CML 301
SOME INTRODUCTION INTO CML, CML SCIENCE, DRUG DEVELOPMENT AND INFORMATION RESOURCES

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CML 101 / BASICS: UNDERSTANDING THE DISCUSSIONS IN CML SESSIONS
What is BCR-ABL?

- CML is a type of 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
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 and in developing countries is 38. It is ultra-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
Tyrosine Kinase Inhibitors (TKIs)

BCR-ABL gene = 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>
</tr>
</thead>
<tbody>
<tr>
<td>1. Imatinib</td>
<td>Glivec/Gleevec</td>
<td>Novartis</td>
</tr>
<tr>
<td>Imatinib</td>
<td>(Various)</td>
<td>Generics companies</td>
</tr>
<tr>
<td>2. Dasatinib</td>
<td>Sprycel</td>
<td>BMS</td>
</tr>
<tr>
<td>3. Nilotinib</td>
<td>Tasigna</td>
<td>Novartis</td>
</tr>
<tr>
<td>4. Bosutinib</td>
<td>Bosulif</td>
<td>Pfizer</td>
</tr>
<tr>
<td>5. Ponatinib</td>
<td>Iclusig</td>
<td>Ariad</td>
</tr>
</tbody>
</table>
First Generation TKI, Second Generation TKI

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

- Dasatinib, nilotinib and bosutinib (Sprycel, Tasigna, Bosulif) 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 (= drug that follows after 1st drug fails).
What is Drug Resistance?

• The cells become resistant to the drug, the drug can not longer keep the CML cells from growing again
• 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

• A LOT ABOUT THIS IS STILL UNKNOWN
What is Drug Intolerance?

- 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
  - Always talk to your doctor about side effects
  - 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
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:
  - "Complete Blood counts" (CBC) = measures hematological response = most superficial response
  - Cytogenetics and FISH = measures cytogenetic response = number of cells carrying the "Philadelphia Chromosome" in the bone marrow
  - PCR = measures molecular response = ratio of BCR-ABL molecules present (also called ‘residual disease’ or ‘molecular test’)


Monitoring CML

- Types of response to treatment

<table>
<thead>
<tr>
<th>Response type</th>
<th>Partial</th>
<th>Major</th>
<th>Complete/Deep</th>
</tr>
</thead>
<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>MCyR</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>
</tbody>
</table>

- 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

- CML Advocates Network, patient summary, www.cmladvocates.net/cmlsummary
Log Reduction

- "Log reduction" is a mathematical term (as is "log increase") used to show the proportion of BCR-ABL eliminated from the sample. Factor 10 = 1 log
- It is another way to express how deep is the response

- Log reduction:
  - 1 log reduction means the number of cells with BCR-ABL is 10 times smaller than initially
  - 2 log reduction means the number is 100 times smaller
  - 3 log reduction means the number is 1000 times smaller (MMR)
  - 4 log reduction means the number is 10,000 times smaller (MR4)
  - 4.5 log reduction means the number is 32,000 times smaller (MR4.5)
PCR, what is all the fuss 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
  - Needs to be standardized (in the international scale) to be comparable between labs

**IF NOT ON THE INTERNATIONAL SCALE, IT IS DIFFICULT TO INTERPRET THE RESULTS**
Treatment Free Remission (TFR) vs Eradicating CML

- **Treatment Free Remission**: describes the status of patients who stop taking TKI and still maintain their CML undetectable or at a very low level
  - Used instead of the word cure, because the disease might still be there, however not progressing even without therapy

- **Eradicating CML**: refers to the potential of treatment to actually cure CML
  - Some new drugs (not TKIs) are being tested to see if they eradicate also the last residual CML stem cell
HOW DOES DRUG DEVELOPMENT WORK?
Phases of Medicines Research & Development

- Research & Discovery
- Non-clinical Development
- Clinical Development Phase I, II & III
- Post-approval Life-cycle management & Pharmacovigilance
Of 8,000 molecule candidates, only 5 ever get into human clinical trials, and only 1 makes it to the market.
In different phases of clinical trials, dosing, safety, efficacy is tested in an increasing numbers of patients.
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**Phase II trials:** Therapeutic effect, optimal dose, toxicity

**Phase III trials:** Large multicentre comparative studies on safety and efficacy of the new medicine compared to standard medicine. Goal: approval

CML examples: IRIS, ENESTnd, DASISION, …
After regulatory approval and reimbursement decision, late-phase trials optimize therapy and collect more (safety) data.

Phase IV trials: Real-life data, therapy optimization of approved drugs, …
Difference between industry-sponsored and investigator-initiated trials – and real world data

Industry-sponsored research

- Industry: More targeted towards assessment and regulatory approval of new drugs, new indications, new regimens

Investigator-initiated trials, academic research

- Academic trials: More focused on therapy optimisation, long-term outcomes, understanding disease biology, real-life care

Patients in clinical trial centers

- Most patients are treated individually outside of clinical trials (= no data, except some registries or real-world data)
Most trials are sponsored by industry and then run at academic hospitals (but this is not either/or)
So what does this mean in CML?

• CML is still a dangerous chronic disease that kills when badly treated, and where no cure exists for most patients.
• Future CML therapies are in different stages of development (phase II to phase IV). Many will not work, some might bring the cure.
• CML is pioneering stopping treatment, but current drugs will only allow every 4th CML patient to stop successfully.
• To interpret the “hope and hype”, we need to look carefully where they are in the development cycle.
Current Research Questions in CML

1. New drugs:
   - Phase I/II trials for new compounds, e.g. ABL001, Ruxolitinib, Nivolumab in combination with existing TKIs. Main goals: Better TFR rates or overcoming resistance.

2. Optimizing current drugs in the market:
   - When is the best time to switch TKI (ELN, NCCN guidelines, milestones)
   - What dose gives best efficacy or reduces serious side effects
   - When and who can stop treatment (TFR)
   - Does the immune system and/or interferon have a role in controlling CML?

3. Improving Quality of life and avoiding serious side effects:
   - The interactions of additional diseases (“co-morbidities”) on CML therapy
   - How to optimize quality of life given specific, also low-grade side effects of TKIs
WHERE TO FIND AND HOW TO BETTER UNDERSTAND CML RESEARCH
1. Discovery of Medicines
2. Pre-clinical development
3. Clinical Development
4. Clinical Trials
5. Regulatory Affairs, Drug Safety, Pharmacovigilance
6. Health Technology Assessment
CML Advocates Network Trial Database
http://www.cmladvocates.net/cmltrials

- Currently 25 CML trials described that are recruiting
- +22 trials that are no longer recruiting
- Continuously updated
Information from medical conferences e.g. ASH, EHA

- ASH Abstracts
- ASH Reports of Giora, Jan
- Free EHA tickets
Other helpful resources that help you and patients to understand CML therapy & research

Your organisation can use them to support patients!

• Patient-friendly summary of Treatment Recommendations of the European LeukemiaNET in 17 languages
  http://www.cmladvocates.net/cmlsummary

• Summary of the CML Adherence Study in 79 countries
  http://www.cmladvocates.net/adherence

• Educational videos on adherence, side effects, testing and monitoring
  http://www.cmladvocates.net/education/educational-videos

• CML Generics Knowledge Base and Webinar
  http://www.cmladvocates.net/generics

• CML Glossary with all common terms used in CML
  http://www.cmladvocates.net/glossary
CML RESEARCH AT CML HORIZONS 2018
Medical Sessions at CML Horizons 2018

Medical #1: CML Management in Countries with Access Challenges
Chairs: Mercedes Arteaga & Rod Padua

• Access to treatment (Eastern Europe)
  Speaker: Andrija Bogdanovic

• Access to monitoring (Africa)
  Speaker: Nicholas Anthony Othieno Abinya

• TFR in low and middle-income countries (Asia)
  Speaker: Raymond Wong

Medical #2: First-line decision making
Chairs: Cornelia Borowczak & Šarūnas Narbutas

• Did the introduction of generics change clinical decisions in first-line therapy?
  Speaker: Gianantonio Rosti

• Pediatrics: New labels of Nilotinib and Dasatinib
  Speaker: Meinolf Suttrop

• Update on Treatment Guidelines
  Speaker: Delphine Rea
Medical Sessions at CML Horizons 2018

Advocacy #3: Stopping CML treatment - clinical data, ‘bad practice, patient information
Chairs: Jelena Čugurović & Felice Bombaci

- Clinical update on TFR studies
  Speaker: Delphine Rea
- Bad Practice examples
  Speaker: Jan Geissler
- Informing patients about TFR
  Speaker: Giora Sharf

Medical #3: Side Effect Management
Chairs: Lisa Machado & Jana Pelouchova

- Long-term side effects of TKIs
  Speaker: Gianantonio Rosti
- Collaboration of cardiologists and hematologists
  Speaker: Tristan Mirault + Delphine Rea
- Side effect management: Nurse experience
  Speaker: Irene Caballes
Medical #4: New Agents / New Regimens
Chairs: Zack Pemberton-Whiteley & Cathy Scheepers

- ABL001/Ascitinib trials
  Speaker: Delphine Rea
- Is there any evidence to use lower TKI doses?
  Speaker: Delphine Rea
- How will therapeutic landscape in CML change in next 5 years in your region?
  Panel discussion with speakers from Asia (Raymond Wong), Africa (Nicholas Anthony Othieno Abinya), Eastern Europe (Andrija Bogdanovic), Europe (Gianantonio Rosti)