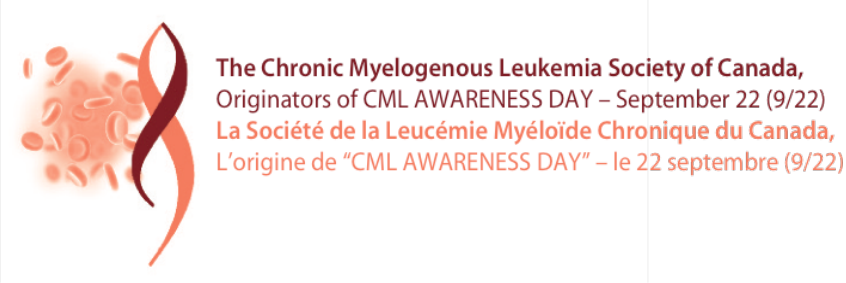

Working Towards a Cure in CML - Breakfast Satellite Symposium - CBMTG

Speakers:
Pierre Laneuville, MD, FRCPC, Assoc. Professor Dept. of Medicine and Oncology, McGill University, Montreal, Quebec

Wanda Hasegawa, MD, FRCP (Course Director)
Assistant Professor, Faculty of Medicine, Division of Hematology, Dalhousie University, Halifax, Nova Scotia

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The Key learning objectives were to:

1.) Review and assess the publications that are contributing to the changes in the CP-CML Canadian Guidelines

2.) Apply the changes to clinical practice that were made to the Canadian CML Guidelines

3.) Identify the role of new and combination therapies while defining the future of CML management

The last Canadian CML Guidelines were established in 2003, updated and published in 2006. Therefore the ELN (European Leukemia Net) Guidelines of 2009 were used as a platform for determining the changes needed to the Canadian CML Guidelines.

What has changed since the ELN 2009 guidelines is that 2nd generation TKI's have mostly received approval for 1st line use, a new importance regarding early molecular milestones and the international standardization of RQ PCR. As well the prospects for the future include additional new therapies and the consideration of treatment discontinuation.

Dr. Laneuville gave a thorough review of the historical data with regards to the IRIS Overall Survival (OS) rates for the imatinib arm (remember that the IRIS study compared IFN and Imatinib in front line setting). The IRIS 8 year up date showed us that 53% of patients on the study have achieved CCyR while 47% of patients actually have, by today's terms an unacceptable outcome, such as no CCyR, safety issues, loss of CCyR, loss + regained CyR and only 7% achieved a response greater than CCyR.

He reviewed the evidence of the Phase III trials of second generation TKI's in Newly Diagnosed CP-CML patients. These are the ENESTnd trial and the DASISION trial. Primary endpoint for the ENESTnd trial was MMR at 12 months and CCyR by 12 months for DAISSON. Note from CAS - be reminded that patients on the DAISSON trial did achieve the same rate of MMR as in the ENESTnd trial, if not slightly better 44% for Nilotinib versus 46% for Dasatinib. Notes from the non-randomized comparison of key study endpoints that Dr. Laneuville presented). Dr. Laneuville pointed out that terms/definitions used in the trials were mostly similar when we look at the IRIS and DAISSON (PFS - progression free survival) terminology but differed when we looked at the MD Anderson terminology (EFS-Event Free Survival) and the ENESTnd (TWP - Time without Progression).

MD Anderson definition of EFS is the most rigorous = Progression to AP or BP, loss of MCyR, hematologic response. Event-free survival (EFS) was measured from the start of treatment to Progression to AP or BP, or the date of lack of achievement of response as per the ELN, of loss of complete hematologic response, loss of complete or major cytogenetic response, discontinuation of therapy for toxicity or lack of efficacy, progression to accelerated or blastic phases, or death at any time. (Notes from CAS - definitions seem to be significantly more liberal with industry sponsored trial data as can be seen by the MD Anderson criteria which showed that the 5 year outcomes on the same population varied significantly from 96% for ENESTnd, 89% for DASISION, 90% for IRIS and 81% for MD Anderson. This would indicate that the true 5 year survival rate might really be considered as an average between 96% and 81% which would really mean about 88.5% in real clinical practice - if of course a patient is being treated at a major CML centre in North America).

The ENESTnd update at 3 years shows a very good rate of cumulative MMR 73% versus 53% for Imatinib. The data for cumulative incidence of MR 4.0 (note the new terminology MR 4.0 is equal to what patients refer to PCRU or in some clinics referred to as CMR 4.0 log reduction. Anything greater than 3.9 log reduction is considered to be CMR now called MR) is also quite good, 50% versus only 26% for Imatinib. ENESTnd update of 3 year MR 4.5 (most major centres in Canada are able to standardize to 4.5 log reductions, and i remind you that this is the criteria for the STIM II trials. Patients must reach this level of response and sustain it for a minimum of two years before they are considered for participation in a stopping trial) data is 32% versus 15% for Imatinib. ENESTnd 3y trial data for progression to AP/BP showed 0.7% for Nilotinib versus 5.02% for Imatinib. The 24 month update on drug related Adverse Events for Nilotinib was again quite favorable, with headache, pruritus and rash being the major concerns for Nilotinib but fluid retention, diarrhea, muscle cramps, nausea, vomiting and neutropenia are the bigger issues with Imatinib, so we clearly see an overall improvement for patients quality of life on Nilotinib versus Imatinib.

The 2 year update of the DASISION data was presented and we must remember that a different endpoint was used, CCyR. Cumulative data for this endpoint was 86% for Dasatinib versus 82% for Imatinib, however, the cumulative incidence of MMR for DASISION was also presented and here we see a rate of 64% for Dasatinib versus 46% for imatinib. Bear in mind that the achievement of MMR is becoming very important for the overall sustainability of good health for the patient, so this improvement in the ability to achieve MMR is vitally important. Cumulative incidence of MR 4.5 for DASISION at 2 years is 17% for Dasatinib versus 8% for Imatinib. Transformation to AP/BC on Dasatinib is 3.5% versus 5.8% for Imatinib. DASISION 2 year update for adverse events shows that only pleural effusion is better with Imatinib and Dr. Laneuville pointed out that pleural effusions with Dasatinib are really more of a concern for patients who are being started on it as a 2nd TKI (this would make a strong argument for using this drug up front). A few moments were given to the topic of high dose Imatinib, but the general consensus is that it really isn't appropriate to increase imatinib doses and delaying getting patients onto 2nd generation TKI's as it may even interfere with patient’s ability to achieve a better and safer level of response to the second generation TKI.

The overall take home message of this part of the session is that the trial data for the 2nd generation TKI's show that they are highly effective and may even replace Imatinib as first line therapy.

Early Molecular Milestones

Review of ELN 2009 milestones shows that optimal responses at 3 months = CHR + MCyR (ph+ ≤65%), PCyR (Ph+ ≤ 35%) at 6 months, CCyR (Ph+ = 0) as 12 months, MMR at 18 months and stable/improving MMR at anytime. Suboptimal responses were expressed as No Cyr (Ph+ ≥95%) at 3 months, less than PCyR (Ph+≥ 35%) at 6 months, PCyR (Ph+ ≤35%) at 12 months or less than MMR at 18 months or loss of MMR with mutations at anytime. Failure was defined, as not hitting any of the milestones in the time frames and warning was High Risk Sokal Score/Ph+ without MMR at 18 months. The Event Free Survival of Imatinib was looked at with regards to suboptimal response and in fact we see that after 72 months, those with sub optimal response actually do worse then those who were reported as a failure. In fact, sub optimal response is equal to or worse then failure.

Combining this with the knowledge gleaned from IRIS 8 year data we see that any event (Loss of CHR, Loss of MCR, AP/BC, death during treatment peak within the first three years of treatment (within the 72 month time frame) - cumulative total of 21% form the IRIS 8 year data and transformation to AP/BC occurred at a rate of 8% with in the first few years. This would certainly indicate that a patient's fate is determined quite early in the treatment program, and therefore argues for a more vigilant control of patient's response and adaptation to therapy.

For 282 patients on Imatinib therapy their MR response at three months correlated with greater overall survival - 93.9% versus 56.9% for those who did not achieve this response. The results from the DASISION for PFS according to BCR ABL level at 3 months (Kaplan-Meier Plots) were much more robust than for the IRIS trials and showed that patients who responded well to either treatment and significantly lowered their BCR ABL levels had better PFS than patients whose level of BCR ABL was greater than 10% at 3 months. The same was true for overall survival (OS) based on 3 month BCR ABL levels for both therapies.

International Standardization of RQ-PCR

IS was developed to allow alignment of BCR ABL values generated by the different laboratories, allowing for molecular results to be compared between sites. We are now closer to standardization after a few approaches: sample exchange with reference lab, Nanogen Kits, Ipsogen Kits, Asuragen Standards and more recently with the Cepheid platform (MMR CMR). Standardization of RQ PCR is an imperative and is becoming the norm in Canada.

With all of the improvements in the therapuetical choices and the wider availability of RQ PCR standardization the question arises as to how are decisions made within the clinical setting. Importantly all trials were never designed to highlight survival as it would have been impossible and required far too many patients, so surrogate endpoints were used such as CCyR, MMR and CMR. It is clear from the current data on the newer TKI's that the surrogate endpoints of MMR and CMR do impart more favorable opportunities for the disease to be stabilized in the chronic phase and in many cases more patients are achieving deeper molecular responses that have been sustained for longer periods of time. It is important to consider this fact as it is becoming clear that the newer TKI's may even perhaps be better suited to replace imatinib in the front line setting.

Update on the Management of Chronic Myeloid Leukemia - Wanda Hasegawa, MD, FRCPC

The Canadian Consensus Group on the Management of CML (CCGM) updated our current Canadian guidelines in 2006 but since then we have two new tyrosine Kinase inhibitors such as Dasatinib and Nilotinib as well as newer milestones for treatment.

The new developments are that the efficacy of Imatinib and durability of response has been confirmed, two other TKI's have been introduced in Canada, there is now international standardization of Q-RT-PCR and an international scale, and early indicators of response predict for treatment failure and disease progression.

The CCGM - CML members met in 2008 to critically review the CML literature from 2006-2008. These recommendations were revised in February 2012 with an updated literature search.
Levels of evidence were graded according to the NCI (National Cancer Institute Guidelines)

Prognostic factors for CML:
Sokal or Hasford
Eutos - Basophils + Spleen size
Age, spleen size, platelet count, % blasts, % eosinophils, % basophils

Baseline investigations were updated with the addition of allowing for use of either/or Sokal, Hasford and/or Eutos. Along with Bone Marrow Aspirate and biopsy as well as Bone Marrow Cytogenetics,

Bone Marrow Fish is no longer recommended. Peripheral blood or bone marrow Q-RT-PCR is still recommended

Monitoring in addition to bone marrow karyotyping at 1 year to confirm CCyR (part of current guidelines), repeating them at least annually if a clonal abnormality additional to Ph+ is present or until MMR or better is achieved (current guidelines), as well as Q-RT-PCR performed every three months, the following is now proposed to be added: If MMR achieved and stable for 2 years, reduced frequency of Q-RT-PCR to every 4-6 months. The rationale is that a lot of transformations will occur in the first few years.

Quantifying Molecular Response

Log Reduction	International Scale	Response
0	100%	Baseline
1	10%	CHR
2	1%	CCyR
≥3	≤0.1%	MMR
>4 or 4.5 or 5.0	≤0.01%	CMR

As with the 2006 Guidelines where the CCGM-CML recommends the use of TKI's as first line treatment for all newly diagnosed CP-CML patients the following has been added:
Imatinib 400mg QD (daily)
Nilotinib 300 mg BID (twice daily)
Dasatinib 100 mg QD (Daily)

Allogenic SCT or clinical trial should be considered for advanced phases of CML

It is becoming the opinion of the CCGM-CML that when we look at the ELN 2009 Response Definitions, then suboptimal response should really be also considered a failure and they would therefore propose that the 6 months response milestones are now the milestones to be reached for the 3 month treatment period.

Log Reduction	International Scale	Response	Response Time Frame
0	100%	Baseline	Pts. Status at Dx
1	10%	CHR	3 months
2	1%	CCyR	12 months
≥3	≤0.1%	MMR	18 months
>4 or 4.5 or 5.0	≤0.01%	CMR	??????

So treatment milestones would look like this:

Complete Hematologic response (CHR) and (proposed to be added) at least a 1-log reduction +/-0.5 (10% IS) at 3 months

Complete Cytogenetic response (CCyR) (2 log reduction; 1% IS) at 12 months

Major Molecular response (≥3 log reduction; ≤0.1% IS) at 18 months

But it is newly noted, "A More rapid response is expected with nilotinib and Dasatinib but optimal response criteria have not yet been determined".

Primary treatment failure criteria remain the same (failure to meet any of the treatment milestones), Secondary treatment failure is loss of any milestone already achieved or progression to more advanced phase of CML

Mutation testing -Proposal to be added:

Mutation testing is recommended in patients who fail to achieve treatment milestones or if there is loss of response
-Includes patients with 0.5 log increase in 2 successive samples with loss of MMR
-ABL Kinase sequencing for mutations
What remains the same is:
Mutational testing should always be performed before switching TKI's - which informs choice of TKI to be used as salvage.

Under Second-Line treatment the following is proposed to be added:
A second generation TKI (nilotinib or dasatinib) is recommended for patients with imatinib resistance/intolerance - choice of TKI may be guided by an individual patient's co morbidities.

Monitoring 2nd generation TKI's in 2nd line:
CBC weekly or bi-weekly until CHR is achieved
Q-RT-PCR every 3 months
Bone marrow test at 1 year after initiation of second line TKI
Repeat cytogenetics and mutation testing if no improvement in milestones or loss of response

Under transplantation:

Allogenic SCT should be considered for all transplant eligible patients with:
T315I mutation - NEW
CML-AP or BC
Evidence of clonal progression by bone marrow cytogenetics
Treatment failure after second-generation TKI - NEW

Not recommended – this represents a NEW section:

Monitoring plasma drug levels (not clinically relevant)
Discontinuation of Imatinib responding patients outside of a clinical trial (because PCR needs to be monitored more closely)
IFN A should be considered only in:
-Women who wish to become pregnant (but they must be informed that it is not as effective as TKI's)
-Patients intolerant to TKI's who are ineligible for SCT or entry into a clinical trial

Key Take home messages:

All three currently approved TKI's should be considered for first line use

3-month milestones should guide treatment choices

Bone marrow karyotyping is important before starting 2nd TKI, but is less important for monitoring stable disease as molecular milestones are more relevant

Prospects for the Future in CML Management - Pierre Laneuville MD, FRCPC

Dr. Laneuville showed an eloquent graph of the annual incidence of CP-CML based on Canadian age distribution, which translates to essentially 536 new CML patients dxed yearly. Additionally he showed another graph showing the impact of imatinib on CML prevalence in Canada and it would show that annual mortality is 1% which is a significant improvement this shows us that more patients are surviving their CML and gaining significant quality years of life which essentially put prevalence for Canada higher than what was originally thought and depending on the age at diagnosis, prevalence could go as high as 10000 patients living in Canada within 20 years with CML. This could have important significant economical repercussions. It is important to also note that even small improvements in treatment milestones, has a significant impact on prevalence.

The concept of a functional cure for CP - CML was addressed. The first thought was that all LSC would have to be completely eradicated in order to stop treatment. The problem being though that early cells (LSC) are not addicted to BCR ABL. One theory is that constant therapy with a TKI forces the early LSC to divide more rapidly whereby they become addicted to BCR ABL and this may be one way to significantly lower the LSC to the point where they become unable to reconstitute CML. This was part of the rational by Mahon for the STIM trial.

Interestingly while it was originally thought that a patient who had achieved CMR and sustained it for ≥2 years and stopped Imatinib, that the loss of CMR would necessitate the re-start of Imatinib. Essentially this is changing, in the STIM II trial patients are only restarted if they lose MMR. It is important to note that once you are in MMR and sustain it for ≥ 3 years it is virtually impossible to lose it (as long as you stay on treatment - note that stopping trials are only offered to those patients who achieve CMR 4.5 and sustain it for ≥ 2 years).

This sets up the rationale for the importance of achieving MMR and it was noted that if no MMR has been achieved by 18 months the probability of achieving it in 60 months is 0.

One of the criteria for the stopping trial is a lower sokal score at diagnosis, lower sokal scores seem to be better able to predict better ability to withdraw treatment and sustain response.

The use of IFN in combinations with TKI was addressed and a slide was presented that showed several trials underway. One appealing theory is that IFN may help recruit & cycle LSC so that they can be killed by the TKI, the Nordic study seems to show better results.

The use of JAK2 inhibitors may help to differentiate LSC and make them susceptible to TKI
Later this year in Canada there will be 2 SMO + TKI trials
There will also be a TKI + PP2A activator (FTY720) Gilenya (NVS)
Another approach is targeting ILIr (Rap), which is s surface protein.
A few words were reserved for compliance and the Marin study was sited. The key take home message for this is that there is a discouraging loss of adherence in the 1st year of therapy and clinicians need to be more vigilant and offer more support.

In summary the annual CML related death has dropped to ~ 1%. There appears to be little room left to further improve OS - small increases in CML -OS = significantly higher prevalence of people living with CML

Drug discontinuation appears feasible with Imatinib <10% (ITT), with 2GTINIB~40-50% (ITT)? Combination TKI+ other agents may improve or move us closer to a cure.

Note: ITT = intention to treat