Management of CML patients treated with TKI: the place of molecular monitoring

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CML: definition

- t(9;22)

CML epidemiology

- CML accounts for 14% of all leukemias
- The incidence is 1.6 per 100,000/year
  - 1 CML = 2 AML = 3 MM = 12 NHL = 37 CLL
  - Increases with age (median 67 y)
- Male predominance: 1.4/1
- The only known risk factor is ionizing radiations (high doses)
  - Exposure to atomic bomb in Nagasaki and Hiroshima induced CML

CML diagnosis

- Symptoms
  - Fatigue, anorexia, weight loss
- Clinical examination
  - Spleenomegaly
- Biology
  - Hyperleucocytosis
  - Circulating bone marrow myeloid precursors (left shift)
  - Increased basophilia
  - Thrombocytosis
- Cytogenetics: t(9;22) = Philadelphia (Ph) chromosome
- Molecular biology: BCR-ABL1

CML: peripheral blood smear

Normal

Chronic phase of CML

Cytogenetic abnormality of CML

Ph chromosome
**Ph chromosome and BCR-ABL1 gene**

*BCR* is a breakpoint on chromosome 22, while *ABL1* is a breakpoint on chromosome 9. The translocation t(9;22) results in the formation of a chimeric protein with tyrosine kinase activity.

**BCR-ABL1: types of transcripts**

- m-bcr ≈ 55 kd
- M-bcr ≈ 2,9 kb
- µ-bcr

**Multiplex-PCR for BCR-ABL1 transcripts**

A multiplex-PCR technique is used to detect the presence of BCR-ABL1 transcripts.

**Constitutively activated tyrosine kinase**

The Bcr-Abl1 protein is a constitutive activated tyrosine kinase.

**Bcr-Abl1 signal transduction pathways**

- JAK/STATs
- GRB2
- CRKL
- CBL
- PI3 kinase
- AKT
- MYC
- BCL-2

**Clinical evolution: CML phases**

<table>
<thead>
<tr>
<th>Phase</th>
<th>Chronic phase</th>
<th>Advanced phases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median time</td>
<td>Median survival</td>
</tr>
<tr>
<td>Variable</td>
<td>6–9 months</td>
<td>3–6 months</td>
</tr>
</tbody>
</table>

*Adapted from Pasternak G et al. J Cancer Res Clin Oncol. 1998;124:643-660*
What are the therapeutic goals in CML?

Disappearance of the symptoms
Modify the natural evolution of the disease → blastic phase
Cure

Criteria for response to R/

Hematologic response

Complete
- Platelet count < 450 x 10^9/L
- WBC count < 10 x 10^9/L
- Differential: no immature granulocytes
- Basophils < 5%
- Non-palpable spleen

Partial (PCR1) = 36-65% Ph+ metaphases
Minor = 66-95% Ph+ metaphases
Minimal = < 5% Ph+ metaphases
None = > 93% Ph+ metaphases

Molecular response

Chemotherapy

- Oral cytotoxic agents
  - Hydroxyurea
  - Busulfan
- Hematological responses in up to 90% of patients
- Major cytogenetic responses are rare (3%-5%)⁴
- Palliative care: no effect on disease progression

Interferon α

- Major cytogenetic response
- Minor or no response


BCR-ABL1: the ideal target for molecular therapy

- Present in the majority of patients with CML (95%)
- The cause of the disease
- Necessary for the initiation of the disease (primary event)
- ABL1 is non-essential for normal cellular functions
  - Abl neg mice are viable

→ Imatinib targets BCR-ABL1

Mechanism of action of Imatinib

Goldman JM, Melo JV. N Engl J Med. 344:1084-1086

IRIS Study
Imatinib versus IFN-α + Ara-C
1316 patients enrolled from June 2000 to January 2001

IRIS Study : Summary of the 12-Month Data

CHR = complete haematological response; MCyR = major cytogenetic response; PD = progressive disease; AP = accelerated phase; BC = blast crisis.

Is CCyR the best surrogate endpoint?
Progression to AP/BP

Towards cure under TKI?

Is MMR the best surrogate endpoint?

• No proven effect on survival...
• Variability of the assay...
• Data on benefit of MMR based on good responders...

But ...

– MMR = very low progression rate
– Loss of MMR signals relapse/progression
– Early MMR predicts complete molecular response → cure?
– MMR underscores the basic oncology principle that less disease is better
  → Less is probably more

Molecular monitoring: difficulties

• RQ-PCR is technically challenging
• Issues concerning comparability of results between centres

→ International standardisation of molecular monitoring for CML to enable testing laboratories to accurately measure key therapeutic molecular milestones in CML (MMR and CMR)

International scale for BCR-ABL1

• Historically (IRIS trial; 2000), the mean BCR-ABL1 levels of 30 CML patients was defined as 100% in each of the three participating laboratories using BCR as a control

• The value corresponding to MMR in each laboratory has been defined as 0.1% (reduction of 3 log from IRIS baseline)

• International Scale (IS) fixed to these key points
Second generation TKI

- **Nilotinib vs. Imatinib in CML-CP (ENESTnd Trial, NEJM 2010, Lancet, 2011)**
  - More frequent and faster MMR
  - Decreased progression to accelerated or blastic phase
  - More frequent CR, room for cure?

- **Dasatinib vs. Imatinib in CML-CP (NEJM 2010)**
  - More CCyR
  - More frequent and faster MMR

**Effect on long term outcome?**

BCR-ABL1 kinase domain mutants

- Are associated with various degrees of TKI insensitivity
- Select resistant clones = most important mechanism of resistance
- Can precede or accompany progression to advanced-phase disease

→ KD mutations above a certain level should be identified as early as possible to reconsider the therapeutic strategy

Activity of Nilotinib on Imatinib-Resistant BCR-ABL1 Mutants

Spectrum of Kinase Inhibition for Imatinib and Novel Compounds

BCR-ABL1 kinase domain mutations

- 90 KD mutations known to date
### Management of CML
Recommendations from the European LeukemiaNet

<table>
<thead>
<tr>
<th>Time</th>
<th>Optimal Response</th>
<th>Suboptimal Response</th>
<th>Failure</th>
<th>Warnings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>High risk</td>
</tr>
<tr>
<td>3 months</td>
<td>CML or Licence/M</td>
<td>N/C</td>
<td>Low Eutop CML</td>
<td>N/A</td>
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<tr>
<td>6 months</td>
<td>At least PCML</td>
<td>Less than PCML</td>
<td>No PCML</td>
<td>N/A</td>
</tr>
<tr>
<td>12 months</td>
<td>CGT</td>
<td>N/C</td>
<td>Less than PCML</td>
<td>N/A</td>
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<tr>
<td>18 months</td>
<td>MMR</td>
<td>Less than MMR</td>
<td>Less than CGT</td>
<td>N/A</td>
</tr>
<tr>
<td>Any time during treatment</td>
<td>Stable or improving</td>
<td>No CML or MMR, MMR, or MM</td>
<td>Loss of CHR, CML, CML, CGT</td>
<td>N/A</td>
</tr>
</tbody>
</table>

New recommendations 2010 are marked in red.

### Conclusion

The next step is:
- to better define CMR (EUTOS project)
- to identify patients cohorts not relapsing after TKI withdrawal