CML 101
Understanding chronic myeloid leukemia
April 2019
Leukemia is a malignant progressive cancer of the blood in which the bone marrow and other blood-forming organs such as the spleen produce increased numbers of immature or abnormal leukocytes (white cells).
What is CML?

- Chronic myeloid leukemia (CML) is a type of blood cancer that begins in the cells in the bone marrow
- A piece of the chromosome 22 and a piece of chromosome 9 break off and swap places

BCR-ABL cancer gene:
- The break on chromosome 9 = ABL
- The break on chromosome 22 = BCR
- People living with CML carry the BCR-ABL gene

- BCR-ABL gene = type of protein known as tyrosine kinase
How do you treat CML?
Tyrosine Kinase Inhibitors (TKIs)

• BCR-ABL gene = type of protein known as **tyrosine kinase**
  (Inhibit = prevent, impede, stop)

• TKIs target BCR-ABL and don’t target normal cells (targeted therapies)
• Currently 5 TKIs for CML available, plus a number of generics/copies

<table>
<thead>
<tr>
<th>Drug</th>
<th>Market Name</th>
<th>Manufacturer</th>
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</thead>
<tbody>
<tr>
<td>1. Imatinib</td>
<td>Glivec/Gleevec</td>
<td>Novartis</td>
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<tr>
<td></td>
<td>Imatinib</td>
<td>Generics companies</td>
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<tr>
<td>2. Dasatinib</td>
<td>Srpycel</td>
<td>BMS</td>
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<tr>
<td>3. Nilotinib</td>
<td>Tasigna</td>
<td>Novartis</td>
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<td>4. Bosutinib</td>
<td>Bosulif</td>
<td>Pfizer</td>
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<tr>
<td>5. Ponatinib</td>
<td>Iclusig</td>
<td>Takeda (Ariad) / Incyte</td>
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What is drug resistance?

- Some times we hear that a patient is resistant to a treatment
  - The cells become resistant to the drug (TKI cannot inhibit the BCR-ABL any more)
  - The TKI stops working for some reason
- Look for other changes in the chromosomes or genes (mutations), so “the key” (TKI) does no longer fit into “the lock” (BCR-ABL)
- Doctors know which TKI works best for which mutation
- Example: mutation T 315i = ponatinib works and the others don’t
What is drug intolerance?

• Some times we hear that a patient is intolerant to a treatment
  • The drug causes side effects that the patient cannot tolerate
  • Caused by drugs also interfering with other body functions and not just BCR-ABL

• Some patients have more side effects than others

• Intolerance is one reason identified in a label, where it is allowed to change treatment to a second line TKI

• A LOT ABOUT THIS IS STILL UNKNOWN
What is an approved label?

• After drugs are developed and tested, they get approved by each country’s Health Authority for use by everyone.

• Depending on how good are the results of the treatment (EFFICACY), they are approved very specifically (LABEL INDICATION).

• Generally, when a drug is first approved in CML, it is often approved for use in adults and not children; and it is approved only for those who are resistant, or cannot tolerate, the drugs already in the market (SECOND LINE TREATMENT).

• After it is proven to be safe, drugs may be approved for patients that...
Iclusig is a kinase inhibitor indicated for the:

• Treatment of adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukemia (CML) or Ph+ ALL for whom no other tyrosine kinase inhibitor (TKI) therapy is indicated.

• Treatment of adult patients with T315I-positive CML (chronic phase, accelerated phase, or blast phase) or T315I-positive Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL).
What if a drug is not approved in a country?

• If a drug is not approved, it means the Health Authority has not given permission to use by patients in that country
  • It can only be used in special circumstances which require special permission from Health Authorities
    o **Clinical trial** (usually sponsored by pharma companies)
    o **Compassionate Use** (some companies agree to supply clinical drug approved for individual cases, for indications where the drug has shown efficacy)
    o **Humanitarian aid** (health authorities might approve importation and use of a drug that is not locally approved, as humanitarian aid)
How do you diagnose CML?

• Clinical diagnosis: enlarged spleen, high white cell count, fatigue, fever, etc.

• Need to confirm that the patient is either philadelphia chromosome positive, or BCR-ABL positive

• CBC (complete blood count)
• FISH (fluorescence in situ hybridization)
• PCR (polymerase chain reaction)
How do we know if the treatment is working?

Monitoring CML treatment

• Monitoring = checking how the treatment is working
  • Is the TKI still inhibiting the BCR-ABL or are the cells becoming resistant?
  • Need to check how deep is the response

• Monitoring CML, different methods:
  • CBC / Blood counts
    = measures hematological response = most superficial response
  • Cytogenetics and FISH = measures cytogenetic response = number of cells carrying the “Philadelphia Chromosome”
  • PCR = measures molecular response = amount of BCR-ABL present
## Monitoring CML
### (Types of response to treatment)

<table>
<thead>
<tr>
<th>Response type</th>
<th>Partial</th>
<th>Major</th>
<th>Complete/Deep</th>
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<tbody>
<tr>
<td>Hematological (H)</td>
<td>PHR</td>
<td>MHR</td>
<td>CHR</td>
</tr>
<tr>
<td>Cytogenetic (Cy)</td>
<td>PCyR</td>
<td>MCR</td>
<td>CCyR (2 log reduction)</td>
</tr>
<tr>
<td>Molecular (M)</td>
<td>PMR</td>
<td>MMR (3 log reduction)</td>
<td>MR4.5 (4.5 log reduction)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>“Undetectable”</td>
</tr>
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- ELN & NCCN = 2 entities that produce guidelines for physicians on
  - When should they switch from one treatment to another
  - How often tests should be performed
PCR, what is all the fuzz about?

- **Prognosis** (ability to predict if a patient will continue to do well for a long time) depends on **how fast** patients achieve response, and on **how deep** is a patient’s response, and whether they meet certain milestones within a certain time.
  - Therapy recommendations (e.g. ELN, NCCN) help to understand the goals of treatment.
  - PCR technology helps doctors know how deep is the response.
  - Current research focuses on the consequences of not having an early, fast response, on what to do after a long period of very deep remission, and how to eradicate CML altogether.

- Traditional PCR technology is not easy to do well, and not available everywhere.
  - Complicated, very dependent on technology and staff.
What is TFR?
(Treatment free remission)

• Even though TKIs should be taken indefinitely, some patients, after many years on a TKI have discontinued therapy and the disease has not come back. These patients have had a very deep remission; undetectable PCR

• Many clinical studies have been done about discontinuation of therapy. In general around 50 percent of patients who try to discontinue therapy are able to maintain “treatment free remission”

• It is still hard to predict which patients will be able to successfully discontinue their TKI treatment
Causes of CML = unknown

• However...

✓ We know it is not hereditary (children of people with CML do not have a higher chance to get it)
✓ We know it is not contagious (it doesn’t pass from one person to the next)
✓ The average age of diagnosis in western countries is 65. It is rare in children (although in developing countries it seems more likely to occur in children and young adults)
✓ It more often occurs in men than women
First Generation TKI, Second Generation TKI

• Imatinib (Glivec) if often referred to as **First Generation** TKI because it was the first one to be developed.

• Dasatinib and nilotinib (Sprycel and Tasigna) are sometimes referred to as **Second Generation** TKI because they came out later than imatinib.

• Ponatinib is sometimes referred to as **Third Generation** TKI.

*Second generation* TKI is **not** the same as *second line* treatment.
<table>
<thead>
<tr>
<th>Phases of CML</th>
<th>WHO Definition</th>
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<tbody>
<tr>
<td>Chronic phase</td>
<td>Peripheral blood blasts fewer than 10% in the blood and bone marrow</td>
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<tr>
<td>Accelerated phase</td>
<td>Blasts 10-19% of white blood cells in peripheral and/or nucleated bone marrow cells</td>
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<tr>
<td>Blast crisis</td>
<td>Peripheral blood blasts ≥ 20% of peripheral blood white blood cells or nucleated bone marrow cells</td>
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Questions?
THANK YOU!