CML HORIZONS 101
AND CML 101

by

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May 26, 2017
Frankfurt, Germany
Goals of this Session

“Everything you ever wanted to know and were afraid of asking”

- Help you navigate the conference
- Help you set goals for yourself at the conference
- Provide you with background to help you follow the medical sessions
CML Horizons
Historical overview

• First meeting organized by Novartis in 2003
  • 25 CML and GIST advocates in Switzerland

• Subsequently Novartis organized New Horizons yearly, CML and GIST together, until 2010

• 2011 onwards, conference organized by the patient community, with multi-sponsorship; CML and GIST split

• Renamed CML Horizons. Supported by Novartis, BMS, Pfizer, Incyte, Leukemia & Lymphoma Society, iCMLf
CML Advocates Network
115 organizations from 86 countries

• Started by 4 advocates
  • Central idea initiated at 2005 New Horizons conference
  • Initial goal: continue the networking in between New Horizons conferences, increase collaboration

• CML Advocates Network today
  • Hosted by the Leukemia Patient Advocates Foundation, Registered global organization in Switzerland since 2011

• Today: 115 organizations, 3 founders, 6 regional representatives as steering committee and 2 Programme Managers
CML Advocates Network

Goals

- Provide a worldwide web directory of CML organizations
- Stimulate collaboration and best practice sharing
- Grow capacity in CML patient advocacy organizations
- Provide educational materials on CML
Who is here?

- 89 delegates (24 newcomers)
- 17 pharma representatives
- 8 speakers
Why are we here?

AUDIENCE GOAL SETTING
Why are we here?

<table>
<thead>
<tr>
<th>Goals</th>
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<tbody>
<tr>
<td>Learn about advances in the treatment of CML</td>
<td>Medical sessions</td>
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<tr>
<td>Learn from others’ experiences</td>
<td>Posters and networking</td>
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<td>Learn about advocacy</td>
<td>Advocacy sessions</td>
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<tr>
<td>Meet industry representatives and speakers</td>
<td>Networking</td>
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<tr>
<td>Produce a report for my group</td>
<td>Note-taking</td>
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How is the conference structured?

4 medical sessions
- CML therapies in 2017
- Discontinuing treatment
- Side effects, pregnancy and fertility
- Generic drugs in CML

6 advocacy sessions (1 more in 2017)
- Patient Advocacy in Research
- Parallel sessions: Management, volunteers and collaborations
- Access: The good, the bad and the ugly
- Best Practice in Advocacy
- Generic drugs in CML
- Joint action and Community Advisory Boards
To whom can I address my questions?

- Logistics: Vanja from Balkan Adriatic
- The management team: Lidija Pecova and Celia Marín
- Any of the Steering Committee representatives!
- Twitter wall using #CMLHZ17

This is your meeting!
Speak out, ask questions!
Make your participation count!
To send your Twitter messages to our “Social Media wall”, include 

#CMLHZ17

in the text of your message.

It will appear in the room, and at walls.io/cmlhz17
Participate in Social Media

using #CMLHZ17 #CourageHope

The most liked and retweeted posts will receive an amazing book 😊
Don’t forget to download the APP CML TODAY

Please, scan the QR code of the card

“CML Today”
the mobile adherence app for CML patients

Download

Iphone

Android
CML 101

UNDERSTANDING THE DISCUSSION IN THE MEDICAL 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 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 = 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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<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>Srpycel</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 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.*
What is Drug Resistance?

- 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

- 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:
  - 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 (also called ‘residual disease’)
Monitoring CML

- Types of response to treatment

<table>
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<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>
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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
- 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 relative number of BCR-ABL eliminated from the sample
- 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
  - 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 focusses 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
Treatment Free Remission (TFR) vs Eradicating CML

- **Treatment Free Remission**: describes the status of patients who stop taking TKI and still maintain their PCR undetectable or very low
  - 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 are drugs developed and approved?

1. **Pre-clinical phase:** this is when a new compound is tested in animals

2. **Clinical Studies:** this is when the compound is tested in humans

3. **Regulatory approval:** this is when the drug company presents the results of the clinical trial to the Health Authorities and asks for approval for a specific set of patients, depending on how the trials were designed. The results of the trial focus on efficacy and tolerance

4. **Post-marketing Surveillance:** after the drug is approved, the Health Authorities still continue to collect data on any side effects of the drug to ensure that the results don’t change from the results of the clinical trial
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 are newly diagnosed (FIRST LINE TREATMENT).

Advocacy note: every advocate should know what drugs are approved in their country and for what specific use (label). Pharma representatives can provide information about their own drug’s situation in your country.
What if a drug is not approved in my 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)

Advocacy note: Running trials and offering compassionate use programs are very expensive to companies. Companies decide where they will seek approval for their drugs
Important terminology about drug development and safety

- **Post-marketing Surveillance**: Health Authorities continue to collect data on side effects of a drug after it has been approved to make sure the drug is safe and no new side effects are discovered.

- **Fast track designation**: Speeds the review of data by FDA, with the purpose of getting important new drugs to the market.

- **Pharmacovigilance**: all activities related to monitoring that drugs are safe for patients. This field is very regulated by Health Authorities.

- **Adverse Event Reporting**: the act of informing Health Authorities of a specific medical occurrence on a patient who is taking a drug.
Treating CML in 2017

- General consensus is to start with one of the TKIs approved for first line treatment

- Glivec (imatinib) is approved for first line treatment in most countries

- Labels vary from country to country. Example: Tasigna (nilotinib) and Spryce (dasatinib) are approved for first line in some countries and second line in some others, and not approved at all in other countries

Advocacy Note:

- Need to know the regulatory process in our country for approval and reimbursement of drugs
Current Research for CML

1. New drugs:
   Phase 1/2 trials for new compounds, e.g. ABL001, Ruxolitinib, Nivolumab
   in combination with existing TKIs

2. What is the optimal way to treat CML given the current drugs in the market:
   When is the best time to switch TKI (ELN, NCCN guidelines, milestones)
   What dose gives best efficacy
   When and who can stop treatment (treatment free remission)
   Does the immune system and/or interferon have a role in controlling CML

3. Quality of life:
   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
Key Clinical Trials focused on response and efficacy

- Current research assumes that all treatments are available, all patients have access to standardized PCR, and focuses on how to use them optimally

<table>
<thead>
<tr>
<th>Trial</th>
<th>Description</th>
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<tbody>
<tr>
<td>IRIS</td>
<td>Original trial that compared imatinib to interferon, and led to Glivec approval - run by Novartis</td>
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<tr>
<td>CML-IV</td>
<td>German study (12 years, still ongoing) comparing Imatinib 400, Imatinib 800, Imatinib+Interferon</td>
</tr>
<tr>
<td>ENEST</td>
<td>Original nilotinib trial by Novartis ENESTnd, ENEST1st, efficacy of nilotinib first line</td>
</tr>
<tr>
<td>DASISION</td>
<td>Compared dasatinib and imatinib first line - BMS</td>
</tr>
<tr>
<td>PACE</td>
<td>Original ponatinib trial - ARIAD</td>
</tr>
<tr>
<td>BELA</td>
<td>Original bosutinib trial - Pfizer</td>
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</table>
Current key clinical trials assessing Therapy-Free Remission (STOP)

Ongoing, but non-recruiting STOP trials:

- **STIM, A-STIM**: French trials stopping Imatinib, academic trials
- **STIM2**: Stopping 2nd generation TKI, academic trials
- **Nordic STIM**: (Imatinib, academic trial)
- **Korean, Japanese STOP trials**: (imatinib)
- **EUROSKI**: (largest STOP study with >700 participants, stopping any TKI, academic trial in 9 European countries)
- **ENESTpath, ENESTfreedom ENESTop**: (Novartis Tasigna Stop Trials)

Ongoing, recruiting STOP trials:

- **TIGER**: (Nilotinib vs. Nilotinib+Interferon, with potential to stop therapy)
- **DECLINE**: (Imatinib to nilotinib escalation in case of non-optimal response, with potential to stop therapy)
- **DASFREE**: (BMS Sprycel stop study)
- **DESTINY**: = De-Escalation and Stopping of Imatinib, Nilotinib or Dasatinib in CML (UK)
- **LAST**: Stopping Tyrosine kinase inhibitors (any TKI, USA)
- **MSIT**: = Malaysia Stop Tyrosine Kinase Inhibitor Trial

See CML Advocates Network Study Database:

[http://www.cmladvocates.net/cmltrials](http://www.cmladvocates.net/cmltrials)
Helpful resources that help you and patients to understand CML
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](http://www.cmladvocates.net/cmlsummary)

• **Reports from the ASH congress in multiple languages**
  [http://www.cmladvocates.net/ashreports](http://www.cmladvocates.net/ashreports)

• **Summary of the CML Adherence Study in 79 countries**
  [http://www.cmladvocates.net/adherence](http://www.cmladvocates.net/adherence)

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

• **Inofficial CML trial registry**, also linking to patient information on trials
  [http://www.cmladvocates.net/cmltrials](http://www.cmladvocates.net/cmltrials)

• **CML Generics Knowledge Base and Webinar**
  [http://www.cmladvocates.net/generics](http://www.cmladvocates.net/generics)

• **CML Glossary** with all common terms used in CML
  [http://www.cmladvocates.net/glossary](http://www.cmladvocates.net/glossary)
World CML Day, 9/22
TODAY WE LIVE, TOGETHER WE FIGHT

Around 22 Sept 2008, the CML Society of Canada announced the creation of the first CML Awareness Day in Canada.

Around 22 Sept 2011, CML patient organisations across collaborated on “International CML Awareness Day”, with 2,100 signatures of the Baveno Declaration, 140 photos of “Faces of CML” collected, 15 countries participating.

Around 22 Sept 2012, 34 organisations held events. World CML Day posters provided.

Around 22 Sept 2013, it became “World CML Day”, using the slogan “All United, All Unique”. 30 countries participated. 8,500 World CML Day pins distributed.

Around 22 Sept 2014, 32 countries. 35,000 pins were distributed. Book “Faces of Courage and Hope” in 50 countries.

Around 22 Sept 2015, 24 countries participated. World CML Day Toolkit first used. Training at this CML Horizons Meeting!

Around 22 Sept 2016, 35 countries participated. World CML Day Toolkit used. Hundreds of images and messages on Social Media.
Not discussed topics, questions

• Phases of CML

• Other treatments: Hydrea, Interferon, Transplant, Synribo (omacetaxine), chemotherapy

• Understanding PCR results

ANYTHING ELSE? THIS IS YOUR CHANCE TO ASK QUESTIONS!