Stopping TKI’s in CML- Are we There Yet?

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Duke Cancer Institute
# Natural History of CML

Accumulation of immature myeloid cells  
New cytogenetic changes

<table>
<thead>
<tr>
<th></th>
<th><strong>Chronic Phase</strong></th>
<th><strong>Accelerated Phase</strong></th>
<th><strong>Blast Phase</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Duration</strong></td>
<td>If untreated, 3-5 yrs</td>
<td>Varies</td>
<td>Median survival of several mos</td>
</tr>
<tr>
<td><strong>Prognosis</strong></td>
<td>Responsive to treatment</td>
<td>Decreased responsiveness</td>
<td>Resistant to treatment</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td>Asymptomatic OR Fatigue Weight loss Abdominal pain or discomfort Night sweats</td>
<td>Progressive splenomegaly Myelofibrosis</td>
<td>Bleeding complications Infection complications</td>
</tr>
</tbody>
</table>

CML: Yesterday, Today and Tomorrow

Today

- Imatinib: 93%alive (censored for non-CML death)
- 1990-2000: 84%alive

<table>
<thead>
<tr>
<th>Year</th>
<th>Total</th>
<th>Dead</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imatinib</td>
<td>302</td>
<td>15</td>
</tr>
<tr>
<td>1990-2000</td>
<td>963</td>
<td>425</td>
</tr>
<tr>
<td>1982-1989</td>
<td>364</td>
<td>273</td>
</tr>
<tr>
<td>1975-1981</td>
<td>132</td>
<td>129</td>
</tr>
<tr>
<td>1965-1974</td>
<td>123</td>
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</tr>
</tbody>
</table>

Proportion Alive vs Years from Referral
A Minute Chromosome in Human Chronic Granulocytic Leukemia

In seven cases thus far investigated (five males, two females), a minute chromosome has been observed replacing one of the four smallest autosomes in the chromosome complement of cells of chronic granulocytic leukemia cultured from peripheral blood. No abnormality was observed in the cells of four cases of acute granulocytic leukemia in adults or of six cases of acute leukemia in children. There have been several recent reports of chromosome abnormalities in a number of cases of human leukemia [including two of the seven cases reported here: Nowell and Hungerford, *J. Natl. Cancer Inst.* 25, 85 (1960)], but no series has appeared in which there was a consistent change typical of a particular type of leukemia.

Cells of the five new cases were obtained from peripheral blood (and bone marrow in one instance), grown in culture for 24–72 hours, and processed for cytological examination by a recently developed air-drying technique (Moorhead, *et al.*, *Exptl. Cell Research*, in press). The patients varied from asymptomatic untreated cases to extensively treated cases of several years’ duration in terminal myeloblastic crisis. All seven individuals showed a similar minute chromosome, and none showed any other frequent or regular chromosome change. In most of the cases, cells with normal chromosomes were also observed. Thus, the minute is not a part of the normal chromosome constitution of such individuals.

The findings suggest a causal relationship between the chromosome abnormality observed and chronic granulocytic leukemia.

Peter C. Nowell

School of Medicine, University of Pennsylvania

David A. Hungerford

Institute for Cancer Research
Historical Perspective

In 1960, Nowell and Hungerford describes, “a minute chromosome replacing one of the four smallest autosomes of chronic granulocytic leukemia cultured from peripheral blood…”

In 1973, Rowley suggests, “...there may be hitherto undetected translocation between the long arm of 22 and the long arm of 9…”

Philadelphia Chromosome Translocation in CML Results in BCR-ABL Oncogene

- Stem cell disorder
- Characterized by myeloproliferation
- Well-described clinical course

Transcription and translation

Inhibition by TKI

Constitutive tyrosine kinase

Phosphorylation of multiple substrates

Mitogenic signaling and genomic instability increased

Apoptosis and stromal regulation decreased

CML
Treatment Options Based on Adverse Effect Spectrum of TKIs in CML

- **Nilotinib**
  - Pancreatic enzyme ↑
  - Indirect hyperbilirubinemia
  - Hypertension
  - Skin toxicity
  - Thrombotic events

- **Imatinib**
  - Edema/fluid retention
  - Myalgia
  - Hypophosphatemia
  - GI effects (diarrhea, nausea)

- **Bosutinib**
  - Diarrhea
  - Nausea/emesis
  - Rash

- **Ponatinib**
  - Pancreatic enzyme ↑
  - Hypertension
  - Skin toxicity
  - Thrombotic events

Common Effects
- Myelosuppression
- Transaminase ↑
- Electrolyte Δ

- **Dasatinib**
  - Pleural/pericardial effusions
  - Bleeding risk
  - Pulmonary arterial hypertension
**Recommendations for Response Monitoring in CML**

**Mutation Analysis**

- If inadequate initial response (failure to achieve PCyR or BCR-ABL ≤ 10% at 3 and 6 mos or CCyR at 12 and 18 mos):
  - RT-PCR > 10% by IS or no PCyR response at 3 mos (Ph+ > 35%)
    - If imatinib was initiated as first TKI, switch is indicated
    - If nilotinib or dasatinib were initiated, consider switching to alternate TKI (except imatinib) or continue TKI
  - Lack of MMR is not failure according to NCCN guidelines; the presence of MMR can, in the absence of cytogenetic data, imply the presence of CCyR
  - For guidance from 5 experts on monitoring response to first-line therapy and switching therapy, an online Interactive Decision Support Tool is available at http://clinicaloptions.com/CMLtool

- Any sign of loss of response (cytogenetic or hematologic relapse):
  - 1 log increase in BCR-ABL transcript levels and loss of MMR

NCCN. Clinical practice guidelines in oncology: chronic myelogenous leukemia. v.3.2014.
Providing Optimal Care for Patients With Chronic Myeloid Leukemia
HEMATOLOGIC DISEASE

Strategies for Stopping TKIs in CML Growing Clearer

SAN DIEGO—In patients with chronic myeloid leukemia (CML), longer treatment duration is associated with an increase in the odds ratio for preserving a major molecular response (MMR) six months after discontinuing tyrosine kinase inhibitor (TKI) therapy, according to recent data from a large study. In contrast, the depth of molecular response was not a predictor of molecular relapse-free survival (MRFS).

In EURO-SKI (European Stop Tyrosine Kinase Inhibitor Study), one of several CML treatment-stopping studies from which new data were presented at the 2016 annual meeting of the American Society of Hematology (ASH), the odds ratio for MRFS was 1.16. Thus, “one additional
<table>
<thead>
<tr>
<th>Study</th>
<th>Finding</th>
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<tbody>
<tr>
<td>Mahon abstract 787</td>
<td>MRFS at 6 months: 62%</td>
</tr>
<tr>
<td>Kadowaki abstract 790</td>
<td>MR4.5 at 1 year: 59%</td>
</tr>
<tr>
<td>Kumagai abstract 791</td>
<td>MRFS at 12 months: 63%</td>
</tr>
<tr>
<td>Pagliardini abstract 788</td>
<td>Disease control at 21.5 months after second discontinuation: 44%</td>
</tr>
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</table>

CML, chronic myeloid leukemia; MR, molecular response; MRFS, molecular relapse–free survival; TKI, tyrosine kinase inhibitor
Loss of MMR by TKI duration: > 8 yrs, 29/86 pts (34%); ≤ 8 yrs, 60/114 (53%)
Loss of MMR by MR4 duration: > 5 yrs, 32/92 pts (35%); ≤ 5 yrs, 57/108 (53%)
Conclusion: ~60% of pts with CP-CML with initial stable, deep MR are likely to remain in TFR after treatment is stopped

## STOP TKI STUDIES

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration</th>
<th>Details</th>
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<tbody>
<tr>
<td>STIM</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>TWISTER</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>EuroSKI</td>
<td>200 (700)</td>
<td></td>
</tr>
<tr>
<td>STIM2</td>
<td>124 (200)</td>
<td></td>
</tr>
<tr>
<td>ENESTop</td>
<td>126</td>
<td></td>
</tr>
<tr>
<td>FREEDOM</td>
<td>190</td>
<td></td>
</tr>
<tr>
<td>LAST</td>
<td>173</td>
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<tr>
<td>IM IFN</td>
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<tr>
<td>IM IFN</td>
<td>42 mos</td>
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<tr>
<td>IM/NIL/DAS</td>
<td>6 min</td>
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</tr>
<tr>
<td>IM</td>
<td>16 mos</td>
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</tr>
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<td>NIL 2\textsuperscript{nd} LINE</td>
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</tr>
<tr>
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<td>12 min</td>
<td></td>
</tr>
<tr>
<td>IM/DAS/NIL/BOS</td>
<td>accru</td>
<td></td>
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EURO-SKI: Conclusion

- EURO-SKI study suggests ~ 60% of pts with CP-CML with deep, durable MR (MR4; BCR-ABL <0.01% for at least 1 yr) on TKIs are likely to remain in remission after TKIs are stopped

TWISTER DATA CONTINUED

- ALL RELAPSED PATIENTS REMAINED SENSITIVE TO IMATINIB RE-TREATMENT
- At 24 MONTHS, STABLE TREATMENT FREE REMISSION WAS 47.1%
STOP 2G-TKI STUDY

- 43% EXPERIENCED MOLEDULAR RELAPSE
- RELAPSES OCCURRED AT A MEDIAN OF 4 MONTHS AND A RANGE OF 1-38 MONTHS
- CUMULATIVE RELAPSE AT 12 MONTHS WAS 35% AND AT 48 MONTHS 44.76%
- NO PROGRESSION TOWARD ADVANCED PHASE CML
THE LAST STUDY

- INFORMED CONSENT
- DOCUMENTED NEGATIVE PCR MINIMUM 2 YEARS
- TWO CONSECUTIVE NEGATIVE PCR FOR BCR/ABL1
- BCR/ABL1 BY PCR EACH MONTH FOR SIX MONTHS
- TRANSCRIPTS EVERY TWO MONTHS FOR SIX MONTHS
- TRANSCRIPTS EVERY THREE MONTHS THEREAFTER
- IF RELAPSE RETURN TO TKI
STUDY OBJECTIVES

- Proportion of patients with CML who develop molecular recurrence after discontinuing TKI.
- Compare health status of patients before and after stopping TKI’s.
- Determine if there are disease or patient related or treatment relate factors that predict recurrence. MR 4.5.
- Develop a risk score to predict risk status and recurrence after stopping TKI.
- Develop and optimal followup schedule.
- Describe health status after resuming TKIs.
INCLUSION CRITERIA

- Age 18 or older
- Able to speak and read English.
- Able to give informed consent
- Diagnosed with CML in chronic phase
- Currently taking imatinib, dasatinib, nilotinib, or bostinib
- Documented undetectable BCR/ABL by PCR for 2 years.
- Undetectable PCR at least three times before screening.
- Two screening PCR’s completed and both < MR4.5
- Compliance demonstrated
EXCLUSION CRITERIA

- Prior stem cell transplantation
- Poor compliance with taking TKI’s
- Unable to follow lab appointment schedule.
- Life expectancy less than 36 months.
- Patients who have receive > 2 TKI/s are not eligible. OK interferon or hydroxyurea.
- Pregnant or lactating women.
WHY CONSIDER STOPPING TKI’S

- REDUCED QUALITY OF LIFE FOR PATIENTS
- COST TO PATIENTS AND SOCIETY
- BY 2050 PREVALENCE OF CML WITH BE 180,000 WITH CURRENT ABOUT 30,000
- ANNUAL COST OF TKI IS AT LEAST $100,000
- SOME PATIENTS MAY NOT REQUIRE LIFE LONG TKI’S
ADVERSE EVENTS

- SERIOUS ADVERSE EVENTS (EXPECTED OR WILD CARDS).
- ALL DEATHS, DISEASE TRANSFORMATION AND TO FUTURE.
- INSTITUTIONAL GUIDELINES
DISCONTINUATION OF TKI THERAPY

- Discontinuation of TKI therapy appears to be safe in select CML patients.
- Clinical studies that have evaluated the safety and efficacy of TKI discontinuation have employed strict eligibility criteria and have mandated more frequent molecular monitoring than typically recommended for patients on TKI therapy.
- Some patients have experienced significant adverse events that are believed to be due to TKI discontinuation.
- Discontinuation of TKI therapy should only be performed in consenting patients after a thorough discussion of the potential risks and benefits.
- Outside of a clinical trial, TKI discontinuation should be considered only if ALL of the criteria included in the list below are met.

Criteria for TKI Discontinuation

- Age ≥18 years.
- Chronic phase CML. No prior history of accelerated or blast phase CML.
- On approved TKI therapy (imatinib, dasatinib, nilotinib, bosutinib, or ponatinib) for at least three years.
- Prior evidence of quantifiable BCR-ABL1 transcript.
- Stable molecular response (MR4; ≤0.01% IS) for ≥2 years, as documented on at least four tests, performed at least three months apart.
- No history of resistance to any TKI.
- Access to a reliable QPCR test with a sensitivity of detection of 24.5 logs that reports results on the IS and provides results within 2 weeks.
  Monthly molecular monitoring for the first six months following discontinuation, bimonthly during months 7–24, and quarterly thereafter (indefinately) for patients who remain in MMR (MR3; ≤0.1% IS).
- Consultation with a CML Specialty Center to review the appropriateness for TKI discontinuation and potential risks and benefits of treatment discontinuation, including TKI withdrawal syndrome.
- Prompt resumption of TKI, with a monthly molecular monitoring for the first six months following resumption of TKI and every 3 months thereafter is recommended indefinitely for patients with a loss of MMR. For those who fail to achieve MMR after six months of TKI resumption, BCR-ABL1 kinase domain mutation testing should be performed, and monthly molecular monitoring should be continued for another six months.
- Reporting of the following to a member of the NCCN CML panel is strongly encouraged:
  - Any significant adverse event believed to be related to treatment discontinuation.
  - Progression to accelerated or blast phase CML at any time.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
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- No history of resistance to any TKI.
- Access to a reliable QPCR test with a sensitivity of detection of ≥4.5 logs that reports results on the IS and provides results within 2 weeks. Monthly molecular monitoring for the first six months following discontinuation, bimonthly during months 7–24, and quarterly thereafter (indefinitely) for patients who remain in MMR (MR3; ≤0.1% IS).
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The 18th Annual
Joseph E. Sokal, MD
Memorial Lecture

Friday, June 25, 2010