<table>
<thead>
<tr>
<th>Disease</th>
<th>Usual phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>acute leukemia</td>
<td>precursor</td>
</tr>
<tr>
<td>chronic leukemia</td>
<td>differentiated</td>
</tr>
<tr>
<td>lymphoma</td>
<td></td>
</tr>
<tr>
<td>myeloma</td>
<td></td>
</tr>
<tr>
<td>Total WBC</td>
<td>Blast</td>
</tr>
<tr>
<td>-----------</td>
<td>-------</td>
</tr>
<tr>
<td>&gt; 60</td>
<td>0</td>
</tr>
<tr>
<td>Leukemoid reaction</td>
<td>0</td>
</tr>
<tr>
<td>Acute leukemia</td>
<td>82</td>
</tr>
<tr>
<td>CML</td>
<td>2</td>
</tr>
<tr>
<td>CLL</td>
<td>0</td>
</tr>
</tbody>
</table>
Acute leukemias

• **Major Categories:**

ALL = acute lymphocytic, lymphoid or lymphoblastic leukemia


versus

ANLL = acute non-lymphocytic leukemia = acute myeloid leukemia (AML)
- includes granulocytic, erythroid, and megakaryocytic lineages
Acute Leukemia

- imbalance between proliferation and differentiation

- majority of cells not dividing
  - therapeutic dilemma
Leukemias - evidence of damage to DNA

- majority have visible chromosome abnormality
- tumor-specific chromosomal translocations, e.g.,
  - t(15;17) acute promyelocytic leukemia
  - t(9;22) chronic myeloid leukemia
  - t(8;14) Burkitt’s lymphoma/leukemia
Types of Genetic Damage (DNA mutations)

- rearrangements
- translocations
- point mutations
- deletions
Proto-oncogenes

• Human genes homologous with genes in viruses which cause cancer in animals
  – e.g., abl is homologous with genetic material in the Abelson murine leukemia virus

• Protein product of proto-oncogenes may have an important normal function in humans:
  – e.g., tyrosine kinase activity of abl
  – e.g., transcriptional regulation by myc

• Conversion to oncogenes by mutational events → enhanced or disturbed function
Conversion of proto-oncogene to oncogene

- Possible mechanisms
  - Unaltered gene product (e.g., myc in Burkitt’s)
  - Altered gene product
    » usually a fusion protein (e.g., bcr-abl in CML)
Gene Products of Oncogenes

- Growth factors
- Receptors for growth factors
- Molecules involved in signal transduction
- Proteins that bind DNA and regulate nuclear functions (e.g., transcription factors)
Genetic damage in leukemias

- Causes
  - radiation
  - carcinogens
    - benzene
    - chemotherapy
  - hereditary chromosome disorders
  - hereditary disorders of DNA repair
  - viruses (eg, HTLV-I)

- Proto-oncogenes → oncogenes
- Inactivation of ‘tumor suppressor genes’
- Multiple events
Myelodysplastic Syndrome (MDS)

• Usually elderly, sometimes prior chemo- or radiotherapy
• Variable cytopenias, often severe
• Macrocytic anemia common
• Neutropenia and thrombocytopenia
• Morphological abnormalities
  – Anisopoikilocytosis
  – Neutrophil hypogranularity and hyposegmentation
  – Macroplatelets
  – Hypolobated megakaryocytes
  – Increasing blast count
• Cytogenetic abnormalities (esp. chromosomes 5, 7, 8)
• Variable response to Epo, GCSF, hypomethylating agents
• Evolution to ANLL
## Oncogene Activation

<table>
<thead>
<tr>
<th>Translocation</th>
<th>Disease</th>
<th>Proposed mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>t(8;14)</td>
<td>some B-cell lymphomas, ALL</td>
<td>↑expression of transcription factor (myc)</td>
</tr>
<tr>
<td>t(9;22)</td>
<td>CML, some ALL</td>
<td>chimeric signalling molecule (bcr-abl)</td>
</tr>
<tr>
<td>t(15;17)</td>
<td>acute promyelocytic leukemia</td>
<td>chimeric transcription factor (pml-rarα)</td>
</tr>
</tbody>
</table>
Acute Promyelocytic Leukemia

- about 7% of all ANLL
- malignant clone shows early differentiation
- cells often contain multiple Auer rods
- disseminated intravascular coagulation common
- t(15;17) almost always present
- sensitivity to arsenical trioxide and retinoic acid
Acute Promyelocytic Leukemia t(15;17)

- Retinoic acid receptor-α (RAR-α) gene on 17q in normal cells

- RAR-α gene product is a nuclear receptor protein acting as transcription enhancer in myeloid differentiation when bound to retinoic acid

- In t(15;17), part of RAR-α gene on 17q is translocated to 15q and fused to another gene, PML

- PML is normally a tumor suppressor gene which modulates transcriptional activation and promotes apoptosis

- The fusion gene product (pml-rarα) of APL causes failure of promyelocytes to differentiate and blocks apoptosis
Retinoic acid induces remissions in APL

- marrow hypoplasia not mandatory
- malignant clone matures to PMN
- leukemic clone replaced by normal cells in marrow
- t(15;17) no longer readily detected
- ‘differentiating agent’
- relapse occurs, necessitating chemotherapy
Tumor-suppressor genes

• inactivation of both alleles of gene allows tumor growth
e.g., p53
  minor DNA damage - promotes repair
  major DNA damage - promotes apoptosis
e.g., retinoblastoma gene
  modulates cell cycling

• ? deleted in therapy-related acute leukemia
Lineage & Stage Specificity in ALL

Acute lymphocytic leukemia

- usually arises in early progenitor B or T cell
- B:T 4:1
- occasional mixed B and T cell phenotype, suggesting malignant event at earlier multipotent lymphoid progenitor cell
<table>
<thead>
<tr>
<th>Feature</th>
<th>ALL</th>
<th>ANLL</th>
</tr>
</thead>
<tbody>
<tr>
<td>usual age group</td>
<td>children</td>
<td>adults</td>
</tr>
<tr>
<td>myeloperoxidase stain</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Auer rods</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>terminal transferase (TdT)</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>cell surface Ag’s</td>
<td>B or T</td>
<td>myeloid</td>
</tr>
<tr>
<td>Ig or T cell receptor gene rearrangement</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>
Flow cytometry in acute monocytic leukemia
## Acute Leukemia

<table>
<thead>
<tr>
<th>Event</th>
<th>Consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marrow failure</td>
<td>neutropenia</td>
</tr>
<tr>
<td></td>
<td>anemia</td>
</tr>
<tr>
<td></td>
<td>↓ platelets</td>
</tr>
<tr>
<td></td>
<td>infection</td>
</tr>
<tr>
<td></td>
<td>weakness, fatigue</td>
</tr>
<tr>
<td></td>
<td>bleeding</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>tubular damage</td>
</tr>
<tr>
<td></td>
<td>acute renal failure</td>
</tr>
<tr>
<td>DIC</td>
<td>↓ platelets</td>
</tr>
<tr>
<td></td>
<td>abnormal clotting</td>
</tr>
<tr>
<td></td>
<td>bleeding</td>
</tr>
</tbody>
</table>
Acute Leukemia

Organ infiltration
marrow involvement
bone pain
enlarged liver, spleen, nodes
hypertrophied gums
meningeal infiltration
   headache, cranial nn. palsies
Acute Leukemia

- blast leukocytosis
- leukostasis in small blood vessels:
  - tachypnea
  - dyspnea
  - tinnitus
  - lethargy
  - stupor
Acute Leukemia - treatment

- intensive combination therapy
- chemotherapy continued beyond remission
- central nervous system prophylaxis (ALL)
- bone marrow transplantation in selected patients
- therapy is dangerous
- supportive measures
  - allopurinol
  - rbc and platelet transfusions
  - antimicrobials
# Acute Leukemia - results of treatment

<table>
<thead>
<tr>
<th></th>
<th>ALL</th>
<th>ANLL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>children</td>
<td>adults</td>
</tr>
<tr>
<td>complete remission</td>
<td>90%</td>
<td>75%</td>
</tr>
<tr>
<td>median survival</td>
<td>6+ yrs</td>
<td>1-2 yrs</td>
</tr>
<tr>
<td>5 yr disease-free survival</td>
<td>70%</td>
<td>20-45%</td>
</tr>
</tbody>
</table>