td>B-cell ALL</td>
<td>L3</td>
<td>5</td>
<td>t(8:14) t(8:22) t(2:8)</td>
</tr>
</tbody>
</table>

**L1** – 85% of childhood ALL  
**L2** – Majority of adult ALL
Prognosis

Favorable Factors:

1. Age 3 to 7 yrs
2. WBC count < 25,000/µL
3. FAB L1 morphology
4. Leukemic cell karyotype with > 50 chromosomes and t(12;21)
5. No CNS disease at diagnosis
## Adverse Prognostic Factors in adult ALL

<table>
<thead>
<tr>
<th>Factors</th>
<th>B– Cell Precursor</th>
<th>T Cell</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>&gt;35</td>
<td>&gt;35</td>
</tr>
<tr>
<td>Leukocyte Count (x10⁹/L)</td>
<td>&gt;30</td>
<td>&gt;100</td>
</tr>
<tr>
<td>Immunophenotype</td>
<td>Pro–B (CD10–)</td>
<td>Pre–T</td>
</tr>
<tr>
<td>Genetics</td>
<td>t(9;22) [BCR–ABL1]</td>
<td>HOX11L2 expression ?</td>
</tr>
<tr>
<td></td>
<td>t(4;11) [MLL–AF4]</td>
<td>ERG expression ?</td>
</tr>
<tr>
<td>Hypodiploidy ?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment Response</td>
<td>Delayed remission (&gt; 4 weeks)</td>
<td>Delayed remission (&gt; 4 weeks)</td>
</tr>
<tr>
<td></td>
<td>Minimal residual disease &gt;10⁻⁴ after induction</td>
<td>Minimal residual disease &gt;10⁻⁴ after induction</td>
</tr>
</tbody>
</table>
TREATMENT
Treatment

• Chemotherapy

• Sometimes stem cell transplantation or radiation therapy
Treatment

4 General phases of chemotherapy

1. Remission Induction

2. CNS prophylaxis

3. Post remission consolidation or intensification

4. Maintenance
Remission Induction

• Initial goal is to quickly induce complete remission

• The induction regimen typically includes a glucocorticoid (prednisone, prednisolone, or dexamethasone), vincristine, and L-asparaginase for children or an anthracycline for adults.
• After Induction Chemotherapy:

• Bone marrow biopsy is obtained

• If > 5% of blasts with > 20% cellularity, then retreatment necessary.

• Stem cell transplant may be necessary if retreatment fails.
CNS Prophylaxis

- Important site of leukemic infiltration is meninges
- Prophylaxis and treatment may include high-dose intrathecal methotrexate, cytosine arabinoside, and corticosteroids
Post remission consolidation or intensification

- Goal is to prevent leukemic regrowth
- Therapy lasts several months and involves drugs with different MOA than drugs used in induction regimen
- Continued low-dose post-remission therapy must be used to ensure prolonged survival. Otherwise recurrence rates can be as high as 90%
Maintenance

• Most regimens include therapy with methotrexate and mercaptopurine

• Duration typically 2.5–3 years

• Patients in continuous complete remission for 2.5 years, risk of relapse is 20%, usually within 1st year
Treatment

• **Continued Supportive Care:**

• Transfusions….
  - Platelets >20,000
  - Hgb >8

• Empiric antibiotic treatment when fever present
Relapse

• Defined as the reappearance of leukemic cells at any site in the body.

• Most relapses occur during treatment or within the first 2 years after its completion.

• Molecular studies suggest that in some cases, especially those with the ETV6–RUNX1 fusion, subsequent mutations of the residual preleukemic clone that were not eradicated during initial treatment account for the "late relapse."

• The marrow remains the most common site of
Relapse

- Between 50 – 70% of children and 40 – 50% of adults who achieve complete remission after initial therapy but then suffer a relapse may be able to go into a second complete remission.
Relapse

• Treatment for relapse after a first remission may be standard chemotherapy or experimental drugs, or more aggressive treatments such as stem cell transplants.

Depends on:
• Children who relapse 3 or more years after achieving a first complete remission have an excellent chance for a second remission without aggressive treatments.

• Those who relapse fewer than 6 months following initial treatment, especially while on chemotherapy, have about a 20% chance of long-term freedom from disease. In such cases,
5 yr survival rates

- Children: 80%
- Adults: 40%
- Percentages include children/adults with all levels of risk factors. For children/adults with high-risk disease, survival rates are much lower, while survival rates are higher for some children/adults with low-risk disease.
• The overall 5-year relative survival for 2001–2007 from 17 SEER geographic areas was 64.4%.

• Five-year relative survival by race and sex was:
  – 63.9% for white men;
  – 64.7% for white women;
  – 60.5% for black men;
  – 64.1% for black women.
Sources

- Lichtman MA, Kipps TJ, Seligsohn U, Kaushansky K, Prchal Jt: Williams Hematology, 8\textsuperscript{th} Edition: http://www.accessmedicine.com