Newsletter

iCMLf International Chronic Myeloid Leukemia Foundation

www.CML-foundation.org – April 2010

Welcome to the second 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 6 months old and it has certainly been a productive 6 months. The aim of the iCMLf is to address the challenges faced by the international CML community, be they patients, carers, clinicians, nurses or scientists. This will be through specific programs, unrestricted grants, clinical trials, education and influence.

The iCMLf Executive Committee at ASH 2009, Michele Baccarani. John Goldman, Brain Druker, Jorge Cortes, Tim Hughes.

In this capacity the Foundation was proud to launch the first Emerging Regions Support and Partnership (ERSAP) project, the ERSAP Preceptorship Program, a unique opportunity for clinicians from developing countries to undertake an intensive educational program to develop and expand their CML management skills. 28 candidates from developing countries are now enrolled and ready to begin this program.

The iCMLf is expanding fast, with the engagement of Jan Geissler (co-founder of the CML Advocates Network) as the communications coordinator based in Germany and Nicola Evans based in Australia as the ERSAP Program Director, the iCMLf has truly become an international organization. There is now a confirmed Scientific Advisory Committee (SAC) of 14 members to provide feedback and support for the activities of the Foundation. SAC member Hemant Malhotra provides an insightful overview of the treatment of CML in India on page 3 of this newsletter. To ensure global influence and representation for the iCMLf, representatives from twenty-eight countries on all continents have agreed to become national representatives of the iCMLf. Countries currently represented are: Germany, Brazil, France, Italy, India, Korea, Spain, Ireland, New Zealand, South Africa, Austria, Czech Republic, Lithuania, Serbia, Israel, China, Hong Kong, United Kingdom, Argentina, Venezuela, Holland, Canada, USA, Belgium, Sweden, Croatia, Finland, and Poland. More countries will be added as the Foundation expands. The first meeting of the SAC and National Representative Board will be held at the iCMLf/ESH meeting in Washington this year. The second Rowley prize, awarded each year by the iCMLf to an individual who has made an outstanding lifetime contribution to our understanding of the biology and/or to progress in treating CML, will also be presented during this meeting.

The mission of the iCMLf is to improve the outcome for patients with with CML globally and the ongoing activities and funding to support this were discussed at the Executive Committee meeting during ASH in December. ASH is always a frantic time and Jan Geissler conveys a comprehensive CML overview from the perspective of a CML patient (page 4).

Moving into the second half of 2010 the iCMLf plans to implement two additional ERSAP projects. The ERSAP Partnership program; in this program hospitals and clinical centres in developing regions will partner with expert CML centres to facilitate exchange of best practices and provide those centres vital support and networks. Tim Hughes outlines the aim and potential impact of the third ERSAP Project, the ERSAP Diagnosis and Testing Program on page 3. The iCMLf welcomes your input discussing this program. Register on the iCMLf website and join the conversation on www.cml-foundation.org/icmlf-forum.

These first three ERSAP programs address enhancing clinician's knowledge, sharing best practice and improving the access to diagnosis and testing facilities. It is through these programs and the future activities of the Foundation that people with CML and their supporting healthcare professionals get the knowledge, skills, therapies and equipment they need to achieve the best possible outcomes.

The iCMLf needs you!

As a charitable Foundation it is only through grants and donations that the iCMLf can positively influence the lives of patients with CML in regions where assistance is most needed. The iCMLf would really appreciate your donations to help achieve its charter.

Please contact us on info@cml-foundation.org to pledge your support.

The ERSAP Preceptorship Program - providing training, education and support for clinicians from emerging countries.

Supported by an unrestricted grant from Novartis Oncology

iCMLf launches global support and partnership program for CML

The iCMLf was proud to introduce the Emerging Regions Support and Partnership (ERSAP) Preceptorship Program at the annual meeting of the American Society of Hematology in December 2009.

This program is a unique opportunity for clinicians from developing countries who treat CML to undertake an intensive educational program to develop and expand their CML management skills.

Clinicians from developing countries may find it difficult to access up-to-date knowledge and skills regarding best practice for the treatment and management of patients with CML. The world of CML is rapidly evolving hence the challenge faced by clinicians in developing regions is how to enhance their education so they can provide optimal treatment and monitoring for 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 urgently needed.

„The improved survival in CML directly attributable to the use of tyrosine kinase inhibitors is so dramatic that these new agents must be made available to the greatest possible number of eligible patients as rapidly as possible throughout the whole world", Professor John Goldman, Chairman of the iCMLf, said.

Nicola Evans
Emerging Regions Support and Partnership Program Director

Learning through practical experience and one to one tuition

The ERSAP Preceptorship Program will enhance clinical knowledge and skills in the treatment of CML through preceptorships at internationally renowned CML centres. 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. Through this practical application of learning, clinicians attending the preceptorship have the opportunity to develop and enhance clinical knowledge to take back and share with colleagues in their country of origin.

Through one-on-one tuition and hands on experience, participants will conclude the program with a practical understanding of the latest information influencing the care of patients with CML. This will include: therapies to treat CML; efficacy, toxicity and the management of side effects, monitoring guidelines, management of resistance, the role of allograft in CML and developments in novel therapies, vaccines and drug cessation. Five specialist CML centers around the globe will each act as hosts for up to six visiting clinicians. The CML expert centers enrolled in 2010 are the Hammersmith Hospital, UK, Royal Adelaide Hospital Australia, S.Orsola-Malpighi University Hospital, Italy, MD Anderson Cancer Centre, USA and OHSU Knight Cancer Institute, USA.

Preceptorships will last for 2-4 weeks depending on the host centre.

The ERSAP Preceptorship Program would not be possible without the dedication and support of the host sites who donate their time and facilities.

"This is our first program and we are very keen to get it going in 2010 and get awareness out there that we are determined to make a difference in managing CML, not just in developed countries but all around the world.", said Professor Hughes, co-founder of the iCMLf.

The mission of the iCMLf is to improve the outcomes for patients with CML by fostering and coordinating global clinical and research collaborations and therefore improving clinical practice and disease monitoring in CML around the world. The launch of the ERSAP preceptorship project, supporting and educating 30 clinicians in 2010 sees the first step on the journey to achieve this goal.

Remarkable global response to the program.

The ERSAP Preceptorship Program has had overwhelming interest in the first 3 months after its inauguration. All program places were filled within 2 months of inception and the first preceptorship will occur in May. Clinicians will be attending from, Africa, India, Nepal, Pakistan, Papua New Guinea, South America and Eastern Europe.

Support for the program has been extensive, recognising the clear need for the increased support and education these preceptorships will provide.

It has been a rewarding first project for the iCMLf to implement and we continue to learn how to meet candidates individual needs as they travel from such diverse countries with varying facilities. For example, due to the high number of French speaking candidates applying for the program the iCMLf plan to initiate a French CML centre of excellence in 2011.

We would be interested in any comments and suggestions you may have about the ERSAP Preceptorship Program, please contact us on the iCMLf discussion forum www.cml-foundation.org/icmlf-forum.

The success of the program so far has been due to the close collaboration of The Max Foundation and I would like to thank the team there for their efforts and enthusiasm.

As all preceptorships are now filled for 2010 the iCMLf welcome further applications for the 2011 program.

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. The application form can be download from the iCMLf website www.cml-foundation.org.

Nicola Evans
Emerging Regions Support and Partnership Program Director

Diagnosis and Monitoring Response in CML: New Challenge for the iCMLf

Prof Tim Hughes

During the ASH meeting in 2009 John Goldman and I had the opportunity to meet with Pat Garcia-Gonzalez and Erin Schwartz from the Max Foundation to talk about our common interests. One of the issues that they raised was the lack of diagnostic and monitoring services for CML patients throughout many of the less developed nations. There are many CML patients who cannot access any therapy (including the GIPAP program) because they can't afford to have a diagnostic test for the disease. In addition, many patients who are able to access imatinib through the GIPAP program have little or no access to any ongoing monitoring tests to determine their response to therapy. The first sign of loss of response in these patients is often clinical evidence of acute phase disease or hematological relapse. In these settings it is usually too late to derive much benefit from second-line TKI therapy.

We would like to work towards providing diagnostic testing and ultimately disease monitoring for CML patients in developing countries. The question which we are now considering is how we could most efficiently achieve PCR testing (or FISH testing if that is appropriate in some settings) in developing regions. It may be necessary to use different strategies depending on the local conditions such as whether an established PCR laboratory is close by and whether there is local infrastructure and skilled staff that would make it realistic to consider setting up RQ-PCR testing for BCR-ABL. Possible solutions would be to (1) establish high quality testing in the patient centre (2) develop a low cost strategy for sending patient samples to a central laboratory for testing or (3) examine point of care PCR testing.

We invite your comments and suggestions. We need better understanding of the scope of this challenge, what possible solutions we should consider, and what sources of funding we could seek for this project. Please use the web-site forum or email us directly with your thoughts and suggestions. We hope you agree that this should be a very high priority for the CML Foundation.

Tim Hughes
iCMLf Executive Committee member

Chronic Myeloid Leukemia - a perspective from India

Dr. Hemant Malhotra is presently Professor of Medicine at the SMS Medical College Hospital & Head of the division of Medical Oncology at the Birla Cancer Center. The SMS Medical College Hospital is a 2000 bedded hospital, one of the leading teaching and patient care center in North India.

Prof Hemant Malhotra

India is a large country with 1.2 billion people and the population is steadily increasing. The majority of the population stays in villages (60 to 70%) and a substantial percentage are still illiterate (30 to 40%). Availability of health care is non-uniform, with medical facilities at par with the best in the world in the metros and large cities and non-existent to rudimentary in interior villages where patients are at the mercy of 'quacks' who still practice medieval medicine (see photos). Only a very small minority of patients (less than 5%) are covered by medical insurance.

Most hematologists and oncologists believe that Chronic Myeloid Leukemia (CML) is the commonest leukemia in adults in India. According to the few existing publications available from the country, age at presentation is at least a decade early as compared to the west, patients present with more advanced disease at diagnosis and have a poorer response to imatinib (possibly due to more advanced disease at presentation).

Generic imatinib is available in India (approximate monthly cost USD 100 to 200, depending on the brand) but many patients are unable to afford even this. As of February 2010, there are 12,224 patients (about 70 to 80% of all CML patients) on GIPAP (Glivec International Patient Assistance Program) Glivec which is provided without cost. Approximately 160 to 170 new applications per month are received by the MAX Foundation – the agency running the GIPAP program in India since 1991. For entry into the GIPAP program, one of the criteria is demonstration of the Ph chromosome by karyotyping or

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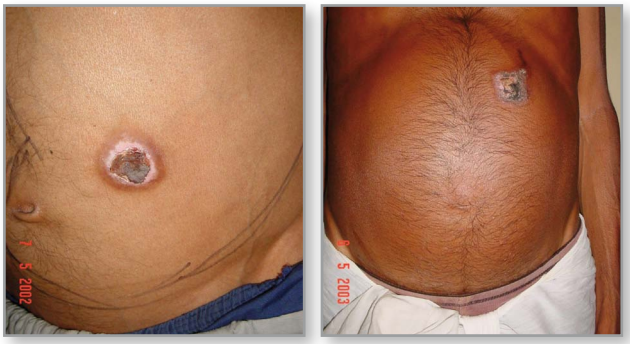
bcr/abl gene by either FISH or RT-PCR. Quite a few patients who would otherwise be candidates for free Glivec under GIPAP, are unable to afford these tests. Most patients on GIPAP Glivec and quite a few on generic imatinib are unable to get 3 or 6 monthly or even annual testing for bcr/abl gene copy numbers for response monitoring and it is quite usual for clinicians to get to know about imatinib resistance only after frank hematological relapse. Even if early molecular relapse is identified in a small subset of patients, only a tiny minority of these would be able to afford second-line treatment.

With regards to CML, priorities in India include availability of free/subsidized, standardized and reliable testing for bcr/abl at all state medical college institutions and cancer centers at diagnosis and for monitoring during therapy for all patients, kinase domain mutational testing at few referral centers and regional cancer centers and GIPAP-like support program for second line drugs (dasatinib and nilotinib). There is also a need to get together a group of clinicians, hematologists & oncologists interested in CML who could address India-specific problems, suggest and implement solutions; and direct India-specific research in the field.

The iCMLf could assist in each one of the above-mentioned priority areas.

Hemant Malhotra
iCMLf Scientific Advisory Committee member



Two middle aged patients of CML at presentation with massive splenomegaly occupying the whole of the abdomen and scars of 'branding' – burning the skin over the spleen by red-hot iron rods.

ASH 2009 Recollection a review by Jan Geissler a CML patient since 2001

***"Actually, why do I always spend the St Nicholas holiday in the US, instead of with my family"**, I asked myself when I boarded the plane to the USA on 4 Dec 2009, in anticipation of a long 16 hour trip to the USA, hiding for days in the dungeons of a large convention center. However, from a patient perspective, it was again worth it. Year by year, more than 20.000 hematologists and healthcare people attend the annual meeting of the American Society of Hematology. All top experts from the CML space are presenting their research here, competing for the hottest piece of news from clinical trials.*

Prof Druker
presenting at ASH 2009

Education Sessions

On the first day, I attended the Education Sessions, providing an overview on the current status quo of managing CML. Brian Druker, Moshe Talpaz, John Goldman and Tim Hughes presented. In the room I felt like a single BCR-ABL gene in a good molecular response – the biggest meeting room in the convention center can probably hold 10.000 people at a time -- a couple of hundred participants interested in CML almost got lost. Dr Brian Druker held a keynote, honoring the 10th anniversary of imatinib given to CML patients. A chart showing the CML survival in the pre-imatinib era again struck me. Before bone marrow transplants were introduced in the 1980s, the only way to treat CML was palliative. Today the key challenges in CML are managing resistances and relapses in those patients that do not achieve good remission, or to investigate whether stopping or less aggressively maintaining therapy in remission is feasible. Overall survival rates in early diagnosed CML are pretty close to the general population. We've come quite far, fortunately.

But we are not yet there. Some patients still become resistant or cannot tolerate the treatments, and all need to cope with a life-long CML therapy. Dr Talpaz and Dr Goldman summarized quite well where we stand in CML therapy today:

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- What we have: effective first line and second line treatment
- What could be improved: managing toxicity, improving response rate and duration, avoiding development of resistance, when to change drugs, coverage of "Archilles heel" mutations
- What is missing: T315I inhibition, elimination of the leukemic stem cells, and treatment discontinuation

I was glad to see how active the CML research community is to close these gaps.

First line CML therapy

In terms of first line therapy after diagnosis, it's been quite simple for newly diagnosed, chronic phase CML patients over the last four to five years: imatinib was the Gold Standard, with clear treatment recommendations which were recently updated. At this year's ASH, all experts seemed to refer to these criteria and recommendations on managing standard treatment, suboptimal response, treatment failure and monitoring.

Now, with the new second generation drugs striving for first line treatment, we can see a number of new options (and new questions) coming up. In the past I have always been a little suspicious about a purely commercially-driven enthusiasm for nilotinib and dasatinib becoming first-line: due to the end of the imatinib patent, or to get a larger piece of an existing huge cake. Now there seems to be first evidence at least that due to the lower progression rates in the first year of nilotinib first-line, a more powerful treatment for induction might actually make sense. Some more years are required to get more clarity. The challenge of adherence to nilotinib due to a twice daily schedule, as well as the requirement not to eat before and after taking the drug, will remain a challenge though. First-line data on dasatinib is expected to be published at EHA2010.

Along these lines I found interesting that High-Dose-imatinib in frontline even chronic phase has come off focus. The latest results from the TOPS and GIMEMA studies after 18 months seemed to have marginalized the "more-is-better" approach.

Prof Goldman also addressed initial therapies combining imatinib with familiar agents (Cytarabine, IFN, Omacetaxine, Arsenicals), or administering three TKIs in varying sequence.

Managing Resistance

Much has been published in recent months about managing resistance to imatinib. While only a relatively small proportion (15%) of patients treated in chronic phase develop a resistance or show suboptimal response, choosing the most promising follow-up treatment has been a key topic of interest. More than 100 different mutations are known today. Only a very small number, mainly the fearsome T315I mutation making up around 15% of all mutations, are resistant to dasatinib, nilotinib and bosutinib. Most other mutations can be overcome by imatinib dose increase or one of the three second line drugs – but which one to pick in which case remains a key question.

A table of sensitivities of mutations based on "IC50" has since been used, which measure the level of inhibition of cells in vitro. However, first question marks came up when people e.g. Dr Laneuville observed discrepancies between IC50-insensitivities in the lab and observed response in real patients. More data on real-life results would need to be collected and documented.

In terms of T315I, Dr Cortes reported about omacetaxine (Homoharringtonine). About 27% of patients achieved a major cytogenetic response, even though it was not very durable (median 5 months). More than half of chronic phase patients with T315I have seen a reduction of T315I clone, but only 9% a complete reduction. There are two new promising targeted therapies to BCR-ABL with T315I, using different mechanisms: Deciphera's DCC-2036 and Ariad's AP24534. Dr Talpaz presented first facts on oral DCC-2036. Dr Cortes presented a phase I study with oral AP24534 where 43% of patients with T315I achieved a major cytogenetic response – encouraging. Furthermore, there were reports of MK0457 and XL228, both aurora kinase inhibitors which block an important signaling pathway in leukemogenesis independent of T315I/BCR-ABL. However these are both given intravenously. Experience with these drugs is still very early, and trials are rare – so as Dr Nicolini presented, bone marrow transplant currently remains the treatment of choice in case of T315I, if a donor is available.

Stopping treatment

Dr Hughes presented the Australian "imatinib cessation" study. In that study, 32 patients were included that had shown complete molecular remission for at least 2 years prior to the study. 17 of them were previously treated with interferon (IFN) and then imatinib, 15 had imatinib as initial therapy. About half of them relapsed within 18 months, most of them within 6 months after cessation of imatinib, independent of IFN pre-treatment.

Dr. Mahon presented the "STIM" (Stop imatinib) study. In the pilot study, patients needed to be in complete molecular response (PCR negative) for at least 2 years before entering the study. 69 patients were included, 34 with previous IFN treatment and 35 only with imatinib. 41 patients relapsed within the first 7 months. There was no difference between the groups that were pre-treated with IFN, or those that did not have IFN before. He concluded that it is possible to stop treatment in patients with sustained complete molecular response, but recommends discontinuing only in a clinical trial with strict molecular monitoring.

Imatinib-Interferon combination

Dr. Guilhot presented the French SPIRIT Trial on 12 month follow-up with 695 newly diagnosed patients. Treatment arms were imatinib-400mg, imatinib-600, imatinib-400+AraC, and imatinib+PegIFN. At 24 months, there was a clear advantage of the imatinib+IFN group, with 46% of patients in optimal molecular response, while only 26% of the imatinib-400mg patients achieved the same. 22% of imatinib-PegIFN patients became PCR-negative, compared to 10% on imatinib only. Overall, 5-10% of patients discontinued imatinib during the first year, and 45% of patients discontinued PegIFN. Average doses of PegIFN were 54µg/week. He concluded that the

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superiority of imatinib+PegIFN combination in term of molecular responses was confirmed at 24 months. There was an observed relationship between duration of PegIFN exposure and the depth of molecular reponses (which seemed to say: better a constant low dose, rather than a high dose of IFN with the risk of interruptions).

In a Nordic CML Study Group (Denmark, Finland, Norway and Sweden) and Israel multicenter study, presented by Dr. Simonsson, a total of 130 newly diagnosed patients were randomized. CML patients had to be in complete hematological remission following 3 months of imatinib induction therapy. The study arms were imatinib-400mg, and the combination of imatinib-400mg and PegIntron. Major molecular response rate at 52 weeks was significantly higher in the imatinib+PegIFN arm (82%) compared to the imatinib-only arm (54%). No unpredictable complications or adverse events were reported.

Interestingly, the presented observation in the German CML-IV Study comparing imatinib, imatinib-IFN combination and high dose imatinib did not come to the same conclusions. Overall survival did not show any significant difference between the arms. When I asked off the record, some were assuming that the difference might be due to "normal" interferon being used in the CML-IV study, while the above studies used PegIFN, leading to better tolerability and hence better exposure of the CML cells to PegIFN.

Lastly, the Italian GIMEMA trial comparing imatinib-400mg with imatinib-400+IFN: While there had been initial advantages of the combination arm, at 24 months these differences were lost. No surprise: the proportion of patients in this trial continuing IFN dropped from 41% at 12 months to 3% at 36 months, and by the end of the fourth year, all patients were off IFN. No information about IFN dosage was given (but some suspected dosage was the problem).

Interferon maintenance

Dr Burchert (Marburg) presented an update to the German PegIFN maintenance study. He reported that while imatinib has shown high efficacy, it fails to eradicate leukemic stem cells and suppresses leukemia-specific immune responses. At the same time, interferon stimulates T-lymphocytes against CML cells. In the study, 20 patients were treated with imatinib+PegIFN. 19 were in complete cytogenetic response, 15 in major molecular response, and 2 were PCR negative. Patients stopped imatinib and continued with interferon only. After 2.8 years, 4 had further improved their response, 9 remained stable, and 5 had a gradual relapse. As a conclusion, Dr Burchert said that achieving PCR negativity would not be a prerequisite for successful imatinib termination and IFN maintenance therapy.

CML in Children

One of the unforeseen surprises was the presentation of data on imatinib treatment of children with CML. Childhood CML is extremely rare, with only 2% of all childhood leukemia cases, so data is very limited. Prof Suttorp from Dresden presented the results of the PAED-II study with 51 patients. The researchers observed an impact on bone metabolism, decreasing bone growth. As a conclusion, Suttorp said imatinib treatment results in high response rates, while side effects are tolerable. Therefore, stem cell transplant has been shifted to a 2nd line strategy also in pediatrics. Changes in bone marrow metabolism and growth impairment are of special concern in not yet grown pediatric patients.

Adherence

The issue of adherence, or compliance to therapy, remains to be a challenge with TKIs. Dr Goldman presented data collected at the Hammersmith hospital. In a trial, they had provided patients with a medication bottle whose cap had some electronics built in. The bottle automatically recorded each time the bottle was opened. That way they observed that more than every fourth CML patient took less than 90% of the prescribed dose and every seventh less than 80%. They found a strong association of response to therapy with adherence rate: the 6-year probability of achieving major molecular response was 28% with those patients taking less than 90% of prescribed doses, and 95% for those that were adherent. The same applied for complete molecular response (0% vs 44%). Interestingly, when comparing the electronic measurement against what patients said to their doctor, patients claimed to be much more compliant than they actually were. This shows the lack of adherence remains largely underestimated.

Summary

It was again a great time at ASH, coming home with the confidence that even though CML therapy has already radically improved over the last years, there is still exciting progress and a lot of enthusiasm to close the existing gaps. For the "last bastion", the T315I, there are a number of new drugs in trials which seem to be targeted, promising and tolerable. In terms of finding a cure, there could of course still be much more progress. The results of the "STOP" trials have not yet been convincing – if the relapse risk is fifty-fifty, I would be hesitant trying it if I can tolerate treatment well, even if re-starters seem to respond again to imatinib.

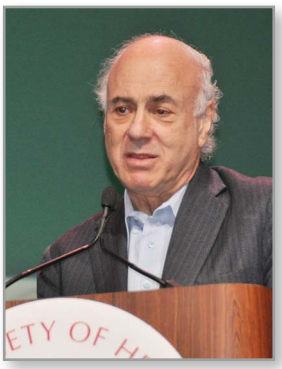
Recent reports from Germany and Sweden about low-dose/PegIFN as maintenance therapy in minimal residual disease – in combination with imatinib or not – are promising. Maybe further research will show who has an immune response to IFN, and those might have a minimal relapse even after stopping all therapies. However, the difference between the trials shows that IFN requires adaptive dosing to be tolerable and effective as a maintenance therapy.

But one of the best ASH messages for me was from childhood CML: For CML kids, whose decisions should be based on the expectation that they should expect another 80 years of life, transplantation has now become second line after imatinib. Chances seem to be good that we CML patients - as long as we adhere to therapy (until someone finds the bullet to kill also the small residual gang of CML stem cells) have the chance to grow very old.

All this is encouraging. And this is why I spend St. Nicholas in the US.

Source: CML Advocates Network
Jan Geissler (CML Patient since 2001), 13 Dec 2009
Full text article: http://cmladvocates.net
Contact: jan@cmladvocates.net
Jan is also the iCMLf Communications Coordinator

Chronic Myeloid Leukemia: Reversing the Chronic Phase



Prof John M. Goldman

Despite considerable scepticism about any possible clinical value of tyrosine kinase inhibitors (TKIs) in the early 1990s, imatinib at an oral dose of 400mg daily has now become standard initial treatment for all CML patients who present in Chronic Phase (CP). After 8 years follow up, the estimated survival for patients treated with imatinib is 85%, which is substantially better than patients treated with interferon alone or interferon plus cytarabine. The adverse effects of imatinib are definitely manageable in most instances.

However, the drug is not perfect. Only approximately 60% of patients are still taking imatinib at standard dosage after 6 years, which means that approximately 40% have needed higher doses of imatinib or alternative therapy. There are three newer TKIs, all of which are more active than imatinib in in vitro assays. Dasatinib (Bristol-Myers Squibb), nilotinib, (Novartis) and the third newest agent bosutinib (Wyeth), which is not yet licensed.

There are now well-defined criteria for imatinib failure; patients still in CP who are judged to have experienced treatment failure with imatinib whether as a consequence of intolerance or of resistance, are routinely offered treatment with either dasatinib or nilotinib. Clinical results are similar with the two agents; 40% to 50% of patients resistant to imatinib will be in complete cytogenetic response 2 years after starting their second-generation TKI.

This poses interesting clinical questions: should one or other of the so-called second-generation TKIs now replace imatinib as primary treatment for CML, and if so, which of the two agents should one choose?

In favour is the observation that the cytogenetic and molecular responses do seem to be much more rapid than those achievable with standard dose imatinib; this could be beneficial if the risk of disease progression is related to the quantity of residual disease in a patient's body and the time that quantity is above a still ill-defined threshold. The adverse effects attributable to both agents seem to be relatively minor or nonexistent in most instances. One could reasonably speculate that the fraction of patients who currently start imatinib but develop resistance while still in CP and then respond to dasatinib or nilotinib would not have developed any TKI resistance if they had started the second generation TKI de novo, and indeed some of those with imatinib resistance who do not respond to second-generation TKIs might never have experienced treatment failure if they started other TKI drugs as initial treatment. These considerations might raise the overall success rate using a second-generation TKI as up-front therapy to 80% or more.

Conversely it could be argued that with 11 years experience of using imatinib, the safety profile is well established and 60% of patients do not need any stronger TKI. Do we really know that more rapid responses translate to superior survival, which must be the ultimate arbiter of whether to start treatment with imatinib or a second generation TKI? Will use of a second-generation increase the proportion of patients in whom we could safely stop therapy? Only time will tell. Finally in some countries considerations of cost also enter the equation.

If you do decide to use a second-generation TKI as primary therapy, which one would you choose? There seems little difference in efficacy. The adverse effect profiles are different; nilotinib is more likely to cause chemical disturbance of liver function and dasatinib more likely to cause pleural or pericardial effusions, but these problems all resolve if the relevant drug dosage is reduced or stopped, in which case one could switch to the other second-generation TKI. Kinase domain mutations may guide choice of therapy in patients resistant to imatinib, but they are exceedingly rare in newly diagnosed patients and thus contribute nothing to choice of initial therapy. Thus there is no good reason for preferring one or other of the newer TKIs.

An interesting compromise strategy would be to use two or three TKIs in sequence. One could, for example, start with imatinib, switch after 6 months to dasatinib (or nilotinib), and then switch again to nilotinib (or dasatinib). At least one such trial is currently in progress. It could prove superior to use of a single second-generation TKI, but this is far from certain. The problem here would be to define realistic endpoints. Studies based on survival would be the gold standard but would also take many years to complete. A more realistic end point might be the incidence of complete molecular response at 1 or 2 years.

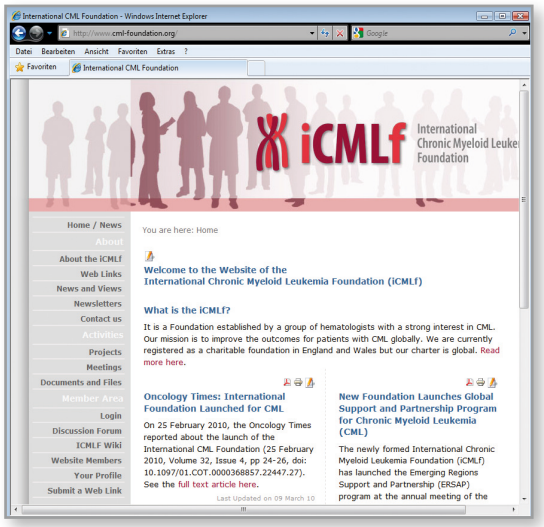
The good news for today is the fact that survival for most patients presenting in CP has improved dramatically compared with 15 or 20 years ago. The challenge is to decide how exactly that survival can be improved further or –better still- how to ensure that therapy can safely be discontinued, as seems to be the case now in a small percentage of patients.

John M. Goldman
Chair, Executive of the iCMLf

This article is a synopsis of the editorial written for the Journal of Clinical Oncology in Jan 2010. The full article including references can be found in the Journal of Clinical Oncology, Jan 2010: 363-365

iCMLf website: A global community for CML researchers, clinicians and carers

"How did we ever do this before we had the Internet?" springs to mind when looking at international networks like the iCMLf, the European Leukemia Net or the CML Advocates Network. The Internet has become indispensable to share knowledge, collaborate and communicate globally. Despite CML being a rare disease, experts on all continents collaborate very closely to improve CML treatment. This worldwide community of hematologists is a perfect example for the Internet era. The iCMLf website aims to strengthen that community collaboration further.



When establishing the iCMLf, we wondered what we could do to support the communication and collaboration between CML experts that are spread all across the world. Despite a small budget, the iCMLf has gone one step further: Rather than just implementing a website presenting the iCMLf activities, we have built an **interactive CML community**. This article illustrates what the iCMLf's website can do for you.

- **Information about the iCMLf**, containing information about the iCMLf's mission, executive structure, scientific advisors, national representatives, partners, sponsors and officers. Additionally, descriptions of our meetings, projects (such as the Emerging Regions Support and Partnership Program) or publications (e.g. Oncology Times recent coverage of the iCMLf).
- **Newsletter Subscription**, allowing visitors to be regularly updated about iCMLf's projects and upcoming meetings via an emailed newsletter. To subscribe, please click on Newsletters and provide your name and email address.
- **Documents and Files**, allowing members access to relevant files and also providing a shared file space for those involved in iCMLf projects. iCMLf project members can easily share files within the team.
- **Discussion Forum** for interactive discussions about iCMLf's Strategy and Priorities. For example tackling diagnostic testing and disease monitoring for CML patients in developing countries. This is the place to share views with the global CML community, and let the iCMLf team know your suggestions. To read and contribute in the forum, you need to register on the website, as the Discussion Forum is available only to registered Members of the website.
- **Find other CML community members** registered on the iCMLf website. Registered members can easily search for other members, e.g. in a country or organization, and contact them individuals. To do so, go to the Member Area of the website, click on Website Members and then on Search Users.

It will be through the engagement of the CML community that the iCMLf will achieve its goals. We welcome and need your participation.

How do I join the iCMLf Community and access the Forum?

All you need to do is register on the website. Go to http://www.cml-foundation.org/login/registers (or Homepage ➠ Login ➠ No account? ➠ Register) and enter your details. You will then receive an email where you need click on a link. Your registration will then be approved and you're ready to go!

If you have any questions or suggestions, please contact Jan Geissler, iCMLf's Communication Coordinator, at jan@cml-foundation.org, or leave a message in the *iCMLf Feedback Forum*.