CML HORIZONS 2015: LEARN, SHARE, GROW
1-3 MAY 2015, BARCELONA, SPAIN

From 1-3 May 2015, the CML Advocates Network welcomed patient leaders in Chronic Myeloid Leukemia (CML) to its annual conference “CML Horizons” in Barcelona, Spain. Delegates from 65 countries worldwide (Europe, North America, Asia, Africa, the Middle East and Latin America) learned from medical experts, shared best practice in patient advocacy, and grew their network in the global patient community.

CML Horizons is a fully community-run conference which has been held for the 13th time this year. The annual conference is run by the CML Advocates Network, hosted by the non-profit “Leukemia Patient Advocates Foundation”.

FRIDAY 1 MAY (DAY 1)

PARALLEL PRE-MEETINGS

- CML 101 (Pat Garcia-Gonzalez)
- Patient involvement in CML research (Jan Geissler)

The pre-meeting started on Friday morning with two parallel sessions, one by Pat Garcia-Gonzalez (USA) on the basics of CML, and how to navigate CML Horizons, and one on patient involvement in research by Jan Geissler (Germany).

Pat Garcia-Gonzalez gave an overview of how CML Horizons started, followed by the main goals of the network, the structure, content and participants’ profiles of the conference: 93 patient advocates (29 newcomers), 18 pharma representatives, and 10 speakers. Attendees were provided with the necessary background to help them follow the medical sessions. For this part of the sessions Pat
Garcia-Gonzalez was helped by Dr. Hari Menon from India. Firstly, they gave a brief overview of CML, the BCR-ABL gene, and how TKI inhibits the BCR-ABL. A list of current treatments was given, explaining the different names used for each drug – the generic names and the manufacturers’ brand names. Also a differentiation between first generation (Imatinib) and second generation (Nilotinib, Dasatinib, Bosutinib and Ponatinib) drugs was highlighted. Furthermore, it was clarified what drug resistance and drug intolerance means, the importance of monitoring the disease and the role that PCR plays in this, together with CBC, Cytogenetics and FISH. As part of the PCR discussion, the lack of standardization of laboratories was also highlighted.

Pat highlighted the importance of not confusing Treatment-Free Remission and eradicating CML, emphasizing that the latter was presently not possible. A full overview was given on the drug approval process, from the pre-clinical and clinical phase to regulatory approval and post-marketing surveillance. Also, the process of label approval was covered, together with the alternative options to access drugs that haven’t yet been approved, such as clinical trials, compassionate use and humanitarian aid. Additional important terminology about drug development and safety was introduced, such as fast track designation, pharmacovigilance and adverse event reporting.

Finally, the session ended with an update of the current treatment used in CML in 2015, together with a list of ongoing clinical trials focused on response and efficacy, and the ones focusing on assessing Treatment-Free Remission.

The second parallel session held by Jan Geissler focused on the current CML research landscape, and how patient advocates can help shape research through collaboration.

Regarding the current research being conducted in CML, the importance of TKI clinical trials was emphasized, such as the need to take into account the willingness of patients to engage, and their potential unwillingness to go beyond certain side effects. Hot topics were also presented, such as access to optimal care, management of side effects, good patient information, pediatric, fertility and data on genetics. The importance of managing expectations with regards to discontinuing treatment was highlighted, as only 40-50% of patients will ever be able stop treatment, and the reasons remain unclear.

Jan also announced the launch of the CML Advocates Network’s Trial Database - a database of 23 currently recruiting trials and 8 ongoing trials. Since the list needs to be updated continuously, members of the CML Advocates Network are encouraged to report about the trials happening in their countries. Attendees were also informed about reliable sources of information, from scientific and medical publications, such as medical conference reports, to educational material, such as that produced by EUPATI.

Jan then moved into explaining how patient organizations can contribute to clinical research, as a driving force of research, a co-researcher, a reviewer, an advisor, an information provider, or merely a research subject. Patients need to be involved in all phases of the research life cycle, by setting the research priorities, designing and planning the research, being involved in the operations and conducting the trials, and taking an important role in communication, dissemination and post-approval. Patient advocates were encouraged to aim for early involvement to achieve maximum impact.

A short overview was given on the CML Advocates Research Group, which had been discussed the year before but didn’t progress as quickly as expected. Members were now encouraged to participate in discussing next steps, roles and tasks. These ideas included the need for developing surveys to collect data, supporting, contributing to and influencing CML studies, building expertise, and setting clear recommendations on how to collaborate with academia and industry on research.

WELCOME TO BARCELONA
(by MARÍA NAVARRO AND GIORA SHARF)

An inspiring opening speech was given by María Navarro (Spain), who focused on the diversity of attending patient representatives from over 60 countries in Europe, North America, Asia, Australia, Africa, the Middle East and Latin America. Based on this diversity and the general objectives of the conference (Learn, Share, Grow) she highlighted the need to collaborate, sharing knowledge and best practices in order to become stronger. The specific aims of CML Horizons, also mentioned by Dr Navarro, are identifying opportunities, being inspired, learning from experts, sharing ideas and networking. To tackle these aims and objectives, attendees would have the opportunity to listen to world-renowned experts in CML and patient advocacy for three days, during both the medical and the advocacy sessions. Before closing her speech she gave
CML Horizons a warm welcome to her city, Barcelona, and wished everyone a fruitful meeting.

Giora Sharf (Israel) then gave a warm welcome to all attendees before opening the first session. He highlighted that the patients’ voice has become very important for all stakeholders, and that the CML community is a very strong network and one of the most active patient communities. CML Advocates now has 102 members from 78 countries. The CML Horizons Steering Committee worked hard to prepare a good educational program, suitable for attendees, no matter whether they come from developed or emerging countries.

All newcomers received a special welcome by Giora Sharf, who also thanked the Steering Committee, Nicole, the speakers and sponsors for their support. Also, the Max Foundation was acknowledged for its help in recruiting new members all over the world.

MEDICAL SESSION #1: CML UPDATE

Chairs: Jana Pelouchová, Yair Bar-David
- Overview CML 1st line, 2nd line, managing resistance (Michael Mauro)
- Managing CML in countries with limited resources (Hari Menon)

Dr Michael Mauro (USA) explained that after 15 years of research in CML, we know that it should be a highly treatable condition worldwide before going on to describe the challenges of resistance. The rapidity of response and passing key milestones make a big difference on deep remission and long-term outcome. However, resistance remains a challenge and BCR-ABL kinase continues to be the driver. In this sense, survival of CML requires attention on reversible early toxicity, quality of life, adherence to therapy, achieving response milestones, and increasingly recognized ‘late effects’ of being on continuous therapy. Dr Mauro then gave an overview of the differences of cytogenetic remission vs deep molecular remission early in time. In any case, results of the IRIS trial had shown that progression or resistance usually come early, and become less likely as therapy moves on. One of the key messages is that early molecular response is of great importance when treating CML.

Dr Mauro then gave an overview of resistance to TKI and the most common mutations that lead to this resistance. Also, an overview of the recommendations on when to consider doing a mutational analysis at diagnosis, in first-line and in second-line settings was provided. The complexity of mutations that lead to resistance came across very clearly, as did the need to develop better techniques to understand these issues. One interesting note was that in 1/3 of patients the type of mutation influences the therapeutic decision. Finally, options for second-line and third-line therapy as well as allogenic transplant were discussed.

Dr Hari Menon (India) gave an overview of CML, using India as an example applicable to many developing countries. Despite the high mortality of cancer and the rapid increase in incidence over the next years, there are still several other challenges that have priority, such as infant mortality or hepatitis. He explained that the first-line therapy in emerging countries continues to be Imatinib, which is largely made available through Glivec International Patient Assistance Program (GIPAP). In fact, more than 70% of patients have access to the treatment through GIPAP. Those ineligible for GIPAP often choose generic Indian brands of Imatinib at a cost of approximately US$60/month.

An overview of the second-line therapies and stem cell transplant was also given. Dr Menon then gave a summary of the studies evaluating efficacy and safety of Imatinib in CML patients in India. In addition, he shared his analysis of the Indian patients enrolled in GIPAP, their cytogenetic response and major molecular response when comparing the originator drug vs generics. He also highlighted the problem in India regarding accessing diagnostics, for which the main reason appears to be the price of these tests. However, there are also other factors, such as underutilization of available facilities, large volumes of patients and non-standardized laboratories. Standardized monitoring strategies are rarely done due to unavailability, cost and a nihilistic attitude towards its implementation.

Regarding Treatment-Free Remission, Dr Menon specified that in developing countries this is not being currently explored, either because patients fear to lose the support from GIPAP or because of the lack of documentation of sensitive diagnostics, access to TKIs when needed, etc.

ADVOCACY SESSION #1: ADVOCACY EXAMPLES ON ACCESS TO TREATMENT & CARE

Chairs: Jelena Cugurovic, Gail Sperling
- Access to therapies (Ananda Plate)
- Access to trials (Zhengchen Liu)
- Access programs (Pat Garcia-Gonzalez)
● Achieving reimbursement (Georges Sayde)

During the first talk of the afternoon, Ananda Plate from Myeloma Patients Europe (Brussels) gave an overview of the current project, the European Atlas on Access to Myeloma Treatment. The rationale of the project is that despite major advances in treatment over last decade, access to therapies is still a key issue in most countries. There are a variety of reasons behind access barriers (policy priorities, budgets, health technology assessment, pricing, etc.). Advocacy to improve access is still largely unsuccessful because the main issues aren’t being understood enough. This is why new approaches to advocacy are needed, including building and using evidence, early engagement and more collaboration, growing skills and training, as well as developing a strategy and better planning.

The methodology used for the project includes a desk review of clinical guidelines / key recommendations, policy documents, unpublished literature and working papers, complemented by a comprehensive survey to patient advocates and clinicians to understand perceived barriers to access.

The expected outputs are a report, with country-specific intelligence on health care systems and a set of recommendations, an implementation phase to strategically guide patient organizations, and an impact assessment and regular update of the document.

Also, an overview of provisional results of the survey on perceived barriers to access in the area of diagnosis, treatment, and governance was given.

To conclude, Ananda provided suggestions on how this could be adapted to other disease areas like CML. In all disease areas, umbrella organizations should play a key role in gathering this kind of evidence and giving strategic support to their national member organizations in order to improve their specific access strategies.

Zhengchen Liu (China) presented the historical background of clinical trials before going into the challenges involving access to clinical trials in his region, such as the information gap of patients, the health technology gap between researchers and clinicians, the financial gap, and the policy gap resulting in slow trial approval.

To overcome this, the New Sunshine Charity Foundation in Beijing, China, has taken several steps. For example, to overcome the health technology gap, the foundation invited physicians to attend CML Horizons, did surveys to accelerate trials, and supported physicians in receiving training and attending international conferences. Regarding the financial gap, the Chinese patient organization supports the China Children Leukemia Group, sponsors clinical research and facilitates a pediatric CML registry/multicenter group in China. To overcome the information gap, its members attend the annual meetings of EHA and ASH, attend scientific sessions, poster sessions, etc., liaise with international physicians, visit the stands of pharma companies at ASH and EHA, and get information on ongoing trials.

Finally, in the case of the policy gap, they work with the Chinese government, co-operate with members of the parliament, and try to enhance international access to clinical trials that take place abroad.

Zhengchen then gave the audience an overview of a survey on Treatment-Free Remission, in which 100 patients participated. The results of the survey were reported to the Beijing Medical Association Meeting. Also, from May to August, 2014, they assisted Dr Qian Jiang with a survey of 1,039 CML patients in China about their target of treatment and their opinion about reaching Treatment-Free Remission. Finally, Zhengchen gave a comprehensive set of recommendations and resources on clinical trials which are available on his slides.

Pat Garcia-Gonzalez (USA) provided some background on the GIPAP and how it came about. In 2001 as Novartis was getting ready to launch Glivec, they developed a program for patients who could otherwise not get access to the drug in certain countries. The Max Foundation went into a partnership with Novartis on this. This new donation model meant that instead of the company giving large amounts of drugs to the government, the administrator would have to identify each patient who has a need, so the company would donate to specific patients.

The donating company decides the specific countries for the program, develops program criteria, donates the drug, and delivers the drug to each treatment provider. The program administrator verifies the identity of the patient and whether the criterion is met, protects confidential patient information, approves patients for entry into the program, and guides patients through the application process.

Pat listed the challenges and best practice solutions of international access programs for targeted therapies, such as verifying the existence, identity and medical need of a patient, drug importation issues, anticipation of the amount needed, receiving regular feedback from clinicians, pharmacovigilance issues,
limitations from the International Donation Guidelines, the broad scope of GIPAP, and having to manage 32,000 active cases and 1,500 physicians in 80 countries.

It was interesting to hear that 30% of all Glivec produced by Novartis is for donation; this is not only for GIPAP. Pat explained that some of the local environments where programs like GIPAP operate have changed in the past decade and companies have developed co-share or co-pay programs. An example from Malaysia showed that when the government became involved in the access program there was more interest from local stakeholders in patient education and disease monitoring.

Finally, Pat gave an overview of the role of patient organizations in access programs. One of these roles is to be a provider of patient support, including information and education. However, the optimal role of the patient organization would be to have a seat at the table when access programs are being discussed. The potential benefit of having patient organizations as a true partner in an access program is huge. In this sense, patient organizations can play a key role in ensuring that the criteria allow patients to maintain their dignity while staying on treatment; they can endorse the program, which ensures public acceptance; they can advocate to their government for involvement in the program, and they can implement education and support initiatives in collaboration with the program administrator to support treatment continuation.

Georges Sayde (Lebanon) gave an overview of health coverage in Lebanon. As he explained, the reimbursement of CML patients in Lebanon is divided into the Ministry of Health, the National Social Security Fund, and other institutions. There is a co-payment of 5% in place for a big proportion of the patients, which is linked to huge challenges, as this co-payment represents half of what an average person in Lebanon earns. The Lebanese patient organization decided to tackle this problem and advocate for free and universal access to treatment for CML patients, which was a big challenge. In order to achieve this, they increased the pressure on the government and started intense discussions with the main decision makers within Novartis. All parties involved made huge efforts to find solutions. In addition, the Lebanese patient organization set up a program to cover the costs of treatment for CML patients. This is sponsored by Novartis. A service provider will mediate between patients and pharmacies in order to relieve the patient of the remaining 5% co-payment.

DINNER AT THE HOTEL

Dinner on the first evening took place in the hotel, with a very inspiring talk by Hiba, Bahija Gouimi’s daughter, who spoke about her mother, the challenges she faced when she was diagnosed, and the great work she is doing as a patient advocate in Morocco.
SATURDAY 2 MAY (DAY 2)

ELECTIONS FOR THE CML HORIZONS STEERING COMMITTEE 2016-2017

The session on elections was introduced by Jan Geissler, who highlighted the importance of the elections every two years. The CML Horizons Steering Committee consists of one elected representative from each of the six major regions plus three CML Advocates Network founders as permanent committee members (Giora Sharf, Jan Geissler, Jana Pelouchová). In 2015 a sixth region (Central and Eastern Europe & West Asia) was introduced. Only one candidate stood for elections for Central and Eastern Europe & West Asia (Jelena Ćugurović from Serbia), Western Europe (Rita O. Christensen from Denmark), and Latin America (Pat Garcia-Gonzalez from the USA) respectively, so these candidates were automatically appointed to the new Steering Committee. The candidates from Asia-Pacific (Rod Padua from the Philippines and Zhengchen Liu from China), Middle East & Africa (Bahija Gouimi from Morocco and Ferdinand Mwangura from Kenya), and North America (Gail Sperling from the USA and Sandra Shaw from Canada) presented their motivation to become members of the new Steering Committee. The newly appointed Steering Committee consists of Rod Padua from the Philippines; Bahija Gouimi for Middle East and Africa, Gail Sperling for North America, Jelena Ćugurović for Central and Eastern Europe and Pat Garcia-Gonzalez for Latin America, Giora Sharf, from Israel, Jan Geissler, from Germany, and Jana Pelouchová, from the Czech Republic. Giora thanked the outgoing committee members Zhengchen Liu and Mina Daban for their valuable contribution in the past term, and encouraged all other candidates to continue to engage with the Network.

MEDICAL SESSION #2: TREATMENT-FREE REMISSION: OPPORTUNITIES AND CHALLENGES

Chairs: Jan Geissler, Felice Bombaci

- Treatment-Free Remission, stop trials, predictors for stopping treatment (Andreas Hochhaus)
- The patient perspective on Treatment-Free Remission, including support needs (Pat Elliott)
- Panel discussion: The psychology of stopping treatment (Pat Elliott, Michael Mauro, Andreas Hochhaus, Cristian Neves)

Dr Andreas Hochhaus (Germany) explained that Treatment-Free Remission is a possibility that only applies to a proportion of patients, and that given the high attention and expectations this topic creates, it’s important to manage these in a sensible way. The lack of data on which patients would best be able to successfully stop treatment, and when, is still a clinical challenge. This is one of the reasons why Treatment-Free Remission should be done only within a clinical trial. Sharing data is also crucial, and is only possible if consistent definitions and monitoring standards are being used.

Regarding TKI discontinuation in CML, to make TKI discontinuation accessible and safe to a higher number of patients, it is necessary to harmonize TKI discontinuation eligibility criteria, molecular monitoring and treatment resumption policies. Also, the evaluation of less stringent criteria for TKI discontinuation than those chosen in pioneer studies STIM and TWISTER seems to be reasonable. Dr Hochhaus presented a list of potential predictors for Treatment-Free Remission and the requirements
for stopping. To avoid relapse as far as possible, an attempt at Treatment-Free Remission should only be done after consolidation of the response (very low residual response or even deep molecular response). A remission is never “complete” as often the PCR fluctuates from month to month, meaning that every patient may have residual disease, even if the immune response is strong enough to keep it under control. Another important point to take into account before considering stopping treatment is the duration of the ongoing treatment before stopping.

Dr Hochhaus gave an overview of the data of recent stop trials, such as STIM, TWISTER, EURO-SKI and STOP 2G TKI.

Pat Elliott (USA) talked about the patient perspective on stopping treatment in the context of CML, including the need to address gaps in patients’ understanding of CML basics; the differences in perceptions of clinicians and patients of the impact side effects have on quality of life; and the need for “patient friendly” information on Treatment-Free Remission to avoid confusion and manage expectations.

There is a generalized lack of awareness of the data coming out of stop trials among patients, and key information about stopping treatment and respective trials is not provided in doctor-patient communication. In this sense, patient advocates have an important role in filling in these gaps.

Pat presented a survey done in April 2015 with 70 CML patients who are in Treatment-Free Remission and in a private online support group. Most respondents (70%) said the main reason for stopping treatment was relief from side-effects and 74% had concerns about long-term effects. Patients were also asked about the concept of “failing Treatment-Free Remission”, psychological concerns, emotional support, the role of health professionals in their dealings with the patient and the personal Treatment-Free Remission experience. These results showed there is also a need for long-term psychological monitoring of these patients.

Pat then talked about her personal experience with stopping treatment. Her recommendations for advocates are to review and share information on Treatment-Free Remission and clinical trials from reliable sources, identify resources for patients who need emotional support, and manage expectations. Her final remarks focused on the need to include the voice of patient advocates – evaluating not only clinical issues, but also the impact on patients’ quality of life, and on removing obstacles that prevent access to treatment and support.

Cristian Neves (Chile) gave an overview of the area he works in as a psychologist and the importance of mental health for CML patients before opening a panel discussion with patient advocates and CML experts.

Panel members expressed several opinions on the questions of how to expect clinicians to give emotional support given the high time pressure in their clinic. Whereas the easiest solution would be to refer the patient to a psycho-ontologist, this might only shift the problem, as psychological support is not reimbursable in many countries. Also, despite the need for psychological support, other more acute cancers and in-patients were usually given priority in this area.

Regarding Treatment-Free Remission, the need for managing expectations was again emphasized, as this is often seen as the ultimate goal of CML as a long-term chronic condition. In this sense, there is a need for individualized long-term-chronic-treatment discussions with every patient at the beginning of his/her treatment, of which Treatment-Free Remission is also part.

Also, there was a discussion of the importance of taking into account the psychological impact for the patient when embarking on Treatment-Free Remission, while waiting for results, and potentially when failing on Treatment-Free Remission, and how patient advocates can play a big role in identifying resources and providing high-quality information on this topic.

**ADVOCACY SESSION #2: WORLD CML DAY**

*Chairs: Sofia Sá Cardoso, Nicole Schröter*

- **Introduction** (Jan Geissler)
- **Training & practical tips** (Danielle Miller)

Jan Geissler presented the history of World CML Day and how a piece of the chromosome 9 and a piece of chromosome 22 led to designate 22 September as World CML Day. An overview of the historical milestones from 2008 and how patient organizations across the world started to engage to celebrate this day was given. For 2015, a toolkit will be created to increase the impact of World CML Day, addressing the public, the community, health care providers and policy makers.
Danielle Miller of the agency ZN Consulting introduced the World CML Day toolkit to the audience. It provides a collection of guidelines, best practices, examples, and templates to support all CML patient organizations in organizing their World CML Day, help them get their messages across and help their audience find out more about CML. The guidelines allow patient organizations to easily pick what they need to create their own communication toolkit, whether organizing events, using social media or getting the attention of the press. The message for World CML Day 2015 is a simple but clear one, with a call to action: Today, Together.

Danielle then presented some examples of how this message can be adapted to different audiences. For example, the general public could be addressed with “Today we live, together we fight”, healthcare professionals with “Today we listen, together we help” patients and relatives with “Today we talk, together we live”, and policy makers with “Today we ask, together we care”.

Once the organization has decided on their messaging, Danielle Miller highlighted the importance of knowing the message by heart and getting their whole team on board. Having a plan with clear definition of roles and responsibilities is also crucial.

MEDICAL SESSION #3: LIVING (LONG) WITH CML

Chairs: Cornelia Borowczak, Rod Padua

- Long-term side effect profiles of CML treatments, cardiovascular & thrombotic events (Andreas Hochhaus)
- Managing CML in children and young adults (Frédéric Millot)
- Panel discussion: What is different for adolescent patients with CML? (Cornelia Borowczak, Rod Padua, Cristian Neves, Frédéric Millot, Andreas Hochhaus)

Dr Andreas Hochhaus focused his talk on the importance of managing co-morbidities, and keeping a close eye on them in order to assess potential side-effects of the CML therapy, and avoid the worsening of these comorbidities. An example of this is the fact that some TKIs increase the blood sugar levels while some others decrease it, which is important to know when managing co-morbidities such as diabetes. Also, modifiable risk factors, such as smoking, abnormal levels of cholesterol, hypertension, diabetes mellitus, can play a key role in controlling co-morbidities and potential side-effects. Furthermore, in some cases it’s highly recommended to bring a cardiologist into the discussions in order to monitor and reduce the risk of cardiac disease.

Dr Hochhaus presented the importance of dosage in TKIs, since dosage is not only important when focusing on efficacy but also on tolerability. Several dose reduction studies are being conducted at the moment.

TKI treatments may add risks to pre-existing diseases, so it is of the utmost importance that the hematologist collaborates with all other specialists, including general practitioners, to ensure the correct management of co-morbidities and side-effects.

There is an unequal degree of knowledge about the impact of co-morbidities on outcome regarding Imatinib, Dasatinib and Nilotinib. However, there is no absolute contraindication for treating a given patient with any of these TKIs. Comorbidities could guide us to establishing a proper baseline evaluation and monitoring, and choosing the right drug depending on the co-morbidity.

To conclude, Dr Hochhaus recommended the treating doctor to keep priorities in mind when using TKIs. The first and main focus should be the anti-leukemic effect; the second should be knowing the toxicity profile of all the drugs that could be used; and the third should be to think about pre-existing co-morbidities. All these three points should be put into balance.

Children leukemias make up 9% of all leukemias, and pediatric CML is extremely rare. Despite rates of survival shifting from 40% in the 1980 to more than 90% after 2000 with the introduction of imatinib, Dr Frédéric Millot (France) expressed the need for the identification of prognostic factors and a pediatric scoring system, to optimize the strategy in the pediatric population.

The International Registry (I-CML-Ped Study) is a pediatric registry which has the purpose of better describing CML in children, to better identify prognostic factors, and to optimize individual treatment strategy.

Dr Millot then gave an overview on the current treatment guideline for pediatric CML, where the first-line treatment for children in chronic phase is Imatinib.

Regarding the adverse events, one important point to take into account is the negative impact of Imatinib on growth of pre-pubertal children. Even though the causes are not yet understood, hypotheses are that
growth hormones are suppressed, bone formation is inhibited, or an early growth plate closure – which causes poor growth and shorter bones – may exist. Some remaining issues on the use of imatinib in children are plasma levels, the impact on early molecular response on the outcome, reduced adherence, fertility, and discontinuation of imatinib in children with undetectable BCR-ABL.

Dr Millot then presented current studies on discontinuation of imatinib in pediatric CML patients with sustained complete molecular response. Between 11% and 25% of children in pediatric prospective trials on pediatric CML in chronic phase discontinued imatinib due to unsatisfactory therapeutic effects. With the STOPIMAPED study, these children can now be offered second generation TKI inhibitors, such as Dasatinib and Nilotinib. However, this is only possible for children above 15 years of age, and within a prospective clinical trial.

To conclude, Dr Millot gave a list of pros and cons regarding hematopoietic stem cell transplantation for pediatric patients in chronic phase, which was presented as being a third-line treatment option.

A panel of experts and parents discussed topics like adherence, overprotection by parents, and the use of adherence as a manipulative tool by adolescents towards their parents. Many of these linked back to the question of whether children with CML need extra psychological support.

Adherence seems more of an issue in young adults, as they are in a moment of life that floats between dependence and independence from the parents. Anything that the adolescent does has a meaning and careful attention should be paid to it. The best way to avoid adherence becoming a tool for children to manipulate their parents is to analyze the family functioning, and see if there is any psychological pre-condition.

One of the biggest challenges of treating children and adolescents with CML may also be the parents, as these tend to over-protect. The aim is that CML patients live a normal life. However, this over-protection by parents often results in a change of living style in those children which is usually not beneficial, e.g. not going to school, not doing sports. The conclusion on this topic was that addressing this issue to parents is crucial in managing CML of children and adolescents. Cristian Neves gave a great overview of his personal experience both as a former pediatric patient and now psychologist. His main message to parents of adolescents with CML was to “give space with care”, meaning that they should pay a lot of attention to what the child does without overburdening.

**ADVOCACY SESSION #3: “MARKETPLACE OF THE REGIONS”**

This was an interactive poster session where all members could present posters on key initiatives and projects. For the first time, the world regions also presented large joint posters summarizing activities across their area. People could vote for the best poster. This year’s award was given at the end of the day to Mina Daban from LMC France.
OFF-SITE DINNER AT THE HOSPITAL DE SANT PAU

A beautiful gala was organized at the refurbished Hospital de Sant Pau. This venue occupies a privileged place in the heritage and culture of Barcelona. Its thorough renovation, which began in 2009, allowed Sant Pau to regain all its former glory, offering a unique space to all attendees, who enjoyed a wonderful meal, and the opportunity to dance and listen to a very typical Catalan music style called Rumba Catalana.

SUNDAY 3 MAY (DAY 3)

ADVOCACY-SESSION #4: ADVOCATING ON GENERICS AND FIGHTING FOR QUALITY OF CARE

Chairs: Šarūnas Narbutas, Mei Ching Ong

- Introduction: How are drugs approved and monitored? (Nicole Schröter)
- CML TKI register & Declaration on Generics (Jelena Ćugurović)
- Debate: Going from fear to action – what can advocacy do? (Pat Garcia-Gonzalez, Sandra Shaw, Jelena Ćugurović, Hari Menon)

Nicole Schröter started by explaining the drug development and approval process in the case of an innovator product. Before a new drug can be tested in humans, it must be tested in animals (pre-clinical stage). If animal testing has proved to be successful, the drug candidate enters the clinical stage (phase I, II and III), where it is tested in an increasing number of subjects. Afterwards the drug candidate moves to the approval stage, which is composed of regulatory approval and HTA. After this, post-marketing surveillance begins. It can take up to 12 years from early research to market availability. The success rate of a drug finally reaching the market is very low (about 2%), and the cost is up to 2 billion euros. Patent protection is granted for 20 or 25 years, depending on the country. During these years the originator company is granted marketing exclusivity on the market. After said period, generic companies may apply for marketing authorization of generic products, which usually takes around two years or more, depending on the country. Because development costs are small (no research!), no clinical studies are required, less marketing campaigns are necessary because the originator drug is already known to doctors, and due to increased competition, generic products can be launched at a much lower cost than the innovator product. It is important to keep in mind, however, that the standards for quality need to be the same for both, at least in the US and the EU, where generic applicants must demonstrate that their product is bioequivalent to the innovator drug (active ingredient in patients’ bloodstream is the same in both).

Nicole gave a comprehensive explanation on the definition, objectives, and role of post-marketing surveillance in monitoring the safety of a drug after it has been placed on the market (market launch), and collecting further data. Pharmacovigilance or adverse event monitoring is the core of post marketing surveillance. This is so important because 5% of all hospital admissions in the EU are due to side effects, these being the fifth most common cause of hospital deaths in Europe. Adverse events can be reported via the pharmaceutical companies, through Individual Case Safety Reports (ICSR) by companies and healthcare professionals, or via direct consumer reporting systems. Also, an overview was given on the consequences of such reporting when important new risks are uncovered. Pharmacovigilance interventions include amendments of labels or leaflets, information to the public, limitation of the use of the drug, or withdrawal from the market.

Jelena Ćugurović (Serbia) presented the CML Advocates Network’s Generics Resource & Knowledge Center: www.cmladvocates.net/generics. It lists comprehensive information on CML generics, copy drugs and substandard drugs. One of the most important components is its unofficial register of CML TKIs providing comprehensive information on five originator TKIs and 77 generic TKIs. CML advocates were called to continuously send updates to the Network about the drugs available in their countries. Jelena presented the Network’s generics toolbox, providing tips on how to advocate for good generic drugs and how to address different stakeholders. She called upon the patient community to share their experiences on how they address the generics issue, in order to make this toolbox even more useful and applicable to all regions.

Another important activity presented during the talk was the CML Advocates Network’s Declaration on Generics, which was discussed and signed off by CML patient organizations after CML Horizons 2014. The points covered in the Declaration are, first, that no generic should be given to the patient without reliable proof of the drug’s quality; second, that further comparative clinical data needs to be collected; third,
that no patient should be switched between drugs without medical reason; fourth, that if a patient is switched between drugs, this should not happen more than once a year; and fifth, that patients who have been switched need to be closely monitored afterwards.

Jelena reflected on the need to advocate for good generics, produced by reliable pharmaceutical companies. The community should focus their fight on avoiding the switch of the drug for non-medical reasons, and achieving regular monitoring for those patients who are switched. Finally, she said that the community of patient advocates has a duty of being well informed about this topic, as this is the only way of efficiently advocating for an improvement regarding the use of generics.

To conclude her talk, Jelena presented some clinical experience of CML patients in Serbia where patients were switched from Glivec to a generic product and between two generic products. In the lack of comparative clinical studies, the data demonstrated the difficulty of assessing whether a generic drug is good for the patient or not, and the danger for a patient of being switched very often due to economic decisions of the government.

Some countries such as India, Canada and some Latin American countries have already collected significant experience in using generics. In India, for example, a parallel access program for those patients who didn’t get into the GIPAP program has yielded data on comparability of some generics and innovator drugs, showing that some generics might generate the same level of response. The challenge is to know about the differences and to choose the right generic product. Canada also has a lot of experience in generics and has an established pharmacovigilance system to monitor marketed drugs. Advocates in Canada are recognized as a legitimate body that supports monitoring adverse events of any TKI. However the reporting system may suffer from double reporting (patient and doctor may report). There is a new patient registry in Quebec that looks at patients that have switched the brand of the drug they are taking.

The panel agreed that the problem doesn’t lie in the nature of generics, but may be on varying quality of the drugs, so it’s important to know the source of the active ingredient and which companies produce generics of good quality. Generation of data on generics is important to reduce anxiety in patients. Patient advocates need to play a key role here, managing that fear and monitoring generic companies and the sources of ingredients. Also, the role of patient advocates in reporting adverse events was discussed as something to be implemented in some countries in the future.

MEDICAL SESSION #4: FUTURE OUTLOOK AND FUTURE WAYS TO DO CML RESEARCH

Chairs: Giora Sharf, Jan de Jong

- Overview: Clinical Drug Development Process (Jan Geissler)
- Beyond TKIs - addressing different pathways (Arnon Nagler)
- Upcoming clinical trials (Michael Mauro)
- Summary: What is the role of CML patient groups in developing the future of CML treatment? (Giora Sharf)

Precisely because of the hope and hype around this topic, CML patient advocates need to understand the development stages of new medicines to assess how likely it is that they will ever get to the patient. Jan Geissler complemented Nicole Schröter’s earlier presentation by explaining the processes and stages of drug development in order to manage patients’ expectations on the products that are currently in the development pipeline. Of 8,000 molecule candidates, only five ever get into human clinical trials, and only one makes it to the market. During the research and development process, dosing, safety and then efficacy of drugs is tested sequentially in different phases of clinical trials.

During the phase of research and discovery, analysis is done on what a new compound could look like and how it could fit into BCR-ABL, or other targets. Then, in non-clinical development, the product is tested on animals, followed by clinical development (phases I, II and III) in humans. Phase II trials test the therapeutic effect, optimal dose, toxicity. Phase III trials (e.g. IRIS, ENESTnd, DASISION) are large multicenter comparative studies on safety and efficacy of the new medicine compared to standard medicine, with the goal of leading to market authorization. Once regulatory approval and reimbursement decisions have been taken, post-approval life-cycle management and pharmacovigilance follow (e.g. phase IV trials) to optimize therapy and collect more real-life data.

Jan reminded the audience to keep in mind the context of CML, which is still a dangerous chronic disease. Even if some people can stop treatment, what we do not know is whether they are cured or not. He also called upon the responsibility of patient
advocates to differentiate between “hope and hype”, as early-stage developments might never make it to patients. To conclude, Jan gave an overview of the CML products that are in pre-clinical, early or late clinical stage.

**Dr Arnon Nagler** gave an overview of many molecules and products that are currently in the pipeline. He explained that CML is stem-cell driven leukemia, and that TKIs provide an effective treatment against the kinase activity of BCR-ABL in mature cells in CML patients, but cannot target the sleeping stem cell population. In this sense, targeting members of key pathways modulated in leukemic stem cells in comparison to normal cells is an attractive therapy for CML.

Stem cell transplant can cure CML. However, the problem of transplant nowadays is that there is no need to transplant CML in chronic phase, so it is done mostly in patients with accelerated phase and blast crisis, where outcomes of transplants are much worse. In addition, side effects of TKIs seem to be more severe in patients that have previously been transplanted.

Dr Nagler then discussed several options for targeting the leukemic stem cell, for example for those patients who are resistant to TKI. Some examples presented by Dr Nagler were the possibility of targeting Oxidative Stress Response, since leukemic stem cells, in comparison with normal hematopoietic stem cells, are more vulnerable to free radicals. There might also be opportunities of combining Fenretinide and Imatinib. Another example is the possibility of targeting CML leukemic stem cells, such as PP2A or ADAR1. Also, there is the potential of going beyond targeting the leukemic stem cell via the microenvironment.

He then gave an overview of the ongoing trials and novel compounds with clinical experience in advanced CML. It is important to note that not all of the drugs presented by Dr Nagler will arrive at the clinical phase or be approved.

All these developments have two very different objectives; one is to do some more for those patients who do respond (eradication or silencing of stem cells); and the other one is to find a solution for patients who fail to respond to the five available TKIs.

In conclusion, even though in CML nowadays we have five effective drugs available (even if not approved in all countries), there is much more to come. So for those patients who need more than TKIs, there are several medicines in the development pipeline, and the scientific community is working to find satisfactory options for this reduced group.

Complementing Dr Nagler’s presentation on early research, **Dr Michael Mauro** talked about clinical trials being set up at the moment or in the near future. First he gave an overview of the most important questions to ask, for example, what more we can do for resistant disease, particularly for advanced phases (accelerated phase, blast crisis, acute lymphoid leukemia), or patients that have failed on Ponatinib and have exhausted available TKI options (due to intolerance or resistance). Another important question is whether we can treat CML better at the time of diagnosis. This is linked to the questions of what is the best drug, whether we can avoid side effects, and whether we can gain early molecular remission and the possibility of Treatment-Free Remission. Other important points are the possibility of harnessing the immune system better, understanding discontinuation approaches, and knowing what to do about vascular event risk.

Dr Mauro presented a very comprehensive list of trials for first-line therapy, incorporation of interferon, optimization of therapies for resistant or intolerant patients, on Treatment-free Remission, and on the ABL1 enzymatic activity.

Some potential options regarding the harnessing of the immune system further in CML and those taking into account vascular risks were also presented.

Dr Mauro concluded his talk by stating that the final answer regarding how to best treat newly diagnosed patients is not yet agreed upon. Other important concluding points were that the resistance of the disease is now less common but more complex; that there is an increased interest in immune modulation in CML; that discontinuation of TKIs is still done within clinical trials; that the vascular risk of TKI therapy needs active attention and further research.

**Giora Sharf** started by reaffirming how patient organizations can largely contribute to clinical research as driving force, co-researcher, reviewer, advisor, information provider, and research subject. The involvement can be done before research starts, by influencing public health policy and research policy; by identifying indications, therapies, patient population, gaps; by uncovering ethical and risk/benefit dilemmas; or by assessing endpoints (PFS vs OS). The involvement can also be done while the research is ongoing, by managing expectations; by helping with patient recruitment and compliance, in understanding and closing the gap regarding side-effect acceptability and reporting; and by increasing patient and public confidence in clinical research. Finally, the involvement of patient advocates can take
place after the conclusion of research, in disseminating the results; in conducting quality of life monitoring in “the field”; and in assessing the value and cost-effectiveness of a drug. At present, the CML patient community is involved in research in patient advisory boards of pharma companies, on study monitoring committees and on study advisory boards (e.g. ENESTop, DASFREE, SIMPLICITY, ENESTpath). We are involved in two Horizon 2020 EU funding proposals, and CML research groups and alliances. Giora concluded his talk by calling upon attendees to contribute to the “CML Advocates Research Workgroup” which was set up in 2014. The next steps for the CML Advocates Research Workgroup are to collect data from patients and patient advocates via surveys; to support, contribute to and influence clinical trials; and to build capacity in the CML community. Also, it is important to find out the best way of collaboration with industry (advisory boards), academic research groups, and publicly funded research projects, and to manage the community’s resources.

CLOSURE OF CML HORIZONS 2015

Giora Sharf closed the CML Horizons 2015 meeting, and thanked the speakers for their time and dedication, the sponsors for supporting the event, the Liberty team for their logistic support, as well as the outgoing Steering Committee and Nicole for their continuous support, which had made this conference a success.

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For Additional Information

- CML Advocates Network website: http://www.cmladvocates.net/
- Web streams and PDF presentations: http://www.cmladvocates.net/cmlhorizons/cmlhorizons-2015

About CML Horizons 2015 and this report

The CML Horizons 2015 conference was hosted by the non-profit Leukemia Patient Advocates Foundation, and was governed and organized by a global steering committee of CML patient advocates.

The CML Horizons Steering Committee 2013-2015 was:

- Gail Sperling (region North America)
- Bahija Gouimi (region Africa)
- Mina Daban (region Europe)
- Giora Sharf (co-founder, permanent member)
- Jan Geissler (co-founder, permanent member)
- Jana Pelouchová (co-founder, permanent member)
- Pat Garcia-Gonzalez (region Latin America)
- Zhengchen Liu (region Asia-Pacific)

Report Editor: Ananda Plate (Myeloma Patients Europe)

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Münzgraben 6, 3000 Bern, Switzerland
www.cmladvocates.net - info@cmladvocates.net