Progress in the Treatment of Chronic Myeloid Leukemia

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Objectives

• Discuss the abnormalities in hematopoiesis found in patients with CML
• Discuss early therapies for CML
• Discuss more recent advances in the biology and treatment of CML
56yo man admitted with abdominal pain and leukocytosis

- 4 days of abdominal pain and diarrhea
- Recently discharged from the hospital
- Temp 100.8  HR 110
- Abdomen diffusely tender to palpation
What is the most likely diagnosis?
56yo admitted with abdominal pain and leukocytosis

- 3 months of gradually increasing abdominal pain, L>R
- Temp 100.8  HR 110
- Abdomen TTP in the LUQ, spleen palpable 8cm below the costal margin
What is the most likely diagnosis?
Figure 12-3 Classical hierarchal map of hematopoietic development

Cantor, A. B. et al. ASH-SAP 2010;2010:331-372
Myeloproliferative Disorders

- Mast cell
  - Systemic mastocytosis
  - Activating mutation KITD816V, FIP1L1-PDGFRα

- Red blood cells
  - Polycythemia vera

- Platelets
  - Essential thrombocytosis

- Eosinophils
  - Chronic eosinophilic leukemia
  - FIP1L1-PDGFRα

- Neutrophils
  - Chronic myeloid leukemia
  - Chronic myelomonocytic leukemia
  - BCR-ABL, TEL-PDGFRβ, BCR-PDGFRα, TEL-JAK2, other fusion TKs

- Monocytes
  - Primary myelofibrosis
Myeloid Malignancies

Myeloproliferative neoplasms
- enhanced proliferation/survival
- normal differentiation
- high white blood cell count
- may progress to AML

Myelodysplastic syndrome
- impaired differentiation
- low blood cell counts
- may progress to AML

Acute myeloid leukemia (AML)
- enhanced proliferation and survival
- impaired differentiation
- limitless self-renewal
Myeloid Precursors

- Myeloblast
- Promyelocyte
- Myelocyte
- Metamyelocyte
- Band
- Neutrophil

"Left shift"
CML clinical features

• ~4500 new US cases per year
• Median age at presentation: 53 years
• 60% men
• Disease is clinically divided into three phases
  – Chronic phase
  – Accelerated phase
  – Blast crisis (lymphoid (ALL) or myeloid (AML))
CML Clinical Features

• Disease is clinically divided into three phases
  – Chronic phase – can be managed/controlled

• Life-threatening
  – Accelerated phase
  – Blast crisis (lymphoid or myeloid)

• Goal of treatment is to prevent transformation/progression
CML Clinical Features

• Approximately 50% have no symptoms at diagnosis, just abnormal counts

• If present, common symptoms include fatigue, night sweats, weight loss, abdominal discomfort, fullness after a small meal

• Uncommonly, symptoms related to increased blood viscosity (headache, shortness of breath)
Hepatosplenomegaly
Chronic Myeloid Leukemia
Peripheral blood smear
CML - blast phase

- failure of normal blood cell development
- responds poorly to medical intervention
  - bleeding, infections, anemia common
- median survival historically 3-9 months
CML - chronic phase

- 85-90 percent of newly diagnosed CML patients are in chronic phase
- Prior to 2000, median duration of chronic phase was ~4-6 years
- Interventions can lead to durable responses in chronic phase
CML – How is the Diagnosis Made?

• Distinguish from other causes of a Leukocytosis
  – Neutrophilia - infection, myelofibrosis, CML
  – Lymphocytosis – CLL
  – Monocytosis – CMML
  – Blasts – AML, ALL
  – Basophilia – CML
  – Eosinophilia – CTD, allergic
CML – How is the Diagnosis Made?

• Distinguish from other causes of a Leukocytosis
  – Must identify that it is clonal
Detecting Mutations: Karyotype Analysis

Direct inspection of the chromosomes achieved by staining. (arrested metaphase cells)

Good for:
Gross chromosomal abnormalities such as massive amplifications, deletions, translocations, inversions, or numerical aberrations.

Typical Protocol:
• Treat white blood cells with a mitosis stimulating agent (phytohemagglutinin)
• After cells begin to divide, arrest cells with Colcemid
• Lyse cells with a hypotonic solution of KCl
• Spread chromosomes onto a microscope slide and apply fixative
• Stain with Giemsa and visualize
Metaphase Spread
First hint at the cause of CML:

46,XX,t(9;22)(q34;q11.2) a.k.a. “the Philadelphia chromosome”

Forrest et al, 2008; Bakshi et al, 2008; Image courtesy of Larry Beauregard, Jr., PhD.
CML BCR/ABL1 fusion gene, the result of a genomic rearrangement
The Philadelphia Chromosome Results in the Fusion of Two Genes and Leads to CML

BCR (Chr. 22) → Ph chromosome → BCR-ABL (activated tyrosine kinase) → CML

ABL (Chr. 9)
Normal Bcr-Abl Signaling*

- The kinase domain activates a substrate protein, e.g., PI3 kinase, by phosphorylation.
- This activated substrate initiates a signaling cascade culminating in cell proliferation and survival.

ADP = adenosine diphosphate; ATP = adenosine triphosphate; P = phosphate.

Downstream Signaling Pathways of Bcr-Abl

Bcr-Abl

Oligomerization and trans-phosphorylation

ERK=extracellular signal-regulated kinase; GCK(R)=germinal center kinase related; MAPK=mitogen-activated protein kinase; PI3K=phosphatidylinositol 3 kinase; SAPK=stress-activated protein kinase; STAT=signal transducer and activator of transcription.

Progression of CML

**Blast Phase**
- >30% blasts
- ~2/3 of patients have myeloid blast crisis
- ~1/3 have lymphoid blast crisis
- Very poor prognosis

**Chronic Phase**
- Myeloid hyperplasia
- <15% blasts
- Natural history of disease progression, 3-5 years untreated

**Accelerated Phase**
- >15%, <30% blasts
- Basophilia >20%
- New cytogenetic abnormalities in 50% to 80% of patients
- Plt <100k

Additional mutations

Bcr-Abl

HSC

CMP

CLP

GMP

MEP

MEG

RBC

Platelets

T cell

B cell

CML-CP

CML-BP (myeloid)

CML-BP (lymphoid)
## Clinical Course: Phases of CML

<table>
<thead>
<tr>
<th>Chronic phase</th>
<th>Advanced phases</th>
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<tbody>
<tr>
<td></td>
<td>Accelerated phase</td>
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<tr>
<td>Median 4–6 years stabilization</td>
<td>Median duration up to 1 year</td>
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</table>

*Cooperating mutations*:

- Loss of p53
- Trisomy 8
- Second Ph
- PAX5 deletion
- Others
How can we treat CML?
Very Early Treatment of CML

• “In the hospital he received arsenical treatment (Fowler's solution) and a little Röntgen ray treatment. He was also given calcium lactate against the haemorrhagic tendency.”

Early Treatment of CML

• How can the excessive cell division be slowed?
• Median survival in 1980 = 3 years
Early Treatment of CML

- **Target: Faster growth**
- **Hydroxyurea**
  - Inhibits DNA synthesis
- **Cytarabine**
  - Disrupts S phase of DNA replication
- **Busulfan**
  - Alkylates and damages DNA
Early Treatment of CML

- **Target:** Faster growth

- **Hydroxyurea**
  - Inhibits DNA synthesis

- **Cytarabine**
  - Disrupts S phase of DNA replication

- **Busulfan**
  - Alkylates and damages DNA

But none of them had a significant impact on the overall prognosis of the disease (Koeffler, NEJM 1981. 304: 1269.)
Early Treatment of CML

- Interferon
  - Made by Leukocytes
  - Observation that interferon lowered WBC when administered to patients for other reasons
Interferon Impairs Granulocyte Maturation and Proliferation

- In Vitro

Table 2. Effect of Human Leukocyte-Interferon on Cell Composition of Aggregates Grown in Agar Culture

<table>
<thead>
<tr>
<th>Interferon Concentration (IRU/ml)</th>
<th>Differential Count of Cells Contained in Clusters (%)*</th>
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<tbody>
<tr>
<td></td>
<td>Myeloblasts</td>
</tr>
<tr>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>10</td>
<td>3.0</td>
</tr>
<tr>
<td>100</td>
<td>9.6</td>
</tr>
<tr>
<td>1,000</td>
<td>6.0</td>
</tr>
<tr>
<td>10,000</td>
<td>8.4</td>
</tr>
</tbody>
</table>

*Average percentage from 50 clusters examined for morphology. Morphological examination of the colonies from dishes with and without interferon revealed normally differentiating cells.

Verma, Blood 1979. 54:1423
Interferon enables temporary control of CML

- Given either in combination with chemotherapy (cytarabine) or as monotherapy
- Very difficult to tolerate
  - Myalgias, fatigue, headache, fever, depression
- Patients lived longer than the prior 3yr average with this therapy
- But no patients were cured
  - ~70% survival at 5yrs
  (Guilhot, NEJM 1997. 337:223)
Immune system control

- Our immune system recognizes disease within the body

- HLA (Human Leukocyte Antigen)
  - Class I (A, B, C)
  - Only expressed by immune-system cells
  - Expressed everywhere (except RBCs, germ cells, neurons)

- Class II (DP, DQ, DR)
  - Only expressed by immune-system cells

Klein. NEJM 2000. 343:702
Immune system control

- Our immune system recognizes disease within the body
- Cancer growth is contributed to by the inability of an immune system to recognize the tumor
Immune system control

- Our immune system recognizes disease within the body
- Cancer growth is contributed to by the inability of an immune system to recognize the tumor
- Is there a way to give a patient a ‘new’ immune system that could recognize the cancer?
Hematopoietic Stem Cell Transplantation

Bone Marrow

Peripheral Blood Progenitor Cells (PBPC)

Umbilical Cord Blood (UCB)

Photo courtesy of Dr. M Linenberger
Hematopoietic Stem Cell Transplantation (HSCT)

- Graft-versus-leukemia effect

Copelan, NEJM 2006. 354:1813
Limitations to Stem Cell Transplant

• In 2000, only 25-30% of patients could undergo SCT for CML
  – Transplant-related mortality - risk of dying from allogeneic transplant about 20-30% within the first year, so only young and very healthy patients were candidates
  – Finding HLA-matched donor for ethnic minorities much more difficult
Improving Transplants (2000-present)

• Reduced-intensity conditioning chemotherapy
  – Older patients and those with other medical conditions are now candidates

• Alternative stem cell sources and expansion of donor registry improves access for non-Caucasians
Transplants by Cell Source
Adult Recipients (18 years and older)

All Patients

Non-Caucasian patients
Role of Cord Blood in Transplants by Patient Race

- **Black/African American**
  - Cord Blood: 44%
  - Bone Marrow or Peripheral Blood: 56%

- **American Indian/Alaska Native**
  - Cord Blood: 37%
  - Bone Marrow or Peripheral Blood: 63%

- **Native Hawaiian/Other Pacific Islander**
  - Cord Blood: 75%
  - Bone Marrow or Peripheral Blood: 25%

- **Asian**
  - Cord Blood: 30%
  - Bone Marrow or Peripheral Blood: 70%

- **White**
  - Cord Blood: 16%
  - Bone Marrow or Peripheral Blood: 84%

Source: National Marrow Donor Program FY 2012
Diversity of Cord Blood Units on the Be The Match Registry® 2012

Minority includes donors who identified their race or ethnicity as:
- American Indian or Alaska Native
- Asian
- Black or African American
- Hispanic or Latino
- Native Hawaiian or Other Pacific Islander

Source: National Marrow Donor Program FY 2012
How you can help

• Become a donor
  – BeTheMatch.org (National Marrow Donor Program)
• Organize a donor drive
• Encourage new parents to donate cord blood at the time of delivery
  – to a Public cord blood bank
Let’s get more specific

• Specific mutation found in all CML
  – Driver mutation

• Could this be targeted and blocked?
Mechanism of Activation of Bcr-Abl

Bcr-Abl

Substrate

Phosphates

Tyrosine

ATP
Mechanism of Activation of Bcr-Abl

Signal transduction cascade
uncontrolled activity

Genetic Instability

Proliferation
Survival
Adherence
Mechanism of Action of Imatinib

Bcr-Abl

Substrate

ATP

Imatinib
Mechanism of Action of Imatinib

Adapted from Goldman JM, Melo JV. *N Engl J Med.* 344:1084-1086
Mechanism of Action of Imatinib

Adapted from Goldman JM, Melo JV. *N Engl J Med*. 344:1084-1086
Phase I Clinical Trial
Chronic phase CML who failed α-interferon

With imatinib, no dose-limiting toxicity observed (25-1000 mg/daily)
400-600 mg daily - achieved maximal inhibition of BCR-ABL kinase activity; clinical efficacy noted

53 of 54 patients (receiving ≥ 300 mg/day) achieved complete hematologic response (WBC returned to normal).
Some patients also achieved a complete cytogenetic response (Philadelphia chromosome no longer detected in bone marrow)

Side effects: mild bone marrow suppression (21%); nausea, diarrhea, rashes, cramps
# Imatinib (Gleevec) - Clinical Efficacy

**Phase III Trial (Chronic Phase CML)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Response Rate (%)</th>
<th>Hematologic</th>
<th>Major Cytogenetic</th>
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<tbody>
<tr>
<td>Imatinib</td>
<td>94</td>
<td>83</td>
<td></td>
</tr>
<tr>
<td>Interferon + Ara-C</td>
<td>55</td>
<td>20</td>
<td></td>
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*O'Brien et al, NEJM, 2003*
FDA Approval, May 2001
Imatinib has dramatically improved survival.
## Incidence And Mortality Of CML

<table>
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<th>Year</th>
<th>Number of Cases</th>
<th>Number of Deaths (%)</th>
</tr>
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<tbody>
<tr>
<td>1997</td>
<td>4300</td>
<td>2400</td>
</tr>
<tr>
<td>2007</td>
<td>4570</td>
<td>490</td>
</tr>
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Based on current data, median survival is expected to exceed 15-20 years.

Next Generations of TKIs

- Dasatinib – improved responses compared to imatinib (DASISION, Kantarjian *NEJM* 2010 362(24): 2260)
- Nilotinib – improved responses compared to imatinib (ENESTnd, Saglio *NEJM* 2010 362(24):2251)
- Ponatinib – effective against T315I mutations
- Bosutinib
Side effects of TKIs

• Common side effects: edema, myalgias (rhabdo), cytopenias, LFTs, CYP450

• Dasatinib – pleural effusions
• Nilotinib – diarrhea, pancreatitis
• Ponatinib – cardiovascular events
• Bosutinib
Can you stop medication?

• In selected patients – yes, but follow very closely
Questions and Thanks
Peripheral Blood Smear
Bone Marrow Aspirate
Some famous people living with CML

Jason Blake

Kareem Abdul-Jabbar