TFR in low and middle-income countries 
(Asia)

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Definition of TFR

- Treatment free remission (TFR) in CML refers to maintenance of deep molecular response without continuing TKI therapy usually after achieving undetectable molecular residual disease (UMRD)
STIM study: Long-term results

Trial commenced in 2007.
At 60 months: 38% in MRD 5.0 (95% CI: 29-47)
# Summary of imatinib TFR studies

<table>
<thead>
<tr>
<th>Study</th>
<th>TKI</th>
<th>Number of patients reported</th>
<th>Required depth of MR</th>
<th>Minimum duration of MR</th>
<th>Median duration of TKI treatment (months)</th>
<th>Trigger to resume TKI</th>
<th>TFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>STIM</td>
<td>IM (± IFN)</td>
<td>100</td>
<td>UMRD (MR5.0)</td>
<td>2 years</td>
<td>50</td>
<td>Loss of UMRD</td>
<td>41%</td>
</tr>
<tr>
<td>TWISTER</td>
<td>IM (± IFN)</td>
<td>40</td>
<td>UMRD (MR4.5)</td>
<td>2 years</td>
<td>70</td>
<td>Loss of UMRD</td>
<td>43%</td>
</tr>
<tr>
<td>A-STIM</td>
<td>IM (± IFN)</td>
<td>80</td>
<td>UMRD</td>
<td>2 years</td>
<td>79</td>
<td>Loss of MMR (61% MMR)</td>
<td>44%</td>
</tr>
<tr>
<td>EuroSKI</td>
<td>IM (± IFN) *</td>
<td>760</td>
<td>MMR</td>
<td>1 year</td>
<td>7 years</td>
<td>Loss of MMR</td>
<td>50%</td>
</tr>
<tr>
<td>KIDS</td>
<td>IM (± IFN)</td>
<td>90</td>
<td>UMRD (MR4.5)</td>
<td>2 years</td>
<td>81</td>
<td>Loss of MMR</td>
<td>59%</td>
</tr>
<tr>
<td>STIM2</td>
<td>IM only</td>
<td>124</td>
<td>UMRD (MR4.5)</td>
<td>2 years</td>
<td>NR</td>
<td>Loss of UMRD (61%**)</td>
<td>34%</td>
</tr>
</tbody>
</table>

*Refers to IM patients only; other TKIs also included in EuroSKI (total 868).

**10-fold increase in BCR-ABL; interim abstract only

Depending on the requirements on deep molecular response and the criteria of defining trigger to resume treatment (or relapse), about 40-60% of patients can achieve successful TFR.
Benefits and risks associated with TFR

**Benefit**
- Cost saving
- Resolution of adverse events
- Improve quality of life
- “Freedom from treatment” and “sense of cure”

**Risks**
- Disease relapse and loss of response to TKI
- Withdrawal symptoms
- Need of close monitoring
- Anxiety of patient
Individualized decision on treatment cessation

• Risk of disease
• Depth and duration of molecular response
• Tolerance to TKI
• Patient’s preference/acceptance
• Availability of accurate molecular monitoring
• Cost of treatment and monitoring
Individualized decision on treatment cessation

- Risk of disease
- Depth and duration of molecular response
- Tolerance to TKI
- Patient’s preference/acceptance
- Availability of accurate molecular monitoring
- Cost of treatment and monitoring

Disease-related
Patient-related
Healthcare system-related
Steps to TFR

1. Treat the patients with the right drug (TKI)
2. Ensure deep response is achieved for an adequate period of time
3. Help them to make an informed decision of treatment cessation
4. Monitor with molecular tests closely
5. Restart treatment promptly if needed
Steps to TFR

Deep molecular response

- Sustained MR\(^4\) or MR\(^{4.5}\) for at least 1 to 2 years

Intensive molecular monitoring

<table>
<thead>
<tr>
<th>RQ-PCR</th>
<th>RQ-PCR every 3(^{rd}) month</th>
</tr>
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<tbody>
<tr>
<td>q4w</td>
<td>q6w</td>
</tr>
</tbody>
</table>

Year 1    Year 2    Year 3
Asia

- Highly heterogeneous socio-economic status and healthcare systems
- A huge population with many living in rural areas
- Reimbursement is highly variable in different countries (sometimes even within the same countries)
Treatment of CML in Asia

• In some high-income countries (e.g. Japan, South Korea, Taiwan), national health insurance provide comprehensive healthcare service including drugs and laboratory tests

• In other high-income countries (e.g. Hong Kong, Singapore), government subsidies also have some limitations (e.g. patients may need to pay part of the treatment cost, restriction in laboratory tests)

• In middle or low-income countries, access to healthcare, reimbursement to drugs and laboratory tests can be limited
  • In some low-income countries, government do not provide TKIs for patients with CML and treatment is dependent on external assistance
  • Molecular monitoring is also limited or even not available especially in rural areas
http://apps.who.int/nha/database/DocumentationCentre/Index/en
Figure 3.3: Prioritization of health in public spending (all sources) by country income groups, 2000–2015

Figure 4.2: Share of external and domestic sources of health spending in low-income countries, 2000–2015

Figure 3.4: Prioritization of health in public spending (domestic sources) by country income groups, 2000–2015

WHO Global Report 2017
Figure 5.3: Out-of-pocket payments as a share of current health expenditure (median) over time by country income groups

WHO Global Report 2017
Challenges of lower-income countries

- Treat the patients with the right drug (TKI)
- Ensure deep response is achieved for an adequate period of time
- Help them to make an informed decision of treatment cessation
- Monitor with molecular tests closely
- Restart treatment promptly if needed

Availability × TKIs Trained healthcare professionals (HCPs)
Accessibility Tests
Challenges in lower income countries: TKIs

Availability
• Usually have first generation TKI
• Not all second generation TKIs are available
• Third generation TKI may not be marketed

Accessibility
• Even if funding is available, usually limited to first generation TKI
• Limited access to second generation TKIs
• Almost no access to third generation TKI

• Cost of drug and side effects are the most important reasons for the patients to attempt treatment cessation
• Cost (reimbursement issue) may lead to inappropriate cessation of treatment (reduce burden to family)
Challenges in lower income countries: Tests (Q-PCR)

<table>
<thead>
<tr>
<th>Availability</th>
<th>Accessibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Standardized and sensitive molecular tests (PCR) may not be available, especially in rural areas</td>
<td>• Limitation in funding for PCR tests</td>
</tr>
<tr>
<td>• Turnaround time may be long (performing tests in batch to save cost)</td>
<td>• Funding may be segregated (drug funding may not be used to perform laboratory tests)</td>
</tr>
<tr>
<td></td>
<td>• Cost of test may be higher than drug cost (generic drug)</td>
</tr>
</tbody>
</table>

• Inadequate evaluation of patients before treatment cessation and monitoring afterward may lead to disease relapse (lower chance of achieving TFR) and even drug resistance
Challenges in lower income countries: Trained HCPs

• It is crucial to have healthcare professionals experienced in managing CML to provide high-quality care to patients, including optimal management to achieve deep response, counselling on TFR and monitoring of patients after treatment cessation.

**Availability**

• Haematologists or oncologists managing CML usually work in large hospitals in major cities.
• Lack of trained HCPs in rural areas especially in large countries.

**Accessibility**

• Patients from rural area may not have the resources or adequate health condition to travel to major cities for treatment.
• Especially important for TFR when frequent monitoring is needed.
# Patient Characteristics and Institutional Requirements for TFR Eligibility

<table>
<thead>
<tr>
<th>ESMO(^1)</th>
<th>NCCN(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient characteristics:</strong></td>
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</tr>
<tr>
<td>• CML-CP</td>
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</tr>
<tr>
<td>• Typical <em>BCR-ABL1</em> transcripts (b2a2 or b3a2) or atypical transcripts that can be quantified over a 4.5-log dynamic range</td>
<td>• Prior evidence of quantifiable <em>BCR-ABL1</em></td>
</tr>
<tr>
<td>• Non-high Sokal risk score at diagnosis</td>
<td>• No history of AP/BC</td>
</tr>
<tr>
<td>• Optimal response to frontline therapy</td>
<td>• No history of resistance to any TKI</td>
</tr>
<tr>
<td>• ≥18 years old</td>
<td>• ≥18 years old</td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th><strong>Institutional requirements:</strong></th>
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</tr>
</thead>
<tbody>
<tr>
<td>• IS-standardized, accurate, sensitive RQ-PCR</td>
<td>• IS-standardized RQ-PCR test sensitive to at least 4.5 logs</td>
</tr>
<tr>
<td>• ≤4-week turnaround of RQ-PCR results</td>
<td>• ≤2-week turnaround of RQ-PCR results</td>
</tr>
<tr>
<td>• Ability to perform RQ-PCR tests every 4 to 6 weeks if required</td>
<td>• Structured follow-up for rapid intervention in case of rising <em>BCR-ABL1</em> transcript levels</td>
</tr>
</tbody>
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\(^1\) ESMO: European Society for Medical Oncology

\(^2\) NCCN: National Comprehensive Cancer Network
Summary

• Treatment-free remission (TFR) has recently emerged as a new goal of treatment in CML

• Individualized balance of benefits versus risks associated with TFR should be done

• Accurate and adequate monitoring is essential in ensuring an informed decision about TFR and safe cessation of treatment

• In resource-limited setting, lack of availability and accessibility to standardized Q-PCR may hamper the achievement of TFR

• We need to ensure that the healthcare system and patients are ready and eligible for TFR to minimize the risks
Thank you

Questions and comments are welcomed