Chronic Myeloid Leukemia: What more is needed?

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University of Chicago
March 2018
## Disclosures – Richard A. Larson, MD

<table>
<thead>
<tr>
<th>Research funding to the University of Chicago:</th>
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<tbody>
<tr>
<td>– Astellas</td>
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<tr>
<td>– Celgene</td>
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<tr>
<td>– Daiichi Sankyo</td>
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<td>– Erytech</td>
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<td>– Novartis</td>
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<tr>
<th>Consultancy/ Honoraria:</th>
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<tr>
<td>– Amgen</td>
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<td>– Ariad (DSMB)</td>
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<td>– Astellas</td>
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<td>– Bristol Myers Squibb (DSMB)</td>
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<td>– Celgene (DSMB)</td>
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<td>– CVS/Caremark</td>
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<td>– Novartis</td>
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<td>– Pfizer</td>
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<tr>
<th>Equity ownership: none</th>
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<th>Royalties: UpToDate, Inc</th>
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CML: Starting, switching, discontinuing

- 10-year follow up from the IRIS study
- Switching based on Early Molecular Response (EMR)
- Aciminib (ABL001; Novartis) – a non-ATP competitive inhibitor of BCR/ABL1
- Discontinuation studies (18 so far)
- Novel agents and combinations
Imatinib Compared with Interferon and Low-Dose Cytarabine for Newly Diagnosed Chronic-Phase Chronic Myeloid Leukemia

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

**CML, March 2018**

The IRIS Trial: Imatinib vs Interferon + AraC

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

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

Overall Survival, %

Patients Events Censored
Imatinib: 553 89 464
IFNα+Ara-C: 553 105 448

Censored observations

Patients at Risk : Events
Imatinib 553 : 0 542 : 6
492 : 41 461 : 57 430 : 71 368 : 82 250 : 88 0 : 89
IFNα+Ara-C 553 : 0 512 : 12
441 : 52 388 : 73 358 : 83 299 : 96 199 : 104 0 : 105

New Engl J Med 2017

THE UNIVERSITY OF CHICAGO MEDICINE & BIOLOGICAL SCIENCES
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>Mean value observed at diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>CHR</td>
</tr>
<tr>
<td>-1</td>
<td>CCyR</td>
</tr>
<tr>
<td>-2</td>
<td>MR³ (MMR)</td>
</tr>
<tr>
<td>-3</td>
<td>MR⁴</td>
</tr>
<tr>
<td>-4</td>
<td>MR⁴.⁵</td>
</tr>
<tr>
<td>-4.5</td>
<td>MR⁵</td>
</tr>
<tr>
<td>-5</td>
<td>BCR-ABL% IS</td>
</tr>
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</table>

BCR-ABL% IS
100%
10%
1%
0.1%
0.01%
0.0032%
0.001%

Safety & Efficacy of Imatinib over 10 years – German CML IV trial

Kalmanti et al. German CML Study Group. Leukemia 2015
These mutations are not detectable when chronic phase CML is first diagnosed.

Occult subclones emerge under selective pressure from TKI therapy.

Redaelli et al, 2009
### 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>
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<tbody>
<tr>
<td>3 months</td>
<td><strong>BCR/ABL ≤10%</strong>&lt;br&gt;<strong>Ph+ cells ≤35% (PCyR)</strong></td>
<td><strong>BCR/ABL &gt;10%</strong>&lt;br&gt;<strong>Ph+ cells 35-95%</strong></td>
<td><strong>No CHR.</strong>&lt;br&gt;<strong>Ph+ cells &gt;95%</strong></td>
</tr>
<tr>
<td>6 months</td>
<td><strong>BCR/ABL &lt;1%</strong>&lt;br&gt;<strong>Ph+ cells 0% (CCyR)</strong></td>
<td><strong>BCR/ABL 1-10%</strong>&lt;br&gt;<strong>Ph+ cells 1-35%</strong></td>
<td><strong>BCR/ABL &gt;10%</strong>&lt;br&gt;<strong>Ph+ cells &gt;35%</strong></td>
</tr>
<tr>
<td>12 months</td>
<td><strong>BCR/ABL ≤0.1% (MMR)</strong></td>
<td><strong>BCR/ABL 0.1-1%</strong></td>
<td><strong>BCR/ABL &gt;1%</strong>&lt;br&gt;<strong>Ph+ cells &gt;0%</strong></td>
</tr>
<tr>
<td>Thereafter</td>
<td>Major Molecular Response [MMR] or better;&lt;br&gt;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 $\leq 10\%$ (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)

Hughes TP, et al. Blood 2014; 123(9); 1353-1360

Nilotinib 300 mg BID

Imatinib 400 mg Daily
Rate of MR\textsuperscript{4.5} By 6 Years According To 3-Month BCR-ABL\textsuperscript{IS} Levels -- ENESTnd

<table>
<thead>
<tr>
<th>Treatment</th>
<th>MR\textsuperscript{4.5} by 6 Years</th>
<th>Patients With MR\textsuperscript{4.5} by 6 Years,%</th>
</tr>
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<tbody>
<tr>
<td>Nilotinib 300 mg BID</td>
<td></td>
<td><img src="chart" alt="Nilotinib 300 mg BID" /></td>
</tr>
<tr>
<td>BCR-ABL\textsuperscript{IS} ≤ 1%</td>
<td>73.6, 52.8, 8.3</td>
<td><img src="chart" alt="Nilotinib 300 mg BID" /></td>
</tr>
<tr>
<td>BCR-ABL\textsuperscript{IS} &gt; 1% - ≤ 10%</td>
<td>75.0, 45.3, 21.4</td>
<td><img src="chart" alt="Nilotinib 300 mg BID" /></td>
</tr>
<tr>
<td>BCR-ABL\textsuperscript{IS} &gt; 10%</td>
<td>72.1, 35.3, 15.9</td>
<td><img src="chart" alt="Nilotinib 300 mg BID" /></td>
</tr>
<tr>
<td>Imatinib 400 mg QD</td>
<td></td>
<td><img src="chart" alt="Imatinib 400 mg QD" /></td>
</tr>
<tr>
<td>BCR-ABL\textsuperscript{IS} ≤ 1%</td>
<td>136, 95, 28</td>
<td><img src="chart" alt="Imatinib 400 mg QD" /></td>
</tr>
<tr>
<td>BCR-ABL\textsuperscript{IS} &gt; 1% - ≤ 10%</td>
<td>43, 133, 88</td>
<td><img src="chart" alt="Imatinib 400 mg QD" /></td>
</tr>
<tr>
<td>BCR-ABL\textsuperscript{IS} &gt; 10%</td>
<td>144, 89, 24</td>
<td><img src="chart" alt="Imatinib 400 mg QD" /></td>
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CML, March 2018
Investigational agents for CML

- **Asciminib** (ABL-001; Novartis)
- Ruxolitinib (JAK2 inhibition)
- **Selinexor** (KPT-330; Karyopharm)
- **Inecalcitol** (Hybrigenics)
- **Venetoclax** (BCL-2 inhibition)
- Other metabolic pathways
  - EZH2 inhibitors
  - Pioglitazone: PPAR-gamma agonist
  - Hedgehog pathway inhibitors
  - Tigecycline
  - Fingolimod (FTY720)
  - Autophagy inhibitors -- chloroquine
Asciminib (ABL001) Is a Potent, Specific Inhibitor of BCR-ABL1 with a Distinct Allosteric Mechanism of Action

- Developed to gain potent BCR-ABL1 inhibition, maintained against BCR-ABL1 mutations that confer resistance to TKIs
- Combine with TKIs to prevent emergence of BCR-ABL1 mutations, increasing the depth of molecular response in a greater number of patients compared with single-agent treatment
Effect of ABL001 on proliferation of BaF3/BCR-ABL cells in absence and presence of IL3
In contrast to nilotinib, ABL001 maintained activity against all BCR-ABL constructs, regardless of mutation, at concentrations below 50 nM.

ABL001 inhibited the proliferation of cells with a T315I mutation in the low nanomolar range; in contrast, nilotinib was inactive at concentrations up to 10 μM.
Combination versus sequential single-agent treatment of ABL001 and nilotinib on the emergence of resistance in KCL-22 xenograft model

KCL-22 CML Xenograft

Tumor Volume (mm$^3$)

0 20 40 60 80 100 200 400 600 800 1000
days post-implant

- Nilotinib (75mg/kg) BID
- ABL001 (30mg/kg) BID
- Nilotinib (75mg/kg) BID + ABL001 (30mg/kg) BID
- Dosing stopped on day 77, all mice remain disease free >176 days

CML, March 2018
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
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)
Conclusions

• ABL001 (aciminib) was generally well tolerated in heavily pretreated patients with CML resistant to (61%) or intolerant of prior TKIs.

• Clinical activity seen in patients with non-mutated 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.

• Phase III trial is randomizing aciminib vs bosutinib for TKI failures.
Selinexor: Exportin-1 (XPO1) inhibition in CML

- Chromosome Maintenance Protein-1 (CMP1)
- Karyopherins $\rightarrow$ transport RNA and proteins out of the nucleus
- Selective inhibitors of nuclear export (SINE)
- Ph+ leukemia $\rightarrow$ increased XPO1 expression
  - SET, IκB, FoxO3a, P53 are transported into the cytoplasm
  - Tumor suppressor PP2A is not activated (by SET).
  - Selinexor led to reactivation of PP2A in the nucleus.
Selinexor (KPT-330) decreased the survival and clonogenic potential in CML-BC and Ph+ B-ALL cells.

Selinexor (KPT-330) increased survival in mice injected with 32D-BCR/ABL leukemia cells.

A 37-year old man with CML in accelerated phase received 4 weekly doses of selinexor

<table>
<thead>
<tr>
<th></th>
<th>Pretreatment</th>
<th>Selinexor (16.5 mg/m²) for 3 doses</th>
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<tbody>
<tr>
<td>WBC (per ul)</td>
<td>&gt;300,000</td>
<td>7000</td>
</tr>
<tr>
<td>Spleen (cm below Left Costal Margin)</td>
<td>13</td>
<td>4</td>
</tr>
<tr>
<td>Bone pain (0 – 4+)</td>
<td>3+</td>
<td>0</td>
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Inecalcitol, an orally active vitamin D receptor agonist
Inecalcitol, an orally active vitamin D receptor agonist

- The vitamin D receptor is a nuclear receptor regulating expression of genes involved in calcium homeostasis and cell proliferation.

- Inecalcitol binds to the vitamin D receptor in a different conformation than the natural vitamin D:
  - Stronger inhibition of cell proliferation
  - Less hypercalcemic toxicity

- Given orally at 4 mg daily.

- Orphan drug status in the US.

- A phase 2 trial in AML is under way in Europe

CML, March 2018
Inecalcitol, a Novel Adjuvant Therapy Inhibiting CML Stem Cells

• Activates a macrophage differentiation pathway in leukemic progenitors

• 3 to 10 times more potent than the active metabolite of vitamin D to inhibit the growth of human AML cell lines

• Stimulated differentiation into more mature and functional myeloid cells

• Induces apoptosis

• In a model of AML genetically induced in mice, the treatment with inecalcitol resulted in a significant delay in the onset of the disease.

Desterke et al. Blood 2015; 126:4020
Inecalcitol, a Novel Adjuvant Therapy Inhibiting CML Stem Cells

• The combination of inecalcitol and decitabine *in vitro*, or in mice *in vivo*, exerted a more potent effect than the addition of the individual activities of each compound alone.

• Decitabine increases expression of the gene coding for vitamin D receptors (by reducing the methylation of its promoter region).

• As a consequence, more vitamin D receptors are expressed and available to be activated by inecalcitol.

Desterke et al. Blood 2015; 126:4020
Venetoclax: targeting prosurvival BCL-2
Targeting of BCL-2 and BCR-ABL in proliferating and quiescent CD34+ cells from TKI-resistant Blast Crisis CML patients.

Carter et al. Sci Transl Med 2016
Remaining challenges in CML

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