Canadian Recommendations for the treatment and management of CML

Presented in Edmonton at the CBMTG meeting, April, 2006

Introduction

An advisory board of Canadian hematologist and oncologists was established in 2004 to establish recommendations for the consistent management of CML by all physicians across Canada and to try to make sure that similar resources are available to patients. They are not called guidelines as this would imply uncontroversial evidence of their validity. As with most developments in medicine, the management of CML is an evolving process, new drugs, tests and philosophies aimed at improving the overall treatment of patients must be evaluated on an ongoing basis. In fact, these are already under review in a number of areas. They are designed to help physicians keep up to date with therapies that are not routine for many of them. Guidelines represent what has been submitted for peer review publication and do not reflect recent changes to the corporate distributed publication. They also do not reflect new drugs that are currently not available in Canada. This will be addressed as they become available.

Dr. Jeffrey Lipton / Dr. Pierre Laneuville

Recommendation 1
Establishes the criteria for determining the staging of CML at time of diagnosis:

0. Chronic Phase (CP) = Blasts <15% Basophiles <20%, Blasts + Promyelocytes <30%
0. Accelerated Phase (AP) = Blasts 15 - 29%, Basophiles > 20%, Blasts + Promyelocytes >30% or platelets < 100 X 10e5/L
0. Blast Crisis (BP) = Blasts > 30% or extramedullary involvement (e.g. chloroma’s)

Recommendation 2
Sokal index for patients to be treated with IM

Recommendation 3
Investigations to confirm diagnosis
1 - Assessment of prognosis (Sokal)
2 - Bone marrow aspirate and biopsy
3 - Baseline bone marrow cytogenetics
4 - Peripheral blood or bone marrow FISH
5 - Peripheral blood or bone marrow Q-RT-PCR

Recommendation 4
1 - The option of allogeneic SCT should be discussed with all eligible patients
2 - All eligible patients should be referred to a transplantation centre for HLA typing and matching of potential donors
3 - Patient choice is determining factor in treatment decision making

Recommendation 5
1 - Patients on IFN-alpha +/- cytarabine who experience intolerable side effects should switch to IM
2 - Assess cytogenetic response in patients on IFN - alpha
3 - All patients less than CCR should be switched to IM
4 - Patients who achieve a CCR on IFN-alpha and are tolerant of therapy should remain on IFN-alpha to be monitored (Dr. Lipton pointed out that there is a potential for some patients, albeit small (versus none with IM) to achieve an immune response, therefore if the treatment is well
tolerated the patient should stay on IFN). It is interesting to note that there are still quite a few patients on IFN, for this very reason.

**Recommendation 6**
For all newly diagnosed patients with CP CML who do not elect related-donor allogenic SCT as first-line therapy, IM or an IRB (investigational review board) approved protocol is recommended.

**Recommendation 7**
Recommended minimum starting dosages of IM:
- CP: 400 mg/day
- AP: 600 mg/day
- BC: up to 800mg/day
- After IFN-alpha failure: 400 mg/day
Recommendation 8

Testing in IM treated patients:

- BM Cytogenetics
  - At diagnosis
  - Annually if MCR maintained

- Q-PCR
  - At diagnosis
  - Every 3 months (FISH may be substituted q3 months until CCR)
  - If $\geq 0.5$ log increase, test should be repeated within 4 weeks. Mutational analysis is recommended

- Abl-kinase sequencing for mutations
  - At confirmed increase of 0.5 log in Q-PCR

Milestones indicating successful progress of therapy:

- CHR: at 3 months
- MCR: at 6 months
- CCR: at 12 months
- MMR: at 18 months

Failure to achieve theses milestones indicates a need to reconsider the therapeutic strategy:

- Allo SCT
- IM up to 800mg/day
- IRB- approved protocol

Once milestones have been achieved, treatment should be maintained indefinitely if patient continues to respond

There is no evidence that patients can stop treatment.

IM discontinuation is justifiable if there is a continued lack of response with 800mg/day

Recommendation 9

Definition of disease progression during IM therapy

- Transformation from CP to AP or BC
- Cytogenetic (clonal) evolution in Ph+ cells
- Loss of CCR
- confirmed increase of $\geq 0.5$ log (Q-PCR) for patients in CCR or better.
- Detection of ABL mutations

Treatment options for patients progressing on IM:

- Transplant-eligible:
  - Allogeneic SCT

Transplant ineligible:
- IM 800 mg/day if no abl mutation that confer complete resistance
- IFN-Alpha +/- Cytarabine*
  - If no response to IM 800mg within 3 months
  - If abl mutations conferring IM resistance
- IRB-approved clinical trial of new, experimental agents
- Hydroxyurea or Busulfan if IFN-alpha is inappropriate
* The efficacy of IFN-Alpha after IM failure is unknown

**Recommendation 10**

The Canadian Consensus Guideline Management - CML strongly recommends standardized Q-PCR testing for all Canadian patients with CML.

Mutational analysis should be regionalized in even fewer centres.