When Should ABL Kinase Mutational Analysis Be Performed in Chronic Myeloid Leukemia (CML)?
[At suboptimal response or failure of first line therapy]

David Steensma, MD FACP
Associate Professor of Medicine, Harvard Medical School
Adult Leukemia Program, Dana-Farber Cancer Institute

ACCME Disclosures
David Steensma, MD

I have the following financial relationships to disclose:
• Member of an independent study data monitoring committee: Amgen
• Scientific advisory board / consulting: Celgene, Novartis, Janssen-Cilag

I will discuss the following investigational or off-label uses:
• Only azacitidine, decitabine, and lenalidomide are FDA approved for MDS therapy; lenalidomide’s approval is limited to lower-risk patients with del(5q).
• The iron chelators deferasirox and deferoxamine are FDA approved for treatment of iron overload related to repeated RBC transfusion.
• All other compounds discussed or specific uses should be considered unapproved, investigational, or off-label in MDS.
Matters in CML are already pretty good, all things considered...

Survival in early chronic phase CML

<table>
<thead>
<tr>
<th>Year</th>
<th>Total</th>
<th>Dead</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imatinib era</td>
<td>230</td>
<td>7</td>
</tr>
<tr>
<td>1990-2000</td>
<td>960</td>
<td>334</td>
</tr>
<tr>
<td>1982-1989</td>
<td>365</td>
<td>265</td>
</tr>
<tr>
<td>1975-1981</td>
<td>132</td>
<td>127</td>
</tr>
<tr>
<td>1965-1974</td>
<td>123</td>
<td>122</td>
</tr>
</tbody>
</table>

- Interferon α, cytarabine, allogeneic stem cell transplant
- Hydroxyurea, busulfan, splenectomy
IRIS Phase III trial of imatinib vs. cytarabine/interferon: overall survival (ITT) in imatinib arm

Estimated overall survival at 8 years was 85% (93%, considering only CML-related deaths)

Survival, deaths associated with CML
Overall Survival

\( ITT: \text{intent-to-treat}; \text{OS: overall survival} \)


...but not perfect.
IRIS Study: imatinib patient status at 60 months

Definitions of unsatisfactory response

- **Primary resistance** = lack of response to initial TKI
  
  Subtypes include:
  - Hematological resistance (only 2-4% of patients)
  - Cytogenetic resistance (15-25% of patients)

- **Secondary resistance** = relapse after initial achievement of hematologic or cytogenetic response

- **“Suboptimal” response** = failure to meet milestones associated with best outcomes
  - ELN guidelines for response are based on IMATINIB and do not apply to 2nd generation TKI (Jabbour E et al. *J Clin Onc* 2011; 29:4260)
  - Note importance of BCR-ABL at 3 months w/ imatinib (Marin D et al. *J Clin Oncol* 2012; 30:232)
Mechanisms of TKI therapy failure in chronic phase CML

- **NON-ADHERENCE**
- ABL kinase domain mutation
  - *Nota bene*: TKIs are not mutagenic; this is Darwinian
- BCR-ABL overexpression (i.e., more target)
- Overexpression of ABCB1 or P-glycoprotein (efflux of imatinib)
- High expression of PTGS1/COX1 (metabolizes imatinib)
- Low activity of hOCT-1 (imatinib importer)
- High activity of ABCG2 (efflux of imatinib and nilotinib)
- Additional non-BCR-ABL driver mutation (e.g. AP/BP)
- Patient taking too low a dose to achieve adequate IC$_{50}$
- Poor absorption


Differential sensitivity of BCR-ABL kinase domain mutation to the 3 front-line TKIs

Deininger M. Hematology: ASH Education Book 2005; pp.419-428

Treatment options based on BCR-ABL kinase domain mutation status

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Treatment recommendation (expert opinion...)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T315I</td>
<td>Stem cell transplant or clinical trial (e.g., ponatinib, omacetaxine)</td>
</tr>
<tr>
<td>V299L, T315A, F317V/I/C</td>
<td>Consider nilotinib; likely resistant to dasatinib</td>
</tr>
<tr>
<td>Y253H, E255K/V, F359V/C/I</td>
<td>Consider dasatinib; likely resistant to nilotinib</td>
</tr>
<tr>
<td>Any other mutation</td>
<td>Unclear; consider high-dose imatinib, nilotinib, dasatinib</td>
</tr>
</tbody>
</table>

Cost of test: $600-1200 (<1 week of a second generation TKI)

Based on NCCN and ELN guidelines (see Soverini S et al Blood 2011)
When should mutation testing be done?

NCCN Guidelines for CML mutation testing

- Recommend ABL kinase domain mutation analysis for chronic phase CML when:
  - Inadequate [suboptimal] initial response or any sign of loss of response in chronic phase CML, and
  - Progression to accelerated or blast phase CML.
Another strategy

Randomized trials underway to assess value of early TKI switching in suboptimal response (i.e., short of frank resistance)


Validation of the new ELN recommendations for Bcr-Abl KD mutation analysis in CML: an analysis of the GIMEMA CML WP studies

Simona Soverini, PhD
Dept of Hematology/Oncology “L. e A. Seràgnoli”
University of Bologna
Italy

ASH Annual Meeting December 2011
Background & Aims

> They came from the expert opinion of the panel members whenever published data were insufficient or contradictory

In order to provide further data to validate or refine these recommendations, we have analyzed the GiMEMA CML WP database recording the results of mutation analyses performed* in CML pts (n=1301) receiving imatinib and/or 2nd generation TKIs between January 2004 and July 2011

* by D-HPLC and/or direct Sanger sequencing

When to perform mutation analysis: ELN

<table>
<thead>
<tr>
<th>Factor Analyzed</th>
<th>N</th>
<th>N positive for KD mutation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>De novo CP CML</td>
<td>58</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>De novo AP/BC CML</td>
<td>12</td>
<td>2 (17%)</td>
</tr>
<tr>
<td>IM Failure (ELN criteria)</td>
<td>166</td>
<td>45 (27%)</td>
</tr>
<tr>
<td>Suboptimal IM Response (ELN)</td>
<td>233</td>
<td>11 (5%)</td>
</tr>
<tr>
<td>Rise in PCR without loss of MMR</td>
<td>70</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Rise in PCR with loss of MMR</td>
<td>89</td>
<td>4 (5%)</td>
</tr>
<tr>
<td>NIL/DAS ‘Failure’ (ELN criteria)</td>
<td>19</td>
<td>11 (58%)</td>
</tr>
<tr>
<td>NIL/DAS ‘Suboptimal’ (ELN criteria)</td>
<td>19</td>
<td>4 (21%)</td>
</tr>
</tbody>
</table>
Some practical tips
What is needed at initial diagnosis?

- CBC+differential; complete metabolic profile including liver tests
- Bone Marrow Aspirate and Biopsy
  - Cytogenetics (20 metaphases)
  - ?FISH, ?QPCR
- Why is a bone marrow necessary?
  - Need to exclude AP/BP-CML.
  - Sokal/Hasford score predictive of response to TKIs
  - Helpful to review entire karyotype (useful for comparison at time of relapse)
  - FISH important for “cytogenetic negative” CML (<5%)
  - FISH may have some role in prognosis, e.g., del9q+

NCCN Guidelines 2012

How to follow your patient?

- CBC+differential, complete metabolic profile
  - Every 3 months; maybe more frequent earlier on
- Bone Marrow Aspirate and Biopsy with Cytogenetics (20 metaphases)
  - Every 6 months until Complete Cytogenetic Remission (CCR)
  - Further bone marrow exams PRN
- Quantitative RT-PCR
  - Every 3 months indefinitely
  - Can go to every 6 months, after 2 years of major molecular response
  - FISH not as helpful
    - Only follow in patients with cytogenetic negative CML (<5%)

NCCN Guidelines 2012
**Pearls**

- Maximize patient adherence by managing adverse events
  - "The most important cell in CML resistance is the neuron"
  - "Once disease is in advanced phase, the game is largely over"
    - Never dose reduce imatinib below 300 mg daily or nilotinib below 400 mg daily or dasatinib below 50 mg daily
    - Heme toxicities (ANC < 1000; Plts < 75K): rare, usually early, and easily managed
- **Never** change dose or therapy based solely on a single PCR
  - Repeat in 1 month
  - Confirm with bone marrow exam before changing therapy
- Mutational Analysis
  - Not useful at initial diagnosis or in responding patients
  - Send at time of any change in therapy (increase in dose or 2nd TKI)
- Stem Cell Transplant
  - Refer at time of 1st failure (want to know donor status)
  - Refer to transplant in patients who fail 2nd TKI, have a T315I or AP/BP-CML
  - May change in the future with ponatinib etc.

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Thank you!