

Welcome to the third newsletter of the International Chronic Myeloid Leukemia Foundation (iCMLf)

Dear Colleagues and friends in the CML community,

The International Chronic Myeloid Leukemia Foundation (iCMLf) is now one year old and when such an important milestone is reached it is an opportunity to reflect on the past and look forward to the future.

The inaugural year for the iCMLf was one of expansion, progress and discovery.



iCMLf advisors hard at work during the first iCMLf advisory committee meeting in Washington DC.

Expansion

With the aim of improving clinical practice and disease monitoring in CML globally, the Directors (all leading haematologists with a strong interest in CML) formed the iCMLf as a not-for-profit foundation. Scientific advisors and national representatives spanning over 30 countries were engaged to foster and coordinate international clinical and research collaborations.

Progress

As the mission and goal of improving outcomes for people with CML globally clarified, the iCMLf Directors formed the strategy to begin this process, focusing on the Emerging Regions Support And Partnership (ERSAP) Program as the first key priority for the Foundation.

The ERSAP Program is the cornerstone of the iCMLf's current activities. Effective treatment for CML is available and has transformed the management and outcomes for patients in the Western world, but many patients in developing countries are unable to access treatment due to cost, or lack of facilities. Clinicians from developing countries may face challenges accessing up-to-date knowledge and skills regarding best practice for the treatment and management of patients with CML. The ERSAP projects directly address these issues and are specifically designed to support, educate and share best treatment practice for clinicians from emerging regions.

As the year progressed the ERSAP Preceptorship Program was launched and clinicians from all continents took part, benefiting greatly from this educational program - a once in a lifetime opportunity for many. An update on the ERSAP Preceptorship Program can be found on page 2.

20 members of the iCMLf advisory committees met during the iCMLf-ESH meeting in September. While brief, the meeting was a

good opportunity to discuss and move forward with key initiatives. In summary, with support from its advisory committees the iCMLf is progressing with 3 key projects in the next 6 months. These projects are designed to spread information about all aspects of managing the patient with CML throughout the world.

- 1) ERSAP Preceptorship Program - intensive preceptorships to enhance clinical knowledge and skills. Open for applications
- 2) ERSAP Virtual Education Program - expert presentations and discussion available electronically and via the iCMLf website. Launched at ASH this year.
- 3) ERSAP Diagnosis and Testing Program - increasing the testing availability in countries where PCR testing for CML diagnosis is either not available, or limited. To begin in January 2011.

The second iCMLf Rowley prize was presented during the CML meeting in Washington. This prize recognises outstanding achievements in understanding and treating CML. An excerpt of the presentation by the recipient, Professor Moshe Talpaz is on page 4.



The 2010 Rowley Prize Medal

Discovery

One of the most rewarding outcomes of the year was forging relationships and partnerships with people and organisations that have goals similar to the iCMLf. We work closely with the team at The Max Foundation on many projects and thank them for their ideas, passion and commitment. The iCMLf also thank our Premium and Major sponsors, Novartis Oncology and Ariad Pharmaceuticals along with all the other Friends of the Foundation who donate time and money. Without your support the activities of the iCMLf would not be possible.

Perhaps there was also discovery in this inaugural year of the limits of what a Foundation can achieve in year one! Walking before running is preferable. Obtaining funding in the time of the global financial crisis is challenging, and it is surprising that even in a disease area with effective treatment, how much must still be achieved to make sure that all patients around the world receive the best possible therapy and care.

And so with the idea that

"Energy and persistence conquer all things."

(Benjamin Franklin)

The iCMLf looks forward into 2011; the launch of two new ERSAP programs, forming further scientific collaborations with clinicians, researchers and nurses and continuing to make a difference for people with CML and the people who treat and care for them.

*Nicola Evans, John Goldman
Tim Hughes, Jan Geissler*

The ERSAP Preceptorship Program – providing training, education and support for clinicians from emerging regions.

The first year for the ERSAP Preceptorship Program is coming to a close and the feedback has been excellent. Clinicians from South America, Eastern Europe, Africa and Asia have taken part in these individualised preceptorships at CML centres of excellence, developing and expanding their CML management skills.

Global Sharing of CML Best Practice Management

Launched in December 2009 the Emerging Regions Support and Partnership (ERSAP) Preceptorship Program is a unique opportunity for clinicians from developing countries who treat Chronic Myeloid Leukemia (CML) to undertake an intensive educational program to enhance clinical knowledge and skills in the treatment of CML.

Clinical data for CML rapidly evolves, posing a challenge for clinicians in developing regions as to how to enhance their education and continue to provide optimal treatment and monitoring for their patients. The aim of the ERSAP Preceptorship Program is to facilitate the sharing of best practice treatment for patients with CML in the areas of the world where this is most needed.



The Adelaide ERSAP Preceptors with Professor Tim Hughes, Dr Les Lukavetsky (Ukraine), Dr Rejiv Rajendranath (India) and Dr Sharat Damodar (India)

2010- A Positive Impact

The ERSAP Preceptorship Program has been a rewarding first project for the iCMLf to implement and we continue to learn how to meet the individual needs of hematologists as they travel from such diverse countries with varying facilities. Reports from the clinicians attending the program have rated the program as exceptionally worthwhile and of great benefit to both the attendee and therefore their patients.

Preceptorships Lead to Future Support Networks

I was fortunate enough to meet four of the preceptors throughout the year and have been overwhelmed by their enthusiasm to share the knowledge gained with colleagues. All of the preceptors have discussed plans for enhancing CML management when returning home, either through increasing diagnosis, improved monitoring, or with new therapeutic protocols. The networks formed with the host laboratory teams and clinical mentors are invaluable to achieve this. This demonstrates the continued benefit and support offered through the preceptorships.

The 2011 ERSAP Preceptorship Program is now open for applications

The iCMLf is very pleased to announce that the ERSAP Preceptorship Program will continue in 2011. Up to 30 preceptorships will be held at nine internationally renowned CML centres. Again participants will be part of the clinical team at the host site for the duration of the preceptorship, undertaking seminars and laboratory work where appropriate.

Wherever possible preceptorships are coordinated with existing CML and hematology training programs. This further increases potential learning and interactions between local and visiting clinicians.

The program is open to hematologists from developing countries with a major interest in CML management. Priority will be given to those hematologists who would not normally have the opportunity to attend international hematology meetings on a regular basis. Further information about the program and the application form can be downloaded from the iCMLf [website www.cml-foundation.org](http://www.cml-foundation.org).

Applications for the program will close on the 10th December 2010. Any applications received after this date will be reviewed if additional preceptorship places become available.

If you have any questions or would like more information about the program please do not hesitate to contact me by emailing nicola.evans@cml-foundation.org.

*Nicola Evans
Emerging Regions Support
and Partnership Program Director*

*The ERSAP Preceptorship Program is supported
by an unrestricted grant from Novartis Oncology*

Report on ERSAP Preceptorship Program: Dr L. Salawu (4th to 15th October, 2010)

On behalf of myself and the department of Haematology and Blood Transfusion, Obafemi Awolowo University Teaching Hospitals Complex, Ile-Ife, Nigeria, I thank the iCMLf and its Board for giving me the opportunity to participate in this year's ERSAP Preceptorship Program at the Hammersmith Hospital's department of Haematology, London. It is a worthwhile experience for me.

Overview of Activities

I was fortunate to be at the Hammersmith Hospital at the time when the yearly "Advances in Haematology" course was to take place. My supervisor, Professor Jane Apperley, graciously permitted me to be part of this course. In addition to latest developments in Haematology, topics relating to all aspects of Chronic Myeloid Leukaemia (CML) were discussed; and this really assisted me in understanding what I observed in terms of diagnosis, management and follow-up of patients with CML at the Hammersmith Hospital.

1. Clinics: I was formally introduced to members of the department by Prof. Apperley on my first day. She then advised me to take part in all

next page

activities of the department as much as I could, particularly those relating to management of CML patients. Thereafter, we were at the CML clinic where I met with two other Consultants in her team. I was also at the clinic with these other Consultants on other clinic days (Two CML clinics per week). I also attended General Leukaemia and Myeloma clinics. In the CML Clinic, I learnt more about the use of other tyrosine kinase inhibitors (TKIs) which we are just beginning to use in Nigeria.

2. Ward Rounds: I was part of Oncology ward rounds, which is usually preceded by a discussion on the patients' progress. I also observed video conferencing in which several Consultants from different hospitals presented cases for which they needed a second opinion.

3. Consultant teaching: I attended the weekly Specialist Registrar (SR) teaching session by Consultant on specific topics which is a form of didactic lecture.

4. Slide review with SRs: I attended several morphology slide reviews with several consultants where new patients' and difficult slides were reviewed with SR. I also accompanied SRs to carry out bone marrow studies and reviewed slides with them.

5. Laboratory: On the second week of my stay, I requested that I be allowed to observe in the laboratory where molecular studies are done. There, I observed how screenings for minimal residual disease (MRD) for monitoring patients' response to therapy and mutation analysis are done.

Beneficial Aspects of the Preceptorship

I have benefited immensely from the CML clinic and the laboratory. In the CML clinic, I was able to observe the use of MRD in management of CML patients and while in the laboratory; I observed the methods of quantitation of the bcr/abl gene and mutation analysis.

Improving the Clinical part of the Program

To improve the clinical aspect of the program, I will suggest that the host Institutions should be requested to develop a specific programme of activities for the preceptors incorporating both clinical and laboratory experience, particularly as it relates to diagnosis and monitoring of CML patients, not necessarily following the departmental activities.

Benefit to my patients: This program has actually opened up a link between my Institution back home and the Hammersmith: samples of patients that needed mutation screening can be sent there, while those that can afford stem cell transplantation when indicated would be referred appropriately as these facilities are not available currently in my hospital.

Conclusion: I once again thank the iCMLf for the opportunity given me to participate in this laudable program. I would support the idea of bringing high quality testing to patients in developing countries as this would also develop the technical manpower of these countries.

ESH-iCMLf 12th International CML Meeting – CHRONIC MYELOID LEUKEMIA – Biological Basis of Therapy



Prof Goldman
convening the 12th
International CML
meeting

The iCMLf is proud to contribute to education in the field of CML in association with the European School of Hematology.

The 12th ESH-iCMLf international conference on CML took place in Washington DC on September the 24th-26th 2010.

Despite the impressive clinical results of tyrosine kinase inhibitors in the management of patients with CML, many unresolved questions remain. The annual CML meetings have become the most important international scientific event in the field and 450 scientists and clinicians attend the meeting each year.

The meeting brings together scientists with new data on the cellular, molecular and immune biology of CML, some of which may eventually translate into new therapeutic

approaches that would enable the clinician to discontinue therapy with the expectation that the leukemia would not recur. As usual this meeting received excellent reviews from attendees on the quality of data and presentations from CML specialists. (The musical interlude was also appreciated!)

Each year the iCMLf presents its annual award (Rowley Prize) to an individual who has made an outstanding lifetime contribution to the understanding of the biology and/or, progress in treating CML. This year the iCMLf Rowley prize was presented to Professor Moshe Talpaz. Dr Talpaz is Associate Chief of the Division of Hematology/Oncology at the University of Michigan Comprehensive Cancer Center. He is one of the leading clinical investigators in hematologic malignancies worldwide. Dr. Talpaz' focus is on the treatment of CML and brings special expertise in immunotherapy, cytokines and biologic response modifiers. Internationally known for his role in the development of targeted cancer therapeutics, Dr Talpaz pioneered the study of interferon in CML. As a pivotal member of the team that developed Gleevec, Dr. Talpaz was instrumental in bringing the new CML treatment to the market. As a leader in the development of novel therapeutics, Dr. Talpaz has unique experience in the building of early Phase clinical trial programs.

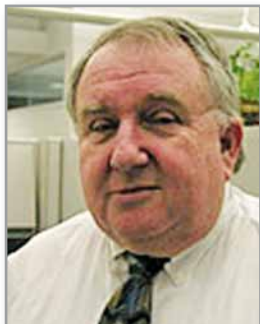
The 13th iCMLf meeting on CML will take place in Estoril, near Lisbon, Portugal on 22 to 25 September 2011. See the ESH website for more details: www.ESH.org



Prof Moshe Talpaz receiving
the Rowley Prize from iCMLf
Chairman Prof John Goldman

Insights from Clinical Research in CML

Excerpts of the Rowley Prize lecture
by Professor Moshe Talpaz



Prof Moshe Talpaz the 2010
Rowley Prize recipient

First of all John thank you very much for the introduction I'd like to thank you, Jorge and Tim for, this very prestigious award and I hope that Janet Rowley can tolerate the fact that a clinical investigator here is receiving this award.

I would like to spend the next 20 mins on a talk that is heavy on speculation and light on data, but actually it's a clinical investigators take on several events in the development of therapies for CML outlining the link, or lack there of between

clinical research and translational and basic research Where we meet, where we are apart and where things look a little different from the two angles.

Prognostication of CML: Is the bench research catching up with the clinical research?

So we'll go back to 1984, Joseph Sokal, has demonstrated that using clinical parameters such as spleen size, basophilia and so forth, he was able to identify prognostic groups that have very different outcomes and we use this prognostic model until today.

And what about today? Jerry Radich is identifying several factors associated with disease progression still preceding the blast crisis and accelerated phase, but I would say, and he will forgive me, that there is still a long way to go in understanding the underpinning of disease progression in CML. There are many many variables we don't know which are associated with this progression. You realise that chronic phase accelerated phase and blast crisis are highly schematic, in reality this is an evolutionary process that goes continuously and we don't have the molecular parameters that predict the evolution of the disease.

Normal Hematopoiesis in CML: When Bench and Clinical Research Meet.

This is an interesting story. We all go with the notion that cytogenetic response is a given, but in the 80's there was the notion that there was no normal stem cell in the bone marrow of CML.

The first one to observe these normal stem cells was Connie Eaves and her team in a series of publications between 1980 and 1984, demonstrating in in-vivo culture, that over time the normal cells prevail whereas the malignant clone subsides and dies out. So normal cells are present in CML.

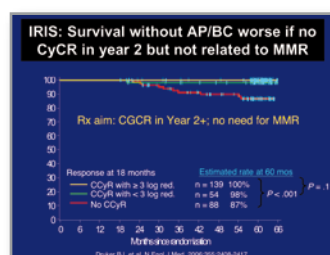
The clinical work that followed this observation was done at the same time when we demonstrated for the first time the selective effect of an agent, interferon, which was able to restore normal hematopoiesis over malignant hematopoiesis. However is the story complete?

» Normal hematopoiesis cannot be recovered in all patients, so it is not a panacea. Not all patients have a reserve of normal stem cells.

- » The likelihood of complete cytogenetic response (CCR) declines with increased disease duration and our ability to restore normal hematopoiesis is declining so our interpretation of cytogenetic resistance is sometimes nothing to do with resistance. It has to do with the fact that there is no pool of normal cells and you cannot restore them
- » The complexity of defects in normal hematopoiesis are not well studied in CML.

The Enigma of Complete Cytogenetic Remission

CCR is really not what you would call a deep remission - it requires 1 to 2 log reduction in the pool of the disease. However it turns out that CCR is an excellent discriminatory element for the patient, between doing well and not doing so well.

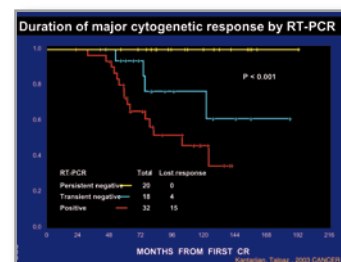


Here is the story on Glivec the IRIS Study as summarised by Brian Druker. This landmark analysis at 2 years shows that the projected outlook for patients that had major molecular response (MMR) and CCR without MMR doesn't differ so much.

This is also supported in a way by Tim Hughes, showing that patients that had 0.1 to 1% disease do virtually the same as patients with less disease. So what is going on about this 1% to 5% disease these patients do so well and patients with deeper responses don't do much better. Its most probably the story of CML is not simply de-bulking and quality, or depth of remission something again more complex. We are using drugs that change the balance between normal and malignant hematopoiesis. Is it the normal hematopoiesis that is now taking shape and governing the disease? I am just raising a series of speculations, don't relate to it simply as a quantitative phenomenon.

The Cure of CML: Is it Possible with Existing Therapies?

This is again the slide from Hagop Kantarjian and my work in 2003 and this is taking about 70 patients in whom treatment was interrupted, not continued. They got CCR, at the time we didn't have quantitative PCR, so it was CCR, treatment was interrupted and this is their fate. Patients that sustained remission by PCR did extremely well. 20 out of 20 patients did not progress off therapy. Patients that had transient PCR negativity had the risk of relapse although not huge, whereas patients who were constantly positive were at constant risk of relapse. Never the less if you look at the data you will see that about 50 patients



next page

have sustained remission (this is out of about 500 patients that were analysed) I calculated at the time 7.8% of the patients who were treated with interferon (in our hands, it is probably a lower number in the real world) have sustained and maintained complete remission. Is this equal to cure?

But here is a more complex story, in a study of 7 patients who were PCR negative and we studied their colonies and when we did PCR on the colonies it turned out that the colonies were positive. These patients were off therapy and they did not relapse. So what is going on here? I called it sustained remission induced by tumour dormancy, well clinically it is tumour dormancy. There is residual disease but it doesn't come back.

The last point of this is do not use the word cure. The argument is the disease can come back and this is what happened. 20 years later 2 patients, 15 years at least without treatment, relapsed, one in accelerated phase and one in blast crisis.

Here is the phenomenon of relapse without therapy many years later that the solid tumour guys see in melanoma, sometimes in breast cancer. This is the clone that is sitting there, it is dormant but it may make a comeback. So the cure and not cure in all of this are intertwined in an interesting story.

Francois Mahon in a French study took 69 patients who were treated with imatinib, achieved sustained CMR and treatment was interrupted. The longest follow up now is 42 months or so. Beyond the 7 months patients did not relapse. (Actually one patient relapsed later, but only one of the many patients). And 40 or 39% of the patients have sustained unmaintained remissions without relapse. That is an interesting piece of data the same phenomenon that happened with interferon happened with imatinib.

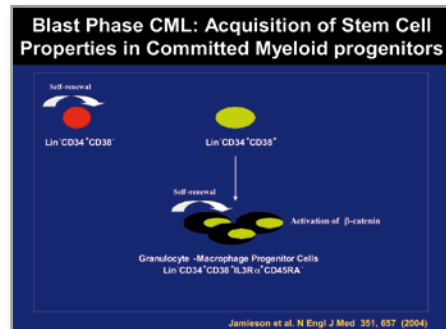
What governs this response? Why does it happen? We have no idea at this point. But the fact is it happens and the question is how do we push it to the next level?

Disease Evolution in CML: Which Cell is the Culprit?

And here I want to take credit. I came up with this concept and I need some witnesses to prove it, totally separate from the research work that was going on at the same time. This is a clinical observation and as a clinical observation it will have flaws it is not fully accurate and it doesn't deal with specific cells, but it has the following speculation.

The yellow bar represents the risk of progression (well actually the risk of death) on hydroxyurea. The orange bar represents the risk of progression on imatinib. What has imatinib done? It allowed us to live with the disease by reducing the risk of progression to a trickle. How does it do it? Does it eliminate the disease? We have already shown data that it does not eliminate the disease.

Here is the work from Catriona Jamieson published in 2004 showing the flexibility of the CML myeloid progenitor. The CD 34+, 38+, the dual positive cell, through activation of the B-catenin pathway, the Wnt pathway, can acquire stem cell properties. In other words the flexibility of the stem cell shows that the blast crisis stem cell is a different cell than the original stem cell, again this is the committed cell. I speculated on this based on a clinical observation that Gleevec doesn't cure, yet the disease doesn't progress – something has to explain it.



Is the development of BCR-ABL a random event? Is it the result of preceding unstable bone marrow, or is it both?

Several publications have been presented on hematopoiesis that is Philadelphia negative yet cytogenetic abnormalities start to appear in patients who are in CCR.

Publications from Bumm (2003) and Cortes (2003) show that anywhere from 6 to 15% of the patients do have novel cytogenetic abnormalities without the Philadelphia chromosome and you have changes like the +8 chromosome, -Y, deletion in 20q, -7 and so forth. Typically they are non-random changes, clustering in specific groups that we see in MDS and other hematologic malignancies.

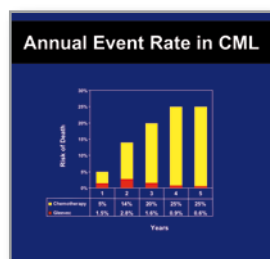
A few additional anecdotes; I have two patients that have the Philadelphia chromosome plus deletions in 5 and deletion in 7 and I said high risk CML, this is clonal evolution, very bad symptoms. We treated them and the Philadelphia chromosome went into complete cytogenetic remission but the -5 and -7 remained.

We are seeing increasing cases which are JAK 2+, BCR-ABL+. I have 3 such patients. In all three of my patients the dominant disease is the JAK 2 + disease. The BCR-ABL disease is marginal. We treat these patients with imatinib. Clinically they don't respond, but the BCR-ABL clone is disappearing, which means again the JAK 2 disease is the dominant disease and BCR-ABL appeared, at least in some cases develops, on a background of unstable bone marrow, which is another basis for research.

It's like archaeological digging, we have brought the disease back to the preclinical phase and it presents for us an excellent opportunity to study the hematopoiesis.

Thank you

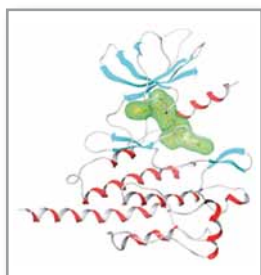
This article contains excerpts from the lecture given on the 24th September 2010 at the iCMLf – ESH 12th International CML Conference: CHRONIC MYELOID LEUKAEMIA - Biological Basis of Therapy. A webcast of the full lecture will be available on www.esh.org



The speculation is the following: What is the source of disease evolution in CML? Is it really in the pluripotent stem cell, or is it more likely focused on the committed myeloid progenitors?

I speculated that the disease progresses through genetic instability in the committed progenitor cells. It's a little off kind of speculation so what is the support for it?

Ponatinib: promising early results with one of the next generation of tyrosine kinase inhibitors



Ponatinib (AP24534) is a potent, orally active, multi-targeted TKI specifically designed to avoid the interaction with the side chain of T315, which hinders the activity of imatinib, nilotinib, and dasatinib against this mutant. Ponatinib not only inhibits native (IC₅₀ 0.37 nM) and T315I (IC₅₀ 2.0 nM) ABL1 kinases, but also other ABL1 mutant isoforms known to confer high levels of resistance to clinically available TKIs, SFKs, VEGFR, fibroblast

growth factor receptor 1 (FGFR1), and PDGFR receptor tyrosine kinases, but not Aurora kinases. In vitro mutagenesis assays demonstrated the ability of ponatinib to suppress the emergence of all known resistant BCR-ABL mutants at clinically achievable dosages. Treatment with ponatinib, but not dasatinib, prolonged survival of mice injected intravenously with Ba/F3 cells expressing BCR-ABL1 T315I.

A phase I study, ponatinib was administered orally at doses of 2, 4, 8, 15, 30, 45 and 60 mg daily to 57 patients: 50 with CML (39 in CP, 6 in AP, and 5 in BP), 3 with Ph+ALL, 2 with myelofibrosis, 1 with MDS, and 1 with multiple myeloma. Of the 53 patients with Ph+ leukemia, 74% had BCR-ABL1 mutations, 94% had failed at least 2 TKIs, and 66% had failed at least 3 TKIs. Among the 12 evaluable patients treated at the highest dose tested (60 mg/d), 4 developed pancreatic toxicity, which constituted the DLT. The most frequently encountered

treatment-related toxicities (any grade) were thrombocytopenia (25%), anemia (12%) elevation of lipase (12%), nausea (12%), rash (12%) arthralgia (11%), fatigue (11%) and pancreatitis (11%). The most important grade 3-4 treatment-related non-hematologic toxicities were elevation of lipase (7%), elevation of amylase (4%) and pancreatitis (4%). Doses over 15 mg/d rendered plasma concentrations over 40 nM consistently. This is important because these concentrations are above the IC₅₀ values for all mutants tested and have been shown to suppress the emergence of all mutants in in vitro induced mutagenesis assays. The CHR rate was 85% in patients with CML CP and the major hematologic response for patients with advanced disease CML or Ph+ALL was 42%. The overall MCyR rate among patients with Ph+ leukemia was 39%, being 46% among patients with CML CP (31% CCyR) and 25% among those with advanced phase CML or Ph+ALL (8% CCyR). When considering only the 17 evaluable patients carrying the T315I mutation, the overall MCyR was 53% (67% for patients in CP). These results, while preliminary, are remarkable and suggest that AP24534 may offer an important treatment option for patients with multi-refractory CML.

A multicenter, international, pivotal Phase II study has recently been initiated for patients in all CML phases.

Full references are available on request.

Jorge Cortes, MD

*Department of Leukemia, The University of Texas,
MD Anderson Cancer Center*

Launching the iCMLf Virtual Education Program

The iCMLf in partnership with The Max Foundation, has developed a Virtual Education Program targeted for physicians managing CML in emerging regions. The Virtual Education Program offers a series of webcast presentations with leading hematologists, as well as an interview with a key opinion leader on the practical aspects of the management of CML.

These presentations provide updated information on treatment advances and best practice in the management of CML, including disease monitoring and new therapies. The sessions specifically address issues of CML care in countries with limited access to monitoring and supplemental treatments.

The Virtual Education Program will be launched during ASH 2010 at a networking meeting for physicians to be held on Saturday, December 4, 2010. Physician attendees to the meeting will have the opportunity to engage in small group discussion with Directors of the iCMLf including Prof John Goldman and Prof Tim Hughes on the challenges and solutions of treating CML in emerging regions, and will receive a copy of the Virtual Education Program on a flash drive. For more information please email info@cml-foundation.org

**Remember the 2011 ERSAP
Preceptorship Applications close
on 10th December 2010.**

**Go to www.cml-foundation.org/projects/ersap-preceptorships to find out more
and download the application form.**



Presented by the International CML Foundation (iCMLf)
in partnership with The Max Foundation



iCMLf Virtual Educational Program Launch

"CML Management in Emerging Regions"

A networking and small group discussion forum with the Directors of the iCMLf including Prof John Goldman and Prof Tim Hughes, on the challenges and solutions of treating CML in emerging regions.

Attendees will receive the iCMLf Virtual Education Program on a flash drive, a series of presentations on best practices in the management of CML.

For physicians treating CML in emerging regions
RSVP at info@thefoundation.org
Light lunch will be served
Use ASH Shuttle from Convention Center

Saturday, December 4, 2010
11:00 a.m. to 12:30 p.m.
Rosen Shingle Creek Hotel
Sebastian Room
Orlando, Florida

Current Patient Management of Chronic Myeloid Leukemia in Latin America



LaLeukemiaNet
Latin American Leukemia Net

The development of imatinib and the second-generation tyrosine kinase inhibitors (TKIs) for the treatment of chronic myeloid leukemia (CML) has greatly improved patient outcomes, and served as important examples of the clinical benefit of targeted therapies. Imatinib is the established standard of care for initial treatment of chronic phase CML. Although most patients have a favorable outcome, some patients are initially refractory and others develop acquired resistance. Second generation TKIs provide alternative therapeutic options for CML patients who fail imatinib. With the availability of more effective therapeutic options, adequate use of therapies and proper monitoring have become increasingly important to optimise patient outcomes. The European LeukemiaNet (ELN) has provided recommendations to guide physicians on how to best treat and monitor their patients to help accomplish the best possible outcome for patients with CML. These recommendations consider the optimal management of patients under ideal circumstances that include wide availability of all therapeutic and monitoring tools.

The extent to which these recommendations are followed in practice is not known. Various factors such as economic limitations, educational differences, and availability of drugs and laboratory tests may affect the extent to which these recommendations are followed. A manuscript recently published in *Cancer* discusses a study in which a questionnaire was developed to assess Latin American physicians' self-reported CML diagnostic, treatment and monitoring strategies. The anonymous and confidential questionnaire was created by the Latin American Leukemia Net (LALNET). Physicians participated from the following countries: Brazil, Mexico, Argentina, Colombia, Venezuela, Peru, Chile, Panama, Nicaragua, El Salvador, Costa Rica, Guatemala, Honduras, Bolivia, Ecuador, and Uruguay. This article illustrates only the key points from the Latin American study and reference to the full manuscript is encouraged.

Therapeutic Management

The survey reflects the change in practice that resulted from the introduction of TKIs, with imatinib widely favored as initial therapy. 92% of respondents had access to imatinib as initial therapy and 42% have access to both second generation TKIs. 79% and 45% of physicians reported approval of the second-generation TKIs dasatinib and nilotinib in their country, respectively. While imatinib 400mg remains the choice for Latin American physicians initiating CML therapy, it is interesting that 10% of participants would treat an 80-year-old patient only with hydroxyurea, while 20% of responders would select a stem cell transplant to manage a 20-year old patient with an HLA-identical donor.

The approach to changing therapy for patients on imatinib suggested some impatience in waiting for an adequate response. Forty-two percent of responding clinicians stated they would consider a change of therapy if there was no cytogenetic response after 3 months of therapy or no complete cytogenetic response (CCyR) at

6 months. These approaches would be more aggressive than those recommended by the European LeukemiaNet.

Regarding patients meeting definitions for failure, 48% and 61% of responders indicated that their preferred course of action would be imatinib dose escalation for patients age 35 years and 50 years, respectively with less than 25% deciding to switch to a second generation TKI, perhaps reflecting the fact that second generation TKIs were not yet fully available throughout Latin America, and the cost of these agents. Among responders, 14% reported not having dasatinib and 44% did not have nilotinib available for their patients. Interestingly, change to a second generation TKI was greatly favored (80% of responders) for older patients (age over 60 years) over dose escalation. One possible explanation for this difference could be a concern about tolerability of higher dose imatinib among older patients. Of note, stem cell transplant was selected as second line therapy by very few physicians, even for the younger patients.

Monitoring Strategies

Some monitoring practices were worth noting. For example, 39% of responders indicated they would use mutational analysis at the time of diagnosis and 55% would test for BCR-ABL kinase domain mutations when managing a patient with a suboptimal response to imatinib treatment. These rates may reflect the intent more than actual practice, since most physicians indicated that they do not have direct access to mutational analysis at their institution. Interestingly, a similar US/European questionnaire by Kantarjian and colleagues reported that U.S. respondents in general were not familiar with BCR-ABL mutation tests. That survey however was done more than 3 years ago when the availability and understanding of the clinical significance of such tests was in its early days. With the broader use of second generation TKIs, this has clearly changed.

To monitor patients with CML treated with imatinib, besides complete blood counts, 72% reported routinely using cytogenetic analysis, 59% qPCR, 30% mutation analysis, and 19% FISH. Cytogenetic analyses are repeated every 6 months by 54% of participants while 31% repeat it every 3 months and 9% only annually. qRT-PCR was reported to be performed every 6 months by 41% every 3 months by 31%. Thirteen percent of participants reported never using qPCR. Mutation analysis was used by 33% of physicians when a patient lost or failed to achieve a hematological response, while 26% identified loss or failure to achieve a CCyR as the reason for performing this test. A ≥ 2 -fold rise in BCR-ABL transcript levels was identified as a reason to perform mutation analysis by 19% of participants.

In this study, a high rate of Latin American physicians (93%) reported that they preferred to conduct frequent visits with their patients to



Prof Jorge Cortes

next page

monitor for imatinib-associated toxicities. This rate was similar to the 90% of U.S. physicians and 97% of European physicians who reported a similar practice.

Economic Impact on Management

The authors discussed the impact that cost may have on treatment choice. The use of transplant has decreased significantly in recent years and nearly all patients throughout the world are offered imatinib as initial therapy. However, investigators in Mexico have published on the favorable results with their stem cell transplant approach and have emphasized the potential cost advantages of a transplant over the long-term use of imatinib. The cost of standard dose of imatinib in Latin America is similar to that in the United States, although there is great variability based on the variability in access programs available in different countries (eg, state coverage, the Gleevec International Patient Assistance Program-GIPAP, etc.). The study by Ruiz-Argüelles et al. reported that the median cost of a non-myeloablative transplant (first 100 days) in Mexico was US\$18,000, and US\$30,000 for a conventional allograft. Subsequent costs are highly variable depending on complications. In contrast, the median cost of standard-dose imatinib in that country was reported as US\$100 per day. Thus, the cost of the first 100 days of transplant would cover 180 days of imatinib. Long term comparisons of the costs would depend on the complications associated with transplant, but it was suggested that a successful transplant with no or minimal long-term complications could have an economic edge. Despite this potential advantage, there are several reasons why transplant may

not have been considered as initial therapy in more patients. These include the non-availability of donors as well as the fact that local experience with this transplant may not be as favorable as those reported in other places.

Wide availability and coverage of imatinib for all patients in need such as occurs for most patients in Brazil, Costa Rica, Panama, Uruguay, and Venezuela according to the responders from these countries would likely influence the selection of this therapy, particularly if it is perceived to be effective and non toxic. Overall, 66% of the participants answered that the majority of their CML patients received state coverage for imatinib therapy. Private insurance, organisations or charity, and self-pay accounted for the remaining 18%, 10%, and 5% of imatinib coverage, respectively.

In Conclusion

The authors concluded that the management of patients with CML frequently deviates from the recommendations published in the literature. The causes of these deviations are variable and should be investigated.

Regional economical, cultural, and other factors should be considered and integrated into guidelines that may be applicable to different areas of the world with the aim of improving the outcome of all patients with CML.

*For correspondence or reprints of the original manuscript
contact Jorge Cortes jcortes@mdanderson.org
Professor Cortes is a Director of the iCMLF*

Maximize Life Global Cancer Awareness Campaign: A call to action aimed at significantly improving the lives of people living with cancer worldwide



This October, in partnership with CML patient organizations and other cancer groups in more than 30 countries, The

Max Foundation launched a worldwide campaign to increase public awareness of the needs of people diagnosed with cancer in low and middle income countries. The campaign includes a drive to collect signatures in support of the World Cancer Declaration.

The Maximize Life Global Cancer Awareness Campaign was launched simultaneously in Seattle at the 'Light the Night' Leukemia and Lymphoma Society (LLS) event on September 25th, and in Washington D.C. at the iCMLF-European School of Hematology (ESH) CML conference from September 24th-26th. These events will be followed by awareness events in multiple locations around the world. All events will feature the opportunity for physicians, survivors and caregivers alike to show their support to cancer survivors through a Tribute Wall.

CML survivors around the world are volunteering their time and efforts to this campaign. The unprecedented access to treatment for their disease in emerging countries has inspired them to form a worldwide movement to eradicate stigma and increase resources for people diagnosed with the disease. Yet, many of people still lack access to diagnosis and monitoring of their treatment, making it difficult to

achieve optimal clinical outcomes and long term survival. The World Cancer Declaration was developed by the International Union Against Cancer (UICC), adopted by the World Cancer Summit 2008, and endorsed by the World Cancer Congress 2008. It sets 11 targets to be achieved by 2020, such as addressing inequalities in access to prevention, diagnosis and treatment; and ensuring that all countries develop a national cancer control plan.

The Max Foundation is a member of the UICC as well as the Non-Communicable Disease (NCD) Alliance. We are joining efforts with these organizations to raise awareness among public officials in preparation for the upcoming United Nations Summit on Non-Communicable Diseases to be attended by Heads of State in September 2011. This Summit will mark the first time in history that the United Nations will address cancer as a global health problem.

Visit www.themaxfoundation.org
to learn more about joining the campaign



*President of UICC Dr. Cazap,
Members of The Max Foundation
team, and UICC CEO Cary Adams
at the 2010 Congress in China*