Does Generic Imatinib Change the Treatment Approach in CML?

Jerald P. Radich, MD

Fred Hutchinson Cancer Research Center/
Seattle Cancer Care Alliance
Educational Objectives

• Describe the current standard of care and the impact of generic imatinib for the management of newly diagnosed patients with CML.

• Identify the challenges associated with the selection of appropriate first-line TKI therapy for the management of patients with CML.
Survival in Early CP-CML

The University of Texas MD Anderson Cancer Center Database.

Year | Total | Dead
--- | --- | ---
Imatinib | 302 | 15
(censored: non-CML deaths)
Imatinib | 302 | 31
1990-2000 | 963 | 425
1982-1989 | 364 | 273
1975-1981 | 132 | 129
1965-1974 | 123 | 123

Start of the TKI era
Interferon
Busulfan, Hydroxyurea

The University of Texas MD Anderson Cancer Center Database.
Relative Survival with TKI by Response to Rx

- 483 pts with CML Rx with imatinib 400mg (n=71), imatinib 800 mg (n=201), dasatinib (n=111) or nilotinib (n=101)
- 5-yr relative survival 94.8% [92.1 - 97.4]

Prevention of blast crisis
Cumulative Incidences 1983 – 2013

--- BU (n = 188, 115 events, recruitment 1983 – 1990)
--- HU (n = 308, 182 events, recruitment 1983 – 1990)
--- IFN mono (n = 134, 67 events, recruitment 1986 – 1990)
--- IFN + HU (n = 226, 92 events, recruitment 1991 – 1995)
--- IFN + HU, study III (n = 621, 145 events, recruitment 1995 – 2001)
--- IFN + HU, study IIIA (n = 669, 82 events, recruitment 1997 – 2002)
--- Imatinib (n = 1340, 48 events, recruitment since 2002)

German CML Study group, unpublished
OS After Progression to AP/BC in the ENESTnd and IRIS Trials

Progression during TKI therapy is not good

Therapy of CML in 2016

• Frontline
  – Imatinib 400 mg daily
  – Nilotinib 300 mg twice daily
  – Dasatinib 100 mg daily

• Second/third line
  – Nilotinib, Dasatinib, Bosutinib, Ponatinib
  – Omacetaxine
  – Allogeneic SCT

• Other
  – Decitabine, Interferon
  – Hydroxyurea, Cytarabine, combination of TKIs
  – Investigational agents, Clinical trials
How to decide on a TKI

- Treatment goals
  - Lengthen survival?
  - Prevent progression?
  - Complete molecular response/discontinuation?

- Co-morbidities (anticipated drug toxicity)

- Compliance (frequency of dose, restrictions)
Treatment goals in CML

**Response goals**
- Early molecular response
- CCyR
- Major molecular response
- Deep/complete MR

**Why?**
- Progression and survival
- Progression and survival
- “Safe haven”
- Discontinuation?
Somewhat bogus comparison of TKIs across randomized trials

<table>
<thead>
<tr>
<th>Outcome, %</th>
<th>Dasatinib&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Nilotinib&lt;sup&gt;2&lt;/sup&gt;</th>
<th>IM 400&lt;sup&gt;1,2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinued</td>
<td>39</td>
<td>40</td>
<td>37/50</td>
</tr>
<tr>
<td>12-month CCyR</td>
<td>77</td>
<td>80</td>
<td>66/65</td>
</tr>
<tr>
<td>5-year MMR</td>
<td>76</td>
<td>77</td>
<td>64/60</td>
</tr>
<tr>
<td>5-year MR&lt;sup&gt;4.5&lt;/sup&gt;</td>
<td>42</td>
<td>54</td>
<td>33/31</td>
</tr>
<tr>
<td>3-month &lt;10%</td>
<td>84</td>
<td>91</td>
<td>64/67</td>
</tr>
<tr>
<td>5-year AP/BC</td>
<td>5</td>
<td>4</td>
<td>7/8</td>
</tr>
<tr>
<td>5-year OS</td>
<td>91</td>
<td>94</td>
<td>90/92</td>
</tr>
<tr>
<td>5-year PFS</td>
<td>85</td>
<td>92</td>
<td>86/91</td>
</tr>
</tbody>
</table>

### The Intergroup trials

<table>
<thead>
<tr>
<th>Outcome</th>
<th>DAS¹</th>
<th>IM 400</th>
<th>IM 800²</th>
<th>IM 400</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCyR</td>
<td>84</td>
<td>69</td>
<td>85</td>
<td>67</td>
</tr>
<tr>
<td>MMR</td>
<td>59</td>
<td>44</td>
<td>53</td>
<td>35</td>
</tr>
<tr>
<td>MR4.5</td>
<td>21</td>
<td>15</td>
<td>19</td>
<td>9</td>
</tr>
<tr>
<td>PFS</td>
<td>93</td>
<td>90</td>
<td>92</td>
<td>80</td>
</tr>
<tr>
<td>OS</td>
<td>97</td>
<td>97</td>
<td>95</td>
<td>90</td>
</tr>
</tbody>
</table>

Survival Based on 3 Months of Molecular Response

Survival After Imatinib Therapy by Molecular Response Achieved at 3 Months


Probability of survival

Time from onset of imatinib therapy (years)

BCR-ABL/ABL < 9.8% OS = 93.3%

BCR-ABL/ABL > 9.8% OS = 57%
## Importance of Testing at 3 Months

**% Survival / TFS by Early Molecular Response**

<table>
<thead>
<tr>
<th>Study</th>
<th>QPCR &lt;10%</th>
<th>QPCR &gt;10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marin (8 year)</td>
<td>93</td>
<td>57</td>
</tr>
<tr>
<td>MD Anderson (10 year)</td>
<td>98</td>
<td>94</td>
</tr>
<tr>
<td>ENEST-nd</td>
<td>97</td>
<td>87</td>
</tr>
<tr>
<td>DASISION</td>
<td>97</td>
<td>86</td>
</tr>
<tr>
<td>BELA</td>
<td>98</td>
<td>88</td>
</tr>
</tbody>
</table>

TFS = transformation-free survival

### Outcome by Response at 3m and 6m

- 528 patients treated with imatinib
- 89/483 (18%) had $BCR-ABL >10\%$ at 3 months

<table>
<thead>
<tr>
<th>Response</th>
<th>No.</th>
<th>3 month</th>
<th>6 month</th>
<th>Survival</th>
<th>PFS</th>
<th>FFS</th>
<th>MMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\leq 10%$</td>
<td>$&lt;1$</td>
<td>342</td>
<td>97</td>
<td>97</td>
<td>87</td>
<td>88</td>
<td></td>
</tr>
<tr>
<td>$\leq 10%$</td>
<td>1-10</td>
<td>42</td>
<td>100</td>
<td>97</td>
<td>79</td>
<td>71</td>
<td></td>
</tr>
<tr>
<td>$\leq 10%$</td>
<td>$&gt;10$</td>
<td>10</td>
<td>89</td>
<td>90</td>
<td>51</td>
<td>56</td>
<td></td>
</tr>
<tr>
<td>$&gt;10%$</td>
<td>$&lt;1$</td>
<td>18</td>
<td>100</td>
<td>100</td>
<td>76</td>
<td>88</td>
<td></td>
</tr>
<tr>
<td>$&gt;10%$</td>
<td>1-10</td>
<td>36</td>
<td>100</td>
<td>94</td>
<td>79</td>
<td>69</td>
<td></td>
</tr>
<tr>
<td>$&gt;10%$</td>
<td>$&gt;10$</td>
<td>35</td>
<td>74</td>
<td>69</td>
<td>11</td>
<td>3.3</td>
<td></td>
</tr>
</tbody>
</table>

Treatment Options Based on Adverse Event Spectrum of TKIs in CML

**Ponatinib**
- Pancreatic enzymes ↑,
- hypertension, skin toxicity,
  - *thrombotic events*

**Nilotinib**
- Pancreatic enzyme ↑,
- indirect hyperbilirubinemia,
- hyperglycemia
- QT prolongation,
- cardiovascular events

**Imatinib**
- Edema/fluid retention,
- myalgia, hypophosphatemia ↑,
- GI effects (diarrhea, nausea)

**Bosutinib**
- Diarrhea, nausea,
- emesis, rash

**Dasatinib**
- Pleural/pericardial effusions,
- bleeding risk,
- pulmonary arterial hypertension

ENESTnd-CV Events

Figure 14.3.1-1.2 (Page 1 of 5)
Kaplan-Meier estimate of time to first cardiovascular event
Safety population
All CVEs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Pat</th>
<th>Evt</th>
<th>Cen</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Imatinib 400 mg qd:</td>
<td>280</td>
<td>10</td>
<td>270</td>
</tr>
<tr>
<td>(2) Nilotinib 300 mg bid:</td>
<td>279</td>
<td>36</td>
<td>243</td>
</tr>
<tr>
<td>(3) Nilotinib 400 mg bid:</td>
<td>277</td>
<td>51</td>
<td>226</td>
</tr>
</tbody>
</table>

Censored observations

At-risk: Events
(1) 280: 0  227: 2  196: 2  173: 4  159: 5  141: 6  125: 8  67: 10  0: 10
(2) 279: 0  240: 4  208: 10 191: 17 177: 20 158: 23 139: 28  71: 36  0: 36
(3) 277: 0  232: 10 209: 17 196: 22 185: 26 161: 39 145: 42  70: 49  0: 51

Hochhaus AE et al. Leukemia 2016;30:1044-1054

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## Arteriothrombotic Events With TKI

<table>
<thead>
<tr>
<th></th>
<th>Imatinib (%)</th>
<th>Other TKI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ENESTnd</td>
<td>3</td>
<td>10-16</td>
</tr>
<tr>
<td>DASISION</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>BELA*</td>
<td>1 (8)</td>
<td>1 (11)</td>
</tr>
<tr>
<td>EPIC</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>PACE* (Ponatinib)</td>
<td></td>
<td>13 (27)</td>
</tr>
<tr>
<td>Bosutinib, phase 2 Trial</td>
<td></td>
<td>6</td>
</tr>
</tbody>
</table>

* Exposure adjusted. Actual rate in parenthesis

## Compliance to Imatinib

(Adagio Study)

<table>
<thead>
<tr>
<th>Actual Imatinib Taken (assessed by pill count)</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>As prescribed</td>
<td>23</td>
<td>14.2</td>
</tr>
<tr>
<td>&gt;the prescribed dose</td>
<td>24</td>
<td>14.8</td>
</tr>
<tr>
<td>&lt;prescribed dose</td>
<td>115</td>
<td>71.0</td>
</tr>
</tbody>
</table>

NCCN recommends evaluating compliance whenever a milestone is not achieved.

"A pill a day keeps the CML at bay"

"Not actual size."

Forehead, Dr. Timothy Hughes
Take these and call me in the morning
Adherence and Molecular Response

Adherence >90%, n=64
Adherence ≤90%, n=23

MMR
CMR

P < 0.0001
P < 0.002

Statistical model of CML response

First slope (α)

Second slope (β)

Roeder et al, Blood 2013;121:378-384

Statistical regression results for 51 IRIS trial patients
Results from mathematical model for IRIS trial and CML IV trial

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to complete eradication of MRD</td>
<td>48.9 y (28-112)/32.8 y (18-176)</td>
</tr>
<tr>
<td>Treatment time to 4.0 log reduction (MR^{4.0})</td>
<td>6.5 y (5.0-9.7)/5.3 y (4.5-9.2)</td>
</tr>
<tr>
<td>Treatment time to 4.5 log reduction (MR^{4.5})</td>
<td>10.7 y (7.7-13)/9.1 y (6.9-13)</td>
</tr>
<tr>
<td>Cumulative cure rate after 15 y of treatment</td>
<td>14%/16%</td>
</tr>
<tr>
<td>Cumulative cure rate after 30 y of treatment</td>
<td>31%/42%</td>
</tr>
</tbody>
</table>

Molecular relapse free survival

200 interim patients – overtime, loss MMR=89

Relapses within 6 months, n=77

At 6 months: 63 % (95% CI: 55% - 69%)
At 12 months: 56 % (95% CI: 49 % - 63 %)
At 18 months: 55 % (95% CI: 47 % - 61 %)

# TKI Discontinuation trials in CML--Update

<table>
<thead>
<tr>
<th>Study</th>
<th>TKI</th>
<th>No. Patients</th>
<th>% off TKI (at X year)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>STIM 1</td>
<td>IM</td>
<td>100</td>
<td>38 (5)</td>
<td></td>
</tr>
<tr>
<td>STIM 2</td>
<td>IM</td>
<td>220</td>
<td>51 (2)</td>
<td></td>
</tr>
<tr>
<td>ASTIM</td>
<td>IM</td>
<td>-</td>
<td>61 (3)</td>
<td>Rx for loss of MR 3</td>
</tr>
<tr>
<td>STIK 2/DADI</td>
<td>NIL or DAS</td>
<td>52/63</td>
<td>48-50 (2-4)</td>
<td>Rx for loss of MR 4</td>
</tr>
<tr>
<td>EURO—SKI</td>
<td>Any</td>
<td>750</td>
<td>50 (2.5)</td>
<td></td>
</tr>
<tr>
<td>ENEST-Freedom</td>
<td>NIL</td>
<td>190</td>
<td>50 (1)</td>
<td></td>
</tr>
<tr>
<td>ENESTop</td>
<td>IM-&gt;NIL</td>
<td>126</td>
<td>58 (1)</td>
<td></td>
</tr>
</tbody>
</table>

CML Frontline Rx

- IM = 2\textsuperscript{nd} generation in OS
- “Deep MR” 2\textsuperscript{nd} gen TKI > IM
  - \(\sim 40\%\) 2\textsuperscript{nd} gen; 25\% IM
  - 25\%->40\% if switch IM->2\textsuperscript{nd} gen (equally durable?)
- Discontinuation equally successful all TKIs
- Imatinib = 2\textsuperscript{nd} generation TKIs in lower risk CML
- Second generation TKIs > IM in progression (and high risk?) CML?
- Long-term toxicities (vascular) 2\textsuperscript{nd} gen. TKI > IM
CML Frontline Rx

*Generic IM*

- Generics = branded IM in potency and toxicity
- \$800,000/QALY for 2nd generation TKIs vs imatinib
- Sun now on 6 m exclusivity clock
  - Generally 70-90% of branded
- Expected price drop
  - Med. ~40% of branded
  - ~15% of branded if > 3 generics
  - In Canada, generics 15-25% of branded

Issues with using generic IM (gIM)

- gIM good for cost-effective, long term use
- But, 2nd gen. TKI better at preventing AP/BC
- 2nd gen. TKI better at deep remissions
  - Cost savings with discontinuation?
- Could a cost-effective strategy be hi dose IM?

Best use of gIM should be guided by treatment goals?
Costs of Treatment-free remission (TFR)

*be careful what you ask for…*

- **TKI**
  - 3 years of Rx and 2 years CMR @ $100,000/year
  - Say 40% get qualifying CMR
  - Say 50% stay in TFR after discontinuation
  - $2,500,000 patient-TFR

- **Transplant**
  - Transplant and 3 years chronic GVHD $1,000,000
  - Survival 85%
  - TFR rates 90%
  - $1,310,000 patient-TFR
The great unfunded trial

Milestones

Generic IM 2nd Gen. TKI

OUTCOMES
1. MR at 12 m
2. PFS
3. Crossover
4. Cost
5. Toxicity

OFF
Simulation of this trial

“Winner” (of QALY) is 2\textsuperscript{nd} generation TKI, then IM
Haven’t built discontinuation into model yet.
Stay tuned.

Rochau, submitted, 2016
What do you want from life?*

WE WANT…
• Cheap meds!
• To not have an MI.
• To prevent blast crisis.
• A CMR and TKI discontinuation.
• Want cake, eat it too.

THUS, WE WILL…
• Use generic IM.
• Exercise! And generic IM.
• Use second gen. TKI.
• Use second gen. TKI.
• High dose IM?

* With apologies to The Tubes, circa 1975
CML Therapy in 2016-my guess

- Generic IM for low and intermediate risk
- Generic IM for older, sicker patients
- Second generation TKIs for higher-risk Sokal
  - until CCyR or MMR, then -> generic IM
  - Indefinitely if nervous
- Second generation TKIs for younger patients in whom Rx discontinuation is important