Living with Chronic Myeloid Leukemia

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Disclosure

Michael Deininger, MD, PhD has affiliations with: Ariad, Bristol Myers Squibb, CTI BioPharma Corp., Gilead, Incyte, Novartis, and Pfizer.
LIVING WITH CHRONIC MYELOID LEUKEMIA

SOME GUIDANCE FOR PATIENTS AND CAREGIVERS

Michael Deininger MD PhD

CML Pioneers

Alfred Donné 1844  John Bennet 1845  Rudolf Virchow 1845
Outline

1. How CML is diagnosed
2. How CML is treated
3. How to deal with side effects
4. When can therapy be stopped?

CML Basics

- 1-1.5 cases/100,000 per year
- Median age > 60 years (developed world)
- More frequent in men (1.5-fold)
- Not heritable and no ethnic or racial differences
- Risk factor: radiation
Chronic Myeloid Leukemia – A Typical Case

- A 38-year old sees his primary care provider because of night sweats, fatigue, weight loss and pain in his left belly
- Physical exam reveals a large spleen
- A complete blood count shows:
  - Hemoglobin (red blood cells): slightly low
  - White blood cells: much increased and with immature cells
  - Platelets: increased

Initial Testing if CML is Suspected

The minimum needed
- History and physical: record spleen size
- Complete blood count and basic metabolic profile
- Bone marrow aspirate and biopsy
- Chromosome analysis of bone marrow cells

What establishes a diagnosis of CML

- The appearance of the blood smear and bone marrow is typical for CML
- The bone marrow analysis shows the ‘Philadelphia chromosome’
- Sometimes molecular tests are done or needed to establish the diagnosis
  - FISH (Fluorescence in situ hybridization)
  - PCR (Polymerase chain reaction)
Philadelphia Chromosome: The Cause of CML

- Chromosome 9q+ with BCR-ABL1 translocation

CML Phases (Stages)

- **Chronic Phase**
  - Maturation lost
  - Additional mutations
  - Rapidly fatal

- **Blastic Phase**
CML Therapy

**Hydroxyurea:** Only initially to lower the white blood cells

**Tyrosine kinase inhibitors (TKIs):** Long-term therapy

**Stem cell transplant (TKIs):** In case of TKI failure

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**Imatinib Greatly Improved Survival in Chronic Phase CML**

Disease Burden & Monitoring

Complete hematologic response: blood counts and spleen normal
Complete cytogenetic response: bone marrow chromosomes normal
Major molecular response: >1,000-fold reduction of CML cells
Deep molecular response: >10,000-fold reduction of CML cells

Recommended Monitoring

<table>
<thead>
<tr>
<th>Test</th>
<th>At diagnosis</th>
<th>On therapy</th>
<th>At failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone Marrow karyotyping</td>
<td>yes</td>
<td>At 3, 6, 12 months or until CCyR, then annually</td>
<td>yes</td>
</tr>
<tr>
<td>qPCR (blood) for BCR-ABL1(IS)</td>
<td>yes</td>
<td>Every 3 months until MMR, then every 3-6 months</td>
<td>yes</td>
</tr>
<tr>
<td>FISH</td>
<td>no</td>
<td>If CCyR documented and qPCR IS unavailable</td>
<td>no</td>
</tr>
<tr>
<td>BCR-ABL1 mutation screen</td>
<td>no</td>
<td>no</td>
<td>no</td>
</tr>
</tbody>
</table>

## Therapeutic Milestones

<table>
<thead>
<tr>
<th>Month</th>
<th>Optimal</th>
<th>Warning</th>
<th>Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 ELN</td>
<td>Ph≤35% or BCR-ABL1&lt;10%</td>
<td>Ph≥65-95% or BCR-ABL1&gt;10%</td>
<td>No CHR or Ph≥95%</td>
</tr>
<tr>
<td>3 NCCN</td>
<td>Ph≤35% or BCR-ABL1≤10%</td>
<td>NA</td>
<td>Ph≥35% or BCR-ABL1&gt;10%</td>
</tr>
<tr>
<td>6 ELN</td>
<td>Ph≤0% and/or BCR-ABL1&lt;1%</td>
<td>Ph≥1-35% and/or BCR-ABL1 1-10%</td>
<td>Ph≥35% and/or BCR-ABL1 &gt;10%</td>
</tr>
<tr>
<td>6 NCCN</td>
<td>Ph≤35% or BCR-ABL1≤10%</td>
<td>NA</td>
<td>Ph≥35% or BCR-ABL1&gt;10%</td>
</tr>
<tr>
<td>12 ELN</td>
<td>BCR-ABL1 &lt;0.1%</td>
<td>BCR-ABL1 0.1-1%</td>
<td>Ph≥0% BCR-ABL1 &gt;1%</td>
</tr>
<tr>
<td>12 NCCN</td>
<td>Ph&lt;0%</td>
<td>NA</td>
<td>Ph≥0%</td>
</tr>
</tbody>
</table>


## CML Therapy – Available TKIs

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Brand name</th>
<th>Generation</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imatinib</td>
<td>Gleevec</td>
<td>1</td>
<td>First line</td>
</tr>
<tr>
<td>Dasatinib</td>
<td>Sprycel</td>
<td>2</td>
<td>First line &amp; imatinib resistance</td>
</tr>
<tr>
<td>Nilotinib</td>
<td>Tasigna</td>
<td>2</td>
<td>First line &amp; imatinib resistance</td>
</tr>
<tr>
<td>Bosutinib</td>
<td>Bosulif</td>
<td>2</td>
<td>Imatinib resistance</td>
</tr>
<tr>
<td>Ponatinib</td>
<td>Iclusig</td>
<td>3</td>
<td>If other TKIs are not indicated</td>
</tr>
</tbody>
</table>

It can be necessary to switch from one TKI to another because of side effects.
I’ve been diagnosed with CML. Which TKI should my doctor pick?

**Things to consider**

- Am I in the chronic phase?
- Am I in the chronic phase, but high risk?
- What other medical conditions do I have?
- What is my lifestyle?

**High Risk CML**

1. **Chronic phase** but aggressive with immature cells, high platelet count, big spleen.

2. **Accelerated phase** or **blastic phase**
   - Treatment must be with a 2-generation TKI
   - Stem cell transplant may be necessary
   - Early referral to a center is important
### Past Medical History

<table>
<thead>
<tr>
<th>Condition</th>
<th>IM</th>
<th>NIL</th>
<th>DAS</th>
<th>BOS</th>
<th>PON</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>POAD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolonged QT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PHT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GI Bleeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IBS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreatitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impaired LF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombembolism</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Few absolute contraindications
- Many better or worse picks
- Clinical judgment crucial

### Side Effects of TKI Therapy

**Things to consider**

- Prior to imatinib average survival with drug therapy was 5 years.
- Stem cell transplant can cause severe side effects or even death.
- All TKIs have side effects.
- Supportive care can frequently mitigate side effects.
- For the provider it’s very important to understand which symptoms are related to the TKI and which are not.

Avoid rapid switching from one TKI to the next or you may quickly run out of options.
Adverse Event Rates on Dasatinib vs. Imatinib

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Any grade</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluid retention</td>
<td>0.2</td>
<td>0.4</td>
</tr>
<tr>
<td>Superficial edema</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Myalgia</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Nausea</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Headache</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Rash</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Anemia</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Dr. Rate Difference (dasatinib-imatinib) with Exact 95% CI

Favors dasatinib
Favors imatinib

Study Drug-Related Non-Laboratory Adverse Events (≥ 10% in Any Group)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>% of Patients Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nilotinib 300 mg BID n = 279</td>
</tr>
<tr>
<td>Nausea</td>
<td>All Grades</td>
</tr>
<tr>
<td></td>
<td>14 &lt; 1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8 1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5 0</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>5 0</td>
</tr>
<tr>
<td>Facial edema</td>
<td>&lt; 1 0</td>
</tr>
<tr>
<td>Eyelid edema</td>
<td>&lt; 1 0</td>
</tr>
<tr>
<td>Periorbital edema</td>
<td>&lt; 1 0</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>8 0</td>
</tr>
<tr>
<td>Rash</td>
<td>32 &lt; 1</td>
</tr>
<tr>
<td>Headache</td>
<td>14 1</td>
</tr>
<tr>
<td>Pruritus</td>
<td>16 &lt; 1</td>
</tr>
<tr>
<td>Alopecia</td>
<td>9 0</td>
</tr>
<tr>
<td>Myalgia</td>
<td>10 &lt; 1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>11 0</td>
</tr>
</tbody>
</table>

Data cut-off: 20Aapr2010
Hughes TP, et al. ASH2010. Absted 207

* At the 24-month data cut-off, one patient in the imatinib arm had a QTcF > 500 msec but no patient in any of the nilotinib arms had a QTcF > 500 msec
* No patients in the study had a decrease in LVEF < 45%
Survival on Imatinib and Nilotinib at 6 Years

<table>
<thead>
<tr>
<th></th>
<th>Nilotinib 300 mg BID (n = 282)</th>
<th>Nilotinib 400 mg BID (n = 281)</th>
<th>Imatinib 400 mg QD (n = 283)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total deaths on study, n</td>
<td>21</td>
<td>11</td>
<td>23</td>
</tr>
<tr>
<td>KM-estimated 6-year OS on study (95% CI), %</td>
<td>91.6 (88.0-95.1)</td>
<td>95.8 (93.4-98.2)</td>
<td>91.4 (88.0-94.7)</td>
</tr>
<tr>
<td>Hazard ratio vs imatinib (95% CI)</td>
<td>0.8934 (0.4944-1.6143)</td>
<td>0.4632 (0.2258-0.9503)</td>
<td>–</td>
</tr>
<tr>
<td>Nominal P value vs imatinib</td>
<td>.7085</td>
<td>.0314</td>
<td>–</td>
</tr>
<tr>
<td>Deaths due to advanced CML, n</td>
<td>6</td>
<td>4</td>
<td>16</td>
</tr>
<tr>
<td>KM-estimated 6-year freedom from death due to advanced CML (95% CI), %</td>
<td>97.7 (96.0-99.5)</td>
<td>98.5 (97.1-100)</td>
<td>93.9 (91.0-96.8)</td>
</tr>
<tr>
<td>Hazard ratio vs imatinib (95% CI)</td>
<td>0.3694 (0.1445-0.9440)</td>
<td>0.2433 (0.0813-0.7279)</td>
<td>–</td>
</tr>
<tr>
<td>Nominal P value vs imatinib</td>
<td>.0302</td>
<td>.0061</td>
<td>–</td>
</tr>
</tbody>
</table>


Survival on Imatinib vs. Dasatinib at 5 Years

<table>
<thead>
<tr>
<th></th>
<th>Dasatinib 100 mg QD (n=259)</th>
<th>Imatinib 400 mg QD (n=260)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of deaths, n</td>
<td>26</td>
<td>26</td>
<td>–</td>
</tr>
<tr>
<td>Estimated 5-year OS, %</td>
<td>90.9 (86.6-93.8)</td>
<td>89.6 (85.2-92.8)</td>
<td>1.01 (0.58-1.73)</td>
</tr>
<tr>
<td>Estimated 5-year PFS, %</td>
<td>85.4 (80.3-89.2)</td>
<td>85.5 (80.4-89.4)</td>
<td>1.06 (0.68-1.66)</td>
</tr>
</tbody>
</table>


*On study treatment and in follow-up after discontinuation of randomized treatment. CI = confidence interval; OS = overall survival; PFS = progression-free survival.
Adherence to Therapy is Crucial For Avoiding Failure

Well-managed CML Impacts Survival Less Than Comorbidities
Recognizing Therapy Failure

- Failure to reach milestones
- Loss of Complete Hematologic Response
- Loss of Complete Chromosomal Response

Do not rush to conclusions

Non-compliance or drug interaction?  Laboratory error or imprecision?

No

Complete diagnostic workup
- Physical exam
- Bone marrow aspirate/biopsy
- Bone marrow chromosomes
- BCR-ABL1 mutation screen

Factors Influencing Selection of Salvage Therapy

- Disease phase (chronic or blastic)
- BCR-ABL1 mutation analysis
- Previous treatment history
- Past medical history
Resistance Due to BCR-ABL1 Point Mutations

- Single BCR-ABL1 Mutants
- T315I

TKI Resistance

- Imatinib
- Nilotinib
- Bosutinib
- Dasatinib
- Ponatinib

Resistance Types:
- Relatively resistant
- Completely resistant


Second Line Therapy: Treatment History is Important

1. Line therapy
   - Imatinib
   - Nilotinib
   - Dasatinib

2. Line therapy
   - Dasatinib
   - Nilotinib
   - Bosutinib
   - Ponatinib

3. Line therapy
   - Dasatinib
   - Nilotinib
   - Ponatinib
   - Bosutinib
   - Omacetaxine
Treatment History and Salvage Therapy – Likelihood of a Complete Chromosomal Response

1. Line therapy
   - Imatinib
   - Nilotinib
   - Dasatinib

2. Line therapy
   - Dasatinib
   - Nilotinib
   - Bosutinib
   - Ponatinib

3. Line therapy
   - Dasatinib
   - Nilotinib
   - Ponatinib
   - Bosutinib
   - Omacetaxine

Likelihood of a Complete Chromosomal Response:

1. Line therapy: 50 - 70%
2. Line therapy: 20% (T315I)
3. Line therapy: 10% (T315I)
### Treatment-Free Remission (TFR)


N = 100

N = 69, minimum 12 months follow-up

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### Maintenance of Deep Molecular Response After TKI Discontinuation in ~ 40% of Patients

**Australian Study**

![Graph showing maintenance of deep molecular response](image1)


**Japanese Study**

![Graph showing maintenance of deep molecular response](image2)

*Estimated TFR 42.7%*

*Takahashi et al. Haematologica. 2012;97(6):903-6*
EuroSKI Study

Recurrence-Free Survival

200 interim patients – overtime, loss MMR=89

Relapse: Loss of MMR at one time point

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%)

Longer Duration of Imatinib Exposure and of Deep Molecular Response Predict TFR

200 interim patients – overtime, loss MMR=89

Factors Associated with TFR in Various Studies

- Exposure to IFN-α
- Low Sokal risk
- Longer TKI treatment duration
- Longer duration of deep response

Withdrawal Syndrome Accompanies TKI Discontinuation in Some Patients

EuroSKI:
- 222 AEs in 98 patients reported
- 57 AEs in 31 patients were related to treatment stop, no grade 4

<table>
<thead>
<tr>
<th></th>
<th>Patients Grade 1-4</th>
<th>Patients Grade 3</th>
<th>AEs Grade 1-4</th>
<th>AEs Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Musculoskeletal pain, joint pain, arthralgia</td>
<td>25</td>
<td>3</td>
<td>19</td>
<td>6</td>
</tr>
<tr>
<td>Other (sweating, skin disorders, folliculitis, depressive episodes, fatigue, urticaria, weight loss)</td>
<td>8</td>
<td>0</td>
<td>18</td>
<td>1</td>
</tr>
</tbody>
</table>

* The Life After TKI Study (LAST; NCT02269267) will specifically look into this
* Patients with chronic myelogenous leukemia may not want to discontinue tyrosine kinase inhibitor therapy (#1584, poster, Saturday)

Treatment-Free Remission – When is it Safe to Try?

Patients who progressed to accelerated or blastic phase or became resistant to a TKI at any time are not candidates.

Otherwise patients considered for TRF must

1. Have completed at least 3 years of TKI therapy.
2. Have maintained a deep molecular response for the past 2 years.
3. Have had dense PCR monitoring for the past 2 years (at least every 3-4 months).
4. Be willing to have frequent (initially monthly) lab monitoring
5. Be willing to go back on therapy if they relapse.

Prior consultation of or referral to a CML center or consultation is recommended.
Summary

- Patients with well-managed chronic phase CML can expect a normal life span.
- Dasatinib, nilotinib and imatinib are acceptable options for frontline therapy of chronic phase.
- Dasatinib and nilotinib should be considered in patients with high risk chronic phase CML.
- In case of side effects, try to manage with supportive care and/or dose reductions, before switching to another TKI.

Summary (continued)

- Failure of first line TKI therapy is a significant event and needs careful workup and a decisive management strategy.
- Progression to accelerated or blastic phase should trigger a referral to a center.
- Treatment free remission is safe only if attempted in the right patients and with proper monitoring; consultation of a center is recommended.
Q&A Session

Ask a question by phone:
• Press star (*) then the number 1 on your keypad.

Ask a question by web:
• Click “Ask a question”
• Type your question
• Click “Submit”

Due to time constraints, we can only take one question per person. Once you’ve asked your question, the operator will transfer you back into the audience line.

SUPPORT RESOURCES

• What to ask: Questions to ask your treatment team: www.LLS.org/whattoask
• Free education materials: www.LLS.org/booklets
• Past CML education programs: www.LLS.org/programs
• Financial Assistance Program for CML patients: www.LLS.org/cml
• Information Resource Center: Speak one-on-one with an Information Specialist who can assist you through cancer treatment, financial, and social challenges.
  ➢ EMAIL: infocenter@LLS.org
  ➢ TOLL-FREE PHONE: (800) 955-4572