<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>low grade lymphoma</td>
<td></td>
</tr>
<tr>
<td>myeloma</td>
<td></td>
</tr>
<tr>
<td>Total WBC &gt; 60</td>
<td>Blast</td>
</tr>
<tr>
<td>----------------</td>
<td>-------</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>
Chronic myeloid leukemia

Chronic phase

increased pool of clonal precursors committed to become myeloid cells

most of the clonal precursors differentiate into mature cells

Leukemias - evidence of damage to DNA

• majority have visible chromosomal abnormality

• tumor-specific chromosomal translocations, e.g.,
  – t(15;17) acute promyelocytic leukemia
  – t(8;14) Burkitt’s lymphoma/leukemia
  – t(9;22) chronic myeloid leukemia (and ALL)
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)

CML - chronic phase

- weakness, weight loss, purpura
- thrombocytosis
- anemia - normal MCV
- splenomegaly
- priapism

- median duration 3-4 yrs
CML - chronic phase

- WBC increased
- Entire granulocytic spectrum on blood film
- Marrow hyperplasia
  - expanded myeloid series
  - eo and basophil precursors
  - megakaryocytes
- Low neutrophil alkaline phosphatase
- Ph chromosome \([t(9;22)]\) present
Ph chromosome: t(9;22)

- reciprocal translocation between long arms of chromosomes 9 and 22

- Ph-negative CML: 9;22 translocation present but not visible

- ABL sequences from 9 translocated into BCR gene on 22 → FUSION GENE
Introduction of BCR-ABL gene into mice

- trans-genic model
- \textit{bcr-} \textit{abl} product expressed
- animals develop CML and/or ALL

<table>
<thead>
<tr>
<th></th>
<th>molecular weight</th>
<th>activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>normal ABL</td>
<td>145,000</td>
<td>weak</td>
</tr>
<tr>
<td>chromosome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>fusion gene</td>
<td>210,000</td>
<td>strong</td>
</tr>
<tr>
<td>chromosome</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**bcr-abl** protein differs from **abl** protein

- cytoplasmic location
- transforms cells *in vitro*
- constitutive (continuous) increased tyrosine kinase activity
- new substrates and binding proteins
- **ras** is activated
- **bcr** component contributes to transforming activity
Chronic myeloid leukemia

Ph chromosome present in precursors of:

- granulocytes
- monocytes/macrophages
- basophils
- eosinophils
- erythrocytes
- platelets
- some B lymphocytes
Treatment of CML - chronic phase

- hydroxyurea
- interferon-α → 10-20% become Ph-negative
- survival better with hydroxyurea or interferon

- imatinib (Gleevec) - targets ABL, potent, low toxicity

- allogeneic transplantation potentially curative
### Marrow and Blood Stem Cell Transplantation

<table>
<thead>
<tr>
<th>Source of cells</th>
<th>Autologous (autograft)</th>
<th>Allogeneic (allograft)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patient</td>
<td>Normal donor</td>
</tr>
<tr>
<td>Myeloablative conditioning</td>
<td>Yes</td>
<td>Usually</td>
</tr>
<tr>
<td>Transplant-related mortality</td>
<td>2-4%</td>
<td>10-30%</td>
</tr>
<tr>
<td>Graft-vs-host disease</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Graft-vs-malignancy</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Greatest curative potential</td>
<td>Lymphoma</td>
<td>Inherited disease, CML</td>
</tr>
</tbody>
</table>

- **Graft-vs-malignancy**
  - Yes: Transplant-related mortality is higher.

**Transplant-related mortality**
- 2-4% for autologous (autograft) vs. 10-30% for allogeneic (allograft)

**Graft-vs-host disease**
- No: Myeloablative conditioning may not be necessary.

**Source of cells**
- Patient: Autologous (autograft) vs. Normal donor: Allogeneic (allograft)

**Myeloablative conditioning**
- Yes: Requires more rigorous conditioning, usually due to the presence of a malignancy.
CML - allogeneic transplantation

- may result in cure
- 10-25% transplant-related mortality
- age, donor limitations
- mechanisms of cure
  - high dose chemoradiotherapy
  - graft vs leukemia
GvHD v GvL

Donor T lymphocytes

Normal cells

Graft versus Host Disease

Leukemic cells

Graft versus Leukemia effect

Frequency of GVHD and relapse after alloSCT

Increasing GVHD

unrelated donor

HLA-identical sibling donor

T-cell depleted

Increasing Relapse

syngeneic
Evidence for an immunologically mediated GVL effect

- Inverse correlation between GVHD and relapse
- In patients whose CML relapses after alloSCT, transfusion of lymphocytes from stem cell donor without additional chemoradiotherapy often induces a complete remission

But I must go and meet with danger there,
Or it will seek me in another place,
And find me worse provided.

William Shakespeare,
*Henry IV*
CML in blastic transformation

• unstable disease
• weight loss, fever, sweats, bone pain
• worsening
  splenomegaly
  anemia
  platelet counts
  blast and promyelocyte counts
  basophilia and eosinophilia
• resistance to therapy
• ‘blastic crisis’ develops in most

• death in weeks or months

CML in blastic transformation

• Blasts of variable phenotype
  myeloid
  lymphoid (early B cell)
  megakaryocytic
  erythroid

• ‘Clonal evolution’
  Ph chromosome with additional mutations
  (e.g., double Ph, trisomy 8, p53 alteration)
**Ph-positive ALL**

- 30-40% of adult ALL
- poor prognosis
- some have same fusion gene as in CML
- different fusion gene in others
  - breakpoints more 5’ in BCR
  - gene product 190,000 daltons
  - even stronger tyrosine kinase activity

**CML as a model of human malignancy**

- origin in a stem cell
- tumor cell phenotype is differentiated (variably)
- clonal
- proliferative advantage
- genetic instability
  - tendency to become less differentiated
Chronic myeloproliferative disorders

- chronic myeloid leukemia
- myelofibrosis with myeloid metaplasia
- polycythemia vera
- essential thrombocythemia

CML, myeloid metaplasia, P vera, essential thrombocythemia

- clonal
- arising in stem cells, with involvement of several cell lines
- JAK2 mutation common
- leukocytosis, thrombocytosis and platelet dysfunction
- splenomegaly
- tendency to convert to acute leukemia
Myelofibrosis with Myeloid Metaplasia

- WBC increased, normal, or decreased
- Differential similar to CML
- anisopoikilocytosis
- tear-drop RBC’s
- nucleated RBC’s
- fibrosis of marrow
  - fibroblasts not part of clone