MINIMAL RESIDUAL DISEASE

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15 slides, 15 minutes
Identify genetic lesions that drive **prognosis** and define **therapy**.

**Cytogenetics (Ph+)**

**Mutation (FLT3-ITD)**

**Gene expression**
Detection of Minimal residual disease (MRD)

MRD+ predicts relapse

Quantification defines risk

Molecular assays of MRD allow for early intervention to prevent relapse.
Disease Burden and Tests

- **Cytogenetics**
  - CCyr: 1-2 log reduction
  - Major molecular remission = 3 log
  - Complete molecular remission = 4-5 log

- **FISH**
- **RT-PCR**

Graph:
- CML (log_{10})
- Treatment over Time

Graph shows a decrease in CML with treatment, indicating a reduction in disease burden.
Molecular response to imatinib predicts outcome

Estimated rate at 54 month

- CCyR with >=3 log reduction: 97%
- CCyR with <3 log reduction: 89%
- No CCyR: 72%

\( p < 0.001 \)
\( p = 0.017 \)
Significance of Sustained MMR and CMR

Event-Free Survival

- **Sustained CMR**
- **Sustained MMR, No CMR (>0 - ≤0.1)**
- **CCyR only**

<table>
<thead>
<tr>
<th>Total</th>
<th>No. of events</th>
</tr>
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<tbody>
<tr>
<td>84</td>
<td>3</td>
</tr>
<tr>
<td>121</td>
<td>17</td>
</tr>
<tr>
<td>15</td>
<td>6</td>
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</table>

p < 0.001
Molecular response at 12 months predicts probability of undetectable BCR-ABL

Probability of undetectable BCR-ABL (%)

- MMR at 12 months (n=24)
- No MMR at 12 months (n=29)

<0.0001

Months on imatinib

0 12 24 36 48 60 72
Early Achievement of Molecular Response With Imatinib Leads to Response Stability

<table>
<thead>
<tr>
<th>Time to MMR</th>
<th>Events</th>
<th>Mean Time to CMR After MMR,* Mos</th>
<th>Probability of CMR,† %</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 6 mos</td>
<td>0/41</td>
<td>24</td>
<td>93</td>
</tr>
<tr>
<td>&gt; 6-12 mos</td>
<td>3/40 (8%)</td>
<td>37</td>
<td>69</td>
</tr>
<tr>
<td>&gt; 12-18 mos</td>
<td>5/33 (15%)</td>
<td>42</td>
<td>37 (n = 43)</td>
</tr>
</tbody>
</table>

*P < .001
†P < .0001

Some patients in complete molecular response can stop imatinib

At 12 mos, the probability of being CMR is 41% (95% CI: 29-52%)

Loss of major molecular response = worse outcome

No Loss of MMR (N=43)
Loss of MMR (N=33)

P = 0.0003
Increasing Bcr-ABL predicts poor outcome

PCR

Advantages

• Very sensitive
• Values have clinical significance
  – MMR = low progression
  – CMR = off therapy?
• Less invasive than bone marrow cytogenetics

Disadvantages

• Technically difficult
• Difficult to standardize
  – Difficulty of adopting the international scale (IS)
Can we eliminate all CML cells?

Late relapses uncommon but can occur >20 years post-transplant!
CML “stem cell” not killed by tyrosine kinase inhibitors

These residual cells may be reservoir for relapse.

Can combination therapy eliminate CML stem cells?

Problem: CML stem cells are very similar to normal stem cells—may be hard to target.
Thanks

1. Organizers
2. Colleagues
3. Audience