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Edition 13

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.

Registered Address:

International CML Foundation
20 Eversley Road
Bexhill-on-Sea, East Sussex,
TN40 1HE - UK

info@cml-foundation.org
www.cml-foundation.org

Board of Directors:

T Hughes (Chair), J Apperley,
M Baccarani, J Cortes,
B Druker, A Hochhaus,
J Radich, C Schiffer

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,

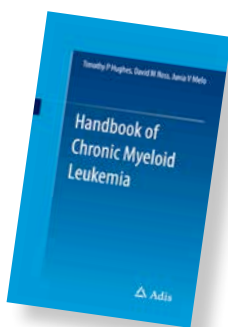
What a busy first half of the year! Welcome to all our new members and partners and thank you to all those who continue to support the efforts of the Foundation. In this newsletter we are pleased to share what we've been working on over the last six months; building on established programs, introducing new initiatives and recognising those who make outstanding contributions to improve CML management around the world.

New CML education available online

We've spent the first half of the year making major additions to the online educational content we offer. There are presentations from the iCMLf Forum for Physicians from Emerging Regions. You can view physicians from Argentina, China and India give their perspectives treating CML with generic therapies, managing paediatric CML and considerations when treating CML over the long term. Professors Michael Mauro, Jeff Lipton and Meinolf Suttorp also give their perspectives. Three modules have recently been added to the Virtual Education Program; Professor Mahon covers the latest information and data on stopping TKIs in CML, Professor Suttorp updates us on the management of children with CML and Pat Garcia-Gonzalez (CEO of the Max Foundation) shares her experiences and thoughts on the management of CML in the emerging economic regions.

This is an extensive library of up to date CML information and education. Have a look and feel free to get in touch with us at info@cml-foundation.org if there are topics you would like to see us cover in the future.

We are delighted to begin a partnership with Springer Healthcare IME this year. Firstly, to bring all our members a PDF copy of the Handbook of Chronic Myeloid Leukemia (2016) which provides a practical, concise up to date overview of the field. Secondly, to bring you monthly updates taken from the latest CML publications. You can read more about our partnership along with an example of the CML stories, 'CML treatment-free remission criteria outlined' on pages 3-5 of this newsletter.



The Emerging Regions Support and Partnership Program

Our programs in the emerging regions, bringing education to physicians and access to CML diagnostics, continue to go from strength to strength. We have 27 physicians participating in the Clinical Preceptorship Program this year, each undertaking a 3-4 week clinical observership at an international CML centre of excellence. This one to one education provides both immediate and long lasting impact for the attending clinicians. On the following page you can read some of the comments on how the program was beneficial, personally to their practice, to their centre and to their patients. The iCMLf Diagnosis and Testing Program is now open for 2016 grant applications. 10 grants of up to \$10,000 are available to support local CML diagnosis and monitoring. See the back page for application details.



Dr Ibe (Nigeria) with Professor Holyoake at the Paul O'Gorman Leukaemia Research Centre, Scotland during her iCMLf preceptorship

Prizes

It is an honour to acknowledge the work of four leaders in the field of CML in 2016. This year the iCMLf prizes are awarded to Professors John Groffen, Nora Heisterkamp (Rowley Prize), Hajop Kantarjian (Goldman Prize) and Associate Professor Susan Branford (iCMLf Prize). Read more about their work on page 6. We are privileged to work with so many dedicated physicians and partners through our programs. Without people donating their time, knowledge and resources the iCMLf would not be able to do the work we do.

We hope you enjoy this edition of the iCMLf newsletter and remember, 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



Clinical preceptorships offer long-lasting benefits

Since its inception in 2010, the iCMLf Clinical Preceptorship Program continues to enhance the knowledge of physicians treating patients with CML in emerging regions. Physicians participate in a 3-4 week intensive observership at one of 12 international CML centres of excellence. Six months after participants return to their home institution, the iCMLf seeks their feedback to understand how their acquired knowledge and skills have impacted their practice. The results of the 2015 surveys of participants have confirmed the many benefits of the program. All respondents agreed that the program was still viewed as useful 6 months after their return.

Below is an overview of the comments replying to the survey questions:

Changes implemented, or applied following the preceptorship:

- Use of TKIs instead of hydroxyurea, however, cost is the main prohibitive factor for patients
- More personal approach for new patients with many treatments started earlier
- Better and more regular monitoring, however, again, cost is the main problem
- Correlating clinical presentation of patient with the laboratory stage of disease

How have skills and knowledge learned benefited patients?:

- Increased awareness on current trends
- Better counselling has helped patient understand disease process, diagnosis, treatment and progression
- Earlier intervention in those with side effects or poor response to treatment – better able to recognise them

Sharing information with colleagues:

- All participants shared the information with their hospital team
- Many made presentations to other hospitals in their country, further extending the reach
- Information session for local GPs
- As a result, students are now interested in doing projects on CML

Plans for the next 12 months:

- Train laboratory staff to improve diagnostics
- Acquire diagnostic laboratories and provide TKIs at reduced costs
- Arrange for mutational analysis at host site
- Research on CML and cytokines
- CML treatment set up in remote area of province where currently no oncology system exists

Reported value:



clinic
(100%)



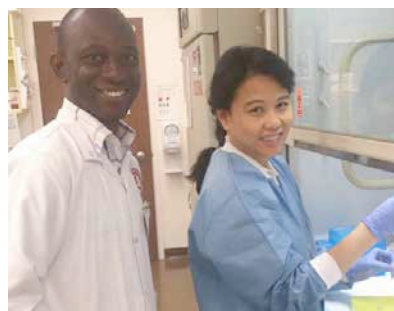
colleagues
(95%)



patients
(100%)

Perhaps one of the most beneficial outcomes of participating in the program is the valuable relationship developed with one of the world's most experienced haematologists. Four out of five participants have maintained contact with their host site lead since their return home and have reported positive outcomes from this including; sending patient samples for TKI mutation analysis, assistance with the preparation of teaching materials and diagnosis of patients with unusual presentations.

The 2017 iCMLf Clinical Preceptorship Program will open in September – please visit www.cml-foundation.org or email melissa@cml-foundation.org for information and application forms.



Dr Jalil (Ghana) at the City of Hope, USA (left)



Dr Tadesse (Ethiopia) in the laboratory at the Fred Hutchinson Cancer Research Center, USA.

“The knowledge and skills after the exposure to an advanced center has helped me in taking bold and confident decision making.”

Dr Gul, Pakistan (attended MD Anderson Cancer Center, USA in July 2015)

New iCMLf educational news services

As part of our online CML education services the iCMLf has recently launched two new resources that complement our other programs, such as the Virtual Education Program and the Clinical Case Discussion Forum.



We are pleased to partner with Springer Healthcare IME to bring you these two new independent educational services, aiming to keep you up-to-date with the latest CML information and guide you through your clinical practice.

IME

Monthly news service covering the latest clinical and scientific advances in CML

The **news service**, provided by **medwireNews** Springer Healthcare's independent news bureau, feature latest advances from key CML publications. Every month you will find three new CML stories on the iCMLf website that are based on articles published in international peer-reviewed journals such as 'Blood', 'Leukemia' or

medwireNews

'Clinical Lymphoma Myeloma and Leukemia', or conference sessions. All the articles are written by highly experienced and knowledgeable writers and contain full references, so you can easily find background information and further reading if desired. The focus is on publications related to the clinical management of CML.

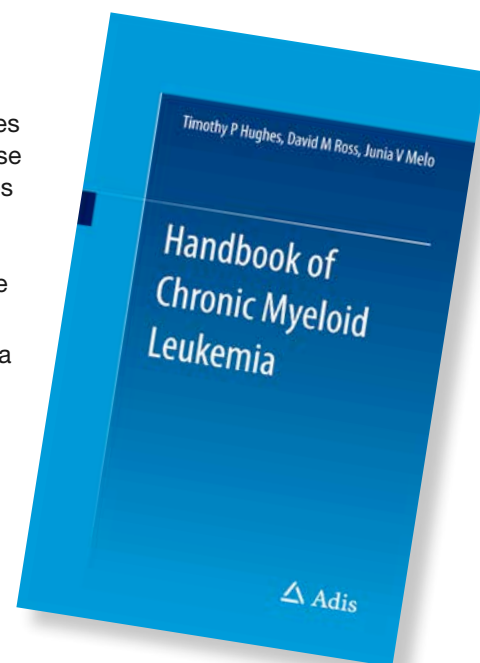
You will find the latest advances from key CML publications on the 'CML publications' page at <https://www.cml-foundation.org/index.php/science-education/scientific-news-cml-2>. You can also sign up to receive these straight to your inbox at <https://www.cml-foundation.org/index.php/about-us/publications>.

Free eBook 'Handbook of Chronic Myeloid Leukemia'

The '**Handbook of Chronic Myeloid Leukemia**' (Timothy P. Hughes, David M. Ross, Junia V. Melo, Springer Healthcare, 2016) - This practical handbook provides healthcare providers involved in the diagnosis and treatment of CML with a concise and up-to-date overview of the field of CML. The book assembles and synthesizes the latest developments and trends in the diagnosis and treatment of CML and provides summaries of the latest progress in TKI trials, the molecular monitoring of CML responses, and the development of new therapies to overcome resistance and to improve patient care.

As a unique offer from the iCMLf, in February this year, all our members received a free eBook of this handbook. If you did not receive your copy please email us at info@cml-foundation.org

We also take this opportunity to thank the authors who donated their writing fees and royalties to support the work of the iCMLf through the 'John Goldman Fund', which provides training and support to hematologists from emerging economic regions (see page 7 for more information).



We thank Novartis Oncology for an educational grant to make these independent initiatives possible

CML treatment-free remission criteria outlined

The article below is brought to you courtesy of the new iCMLf news service in partnership with medwireNews. It gives an overview of the recent perspectives article in *Blood*. Moving treatment-free remission into mainstream clinical practice in CML by Timothy P. Hughes and David M. Ross

medwireNews: Treatment-free remission (TFR) may be feasible in many patients with chronic myeloid leukaemia (CML), say researchers who set out clinical and logistical requirements for discontinuing tyrosine kinase inhibitor (TKI) therapy.

“We have proposed some criteria for patient selection and some criteria for institutional capability to supervise a TFR attempt, primarily access to timely and accurate standardized RQ-PCR [real-time quantitative reverse transcriptase polymerase chain reaction] results”, say Timothy Hughes and David Ross, from the South Australian Health & Medical Research Institute in Adelaide.

“If all of these criteria can be met, then we believe that TFR should become a routine part of clinical practice”, they write in a perspective in *Blood*, acknowledging that ensuring the laboratory technology is available is a “new challenge for the global CML community”.

The authors explain that the nine-fold increase in patients living with CML means provision of life-long TKI therapy is a “substantial and growing financial burden”, especially in countries where generic imatinib is unavailable and for patients who do not tolerate or respond to imatinib.

In addition, many patients may now experience chronic CML as a “syndrome of TKI side effects”, with those who achieve a deep molecular response (MR) often questioning whether they may stop treatment.

Several studies have successfully achieved TFR in imatinib-treated patients who had maintained an undetectable minimal residual disease (UMRD) or MR4.5 (BCR-ABL $\leq 0.0032\%$) for at least 2 years, as well as demonstrating that patients regained UMRD within 6 months of restarting treatment after UMRD loss.

And the multinational EuroSKI study is now assessing TFR in TKI users based on the less stringent criterion of MR4.0 (BCR-ABL $\leq 0.01\%$) for at least 12 months, with return to treatment on loss of a major molecular response (MMR; BCR-ABL $\leq 0.1\%$), the authors say.

In addition, the Korean Imatinib Discontinuation Study and the STIM2 study aim to determine the impact of Sokal score and imatinib response kinetics in treatment-naïve patients, removing any potential confounding from prior interferon (IFN) therapy.

The possibility of TFR in patients treated with nilotinib and dasatinib is also under investigation, with initial findings of the DADI study indicating a TFR rate of 58% for patients who switch from imatinib to dasatinib for intolerance or patient preference but around 8% for those who did not achieve an optimal response to imatinib.

Hughes and Ross emphasize that while most successful TFR patients have discontinued treatment after 5 to 8 years, with only a small proportion doing so after 3 years, it is not yet possible to conclude that a shorter duration of TKI therapy will reduce the likelihood of TFR.

They found just one known case of disease progression and death following TFR out of attempts in over 1000 patients, describing a woman who did not begin imatinib therapy until 10 years after diagnosis. She lost MMR after stopping imatinib and, although the patient responded to further treatment, she experienced blast crisis 8.5 months later.

In addition, there have been reports of imatinib withdrawal syndrome, described as persistent but self-limiting myalgia or arthralgia that can be managed with pain relief and nonsteroidal anti-inflammatory agents.

Hughes and Ross observe that the small number of patients with atypical BCR-ABL1 transcripts, or whose BCR-ABL transcript type at diagnosis is unknown, and whose MR endpoints cannot be reliably determined, are not suitable candidates for TFR.

The authors also note that patients with a history of TKI resistance should be informed they have a low likelihood of maintaining TFR, although it should not be ruled out if quality of life is adversely affected by treatment toxicity.

Table 1.

Institutional requirements for safe supervision of TFR
1. Availability of high quality internationally standardized, accurate, sensitive RQ-PCR laboratory
2. Rapid turn-around of RQ-PCR test results – within 4 weeks
3. Capacity to provide RQ-PCR tests every 4-6 weeks, when required
4. Structured follow-up established to enable rapid intervention if BCR-ABL is rising

They recommend that TKI withdrawal should be undertaken only when highly sensitive RQ-PCR testing is available to detect first signs of relapse, with monitoring at 2 to 3 month intervals required indefinitely.

“In order to minimize unnecessary anxiety it is important to explain that molecular relapse is completely different from haematological relapse, and that clinically relevant consequences of molecular relapse are rare”, the researchers add.

Future studies should focus on the role of TFR in patients undergoing combined TKI and IFN therapy; the feasibility of a second TFR attempt in patients whose initial trial results in loss of MMR but is later regained on a return to TKI therapy; and the search for biomarkers that predict the likelihood of successful TFR.

Hughes and Ross summarise that TFR research findings so far “are sufficiently reassuring that we feel comfortable in offering all eligible patients a supervised test of TKI withdrawal.”

“The optimum eligibility criteria are open to debate, but the available data suggest that should have a minimum of 12 months of deep [MR] with MR4.0 or better”, they write, albeit that such recommendations are restricted to patients with adult chronic phase CML and no history of accelerated phase or blast crisis.

“In patients who have achieved a second chronic phase we would be very reluctant to ever stop TKI outside of a clinical trial”, the authors say.

Hughes and Ross conclude: “There are still many unanswered questions concerning TFR, so eligible patients should be strongly encouraged to participate in clinical trials where possible.

“The absence of a suitable trial should not preclude a patient from stopping TKI treatment, but outside the structure of a clinical trial it would be useful to have consensus recommendations to guide those clinicians for whom TFR represents a new area of practice.”

By Lynda Williams, Senior medwireNews Reporter

medwireNews is an independent medical news service provided by Springer Healthcare Limited.

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Blood 2016; Advance online publication

Free abstract <http://www.bloodjournal.org/content/early/2016/03/24/blood-2016-01-694265>

Figure 1 Proposed criteria for patient selection

Criteria	GREEN	YELLOW	RED
Institutional criteria met (per Table 1)	Yes	-	No
Sokal score at diagnosis	Non-high	High	-
BCR-ABL transcript at diagnosis	Typical – B2A2 or B3A2	Atypical, but can be accurately quantified	Not quantifiable
CML past history	CP only	Resistance or KD mutation	Prior AP or BC
Response to first line TKI therapy	Optimal	Warning	Failure
Duration of all TKI therapy	>8 years	3-8 years	<3 years
Depth of deep molecular response	MR4.5	MR4.0	Not in MR4.0
Duration of deep molecular response monitored in a standardized laboratory	>2 years	1-2 years	<1 year

KD= kinase domain; AP= accelerated phase; BC=blast crisis

ALL GREEN lights: strong recommendation to consider TKI withdrawal

ANY YELLOW lights: only consider TKI withdrawal in high priority circumstances (e.g. significant toxicity or planned pregnancy)

ANY RED lights: TKI withdrawal not recommended except in clinical trial



iCMLf Prizes for outstanding contributions to CML management

Again in 2016, the Foundation called out to the CML community to nominate persons who made significant contributions to the understanding and management of CML. From the list of many nominations a panel of past prizewinners, iCMLf Directors and advisors have chosen the following people to recognise for their incredible achievements for patients with CML.

Recipients of the three 2016 iCMLf awards will receive their prize medals at the annual John Goldman Conference on CML in Houston in September. All winners will give a keynote lecture at the award ceremony.

You can nominate colleagues and mentors for the 2017 iCMLf Prizes by emailing nicola.evans@cml-foundation.org.

ROWLEY PRIZE - Professors Groffen and Heisterkamp

The 2016 Rowley Prize is awarded to **Professor John Groffen** and **Professor Nora Heisterkamp** to recognise their roles as co-discoverers of the fusion of the BCR and ABL genes on the Philadelphia chromosome in CML. This historical milestone of CML research led to the development of small molecules that inhibits the tyrosine kinase activity of BCR-ABL, which was the first rationally designed cancer therapeutic.

The **Rowley Prize** is designed to recognise persons who have made major contributions to the understanding of the biology of CML. Previous winners are; Brian Druker, Moshe Talpaz, John Goldman, George Daley, Connie Eaves, Owen Witte and Richard Van Etten.



GOLDMAN PRIZE - Professor Hagop Kantarjian

The 2016 Goldman Prize is awarded to **Professor Hagop Kantarjian** in recognition of his ground-breaking discoveries in his role as key clinical investigator, including the development and testing of first- and second-generation tyrosine kinase inhibitors – new targeted-therapies that significantly improved prognosis and survival in patients with CML.

The **Goldman Prize** is the clinical equivalent of the Rowley Prize recognising outstanding lifetime contributions to the management of patients with CML. Previous winners are; Rüdiger Hehlmann and Michele Baccarani.



iCMLf PRIZE - Associate Professor Susan Branford

The iCMLf has awarded the 2016 iCMLf prize to **Associate Professor Susan Branford**. This award recognises the critically important work she has performed to improve the quality and availability of reliable molecular testing for CML in the emerging regions. Her efforts have significantly impacted and improved the management of so many CML patients in these regions.

The **iCMLf Prize** was introduced as a third prize to recognise outstanding contributions to the improvement of CML treatment in the emerging economic regions. The iCMLf Prize was formally named the ERSAP (Emerging Regions Support and Partnership Prize) and was first awarded in 2015 to Pat Garcia-Gonzalez, CEO of The Max Foundation.



The iCMLf Goldman Fund - Supporting young physicians from the emerging regions

The iCMLf has established a special fund in memory of Professor John Goldman. The 'Goldman Fund' will be used specifically for the training of young CML clinicians and scientists from the emerging regions. This was something that John was passionate about.

The Goldman Fund supports young physicians to attend and present their work at the annual **John Goldman Conference on CML**.

Speakers at this premier CML meeting present the newest and often unpublished data that relate to the biology of CML and aspects of CML treatment. Using the Goldman fund to support people from the emerging regions to this meeting gives them access to the latest advances and ideas in the management of CML along with opportunities to build lasting, constructive networks with colleagues from around the world.

Scientists from Nigeria and Ukraine supported by the Goldman Fund in 2015

In 2015 two young scientists from Nigeria and Ukraine came to the meeting in Estoril and presented their work to the CML community.

Dr Adeagbo Babatunde (PhD) from Ile-Ife, Nigeria

'It was an honour for me to present my data at this well-known conference on CML following in the footsteps of so many renowned scientists and 'big names' such as Professor John Goldman'



Dr Babatunde serves as lecturer at the Faculty of Pharmacy at the Obafemi Awolowo University in Ile-Ife. He presented his poster on 'Pharmacokinetics on imatinib in Nigerians with CML' during the interactive poster walks on the biology of CML.

Dr Kostyantyn Kotlyarchuk (MD) from Lviv, Ukraine

'I have benefited greatly from the opportunity to spend four days of CML education from top lectures and have brought a lot of new ideas with me on how to further improve CML management at home'



Dr Kotlyarchuk serves as a Research Associate at the Department of Hematology at the Institute of Blood Pathology and Transfusion Medicine in Lviv. He presented his poster on 'Pregnancy in chronic myeloid leukemia – an analysis of 19 cases' during the interactive clinical poster walks.

Donate in John's memory

A special thank you to those who have already donated to the Goldman Fund. It's thanks to your contribution that the Fund comes to life supporting young physicians from the emerging regions. We appreciate every donation that allows us to bring more young scientists to the John Goldman Conference on CML over the coming years.

To donate to the iCMLf Goldman fund visit us at the 'John Goldman Fund' page at www.cml-foundation.org/index.php/about-us/john-goldman



Upcoming iCMLf activities

Apply Now!

iCMLf Diagnosis and Testing Program: 2016 grants

The iCMLf Diagnosis and Testing Program offers seeding grants to hematology institutions in emerging economic regions. The program is to facilitate diagnosis, testing and long-term disease monitoring of CML patients where it is limited, or not currently available.

Building on the success of the previous thirty-two projects awarded iCMLf grants, the Foundation will offer further funding in 2016 for ten new proposals with a funding of up to \$10,000.

Expressions of interest are welcome to melissa@cml-foundation.org.

Applications close on the 15th July 2016.

Read more www.cml-foundation.org/index.php/emerging-regions/diagnostics-program

18th Annual John Goldman Conference on **CHRONIC MYELOID LEUKAEMIA: BIOLOGY AND THERAPY** HOUSTON, TX, USA SEPTEMBER 15-18, 2016



Sessions include:

- John Goldman Prize
- Janet Rowley Prize
- iCMLf Prize
- Keynote Lectures
- Brief Oral Communications Selected From Submitted Abstracts
- Special Lectures
- Workshops for Non-Clinical Scientists
- Symposia
- Mentored Clinical and Biology Posters Walks

Chairs: J. Cortes, T. Holyoake, T. P. Hughes

To register and for further information: www.esh.org Email: pauline.jaillard@univ-paris-diderot.fr

SAVE THE DATE



Presented by the International CML Foundation and in partnership with The Max Foundation

iCMLf Forum for Physicians from Emerging Economic Regions

'Overcoming challenges treating CML'

Featuring practical innovations sharing experiences and discussion with CML experts. Held during the annual American Society of Hematology meeting.

San Diego, California Friday 2 December 2016

To register your interest and reserve your place, please email melissa@cml-foundaton.org