Newsletter

iCMLf International Chronic Myeloid Leukemia Foundation

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Edition 8

About the iCMLf

The International CML Foundation (iCMLf) is a Foundation established by a group of leading hematologists with a strong interest in CML. The mission of the iCMLf is to improve the outcomes for patients with CML globally. The Foundation is registered as a charitable organisation in England and Wales but its charter is global. Its aims are to foster and coordinate global clinical and research collaborations and to improve clinical practice and disease monitoring in CML, especially in emerging economic regions. Scientific advisors and national representatives spanning over 30 countries provide guidance and advice to further the aims of the iCMLf.

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Please support the iCMLf! Your donations and unrestricted grants enable us to support the opportunity for all CML patients to have the best possible outcome no matter where they live.

Dear Colleagues,

"This is the greatest scientific community one can belong to" said Professor Connie Eaves on receiving the 2013 iCMLf Rowley prize from Professor John Goldman at the 15th International CML Conference. This statement epitomises what the iCMLf aspires to. A scientific community which, working together through research, education, discussion and practical innovations, will improve global CML outcomes.

The International CML Conference, co sponsored by the iCMLf and ESH, is the ideal opportunity for this community focused on CML to come and discuss the latest innovations in therapies and research. Each year the iCMLf awards the annual Rowley prize at this meeting and this year's recipient was Dr Eaves from Toronto for her outstanding contribution to the field. Dr Eaves' opening keynote "The Stem Cell State: Embracing Complexity" set the tone of the meeting and an overview of her presentation can be found on pages 6-7.

During the international CML congress the iCMLf Directors and Advisors gathered for their annual meeting to discuss the foundation´s current and future strategies and activities. The advisors' conversation reconfirmed need for the iCMLf to continue to focus on expanding CML education worldwide. In doing so the foundation will continue to concentrate on projects for emerging regions such as the preceptorship program and the diagnostic and testing program, but will at the same time expand to a more global level launching international programs such as a new global research initiative.

Continuing to enhance and influence best practice CML management worldwide the iCMLf has now delivered over 80 clinical preceptorships, 56,000 online educational programs and 2,000 diagnostic tests have been provided to date. These results are due to the emerging regions support and partnership program, with projects dedicated to improving the management of CML in the emerging regions where this assistance is most needed. Three projects with this mandate are currently open for expressions of interest; the iCMLf Forum for Physicians from Emerging Regions will be held at ASH on December the 4th, the 2014 iCMLf Preceptorship Program is open for applications and the 2014 iCMLf Diagnosis and Testing Program is also open for grant proposals. For more information on these projects and how to apply see page 3.

The iCMLf Directors meeting in Estoril.

Part of the iCMLf's current efforts to add benefit to the CML scientific community lies in our online platform. As an example, the interactive, online clinical case discussion forum is an ideal way to seek a second opinion on a challenging CML case, or to share a case you think others could learn from. Go to *www.cml-foundation.org/caseforum* to see the latest discussions. An overview of a recent pediatric case discussion can be found on pages 9-11.

In an effort to expand the global reach of the Foundation and the magnitude of voices raising awareness of the needs of people with CML to achieve optimal outcomes, the iCMLf have opened up membership to anyone, with an interest in CML. In the words of Henry Ford, *"coming together is a beginning, staying together is progress and working together a success".* Become a member of the iCMLf, join our community and together we will continue to work towards improving outcomes for CML patients worldwide.

Your iCMLf team

The Emerging Regions Support and Partnership Program

As the iCMLf is committed to improving the quality of care for CML patients internationally, the first priority for the Foundation was to establish a support program for clinicians working in emerging economic regions. This was designed for those who may not have easy access to appropriate monitoring assays and who are likely to face difficulties in their efforts to update their knowledge and skills regarding best practice for CML patients.

The Emerging Regions Support and Partnership (ERSAP) Program is designed to address this by:

1) Providing educational opportunities that specifically address issues faced by clinicians from these regions.
2) Increasing access to CML diagnostics. Building local capacity to diagnose and monitor CML patients will increase the number of patients able to access optimal treatment.
3) Establishing supportive one-to-one relationships between key centres of excellence and clinicians in emerging economic regions who have a significant commitment to CML patients.

The ERSAP Program is regarded as the Foundation's highest priority and will remain the iCMLf's major focus of activity and fundraising over the coming years.

The story so far…

iCMLf Clinical Preceptorship Program

- 80 preceptors from 43 different countries

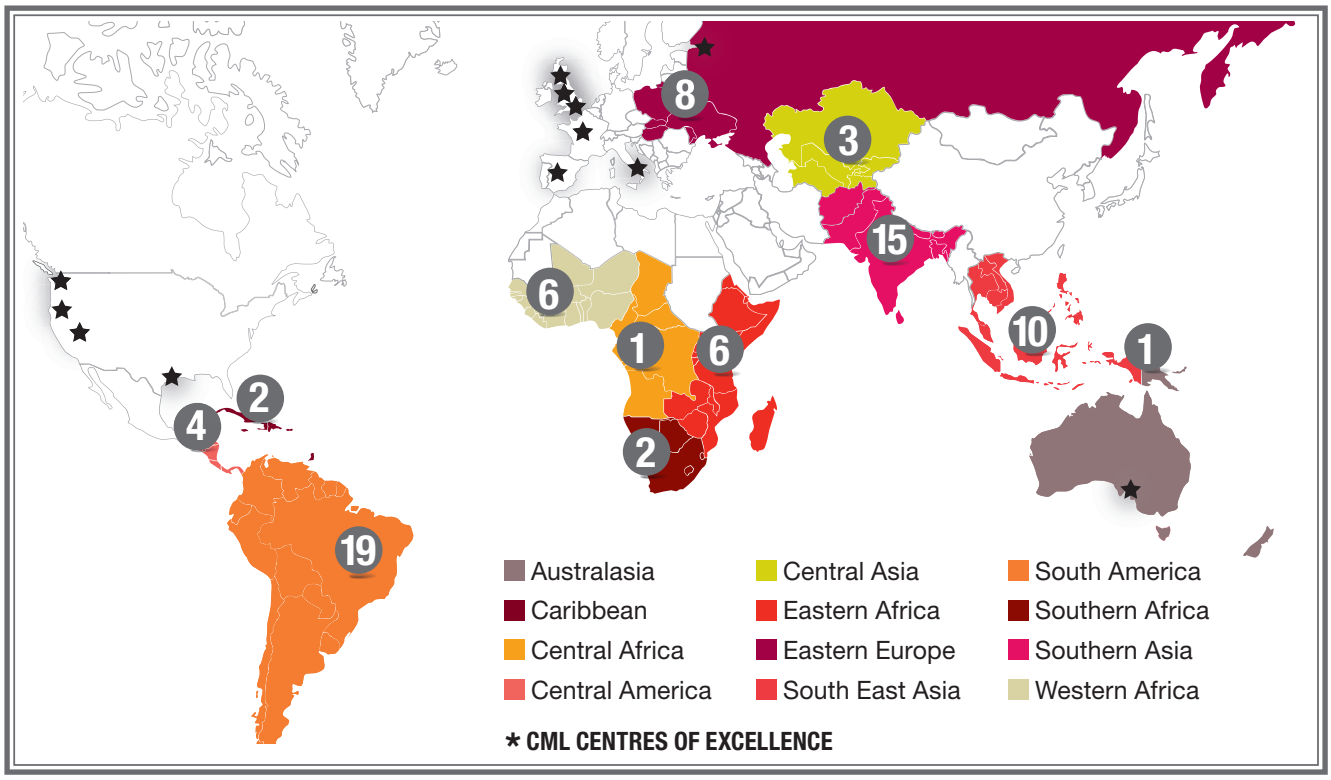
iCMLf Virtual Education Program

- Over 56,000 online education programs delivered
- English, French and Spanish modules available

iCMLf Diagnosis and Testing Program

- 2,000 diagnostic tests delivered
- GeneXpert equipment which provides bench top testing for BCR-ABL1 (the CML fusion gene) installed and operating in Uzbekistan, Honduras, Ghana, Ethiopia, Nigeria
- Building local capacity for CML analysis in India, Nepal, Ghana, Ethiopia and Uzbekistan
- Facilitating access to external CML diagnostics in Kenya, Indonesia and Philippines

Countries with attending iCMLf preceptors 2010-2013.



Each individual test gives the hematologist and patient important knowledge about the disease status. Each machine, training program, standardisation initiative, reference site set up, allows the potential for 1,000's if not 10,000's more!

Three of the ERSAP Projects are currently open for participants.

iCMLf Clinical Preceptorship Program

This program is designed for clinicians from emerging regions with a specific interest in the treatment of CML and a significant CML patient load. The program enhances clinical knowledge and skills in the treatment of CML through preceptorships at internationally renowned CML centres. The program caters for up to thirty haematologists who undertake preceptorships lasting three to four weeks.

Participants are part of the clinical team at the host site for the duration of the preceptorship, participating in seminars and laboratory work where appropriate. Preceptorships are currently held in five languages; English, French, Italian, Russian and Spanish.

Further information and an application form are available from *melissa@cml-foundation.org.* The first intake of **applications will close on 16th December 2013**. Applications received after this date will be reviewed if additional preceptorship places become available.

iCMLf Diagnosis and Testing Program

Through the Diagnosis and Testing Program the iCMLf will enhance facilities at a local level to either bring high quality testing to the patient, or to develop a low cost strategy for sending patient samples to a central reference laboratory for testing.

iCMLf Funding

Building on the success of the 2011 program, in 2014 the iCMLf grants available to increase access to CML diagnostics are as follows:

1) Phase II funding of $20,000. Previous grant awardees that have achieved outstanding results will be invited to apply this funding.
2) Phase I funding of $10,000.
    a) Previous grant awardees that have had good outcomes with their initial funds will be invited to apply for further $10,000 funding.
    b) Up to ten new proposals will be awarded iCMLf grants

All iCMLf grants will be awarded based on evaluation of submitted proposals. The proposals should clearly demonstrate how the funded activity would improve long term access to CML diagnosis and testing. Resource sustainability is an important criterion for iCMLf funding in 2014.

For further information on the iCMLf Diagnosis and Testing Grants Program in 2014, please email *nicola.evans@cml-foundation.org* or visit the iCMLf website *www.cml-foundation.org.* **Grant applications close on the 1st February 2014.**

iCMLf Sample Shipments

To help address some of the short term challenges a further Diagnosis and Testing project will be implemented. iCMLf Sample Shipments, in 2014 the iCMLf will link five centres in emerging regions with a CML centre of excellence (the reference site). The reference site will conduct free PCR analysis on samples sent by the centre and work with the centre to establish local capacity for PCR analysis within the 12 months. Support will be in the form of clinical and laboratory guidance and mentoring and potentially training. Sample shipments will be funded by the iCMLf.

There will be a call for proposals for this program in early 2014.

Dr Dorado (Philippines) and Dr Timothy (Papua New Guinea) with Professor Hughes during their preceptorships in Australia.

iCMLf Forum at ASH in New Orleans

Don't forget to join us at the 4th iCMLf Forum for Physicians from Emerging Regions. This meeting held during the annual American Society of Hematology meeting, is a unique opportunity for physicians treating CML in these regions to meet and share their experiences. Discussion is focused on the specific challenges faced treating CML with limited resources. The iCMLf experts give practical recommendations for hospitals and patients with limited access to therapies, diagnostics and even medical practitioners.

There will be three key presentations at the 2013 iCMLf Forum:

1) **Dr Lilian Pilleux, Chile** – Implementation of molecular monitoring of p210 BCR-ABL fusion transcript for CML patients at the Hospital of Valdivia, Chile.
2) **Dr Ya-Zhen Qin, China** – An efficient way for multi-centers to simultaneously derive and validate conversion factors for the conversion of BCR-ABLIS in chronic myeloid leukemia: a practice from China.
3) **Dr Benneh, Ghana –** Overcoming challenges treating CML, best practice from Ghana.

These presentations were selected by the iCMLf Directors from submitted abstracts outlining projects implemented to improve CML management. We hope by sharing these real life examples of enhanced CML care despite the challenges involved, others can learn and implement these ideas. In this way we move steadily towards improving global outcomes for all CML patients.

The iCMLf Forum for Physicians from Emerging Economic Regions is a partnership project with the MAX Foundation and we look forward to seeing you there. Contact *melissa@cml-foundation.org* for more information.

Latest updates on biology and clinical research and therapy are presented at the International Conference on CML

The 15th International Conference on CML: Biology and Therapy took place in Estoril, Portugal, from September 26-29, 2013. This leading international CML meeting was again co-sponsored by the iCMLf and the European School of Haematology (ESH). The conference, chaired by three of the iCMLf Directors; John Goldman, Jorge Cortes and Tim Hughes, focuses on the latest up-dates on biology and clinical research and current therapeutic approaches.

"This is a remarkably successful meeting that enables clinicians and scientists with a CML focus to exchange their latest findings and share emerging concepts." said Professor Tim Hughes at the meeting's conclusion.

Meeting highlights

The latest updates in therapy and research in CML were reviewed from clinical and scientific perspectives:

1) Nine different scientific sessions highlighted the latest research findings in CML.

   Topics included; molecular genetics and leukemic stem cells, molecular biology, progression to blastic transformation, and predicting and monitoring response to CML. New clinical strategies in CML, novel therapeutic approaches and immunology and immunotherapy were also discussed.
2) The new session dedicated to CML in children was well received.
3) Poster presentations including a series of poster walks were a strong focus, covering over 100 abstracts of key scientific and clinical findings.

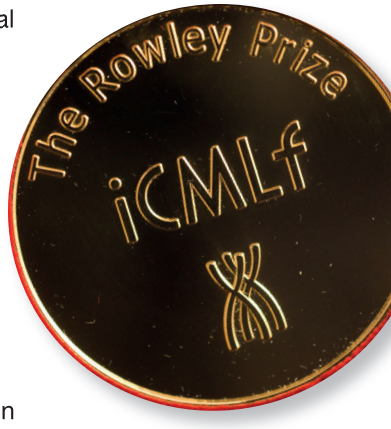
iCMLf awards 2013 Rowley Prize to Professor Connie Eaves

Named in honour of Dr Janet Rowley the iCMLf Rowley Prize is an annual award recognising outstanding work in the field of CML. The 2013 Rowley Prize awardee is Professor Connie Eaves, a distinguished scientist at the Terry Fox Laboratories in Canada.

Professor Eaves' areas of major contribution to the field of CML include:

- defining erythroid abnormalities in CML & MPN
- cell cycle dysregulation in CML
- development, refinement and clinical application of long term cultures for "purging" CML autografts
- competitive repopulation assay
- expansion of haematopoietic stem cells
- identification of quiescent stem cells in CML
- development of 'STEMCELL Technologies Inc.'

Having received her PhD in immunology from the university on Manchester, Dr Eaves worked as an Associate Professor at the university of British Colombia, as a Professor of Medical Genetics and as Deputy Director and Director at Terry Fox Laboratories. She continues to work there as a distinguished scientist.



Her current interests are in normal and leukemic stem cells, normal and malignant breast stem cells and the derivation of hemopoietic cells from human embryonic and induced pluripotent stem cells.

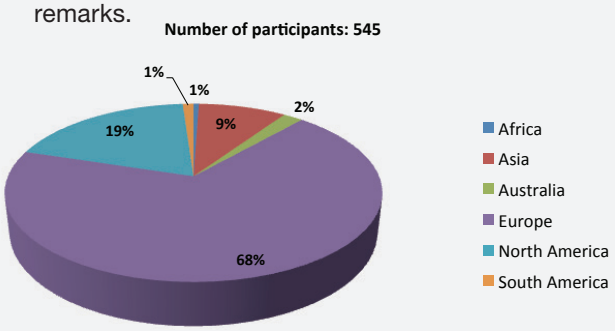
The Rowley Prize is awarded at the International CML Conference each year and the recipient presents the opening keynote lecture. After receiving her Rowley Prize medal from John Goldman, the iCMLf chairman, Professor Connie Eaves spoke about "The stem cell state: embracing complexity". A précis of her lecture can be read on the following pages.

Professor Goldman said: "Connie is a most deserving winner of the 2013 Rowley prize. No single person has contributed more in recent decades to our understanding of the biology and kinetics of CML stem and progenitor cells".

John Goldman awarding the 2013 iCMLf Rowley Prize to Dr Connie Eaves.

The scientific program also included special lectures, brief oral communications, three satellite symposia and workshops for non-clinical scientists that looked at the next generation sequencing and methods for more sensitive mutation detection.

Over 540 people from 43 different countries attended the meeting. The group of participants represents the increasing global nature of the CML scientific community: *"The number of attendees from Emerging Regions significantly increased compared to previous years",* emphasised John Goldman during his opening remarks.



Opening keynote presentation from the 2013 International CML Conference

The Stem Cell State: Embracing Complexity

Connie J Eaves

Terry Fox Laboratory

British Columbia Cancer Agency and the University of British Columbia

Studies of Chronic Myeloid Leukemia (CML) have taught us many important lessons about normal and malignant cell biology. In fact, investigations of CML have laid the very foundations of current concepts about how tissues maintain a constant output of cells throughout life. Importantly, they helped to establish the idea that the production of all blood cells is a hierarchical process that originates in a rare, self-maintaining population of undifferentiated cells.

What were the critical observations that led to these ideas? First and foremost was the discovery that CML is a disease with a singular, readily detectable, genetic basis. This allowed patients with CML to be clearly identified, and led rapidly to evidence that the chronic phase clone typically includes apparently normally differentiating blood cells of multiple lineages (not just the hyper-activated granulopoietic lineage) - implying their common origin from a deregulated multi-potent hematopoietic stem cell. In addition, early studies (in this pre-Gleevec era) revealed an important association of new chromosomal abnormalities with the inevitable progression of the disease to a more advanced and rapidly fatal acute leukemia.

These basic concepts of the hierarchical organization of normal hematopoiesis and the complex, multi-step nature of the leukemogenic process prompted us to focus on the development and use of robust methods for identifying human cells at different early stages of normal human hematopoietic cell differentiation. These biological “assays” are designed to detect the outputs of different types of mature blood cell progeny for defined periods of time under conditions that are not limiting. Initially, supportive in vitro systems were used to elicit the cell output potentialities of different cell types. More recently it has become possible to use transplanted irradiated, immunodeficient mice for the same purpose. An important feature of all of these assays is their ability to measure the clonal outputs of the relevant starting cells.

Application of these methods to samples of cells obtained from CML patients with chronic phase disease led to several seminal findings which have informed our understanding of the structure and regulation of the abnormal clone. One was the frequent detection in of an undiminished, but functionally suppressed, residual compartment of primitive normal hematopoietic cells in CML patients. This finding was clinically important because it encouraged the subsequent successful development of approaches to curing CML without the need to reconstitute the hematopoietic system from a transplant. A related finding was the very tiny number of CML stem cells present which, although mostly quiescent at any given moment, rapidly outcompete the co-existing normal stem cells to gain dominance of the system as they begin to differentiate. This unique ability of primitive CML cells may be explained by their ability to transiently activate an autocrine/paracrine IL-3/G-CSF mechanism as soon as they begin to divide. A third unexpected finding was the deficient self-renewal activity that is also a consistent feature of very primitive CML cells when they are compared to their normal counterparts tested under the same optimal stimulatory conditions.

Use of these functional methods for detecting primitive chronic phase CML cells enabled our group to also identify a series of samples in which the primitive compartments had become dominated by CML cells - even though no signs of disease progression had yet appeared. Access to these primitive CML cells made it possible to isolate them prospectively and use them to confirm growing evidence of their relative insensitivity to Gleevec and other tyrosine kinase inhibitors (TKIs) now used clinically to treat CML patients. We also characterized a number of other features of these primitive CML cells and identified several properties likely to contribute to their TKI resistance. These included a very high level of expression of the BCR-ABL fusion gene (100 times higher than the level of BCR-ABL expression in the bulk mature CML cells). We also noted an extreme genetic instability in primitive CML cells that affects the abl SH1 kinase domain in particular and is detectable even before any exposure to Gleevec. Nevertheless, for many CML patients, the future looks bright, in terms of the durable remissions they can anticipate after a few years of TKI treatment.

So what are the remaining biological challenges? A major one is the variable nature of the disease in individual patients, and hence, anticipating how each will respond to a particular therapy. Given the clonal nature of the disease we hypothesized that the variable behaviour of each CML clone is likely to be influenced in part by intrinsic causes of heterogeneity that exist within the normal hematopoietic stem cell compartment. Accordingly, we have spent some effort to first examine this latter issue. These studies have provided strong evidence of both molecular and cellular heterogeneity within the originally singular concept of the hematopoietic stem cell state. They include the discovery of subsets of hematopoietic stem cells with sustained, but not fixed, differentiation programming options, developmental changes in a specific chromatin regulatory network in hematopoietic stem cells that alter their optimally stimulated self-renewal activities, as well as differences in how external cues regulate their viability, mitogenesis and self-renewal. It thus seems likely that obtaining deeper knowledge of these mechanisms and their operation in individual CML patients may be important to identifying their response profiles and strategies for improving the treatment of those who cannot be cured with current therapies. Powerful new tools for manipulating and tracking clones of normal and leukemic human hematopoietic cells over prolonged periods in immunodeficient mice should help to accomplish this goal.

A second strategy now emerging is focused on creating advanced phase human malignancies de novo from defined normal human cell types. The appeal of this approach is the extent to which it controls variables that are not defined when “naturally arising” malignancies are studied. Specifically, de novo tumorigenesis experiments make possible an analysis in real time of how properties of particular types of starting cells change following their manipulation in a variety of defined ways. It is thus anticipated that this approach may simplify the problem of elucidating the genetic and biologic basis of key malignant properties in a sea of accumulated heterogeneity. In CML, the advantage of access to chronic phase cells makes it possible to identify specific mutations and signalling pathways that confer the features of accelerated phase and advanced stage CML in the very cells from which more aggressive subclones emerge. We have now established the feasibility of this approach and look forward to its future exploitation to accelerate our knowledge of how to eliminate remaining treatment limitations.

“The most important question now is how do we understand how to live with a clone with expressed disease?” Dr Eaves, concluding her lecture at the International CML Conference in Estoril.

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World CML Day on 9/22 - Hematologists and patient organisations around the world raise awareness of CML

World CML Day on 22nd September raises public awareness about the needs of patients living with CML. Following the motto “all united, all unique”, World CML Day reminds us that a close collaboration between scientists, clinicians and patient organisations is key to improving the outcomes for patients with CML around the world.

Dr Hemant Malhotra speaking on World CML Day.

In 2013 numerous events were organised by patients, hematologists and medical associations to recognise the day around the world.

As an example of the importance of physician events to raise awareness of optimal CML management, Dr Hemant Malhotra, Professor of Medicine and Head of Medical Oncology Division at the SMS Medical College Hospital in Jaipur and Scientific Advisor to the iCMLf, gives an overview of the local activities for World CML Day and a perspective of why this is imperative.

“CML is the commonest adult leukemia in India, being much more common than CLL and also AML. The reasons for this are unclear. Since the availability of imatinib, the leukemia and its symptoms can be controlled for prolonged periods of time in the majority of patients. The generic version of imatinib has been available in India for several years and is made and marketed by several pharmaceutical companies. Because of this competition, the costs have come down to a level that most patients are able to afford the drug. One month treatment of the CML-CP patient put on the cheapest generic imatinib in India today costs only Rs. 3000/- (USD 50). Several government institutions including my own are on the threshold of providing free imatinib to patients coming to the hospital.

CML experts, physicians, medical oncologists and hematologists, in India are now faced with a peculiar situation. Private practitioners and clinicians working at district level hospitals and clinics are initiating therapy with imatinib in patients with just leucocytosis and splenomegaly without confirming the presence of the Ph chromosome (karyotyping) or bcr/abl gene expression. As a result, a significant number of patients of non-CML, bcr/abl negative, myeloproliferative neoplasms and leukemoid reaction are unnecessarily prescribed the drug. These patients, when there is no response, are then seen by the oncologist, or hematologists. Also, monitoring of response of the disease by the unaware clinician is not done and early relapses are not picked up.

One of the priorities for the Indian oncology and hematology academic organizations is now to educate the physicians on the minimal workup required for the suspected CML patient and mandatory monitoring to be done once imatinib is initiated.

Towards this end the Indian Society of Medical and Pediatric Oncology (ISMPO) in conjunction with the iCMLf, conducted a CME Program on CML at the Jodhpur Medical College on the eve of World CML Day on 21 Sept 2013. The physicians of the city were updated on the latest advances in the management of CML by expert lectures and case-based panel discussions. More than 50 physicians participated this activity. A similar program was organized at Jaipur under the auspices of the Jaipur Branch of the Association of Physicians of India on October 26, 2013 and was attended by more than 100 physician and medicine residents.

Another initiative, which is of importance to developing countries, is the availability of reliable bcr/abl testing by RQ-PCR. Even though there are several private labs in the country conducting this test, the quality control at these labs is questionable and it is not unusual to find bcr/abl transcripts levels ‘yo-yoing’ quite significantly. Efforts are ongoing in India to establish good molecular labs at selected academic centers, which can serve as reference centers not only for testing but also for training of technicians and other lab personals. The iCMLf has taken a lead in this initiative by providing initial funding for setting up testing facilities at several institutions across the country.

The workup and management of the newly diagnosed patient of CML in India today has undergone a sea change in the past decade. However, there is still a long way to go. Oncologists and hematologists are working towards improving the care given to these patients. We will continue our effort till each and every patient of CML in India gets the appropriate work up and the best possible treatment for all stages of the disease.”

We stand together on 9/22 to recognise World CML Day and look to a future where all people with CML receive the best possible therapies and management wherever they reside.

iCMLf experts discuss challenging CML cases online

Do you have an interesting case that you think would interest the iCMLf community? Would you like a second opinion on a challenging CML case?

To share and enhance best practice management of CML, experts and interested clinicians can discuss difficult or interesting CML patient cases on the iCMLf website. Clinicians submit a brief history of the patient and the case for discussion by posting it in this forum *(www.cml-foundation.org/index.php/forumm/7-difficult-cases-in-cml)*

Each case is forwarded to the iCMLf moderators for a brief independent response. Moderators of the online iCMLf case discussion forum are members of the iCMLf scientific advisory network.

An example of a recent case and the following discussion is outlined below;

I would be very grateful for any further thoughts you may have about this young patient of mine.

Ph+ CML was diagnosed at age 2.5y. Additional abnormalities seen in the Ph+ population –Y and +8. Commenced on imatinib 340mg/m^2 and had suboptimal response, remaining at PCYR and QPCR 10% with 9 months into therapy despite and increase in dose at 6 months.

Lab did sensitivity testing and mutational analysis (neg) for us at that stage.

We commenced dasatinib at that time 60mg/m^2. Family were reluctant to consider SCT.

After 12 months dasatinib therapy QPCR 0.115%. Dose was increased 40mg daily (53mg/m^2) to 50mg daily (67mg/m^2) due to growth.

After 24 months dasatinib therapy QPCR 0.035% MMR.

After 36 months dasatinib therapy QPCR equivocal.

March 2013 QPCR 0.007%

June 2013 QPCR 0.365%

Patient has tolerated therapy reasonably well. There are no compliance concerns. Growth is somewhat slowed.

Currently on 50mg at 0.86m^2 = 58mg/m^2.

Has not had a BMA for morph and cytogenetics/FISH for some time so I will arrange this.

Does the child needs sensitivity testing and mutational analysis at this point?

Is a dose increase advisable and should SCT again be considered?

iCMLf Experts Discuss Challenging CML Cases Online ...continued

Tim Hughes – Australia

The most common cause for a rise in BCR-ABL of this type is a loss of drug compliance but I gather that you are quite confident that this is not the case. The next possibility to consider would be that this is just assay fluctuation – very unlikely with this rise but I would want to see more than one result before I was convinced of the rise. The doubling time here is short (10-20 days). In our recent publication on doubling times (Branford et al, Vol 119, 2012 Blood) this very rapid rise was associated with transformation to blast crisis OR drug cessation. By contrast most cases of resistance with mutations had doubling times of 40+ days.

So I agree a marrow examination with cytogenetics and RQ-PCR as well as a repeat mutation screen would be important at this stage.

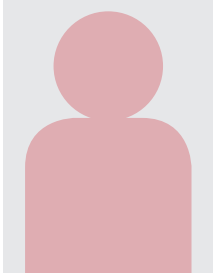
Assuming that this rise in confirmed and that no mutation or evidence of blast crisis emerges the options would be;

1. Increase dasatinib dose to >80 mg daily. Possible if his tolerance to 50 mg is very good with minimal cytopenia.
2. Switch to ponatinib. Limited experience in children and I am not sure that the compassionate program extends to children but if this is acquired resistance to dasatinib then it is more likely that he will achieve a deep and durable molecular response to ponatinib than he would achieve with higher dose dasatinib. It does have worrying toxicities though (pancreatitis and thrombotic events) so the risks are higher.
3. Proceed to an allograft – I would favour this if you can't achieve molecular control with (1) or (2).

   Sensitivity studies aren't possible unless the BCR-ABL level is >10%.

Whatever you do you should monitor response with monthly RQ-PCR to give you the earliest indication of if and when to proceed with the allograft option.

Nobuko Hijiya
– United States of America



Tim, we had a patient with Ph+ALL and T315I mutation and received ponatinib through the compassionate program. However, I am curious to know why ponatinib if it is not T315I mutation. We have a little more experience with nilotinib in children although less in younger population.

I would definitely look at mutation. If there is mutation and there is a good matched donor, HSCT would be a good option.

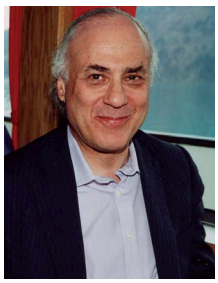
Jeff Lipton – Canada

The presenting cytogenetics were of a major concern to begin with and the response to various drugs worrisome as well. As Tim suggested, there may be some mileage with dose or drug switches, but this kid is a ticking bomb for going acute. If there is a reasonable donor available, I would strongly favor an allograft. This is probably going to be necessary at some point in the future and the results of doing this in CP1 far exceed those of doing it in advanced disease whether or not CP2 can be achieved.

Guiseppe Saglio – Italy

I agree with Tim that strict molecular monitoring is essential and it is important also to check again for the presence of mutations. If and as soon as the BCR-ABL level will be above 1%, it is important also to perform BM aspiration in order to evaluate morphology as well as cytogenetics. In case of an emergence of a dasatinib resistant clone (even at the present dose) I would take in great consideration the SCT option, as I do not believe that ponatinib at this moment is available for pediatric cases and furthermore we do not have any information on its long-term effects on growth.

John Goldman
– United Kingdom



This is certainly a challenging problem. If adherence seems not to be a problem, then I would do nothing until you have repeated the RQ-PCR (very soon) and confirmed the substntial rise you have observed between March and June. If not confirmed then probably make no changes.

If confirmed it would indeed be worth doing a marrow aspirate and KD mutation analysis. Treatment options then include ponatinib and SCT, probably in that sequence.

Jeff Lipton – Canada

Again I refer you to the presentation. 2 additional chromosome abnormalities in a child. By the German and Italian data, this child was bad risk to begin with. Regardless of the reason this is happening now, he is in trouble. Before he goes acute, the allograft is the best option. There is not data to suggest playing around with additional TKIs will help

Guiseppe Saglio – Italy

At the moment probably not, but in the future we could expect some changes. Whereas in the previous 2006 and 2009 editions, the ELN recommendations for CML treatment and monitoring were indicating the cytogenetics analysis as the main method to evaluate the response to TKI treatment of CML patients at early times points (3 and 6 months), the 2013 edition recently published suggests that a strict molecular monitoring at these time points is also highly recommended and to be performed with a standardized method of RQ PCR. This is a consequence of a number of studies that have provided evidence that a BCR-ABL level above 10% at 3 months or above 1% at 6 months is predictive of an inferior outcome in terms of PFS and of OS with a statistical significance and more predictive of a corresponding achievement of a PCyR response at 3 months or of a CCyR response at 6 months.

A) Within this context, the labs are expected to focus their efforts to standardize with great precision the detection of these levels of BCR-ABL in addition to MMR, that according to ELN 2013 recommendations still remains a step to be achieved within 12 months in order to have an optimal response. This would probably be more probably achieved using the Cepheid machine, that could indeed present several advantages with respect to the more traditional methods, like an decreased need of sample exchanges to establish the conversion factor of an individual lab and a more rapid availability of the results of the analysis, because the entire process requires only 2-3 hours. The latter is a important aspect to be considered, because the BCR-ABL level at 3 or 6 months is expected to be the basis to drive a possible change in the therapy.

B) On the other side, a great deal of attention has been recently focused of the precise definition of minimal amounts of residual disease (MR4, MR4.5 and MR5) as this could represent the basis to enroll the patients in trial leading the CML patients to treatment discontinuation. This could be ideally achieved with new methods of digital PCR, that do not need a control gene (and therefore no need of standardization) and could detect the residual copies of BCR-ABL transcripts with great precision.

Go to the iCMLf website to see more, or submit a case for the moderators.

We welcome your cases

**As a full clinical history maybe necessary for accurate comment, cases are only accepted from clinicians. Interested individuals are welcome to view and make comments on the Forum provided their qualifications are included with any comment.*

"Coming together is a beginning; keeping together is progress; working together is success."
- Henry Ford

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