Chronic Myeloid Leukemia – Starting and stopping TKI therapy

Richard A. Larson, MD
University of Chicago
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Disclosures

• Research support to the University of Chicago
  – Ariad
  – Bristol Myers Squibb
  – Novartis
  – Pfizer

• Consultancies & Honoraria
  – Ariad
  – Bristol Myers Squibb
  – Novartis
  – Pfizer

• One investigational agent: ABL001
CML: Starting, switching, discontinuing

• 10-year follow up from the IRIS study

• 5-year follow up on the TIDEL-II study – switching based on Early Molecular Response (EMR)

• ABL001 (Novartis) – a non-ATP competitive inhibitor of BCR/ABL1

• Discontinuation studies
  – Euro–SKI
  – ENESTfreedom
Imatinib Compared with Interferon and Low-Dose Cytarabine for Newly Diagnosed Chronic-Phase Chronic Myeloid Leukemia

![Graph showing major cytogenetic response over months after randomization for Imatinib and combination therapy.](image)

P < 0.001

Five-Year Follow-up of Patients Receiving Imatinib for Chronic Myeloid Leukemia

The IRIS Trial: Imatinib vs Interferon + AraC

At 10 years
83.3%
(95% CI, 80%-87%)

78.8%
(95% CI, 75%-83%)

Overall Survival, %

Months Since Randomization

Patients at Risk: Events

Imatinib: 553: 0 542: 6

IFNα+Ara-C: 553: 0 512: 12

New Engl J Med 2017
Long-Term Outcomes of Imatinib Treatment for CML: IRIS

• Median follow-up now 10.9 years.

• Among patients on the imatinib arm, the estimated 10-year overall survival rate was 83.3%.

• 82.8% achieved a complete cytogenetic response.

• Imatinib-related serious adverse events were uncommon and most frequently occurred during the first year of treatment.

• The efficacy of imatinib persisted over time:
  – Late progression events were rare.
  – Chronic imatinib administration did not have cumulative or late toxicities.
Quantitative RT-PCR for BCR-ABL1 transcripts (International Scale)

<table>
<thead>
<tr>
<th>Log reduction</th>
<th>BCR-ABL% IS</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100%</td>
</tr>
<tr>
<td>-1</td>
<td>10%</td>
</tr>
<tr>
<td>-2</td>
<td>1%</td>
</tr>
<tr>
<td>-3</td>
<td>0.1%</td>
</tr>
<tr>
<td>-4</td>
<td>0.01%</td>
</tr>
<tr>
<td>-4.5</td>
<td>0.0032%</td>
</tr>
<tr>
<td>-5</td>
<td>0.001%</td>
</tr>
</tbody>
</table>

Mean value observed at diagnosis:
- CHR
- CCyR
- MR³ (MMR)
- MR⁴
- MR⁴.5
- MR⁵

## 2013 European LeukemiaNet Recommendations for newly diagnosed CML

<table>
<thead>
<tr>
<th>Time:</th>
<th>Optimal Response</th>
<th>Warning</th>
<th>Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 months</td>
<td>BCR/ABL ≤10% &lt;br&gt; Ph+ cells ≤35% (PCyR)</td>
<td>BCR/ABL &gt;10% &lt;br&gt; Ph+ cells 35-95%</td>
<td>No CHR. &lt;br&gt; Ph+ cells &gt;95%</td>
</tr>
<tr>
<td>6 months</td>
<td>BCR/ABL ≤1% &lt;br&gt; Ph+ cells 0% (CCyR)</td>
<td>BCR/ABL 1-10% &lt;br&gt; Ph+ cells 1-35%</td>
<td>BCR/ABL &gt;10% &lt;br&gt; Ph+ cells &gt;35%</td>
</tr>
<tr>
<td>12 months</td>
<td>BCR/ABL ≤0.1% &lt;br&gt; (MMR)</td>
<td>BCR/ABL 0.1-1%</td>
<td>BCR/ABL &gt;1% &lt;br&gt; Ph+ cells &gt;0%</td>
</tr>
<tr>
<td>Thereafter</td>
<td>Major Molecular Response [MMR] or better; Tolerating the drug; good adherence; monitored every 3 mos</td>
<td>-7 or del(7q) in Ph- cells</td>
<td>Loss of CHR or CCyR; confirmed loss of MMR. ABL mutations. New chromosome abnormalities</td>
</tr>
</tbody>
</table>

Baccarani et al. Blood 2013 Aug 8;122(6):872-84
What is an Early Molecular Response?

- **BCR/ABL1** transcript level ≤10% (International Scale)
  - At 3 months
  - At 6 months

- **Importance**: predicts for MMR and Survival

- **Limitations**: not yet clear whether altering therapy for qRT-PCR level >1% leads to a better outcome.

- However, switching at 3 or 6 months if the **BCR/ABL1** level is still >10% seems reasonable.
Outcomes (MMR by 1-2 yrs) by EMR at 3 months (ENESTnd)

Nilotinib 300 mg BID

Imatinib 400 mg Daily

Hughes TP, et al. Blood 2014; 123(9); 1353-1360
Rate of MR$^{4.5}$ By 6 Years According To 3-Month BCR-ABL$^\text{IS}$ Levels

![Graph showing the rate of MR$^{4.5}$ achievement at 6 years according to 3-month BCR-ABL$^\text{IS}$ levels for different treatments.](image)

- **Nilotinib 300 mg BID**:
  - $BCR-ABL^\text{IS} \leq 1\%$: 73.6, $P = .001$
  - $BCR-ABL^\text{IS} > 1\% - \leq 10\%$: 52.8, $P < .0001$
  - $BCR-ABL^\text{IS} > 10\%$: 8.3

- **Nilotinib 400 mg BID**:
  - $BCR-ABL^\text{IS} \leq 1\%$: 75.0, $P < .0001$
  - $BCR-ABL^\text{IS} > 1\% - \leq 10\%$: 45.3, $P = .02$
  - $BCR-ABL^\text{IS} > 10\%$: 21.4

- **Imatinib 400 mg QD**:
  - $BCR-ABL^\text{IS} \leq 1\%$: 72.1, $P < .0001$
  - $BCR-ABL^\text{IS} > 1\% - \leq 10\%$: 35.3, $P = .002$
  - $BCR-ABL^\text{IS} > 10\%$: 15.9

Patients With MR$^{4.5}$ by 6 Years, %

- **Nilotinib 300 mg BID**: n = 144, 89, 24
- **Nilotinib 400 mg BID**: n = 136, 95, 28
- **Imatinib 400 mg QD**: n = 43, 133, 88

Upfront imatinib with selective early switching to nilotinib leads to excellent achievement of deep molecular response in chronic phase CML: 5 year (final) analysis of the TIDEL II study

David T Yeung, Michael P Osborn, Deborah L. White, Susan Branford, Tracey Gerber, Belinda Butcher, Samar Issa, Devendra K Hiwase, Mark S Hertzberg, David Gottlieb, Anthony P Schwarer, Robin Filshie, Christopher K Arthur, Yiu Lam Kwan, Cecily J Forsyth, David M Ross, Anthony K Mills, Andrew P Grigg, and Timothy P Hughes on behalf of ALLG
Nilotinib 400 mg BID

Cohort 2 treatment schema (N=105)
Newly diagnosed chronic phase CML, started Imatinib 600 mg daily

<table>
<thead>
<tr>
<th>IM 600</th>
<th>TIDEL-II = ELN Targets (Baccarani et al. Blood 2013)</th>
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<tbody>
<tr>
<td>Trough IM &lt;1000ng/mL</td>
<td>Nilotinib 400 mg BID</td>
</tr>
<tr>
<td>BCR-ABL ≤ 10% IS</td>
<td></td>
</tr>
<tr>
<td>BCR-ABL ≤ 1% IS</td>
<td></td>
</tr>
<tr>
<td>BCR-ABL ≤ 0.1% IS</td>
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Day 22  Month 3  Month 6  Month 12  Month 60
MMR achievement stratified by TIDEL-II targets

Intolerance

No target failure

No MMR at 12 mos, n=30

>1% at 6 mos, n=23

>10% at 3 mos, N=25

TIDEL-II, ASH 2016, Abstract #939
TIDEL-II as a frontline strategy

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<th>DASISION</th>
<th>ENESTNd</th>
<th>TIDEL-II</th>
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<tbody>
<tr>
<td></td>
<td>DAS</td>
<td>IM 400</td>
<td>IM 400</td>
</tr>
<tr>
<td>OS, 5 yrs</td>
<td>91%</td>
<td>90%</td>
<td>92%</td>
</tr>
<tr>
<td>Blast Crisis</td>
<td>5%</td>
<td>7%</td>
<td>8%</td>
</tr>
<tr>
<td>EMR failure</td>
<td>16%</td>
<td>36%</td>
<td>33%</td>
</tr>
<tr>
<td>5yr MMR</td>
<td>76%</td>
<td>64%</td>
<td>60%</td>
</tr>
<tr>
<td>5yr MR4.5</td>
<td>42%</td>
<td>33%</td>
<td>31%</td>
</tr>
<tr>
<td>Withdrawn</td>
<td>39%</td>
<td>37%</td>
<td>50%</td>
</tr>
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At 5 years:
77 on Imatinib
33 on Nilotinib

1. Cortes et al. JCO 2016;34:2333-40
Conclusions

- TIDEL-II is associated with high molecular response & excellent Transformation-free Survival.
  - MMR in 86%
  - MR4.5 in 60% - good platform for Discontinuation studies

- TIDEL-II provides a schema to maximise the utility of imatinib and the selective switching to nilotinib.
Expanded Phase I Study of ABL001, a Potent, Allosteric Inhibitor of BCR-ABL1, reveals Significant and Durable Responses in Patients with CML-Chronic Phase with Failure of Prior TKI Therapy

Timothy P. Hughes, Yeow-Tee Goh, Oliver Ottmann, Hironobu Minami, Delphine Rea, Fabian Lang, Michael Mauro, Daniel J. DeAngelo, Moshe Talpaz, Andreas Hochhaus, Massimo Breccia, Jorge Cortes, Michael Heinrich, Jeroen Janssen, Juan-Luis Steegmann, François-Xavier Mahon, Ally He, Varsha Iyer, David Hynds, Gary J. Vanasse, Dong-Wook Kim

American Society of Hematology Annual Meeting 2016 Abstract # 625
ABL001 is a potent, specific inhibitor of BCR-ABL1 with a distinct allosteric mechanism of action.

- Developed to gain potent BCR-ABL1 inhibition and maintained against BCR-ABL1 mutations that confer resistance to TKIs.

- Potential to combine with TKIs to prevent the emergence of BCR-ABL1 mutations, increasing the depth of molecular response in a greater number of patients compared with single-agent treatment.

ATP, adenosine triphosphate; TKI, tyrosine kinase inhibitor.
Responses in Patients With CML Treated with Single-Agent ABL001 BID with ≥ 3 Months Exposure

Hematologic Disease (CHR relapse)
- CHR 88% (14/16)

Cytogenetic Disease (> 35% Ph+)
- CCyR 75% (9/12)

Molecular Disease (> 0.1% IS)
- MMR 20% (10/50)
- ≥ 1-log reduction 30% (10/33)

Molecular Disease (≤ 10% IS)
- MMR 42% (16/38)
- ≥ 1-log reduction 48% (12/25)

Disease Status at Baseline

a Patients had ≥ 6 months of treatment exposure or achieved response within 6 months.
b BCR-ABL1IS reduction achieved.
c Patients had ≥ 12 months of treatment exposure or achieved response within 12 months.
Conclusions

• ABL001 was generally well tolerated in heavily pretreated patients with CML resistant to or intolerant of prior TKIs.
  – 61% patients were resistant to their last TKI

• Clinical activity seen in patients with nonmutated BCR-ABL1 as well as across multiple TKI-resistant mutations.
  – 42% achieved MMR by 12 months
  – Only 1 patient with progressive disease had detectable mutations in both kinase and myristoyl domains.

• Dose of 40 mg BID recommended for patients with CML-CP without T315I mutations.
Is it ever safe to discontinue TKI therapy in CML?

Prospective discontinuation studies
Relapse defined as BCR-ABL > 0.1% (loss of MMR) at one time point
Molecular relapse-free survival (n = 750)
EURO-SKI Study

<table>
<thead>
<tr>
<th>Month</th>
<th>Molecular RFS %</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>62</td>
<td>59-67</td>
</tr>
<tr>
<td>12</td>
<td>56</td>
<td>52-59</td>
</tr>
<tr>
<td>24</td>
<td>52</td>
<td>48-56</td>
</tr>
<tr>
<td>36</td>
<td>47</td>
<td>44-53</td>
</tr>
</tbody>
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Events:
- Molecular relapse  n = 348
- Death in remission  n = 5

For patients who resumed treatment, median time to restart was 4.1 months

FX Mahon et al. Blood 2016; 128: #787

CML, March 2017
Treatment-Free Remission in Patients With CML-CP Treated With Frontline Nilotinib: Results From the ENESTfreedom Study

Primary Endpoint and Treatment-Free Survival

- 98 of 190 patients (51.6%; 95% CI, 44.2-58.9%) remained in TFR after 48 weeks (primary endpoint)

- Statistical criterion for trial success was that the lower limit of the 95% CI of the observed primary endpoint be >50%

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a Defined as the time from the start of TFR until the earliest of any of the following: loss of MMR, reinitiation of nilotinib for any reason, progression to accelerated phase/blast crisis, or death due to any cause.

Presented by: Prof Andreas Hochhaus
50% of all retreated patients achieved MMR and MR^4.5 by week 8 and week 15 after treatment reinitiation, respectively.
Case History (2007)

- 28 year old unmarried woman
- WBC 300,000/uL
- Marked splenomegaly
- Bone marrow: 99% cellular with granulocytic hyperplasia
- Cytogenetics: 46 XY, t(9;22)(q34;q11)
- Diagnosis: chronic myeloid leukemia in chronic phase
- Sokal risk score -- not reported
Case History (II)

- Started hydroxyurea and Imatinib 400 mg daily
- Grade 2 myalgia & arthralgia
- Imatinib increased to 600 mg daily due to elevated platelets. Grade 2 nausea & vomiting.
- 19 months later: Bone marrow biopsy showed hematologic remission. FISH for \textit{BCR/ABL1} was negative.
Case History (III) [now October 2012]

- First seen at University of Chicago
- Q-RT-PCR on blood -> 0.04% (IS)
- February 2013: married and stops oral contraceptives.
- October 2013: Q-RT-PCR = 0.01% (IS)
- June 2014: pregnant! Stops imatinib.
BCR/ABL1 transcript levels by quantitative RT-PCR (%IS)

Transcript levels (%IS)

- Undetectable
- MR4.0
- MMR
- ~CCyR

Imatinib 600 mg

Phases:
- Pregnant

Levels:
- 0.001
- 0.01
- 0.1
- 1
- 10

Dates:
- Oct-12
- Jan-13
- Apr-13
- Jul-13
- Oct-13
- Jan-14
- Apr-14
- Jul-14
- Oct-14
- Jan-15

Notes:
- 0.2%
Case History (III) [now October 2012]

- First seen at University of Chicago
- Q-RT-PCR on blood -> 0.04% (IS)
- February 2013: married and stops oral contraceptives.
- October 2013: Q-RT-PCR = 0.01% (IS)
- June 2014: pregnant! Stops imatinib.
- February 2015: healthy baby boy delivered by C-section.
- Breast fed for 2 months.
- April 2015: starts dasatinib due to prior GI toxicity while on imatinib.
BCR/ABL1 transcript levels by quantitative RT-PCR (%IS)

<table>
<thead>
<tr>
<th>Imatinib 600 mg</th>
<th>Dasatinib 100 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>~CCyR</td>
<td>Pregnant</td>
</tr>
<tr>
<td>MMR</td>
<td></td>
</tr>
<tr>
<td>MR4.0</td>
<td></td>
</tr>
<tr>
<td>Undetectable</td>
<td></td>
</tr>
</tbody>
</table>

Transcript levels (%IS)


CML, March 2017
Remaining challenges in CML

• Managing acute and chronic toxicities of TKI therapy.
• Treating resistant and blast phase disease.
• Identifying which patients can safely stop TKI therapy.