Chronic Myeloid Leukaemia (CML): Overview

March 2007
Introduction

Objective: To provide an overview of chronic myeloid leukaemia (CML), including relevant biology, epidemiology, pathophysiology, clinical presentation, and current treatment approaches.

Topics covered in this slide module
• Haematopoiesis
• Haematological malignancy and leukaemia
• Cellular signal transduction
Introduction (cont’d)

Other topics covered in this slide module

• Epidemiology of CML
• Cytogenetics and molecular biology of CML
• Clinical presentation and natural history of CML
• Therapeutic options for CML
Haematopoiesis: Blood Cell Lineages

- Haematopoiesis: process by which blood-cell lineages are produced by bone marrow
- WBCs (white blood cells, or leukocytes) subdivided into
  - Myeloid lineages
  - Lymphoid lineages
- Granulocytes massively expanded in CML

Diagram reproduced with permission from W.H. Freeman Company, New York, NY, USA.
Stem Cells and Haematopoietic Differentiation

- Haematopoietic stem cells capable of
  - Self-renewal
  - Differentiation
- Differentiation and proliferation controlled by molecular signals
  - Contact with stromal cells in bone marrow
  - Growth factors

Signal Transduction and Tyrosine Kinases

Haematological Malignancy and Leukaemia

- Haematological malignancies
  - Cancer of blood cells
  - Involves acquisition of growth advantage by single cell
  - Uncontrolled growth results in expansion of clonal population of cells
- Leukaemia: haematological malignancy in leukocyte cell lineage

Neoplastic transformations initiated by:
- Point mutation
- Chromosomal loss, duplication, or inappropriate recombination
- Loss of expression of a gene that inhibits cell proliferation or promotes apoptosis

Diagram courtesy of National Cancer Institute, USA.
Types of Leukaemia

- Leukaemia classified according to:
  - Cell lineage (myeloid or lymphoid)
  - Degree of terminal differentiation
- Acute (eg, AML, ALL)
  - Primitive progenitor cell with limited capacity for further maturation
  - Evolves rapidly, requires prompt intervention
- Chronic (eg, CML, CLL)
  - Primitive progenitor cell with capacity for further maturation
  - Generally progresses in indolent manner

ALL, acute lymphocytic leukaemia; AML, acute myeloid leukaemia; CLL, chronic lymphocytic leukaemia.
CML: Epidemiology

- Leukaemia accounts for ~3% of all cancers in humans\textsuperscript{1-3}
  - Incidence: 5-10 cases per 100,000 population
- CML accounts for 15%-20% of all adult leukaemias\textsuperscript{4,5}
  - Incidence: 1-2 cases per 100,000 population\textsuperscript{4,6}
  - Occurs slightly more frequently in men than women (1.4-2.2:1)\textsuperscript{7}
- Median patient age at diagnosis: 55-60 years\textsuperscript{7}
- CML is rare in persons aged ≤19 years (~1-2 cases per million population)\textsuperscript{6}
- CML was the first cancer to be shown to be caused by an underlying genetic abnormality\textsuperscript{8}

CML Pathogenesis: Philadelphia (Ph) Chromosome

- CML first cancer demonstrated to have underlying genetic abnormality \(^1,2\)
  - Associated with Ph chromosome
- Result of translocation between chromosomes 9 and 22 \(^3\)
- Detected in \(~95\%\) of patients with CML \(^4\)


**BCR-ABL Oncogene**

- Ph chromosomal translocation splices 2 genetic segments in an abnormal hybrid\(^1\)
- *BCR* gene of chromosome 22 in continuity with *ABL* proto-oncogene of chromosome 9\(^1\)
- Hybrid *BCR-ABL* gene encodes a continuously activated BCR-ABL fusion protein\(^2\)
  - Drives leukaemic transformation, causing CML

Figure reprinted with permission from Goldman JM et al. *N Engl J Med.* 2003;349:1455.

BCR-ABL Tyrosine Kinase and Intracellular Signal Transduction

- BCR-ABL has tyrosine-kinase activity and participates in intracellular signal transduction\(^1\)
- Activity imparts growth advantage to leukaemic cells\(^2-4\)
  - Increased proliferation and cytokine-independent growth
  - Inhibition of apoptosis
  - Alteration of adhesion pathways

Figure reprinted with permission from Goldman JM et al. *N Engl J Med.* 2003;349:1457.

# Clinical Presentation of Ph+ CML

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Chronic</th>
<th>Accelerated</th>
<th>Blast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median duration prior to availability of imatinib therapy</td>
<td>5-6 years</td>
<td>6-9 months</td>
<td>3-6 months</td>
</tr>
<tr>
<td>WBC count</td>
<td>≥20 × 10⁹/L</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Blasts</td>
<td>0%</td>
<td>≥10%</td>
<td>≥30%</td>
</tr>
<tr>
<td>Basophils</td>
<td>↑</td>
<td>≥20%</td>
<td>–</td>
</tr>
<tr>
<td>Platelets</td>
<td>↑ or normal</td>
<td>↑ or ↓</td>
<td>↓</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>Myeloid hyperplasia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytogenetics</td>
<td>Ph+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCR-ABL</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Ph+, Philadelphia chromosome positive.

CML: Chronic Phase

- Majority (>80%) of cases of CML diagnosed in chronic phase
- Defined by
  - Elevated WBC count (≥20 × 10⁹/L)
  - Relative lack of blasts (<10% in peripheral blood and bone marrow)
- Prior to imatinib, median duration: 5-6 years
- Effect of imatinib on duration of chronic phase has yet to be quantified

CML: Accelerated Phase

- Second and intermediate phase in CML\(^1\)
- Defining criterion: ≥5% to ≥19% blast cells in blood or marrow\(^2,3\)
- Thrombocytopenia and progressive anaemia may mark onset\(^1,3\)
- Characterised by general worsening of symptoms\(^4\):
  - Fever of unknown origin
  - Bone pain
  - Symptoms related to splenomegaly or hepatomegaly
- Median duration (range): ~3-18 months\(^5\)

CML: Blast Crisis

- Final disease phase characterised by ≥20% to ≥30% blasts in peripheral blood or marrow\textsuperscript{1-3}
- Increased symptomatology\textsuperscript{1}
  - Fatigue related to progressive anaemia
  - Bleeding
  - Infectious complications
  - Lymphadenopathy
  - CNS dysfunction
- Phase is rapidly fatal, with median survival ranging from 3 to 12 months\textsuperscript{4}

CNS, central nervous system.

2006 European LeukemiaNet Recommendations
Ph+ CML Treatment Response Definitions

Haematologic Response (HR)
- Platelets: <450 × 10⁹/L
- WBCC: <10 × 10⁹/L
- Differential without immature granulocytes and <5% basophils
- Nonpalpable spleen

Complete (CHR)

Cytogenetic Response (CyR)
- Complete (CCyR) Ph+ 0%
- Partial (PCyR) Ph+ 1%-35%
- Minor Ph+ 36%-65%
- Minimal Ph+ 66%-95%
- None Ph+ >95%

Molecular Response (MR)
[BCR-ABL to control gene ratio according to International Scale (IS)]
- Complete Transcripts nonquantifiable and nondetectable
- Major (MMR) ≤0.1%

Major = partial + complete

WBCC, white blood cell count.
*Standardised baseline represents 100% on IS; 0.1% = 3-log reduction from standard baseline.
# 2006 European LeukemiaNet Recommendations for Monitoring Response

<table>
<thead>
<tr>
<th></th>
<th>Haematologic Response(^1)</th>
<th>Cytogenetic Response(^1)</th>
<th>Molecular Response(^2)</th>
</tr>
</thead>
</table>
| **Frequency**            | • Every 2 weeks until a complete response has been achieved and confirmed  
                           • Every 3 months unless otherwise required  | • Every 6 months until a complete response has been achieved and confirmed  
                           • Then every 12 months  | • Every 3 months |
| **Methods**              | • Complete blood count (CBC) with differential  | • Conventional cytogenetic examination  
                           • FISH (only before treatment)  | • RQ-PCR |

FISH, fluorescence in situ hybridisation; RQ-PCR, reverse transcription quantitative polymerase chain reaction.

Molecular Response

Decreasing residual leukaemia

BCR-ABL/ABL Ratio, %

0

0

1

0.1

0.01

0.001

10

100

Leukocytosis

Ph+

Ph− but RT-PCR positive

RT-PCR negative

Cure?

Total Number of Leukemia Cells

10^1

10^2

10^3

10^4

10^5

10^6

10^7

10^8

10^9

10^10

10^11

10^12

10^13

Reproduced with permission from Goldman J. *Curr Opin Hematol.* 2004;12:34.

Ph−, Philadelphia chromosome negative; RT-PCR, reverse transcription polymerase chain reaction.

2006 European LeukemiaNet Recommendations: Criteria for Satisfactory Response to Imatinib Treatment

**Treatment Failure**
- **3 months**
  - No HR
  - <CHR
  - No CyR
- **6 months**
  - <CHR
  - No CyR
- **12 months**
  - <PCyR
  - <CCyR
- **18 months**
  - <CCyR
- **At any time**
  - Loss of CHR
  - Loss of CCyR
  - Mutation with a high level of insensitivity to IM

**Suboptimal Response**
- **3 months**
  - <CHR
- **6 months**
  - <PCyR
- **12 months**
  - <CCyR
- **18 months**
  - <MMR
- **At any time**
  - ACA in Ph+ cells
  - Loss of MMoIR
  - Mutation with a low level of insensitivity to IM

**Warnings**
- High risk
- Del 9q+
- ACA in Ph+ cells

**At diagnosis**
- <MMR

**12 months**
- <MMR

**At any time**
- Any rise in transcript level
- Other chromosomal abnormalities in Ph- cells

ACA: additional chromosome abnormalities; CCyR: complete cytogenetic response; CyR: cytogenetic response; CHR: complete haematological response; HR: haematological response; MMR: major molecular response; PCyR: partial cytogenetic response.

*To be confirmed on 2 occasions, unless associated with progression to AP/BC. †To be confirmed on 2 occasions, unless associated with CHR loss or progression to AP/BC. ‡Mutations need to be interpreted within clinical context. §To be confirmed on 2 occasions, unless associated with CHR or CCyR loss.

Therapeutic Options for CML

- Imatinib current recommendations
  - US NCCN clinical practice guidelines: emphasise the use of SCT and imatinib¹
  - European LeukemiaNet recommendations: imatinib is the preferred initial treatment for most patients with newly diagnosed chronic-phase CML²

- Allogeneic SCT
- IFN-α
- Chemotherapy with hydroxyurea or busulphan
- Second-generation TKIs (when imatinib resistance/intolerance is seen)

IFN-α, interferon alpha; NCCN, National Comprehensive Cancer Network; SCT, stem-cell transplantation; TKIs, tyrosine kinase inhibitors.

Response to Imatinib in Patients With Chronic-Phase CML

Failure
- Imatinib treatment at the current dose is no longer appropriate
- Dose escalation or other treatments are recommended

Suboptimal response
- Continuation of imatinib treatment may still have a substantial benefit
- Long-term outcome of the treatment not likely to be as favourable

Warnings
- Standard dose of imatinib may not be the best option
- “Warnings” are flexible and don’t necessarily mean action needs to be taken
- More careful monitoring is required
- Dose escalation or other treatments are recommended

**Chronic-Phase CML: European Treatment Recommendations**

Imatinib 400 mg daily is the preferred initial treatment for most patients with newly diagnosed chronic-phase CML.

<table>
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<th>Response to Imatinib</th>
<th>Treatment Recommendations*</th>
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<tr>
<td>Suboptimal response</td>
<td>• First choice: imatinib dose escalation to 600 or 800 mg daily</td>
</tr>
<tr>
<td></td>
<td>• AlloHSCT</td>
</tr>
<tr>
<td>Failure</td>
<td>• Imatinib dose escalation to 600 or 800 mg daily</td>
</tr>
<tr>
<td></td>
<td>• AlloHSCT</td>
</tr>
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</table>

*When other treatment options are not available, continuation of imatinib treatment or hydroxyurea should be considered.

alloHSCT, allogeneic haematopoietic stem-cell transplantation.

## Chronic-Phase CML: Treatment Recommendations

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<tr>
<td>Warnings</td>
<td>• Standard treatment: 400 mg daily imatinib</td>
</tr>
<tr>
<td></td>
<td>• Dose escalation, alloHSCT, or investigational agents</td>
</tr>
<tr>
<td>Intolerance or toxicity</td>
<td>• AlloHSCT*</td>
</tr>
<tr>
<td></td>
<td>• rIFN-α ± LDAC*</td>
</tr>
</tbody>
</table>

*Must be weighed against investigational trials of new agents.

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rIFN, recombinant interferon; LDAC, low dose arabinosyl cytosine.

Event-Free Survival and Survival Without AP/BC on First-Line Imatinib

Progression events:
- 6.3% AP/BC
- 5.1% loss of MCR
- 2.5% loss of CHR
- 1.6% CML-unrelated deaths

Estimated rate at 60 months (with 95% CI)
- Survival without AP/BC: 93% (90-96)
- EFS: 83% (80-87)

Months Since Randomisation

AP, accelerated phase; BC, blast crisis; EFS, event-free survival.
Survival Rates for Stem Cell Transplantation

- First chronic phase (n = 1903)
- Accelerated and second chronic phase (n = 744)
- Blastic phase (n = 159)

P = 0.0001

Years After Transplant

% Survival

National Marrow Donor Program overview slide presentation.
A Minority of Patients Treated With IFN-α in Early Chronic-Phase CML Achieve CCyR

- CyR correlates with prolonged chronic-phase duration and survival
- At doses that induce CyR, IFN-α therapy is associated with issues of tolerability and side effects

Chemotherapy: Hydroxyurea and Busulphan Are Palliative for Symptoms of CML

- IFN-α ($n = 133$) median survival 66.0 months
- Hydroxyurea ($n = 194$) median survival 56.2 months
- Busulphan ($n = 186$) median survival 45.4 months

IFN-α vs busulphan: $P = 0.008$

Adapted with permission from Hehlmann R et al. Blood. 1994;84:4064-4077.
Imatinib Treatment in CML: US Recommendations

- HSCT candidate
  - Donor available and prefers HSCT
    - HSCT
  - No donor available or Declined HSCT
- Not HSCT candidate
  - Imatinib 400 mg PO daily
    - 3-month evaluation
      - Not in haematological remission, or
        - In haematological relapse
          - Dasatinib and HSCT, or
            - Clinical trial
    - Haematological remission
      - Continue imatinib

HSCT, haematopoietic stem-cell transplantation.
Imatinib Treatment in CML: US Recommendations (cont’d)

- Major or minor CyR:
  - Continue same dose or increase to maximum of 600-800 mg

- 6-month evaluation:
  - No CyR:
    - Increase dose of imatinib to 600-800 mg, or
    - Dasatinib, or
    - Clinical trial, or
    - HSCT

- 12-month evaluation:
  - Complete CyR:
    - Continue imatinib
  - Partial CyR:
    - Increase dose to maximum of 600-800 mg or
    - Continue same dose
  - Minor or no CyR:
    - Dasatinib, or
    - Clinical trial, or
    - HSCT

CyR, cytogenetic response;
Imatinib Treatment in CML: US Recommendations (cont’d)

- Complete CyR → Continue imatinib
- 18-month evaluation
  - Partial CyR Minor or no CyR
    - Increase dose to maximum of 600-800 mg, or
    - Dasatinib, or
    - HSCT, or
    - Clinical trial

Summary and Conclusions

- **CML**
  - Accounts for 15%-20% of all adult leukaemias
  - Ph chromosome detected in ~95% of patients with CML

- **Ph chromosome**
  - Translocation of 2 segments – t(9;22) – resulting in an abnormal hybrid BCR-ABL oncogene
  - Encodes constitutively active BCR-ABL protein-tyrosine kinase
  - BCR-ABL activity drives development of CML
Summary and Conclusions (cont’d)

- CML diagnosed in all phases on basis of common symptoms, signs, and laboratory findings
- Goal of therapy: stabilise blood counts and achieve haematological and cytogenetic response
- Overall goal: complete molecular response
  - No BCR-ABL transcripts detected in peripheral blood by quantitative RT-PCR
Summary and Conclusions (cont’d)

- Imatinib is the standard of care for CML in all phases
  - Demonstrated to be well tolerated in all studies
  - Improved efficacy in comparison with previous systemic therapies
- Other treatment options for CML
  - Allogeneic SCT
  - IFN-α
  - Chemotherapy with hydroxyurea or busulphan
  - Second-generation tyrosine kinase inhibitors