Newsletter

iCMLf International Chronic Myeloid Leukemia Foundation

www.CML-foundation.org –– September 2009

Welcome to the first newsletter of the newly formed International Chronic Myeloid Leukemia Foundation (ICMLF)

What is the ICMLF?

It is a Foundation established by a group of hematologists with a strong interest in CML.
Our mission is **to improve the outcomes for patients with CML globally**. We are currently registered as a charitable foundation in England and Wales but our charter is global.

What are our aims and priorities?

The aims of the International CML Foundation (ICMLF) are to foster and coordinate global clinical and research collaborations and to improve clinical practice and disease monitoring in CML. There are numerous activities that could come within this broad charter but the initial focus is to meet the needs in CML that are not already being met by other groups, particularly those needs that are best met by a global organization.

What are our guiding principles?

1. A focus on chronic myeloid leukemia and related disorders
2. A truly independent not-for-profit foundation
3. Collaboration with, but independence from, the pharmaceutical industry
4. A global foundation with broad representation from all geographic regions
5. Priorities and policies determined by hematologists and scientists involved in CML research and patient care
6. Close consultation and cooperation with CML patient groups
7. Active collaborations with key national and regional leukemia groups

The ICMLF is co-sponsor of the International Meeting on CML with the European School of Hematology being held in Bordeaux, September 11-13 2009 and will provide scientific leadership for future annual meetings (eg in Washington DC in September 2010)

Agenda-Link

ICMLF Executive:

John Goldman (Chair)
Jorge Cortes
Brian Druker
Michelle Baccarani
Timothy Hughes

Donations

The ICMLF does not receive government funding. Initially we have sought funding from the pharmaceutical industry to enable us to start our high priority programs. This funding is in the form of unrestricted grants where the money is used according to the discretion of the ICMLF without an expectation of benefit to the supporting company. We are seeking support from a broad range of company and will at all costs avoid any perceived or actual "domination" by any single Pharma company. Over the longer term we hope that fund raising from the community and from private individuals will be our main source of support.

If you would like to donate to our foundation please contact us on info@cml-foundation.org. You can choose to donate to our general fund which will help us to run the Foundation, maintain the web-site and support our general activities. There is also the opportunity to donate to support our ERSAP fund which is dedicated to the programs set out below.

The ICMLF Scientific Advisory Committee (SAC)

The SAC will be responsible for providing feedback and support at the national level for the activities of the Foundation. About 50 haematologists, scientists, nurses, and patient representatives will be invited to join the SAC.

The ICMLF Commitment to the Emerging Regions Support and Partnership (ERSAP) Program

The ICMLF is committed to improving the quality of care for CML patients internationally. We have set as one of our first priorities a support program for clinicians working in the emerging economic regions who may not have easy access to appropriate monitoring assays and are likely to face difficulties in their efforts to update their knowledge and skills regarding best practice for CML patients.

Our initial program is designed to establish a supportive relationship between international CML centres of excellence and clinicians in developing regions who have a significant commitment to CML patients.

We propose to establish a dedicated ERSAP fund to support our long term goals in the emerging regions.

ICMLF Coordinator for the ERSAP Programs

We are seeking to employ a Program Coordinator to run the Emerging Regions Support and Partnership (ERSAP) Programs. Initial programs starting in 2010 will be the Preceptorship and Partnership Programs. The successful applicant will work under the supervision of Professor John Goldman in London. Funding is currently available for this position for 12 months but ongoing support is anticipated.

Their duties would include:

- In consultation with the ICMLF executive group develop a detailed plan and funding model for the Programs
- Liaison with the executive to expand the scope of ERSAP programs as funding allows
- Actively seek funding for the ongoing activities of the ERSAP programs
- Report on the progress of the programs and making adjustments to the program as directed and as required by budgetary reviews.
- Establish contractual arrangements with the CML specialist centres running Preceptorship and Partnership programs.
- Effectively communicate the availability of the Programs to hematologists globally and promote the programs as appropriate.
- Coordinate the selection of appropriate clinicians and centres to join the Programs.
- Coordinate the clinicians preferences with the available centres and draw up a 12 month program for each CML centre
- Liaise with the CML centres to ensure the successful running of the Programs. This may require a site visit from time to time

Enquiries to info@cml-foundation.org

Two ERSAP projects we aim to open in 2010

1. Establish a Preceptorship Program for clinicians from developing regions

Program Funded with an unrestricted grant from Novartis

This program will be open to haematologists from developing countries with an interest in therapy and monitoring of CML patients. The Preceptorships will be available at designated specialist CML centres that sign up for the program. We will initially run programs at 5 international CML centres but this number can be increased if more funding becomes available. The preceptorships will be designed to provide one-on-one tuition and practical experience tailored to the needs of the applicants. The duration and nature of these training courses will vary according to the preference of the CML centre and the needs and priorities of the applicants.

The preceptorships will be open to 6 clinicians per year at each centre. They will usually run for 3-4 weeks but this is flexible. It is expected that the visiting clinicians will attend CML clinics as well as join the normal activities of the clinical team. They will be observers only. Some centres may prefer to have all 6 clinicians attend at the same time to make teaching activities more efficient while others might prefer to have 3 pairs of clinicians attending at separate times. However the program is configured, it would provide training for 30 clinicians per year.

2. Establish one-to-one partnerships between CML centres of excellence and major CML centres in developing regions.

Funding currently being sough

We propose to foster collaborative relationships between CML centres of excellence in developed regions with CML centres in developing regions. These partnerships will enable an emerging centre (or several centres working together in one region) to form a partnership with an established centre of excellence to facilitate exchange of scientists, clinicians and nurses involved in CML care, monitoring and research, to run joint clinical trials, joint data bases, share protocols, exchange samples, run joint workshops etc. The specific activities will be determined by the partners, subject to available financial support. It will be the responsibility of each partnership to agree on the annual program, which might for example include planning workshops where clinicians from both sites meet face-to-face or a series of staff exchanges.

Specific Aims

- Foster partnerships between CML centres that will become established and continue beyond the 3 year support program.
- Enable medical and scientific staff from partnering centres to undertake exchanges in partner centres and receive/provide on-site training.
- Improve understanding about the challenges confronting the emerging centres and identify the most effective assistance that can be provided
- Provide the opportunity for CML experts from the partnering centre to visit, teach and learn about the problems confronting medical staff and scientists at the regional centre
- Enable exchanges of scientific staff to facilitate training and standardisation of monitoring assays as well as fostering research collaborations
- Fund face-to-face workshops to facilitate the running of joint clinical trials and research collaborations
- Facilitate best practice for CML patients in the emerging regions.

The Rowley Prize

Dr Janet Rowley has kindly given us permission to name this new award in her honour. Dr Rowley MD is the Blum-Riese Distinguished Service Professor of Medicine, Molecular Genetics and Cell Biology and Human Genetics at the University of Chicago.

In 1973 she made a seminal discovery in CML when she used newly developed chromosome banding techniques to show that the Philadelphia chromosome is formed by a translocation between chromosomes 9 and 22.

This discovery led to the eventual identification of the fusion gene BCR-ABL and ultimately to the development of targeted inhibitors of this leukemia-specific oncoprotein. This is one of many major contributions made by Dr Rowley and her team to our understanding of the molecular biology of leukemia and other cancers. She was recently awarded the Presidential Medal of Freedom, the highest civilian honour awarded in the USA.

The Rowley Prize will be awarded each year by the ICMLF to an individual who had made an outstanding lifetime contribution to our understanding of the biology and/or to progress in treating CML.

We are very pleased to announce that the first winner of the Rowley Prize for 2009 is Dr Brian Druker.

Dr Druker is Joint Professor, Cell and Developmental Biology and JELD-WEN Chair of Leukemia Research at the Oregon Health and Science University. He is also an HHMI scholar. Dr Druker was responsible for bringing imatinib, the first tyrosine kinase inhibitor, to the clinic for patients with CML. Imatinib has transformed the lives of thousands of patients with CML. While there are many scientists and clinicians who made critical contributions to developing this drug and to clinically validating its effectiveness and safety, Dr Druker's role was indisputably fundamental. Janet Rowley was thrilled to hear that Dr Druker would be the first recipient "I admire Brian immensely and would be so honored to have him be the first recipient of a prize named after me." Dr Druker will present the Rowley Prize oration at the start of the CML meeting in Bordeaux.

Past meetings on CML – how we got to number 11 this year

The International CML meeting being held in Bordeaux is number 11 in a series that started in 1987

The characterization of the breakpoint cluster region on chromosome 22 reported by Groffen and colleagues from Rotterdam in 1984 was followed rapidly by the identification of the BCR-ABL fusion mRNA by Canaani and colleagues the following year. It seemed to many in the field that these were important starting points for unravelling more of the molecular basis of CML and so the first meeting to review all that was known of the biology of CML was convened by John Goldman and Robert Gale in Annapolis in 1987. Just 35 people attended. The BCR gene of which the original bcr formed just a small part was named at that time. As second CML meeting was held in Cape Cod in 1990 and a third meeting by organised again by Gale and Goldman along with David Baltimore on Martha's Vineyard in 1992 – a charming location selected for his summer holiday this year by the US president. The major topics at that meeting were little different from those discussed subsequently, namely molecular biology, cell biology, Ph-positive ALL and therapy.

The next CML meetings took place on the other side of the Atlantic. One was organised in Portofino by Angelo Carella and another in Jerusalem organized by Eliezer Rachmilewitz in 1996. It was very clear by that stage that interferon alfa and allotransplants were both major steps forward in treatment of CML but autotransplants with blood cells collected after chemotherapy was also becoming an attractive concept. It was at the Jerusalem meeting that we were updated with the status of the tyrphostins, which already showed some promise in their ability to inhibit the ABL kinase activity. We also had an update on the preclinical work with Ciby-Geigy compound named CGP-57148B, which also showed great promise.

The modern era started with a small meeting in Bordeaux organised by Josy Reiffers that immediately preceded a larger meeting on CML in Biarritz in 1999.

At the first of these two linked meetings we heard the first clinical results of using CBP-57148B, by now renamed STI571, for treating interferon resistant CML in CP. They excited all who heard them. The IRIS study started the following year.

The first meeting organised with help from the European School of Hematology took place in Rapallo 2000 and the ESH has been involved ever since. More recently there have been meetings dedicated to CML in Italy, France and the USA. We meet again in Bordeaux this year. Next year's meeting will take place in Washington DC from 23 to 26 September 2010, like this year under the joint auspices of the new International CML Foundation and the ESH, so make a note in your diary or Blackberry now. The plan is to continue annual meetings on one or other side of the Atlantic until all the problems of CML are solved, which may still be some years away!

Angelo Carella
Robert Gale
John Goldman

References:

Goldman JM, Grosveld G, Baltimore D, Gale RP. Chronic myelogenous leukemia – the unfolding saga. Leukemia 1990; 4: 163-167

Carella AM, Melo JV, Goldman JM. Portofino International Conference on chronic myelogenous leukemia. Exper Hematol 2001; 29: 1147-1156

CML meetings in recent years

1999 - Bordeaux & Biarritz
2000 - Portofino/Rapallo, Italy
2002 - Bordeaux, Relais de Margaux
2003 - Rapallo, Italy
2005 - Genoa, Italy
2007 - Mandelieu, France
2008 - Boston, USA

GIPAP, historical perspective and current objectives

Since early 2002, the Glivec International Patient Assistance Program (GIPAP) has provided a bridge to Glivec access for CML patients from 80 countries in Latin America, Africa, Asia Pacific and Eastern Europe. Developed and sponsored by Novartis and launched just a few months after the drug received FDA approval, the program has provided unprecedented access to state of the art treatment in so-called developing countries almost simultaneously with the Western World. As a result, for the past eight years more than 1,000 hematologists and 30,000 CML patients in developing countries have been able to benefit from access to Glivec treatment.

GIPAP operates in designated countries with program guidelines developed by Novartis in line with WHO recommendations for international drug donations. As such is serves patients who have confirmed Ph+ CML disease, following the locally approved indication. The program is administered in most countries by The Max Foundation and eligible patients must verify that they do not have reimbursement, insurance or other means to access treatment. As administrator, The Max Foundation liaises with each GIPAP physician, confirms the need and qualifications of each patient and informs Novartis of the approval. Novartis, in turn, supplies the drug on a patient-by-patient basis to each physician for a period of three months at a time.

A program of this magnitude for an oncology product in countries with stressed healthcare systems had never been implemented before and has presented unique challenges which include: issues with drug importation and control of drug distribution in-country; lack of needed resources available for treating physicians; and lack of diagnostic capabilities at the medical centers. On the patient side, poverty and distance from the qualified hematologists can affect treatment adherence.

Support systems established early on in the development of the program have served to offset some of the challenges inherent to the environment.

Some of the main medical centers in countries with large populations, such as India, are provided with clinical coordinators that support physicians in the administrative process. The Max Foundation established a network of local advocates who facilitate internet related administrative work for physicians; as well as follow patients one-on-one providing support with transportation issues and access to diagnostics among other services. Further, The Max Foundation developed a web based application that allows the team to communicate with physicians in real time to coordinate the care of each patient.

Today GIPAP continues to serve more than 20,000 CML patients some of whom have been on Glivec treatment for eight years. In many of the countries where GIPAP used to be the only means for access to treatment, new, more sustainable access models, are currently being launched in collaboration with local MOH and other local stakeholders. In several countries, newly diagnosed patients can now access services and support from formal patient organizations established by CML patient leaders; and disease management programs are being rolled out to support compliance.

GIPAP has shown that access to oncology products in developing countries can be a key factor in the development of stronger healthcare systems by showing the many benefits of early diagnosis and good treatment. Still one must pose the question, “Now what?” My response would be that it is up to all stakeholders to join in partnership and ensure sustainable access to the newest treatments, and this is where the global community will benefit from the leadership of the International CML Foundation, a meeting of the minds to further research to help patients all around the world.

Pat Garcia-Gonzalez
Executive Director
The Max Foundation

International Standardisation for *BCR-ABL* RQ-PCR in CML

How close are we to achieving the ultimate goal of global standardization for BCR-ABL measurement by RQ-PCR in CML?

Over recent years various studies have demonstrated that serial analysis of *BCR-ABL* mRNA levels by real-time quantitative PCR (RQ-PCR) accurately reflects the level of leukemic inhibition induced by therapy and provides an effective monitoring strategy for patients with CML. Since the introduction of *BCR-ABL* kinase inhibitor therapy, molecular monitoring has become particularly relevant since most *de novo* treated patients achieve a complete cytogenetic response (CCR) soon after initiating therapy. Once CCR is achieved, residual disease can be tracked at the molecular level.

The IRIS trial was the first formal demonstration of the dramatic superiority of imatinib over interferon based regimens. RQ-PCR analysis for the trial was centralised in three centres – Adelaide, London and Seattle – that used different laboratory procedures. It was observed that reproducible differences in median *BCR-ABL* values were being measured between the three centres at specific timepoints which prompted the need for an urgent alignment of their respective results. In the absence of any independent reference materials, the decision was made that each centre would measure the level of disease in a common set of 30 pretreatment samples, and that patient results would be normalised to this standardised baseline. Reanalysis of the data showed improved comparability of results between the three laboratories and the standardised baseline was used to normalise all IRIS RQ-PCR results. Thus, major molecular response (MMR) is defined as a three log reduction from the IRIS standardised baseline and not a three log reduction from pretreatment material for each case. MMR corresponds to a level of disease approximately 1 log below that at which CCR is achieved and is considered as an important therapeutic milestone.

There are a range of RQ-PCR techniques in use throughout the world and therefore variation in *BCR-ABL* levels reported by different laboratories is inevitable. Even laboratories using the same technique may report different values. Whilst this variation is not necessarily a major drawback when tracking an individual patient's response in a single centre, it does limit the accuracy with which MMR can be gauged and makes the comparison of *BCR-ABL* values between laboratories difficult. One problem for laboratories trying to establish the level representing MMR has been in the determination of an appropriate *BCR-ABL* value that represents the baseline. This is not a simple task and imprecision can occur depending on the RQ-PCR technique in use, the patients selected for analysis and the control gene that is employed to normalise results of the assay.

To overcome these difficulties an international reporting scale (IS) has been established which abolishes the requirement to determine a baseline value. The IS expresses detectable disease as a percentage and, critically, this scale is essentially identical to that used in the IRIS trial, with 100% IS defined as the standardised baseline and 0.1% IS corresponding to MMR. Over the past few years pilot studies initiated by the Adelaide laboratory have established that individual testing labs can align their reporting scale to the IS by exchange of samples and derivation of a laboratory specific conversion factor (CF). Whilst this process works well, it is not possible for a single reference laboratory to standardise all other testing laboratories in the world and the concept of regional or national reference laboratories has been developed, particularly in Europe through the European Treatment and Outcome Study (EUTOS) within the European LeukemiaNet. The aim is that selected laboratories who have established a validated CF with Adelaide can then exchange samples with other laboratories and thereby propagate traceable CFs to local centres.

Whilst the development of CFs is a major step forward, it is obvious that this approach represents a pragmatic compromise between what is desirable and what is currently achievable. Ideally, any testing laboratory should be able to readily access reference standards that enable them to convert patient results directly to the IS, provided that their assay conforms to accepted quality assurance criteria. A program to develop such reagents is well underway.

Although standardisation of *BCR-ABL* RQ-PCR testing is a complex and expensive process, we believe that it is both desirable and achievable. Our goal is to engage as many testing laboratories and clinical centres as possible in this process. The International *BCR-ABL* standardization group is open to all who are interested and meets regularly at the annual American Society of Hematology and European Hematology Association meetings. The group aims to improve the quality and comparability of *BCR-ABL* RQ-PCR testing through promulgation of the IS as well as providing a forum for presentation and discussion of other *BCR-ABL* related laboratory issues. Please contact us if you would like to be added to the mailing list.

Susan Branford (Susan.Branford@health.sa.gov.au)
Nick Cross (ncpc@soton.ac.uk)

"CML Advocates Network" fosters collaboration of patient groups world-wide, welcomes ICMLF launch

Patient groups representing rare cancers like leukaemia greatly benefit from sharing knowledge as well as collaborating with other groups and the oncology community. The CML Advocates Network, founded in 2007, is both a virtual network and an internet platform, now connecting 40 leukemia patient groups from 30 countries.

The main objectives of the "CML Advocates Network" are:

- To provide a worldwide web directory of CML patient groups, to allow patients to find national support groups in another country.
- To provide a communications platform for CML patient representatives, in order to share best practice in the field of cancer patient advocacy.
- To build a knowledge base on patient advocacy.

The network is solely run by patient groups, and is maintained without any government or industry support. This ensures its financial independence from commercial or political interests.

"We would like to help CML patient groups cooperate more closely on a global level. Our goal is to support leukemia patients to help each other across borders as well as to access news from research, trials and clinical care. Many patient organisations face similar challenges, but have different levels of experience and varying national and local health care systems. The network helps us to learn from each other, to share information and best practice", said Jan Geissler, chair of Leukämie-Online e.V.

"The CML Advocates Network has been very well received by CML groups worldwide, which underlines our core rationale of alliance building as the single most important component of effective patient advocacy on the ground", said Sandy Craine, Director of The CML Support Group (UK). The informal global network patient groups has already proven to be very effective in sharing information about progress in treatment, clinical trials, and built capacity in cancer patient advocacy. Joint work has helped create and make articles available about building a support organisation, fundraising for non-profit organisations, building strategic alliances or creating patient friendly websites. The network has run joint campaigns to improve patient access to adequate treatment in countries where substantial deficits existed.

"We very much welcome the launch of the International Chronic Myeloid Leukemia Foundation, and hope to collaborate closely to improve the outcomes for patients with CML globally", said Jan Geissler. "There is a huge potential if patient groups, researchers and clinical centers work closely together to provide the best possible information and care to patients. We warmly wish the ICMLF a successful start!"

Contact

CML Advocates Network
http://www.cmladvocates.net
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HEMATOPOIETIC STEM CELL TRANSPLANTATION IN CML

Few examples in clinical medicine demonstrate such a fascinating interaction as chronic myeloid leukemia (CML) and hematopoietic stem cell transplantation (HSCT). CML did provide first proof of principle that an incurable disease was amenable to successful treatment, that immune mediated mechanism could control a malignancy and that the risk of HSCT could be quantified by a few key factors. HSCT was nearly abandoned at the introduction of targeted therapy with imatinib. Today, it has a clear position and exemplifies the modern risk adapted approach.

The disappearance of Philadelphia chromosome in patients given intensive chemo-radio therapy and bone marrow from their syngeneic twin donors more than 30 years ago marked the beginning of a new area in the treatment of CML: it became possible to cure patients from their disease. The concept was rapidly adopted. Allogeneic HSCT became the treatment of choice for young patients with CML and a compatible donor. At the end of the century, CML was the most frequent indication for an allogeneic transplant with more than 2'000 HSCT worldwide. Imatinib changed this trend and numbers of HSCT for CML began to decline even years before the results of the first clinical trials with imatinib were published. Numbers of HSCT declined primarily for first chronic phase but remained relatively stable for advanced stages. The large number of early transplants gives clear information on the long term expectations More than 40% of the patients transplanted in first chronic phase are alive without the disease beyond 20 years after the transplant, about 20% of those transplanted in accelerated phase and about 10% of those transplanted in blast crisis. No other form of treatment has yet achieved these results and transplant results have substantially improved since. In addition, outcome is not erratic. Five key pre transplant risk factors, stage of the disease, age at the time of the transplant, time from diagnosis to transplant, donor type and donor recipient sex combination provide for a score from 0 to 7, with decreasing survival with increasing score due to increasing transplant related mortality. The predictive value of this risk score has been confirmed in several independent series, with different transplant technologies and holds for all allogeneic HSCT for a hematological malignancy.

Risk assessment can further be fine tuned by integrating additional elements, such as CMV serostatus, cytokine polymorphisms or co morbidity score. Hence, risk assessment of the transplant has become a reality. Indeed, in a recent series of the German CML study group, survival of 56 patients transplanted in first chronic phase with high risk disease and low risk donors showed a survival probability at 3 years of 90% with less than 10% transplant related mortality.

Based on these data, the new updated European Leukemia Net recommendations for the treatment of CML include this risk adapted approach and give guidance on when to search for a donor and when to proceed to a transplant. Early recognition of a failed response to imatinib is essential in order to initiate donor search and to proceed to HSCT in time. This has become even more important, since most failures occur within the first two years of treatment. HSCT is recommended for all patients in accelerated phase, blastic transformation or with T315I mutation; it is recommended for all patients who failed second line TKI therapy and for those who failed first line therapy with a low EBMT risk score. Last, HSCT might be the most cost efficient approach in some countries with limited resources.

Physicians treating patients with CML have been intensively trained in the use of imatinib and other tyrosine kinase inhibitors. It is now time to inform more in-depth patients and physicians about the modern risk adapted strategy for HSCT. Patients with failed response and optimal donor should proceed to the transplant whenever possible before transformation has occurred. Such a strategy will save lives and costs and improve overall outcome.

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