



**London Health Sciences Centre**  
London Regional Cancer Program

# **Chronic Myelogenous Leukemia (CML)**

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## **Hematology Practice Guideline**

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This guideline is a statement of consensus of the Hematology Disease Site Team regarding their views of currently accepted approaches to treatment. It is not intended to replace the independent medical judgment of the physician in the context of individual clinical circumstances to determine any patient's care or treatment.

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## Background/Overview

The Hematology Disease Site Team has and will be following the Guidelines recently published by the Canadian Consensus Group<sup>1</sup> with respect to the diagnosis, treatment and follow-up of patients with CML. This is summarized in a patient care flowchart (Attachment #1).

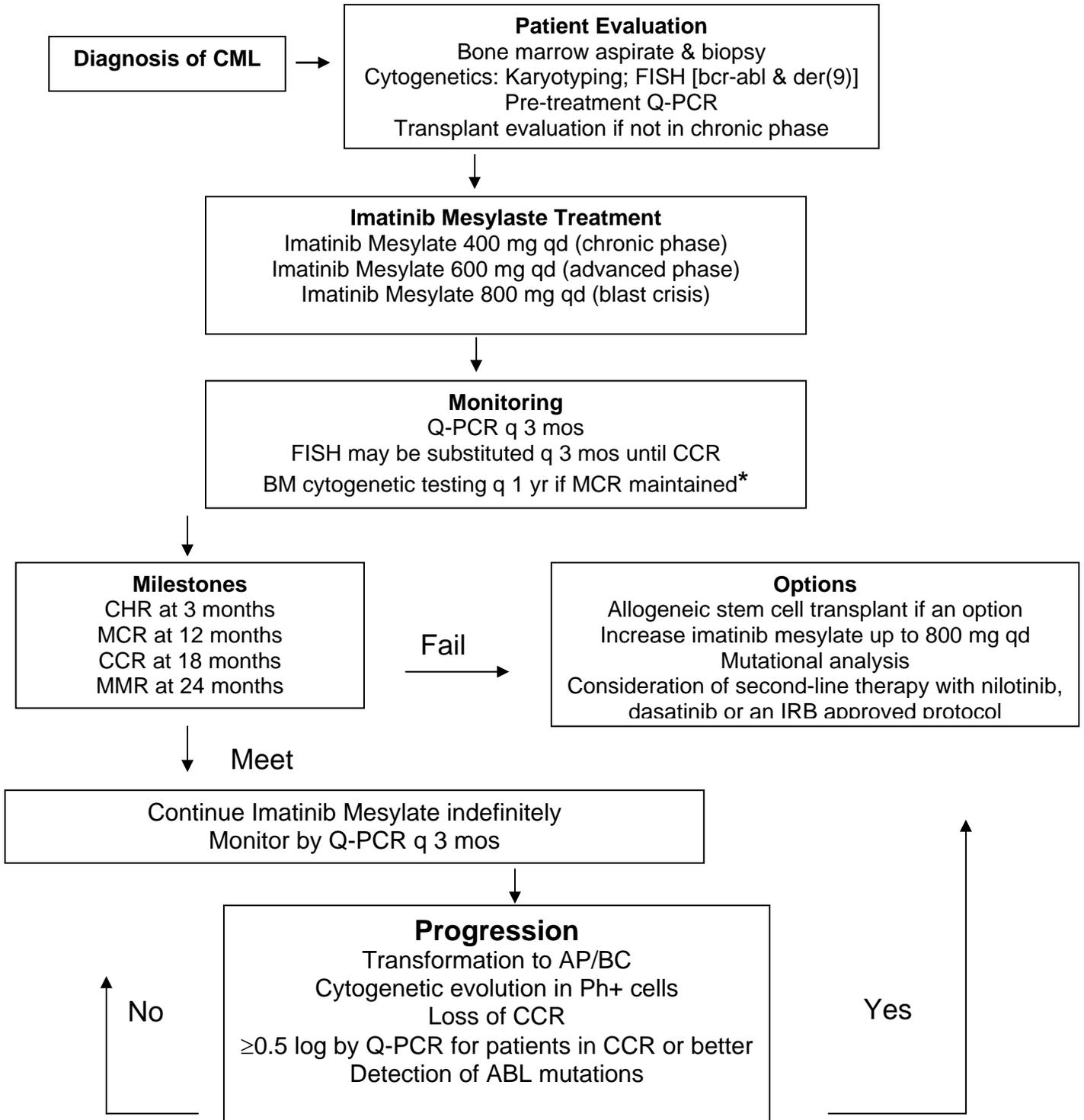
An updated summary of the guidelines can be found at:

URL: <http://cmlrecommendations.ca>  
ID: cmlcases  
PASSWORD: online

A copy of the Summary of Recommendations is appended (Attachment #2). Differences between the Canadian Recommendations and our current practice at the LRCC are highlighted (in blue font) after each of the ten recommendations.

# Treatment

## Attachment #1: Patient Treatment Algorithm



\* Optional

## **Attachment #2: Guideline Summary**

### **Summary of Recommendations of the Canadian Consensus Group on the Management of Chronic Myelogenous Leukemia (CCGM-CML)**

Differences between the Canadian Recommendations and our current practice at the LRCP are highlighted (in blue font) after each of the ten recommendations.

#### **Definitions:**

- Complete hematologic response:
  - WBC <10 x 10<sup>9</sup>/L with normal differential
  - Hb >110g/L
  - Platelets <500 x 10<sup>9</sup>/L
  - No signs or symptoms of disease (splenomegaly)
  
- Cytogenetic responses:
  - Complete cytogenetic response: 0% Ph-positive metaphases
  - Major response: 1-34% Ph-positive metaphases
  - Minor response: 35-95% Ph-positive metaphases
  - No response: Persistence of 100% positivity.
  
- Major molecular response: A greater than 3 log reduction of the bcr-abl transcript.

#### **Recommendation #1**

The CCGM-CML recommends the following categorization of CML stages, as defined by IRIS investigators:

- Chronic phase (CP): The presence of <15% blasts, <20% basophils and <30% blasts plus promyelocytes in peripheral blood and marrow.
- Accelerated phase (AP): The presence of at least 15% blasts in blood or bone marrow, at least 30% blasts plus promyelocytes in blood or bone marrow, and at least 20% peripheral basophils or thrombocytopenia (platelets <100 x 10<sup>9</sup>/L).
- Blast crisis (BC): The presence of at least 30% blasts in blood or bone marrow or extramedullary involvement, eg, chloromas.

## Recommendation #2

The CCGM-CML recommends the use of the Sokal index for newly diagnosed patients with CML, until further investigation validates a more reliable prognostic score for patients who are considering imatinib mesylate.

### **LRCP convention:**

[Determination of the Sokal index is optional as it requires complex calculations and does not currently impact on prognosis or the management of CML patients.]

## Recommendation #3

The CCGM-CML recommends the following investigations at diagnosis for all patients with suspected or confirmed CML:

- Assessment of prognosis (Sokal)
- Bone marrow aspirate and biopsy
- Baseline bone marrow cytogenetics
- Peripheral blood or bone marrow fluorescence in situ hybridization (FISH) for deletion of chromosome 9
- Peripheral blood or bone marrow quantitative real time polymerase chain reaction (Q-PCR)

## Recommendation #4

The option of allogeneic stem cell transplantation (SCT) should be discussed with all transplantation-eligible patients.

All transplantation-eligible patients should be referred to a transplantation centre for human leukocyte antigen (HLA) typing and matching of potential donors as advanced preparation for allogeneic SCT in case this option is chosen as first-line therapy or in the event of imatinib mesylate failure, to ensure the patient proceeds to transplantation in a timely manner. Allogeneic SCT as first-line therapy is an acceptable option that may be selected by some patients based on personal preference after discussion of the pros and cons versus imatinib mesylate therapy.

Patient choice is the determining factor in treatment decision-making.

### **LRCP convention:**

[Allogeneic SCT is not generally considered as the first-line therapy at our center for non-high risk CML patients. Since we are a SCT center, referral and preparation can be expedited for high-risk patients.]

## Recommendation #5

The CCGM-CML recommends that patients on a pre-existing regimen of interferon-alpha (IFN- $\alpha$ ) with or without cytarabine who experience intolerable side effects switch to imatinib mesylate.

The CCGM-CML recommends the assessment of cytogenetic response in patients who are initially treated with and remain on IFN- $\alpha$ . All patients with less than a complete cytogenetic response (CCR) should be switched to imatinib mesylate. Patients who achieve a CCR on IFN- $\alpha$  and are tolerant of therapy should remain on IFN- $\alpha$  and be monitored.

## Recommendation #6

For all newly diagnosed patients with chronic-phase CML who do not elect related-donor allogeneic SCT as first-line therapy, imatinib mesylate is recommended.

## Recommendation #7

The CCGM-CML recommends the following **minimum** starting dosages of imatinib mesylate for patients with CML:

- Chronic phase: 400 mg/day
- Accelerated phase: 600 mg/day
- Blast crisis: up to 800 mg/day
- In patients who switch to imatinib mesylate after failure of IFN- $\alpha$  with or without cytarabine, the CCGM-CML recommends a starting dose of 400 mg/day of imatinib mesylate.

## Recommendation #8

The CCGM-CML recommends the following tests and frequency of testing to monitor hematologic, cytogenetic, and molecular responses in all patients on imatinib mesylate and guide therapeutic decision-making:

Bone marrow cytogenetic testing

- At diagnosis
- q1 year, if major cytogenetic response (MCR) is maintained Q-PCR
- At diagnosis and q3 months (FISH may be substituted q3 months until CCR) (FISH and Q-PCR should be performed at standardized laboratories)
- 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 the Q-PCR (*abl* sequencing should be performed at standardized laboratories)

**LRCP convention:**

[Current practice at our institution is to defer the annual bone marrow examination and repeat karyotyping if the patient maintains a log reduction of < 3.]

The CCGM-CML recommends the achievement of the following therapeutic milestones, to indicate the successful progression of imatinib mesylate therapy in chronic-phase patients with CML:

- Complete Hematologic Response at 3 months
- Major Cytogenetic Response at 12 months
- Complete Cytogenetic Response at 18 months
- Major Molecular Response at 24 months

Failure to achieve these therapeutic milestones within the specified time limits indicates a need to reconsider the therapeutic strategy and the CCGM-CML recommends the following alternatives:

- Allogeneic SCT if an option
- Increasing the dose of imatinib mesylate up to 800 mg/day
- Consideration of an IRB approved protocol
- On continued lack of response, despite maximum dose escalation, discontinuation of imatinib mesylate treatment and consideration of alternative therapy is justifiable
- Once the milestones have been achieved, treatment should be maintained indefinitely as long as the patient continues to respond

**LRCP convention:**

[Consideration of initiating second-line therapy with nilotinib or dasatinib. Use of mutational analysis, which is available at University Health Network, to guide choice.]

**Recommendation #9**

The CCGM-CML recommends the following definition of disease progression in *compliant* patients on imatinib mesylate therapy:

- Transformation from CP to AP or BC
- Cytogenetic (clonal) evolution in Ph<sup>+</sup> cells
- Loss of CCR
- Confirmed increase of  $\geq 0.5$  log (Q-PCR), for patients in CCR or better
- Detection of *abl* mutations with loss of response

For patients in whom imatinib mesylate fails, the CCGM-CML recommends:

- Allogeneic SCT for all transplantation-eligible patients
- Dose escalation up to 800 mg/day of imatinib mesylate in transplantation-ineligible patients who do not have *abl* mutations that confer complete resistance to imatinib mesylate
- IFN- $\alpha$  +/- cytarabine therapy for transplantation-ineligible patients who fail to respond to dose escalation within 3 months or who have mutations of *abl* that confer resistance
- IRB approved therapeutic protocols for clinical trials of new, experimental agents\*
- Treatment with hydroxyurea or busulfan in patients in whom IFN- $\alpha$  may be deemed inappropriate\*

\* The efficacy of IFN- $\alpha$  after imatinib mesylate failure is unknown as there are no available data.

### **Recommendation #10**

The CCGM-CML strongly recommends standardized Q-PCR testing for all Canadian patients with CML. Mutational analysis should be regionalized in even fewer centres.

#### **LRCP convention:**

[[We are participants in Canadian standardization activities.](#)]

### **Reference:**

1. Laneuville et al. Recommendations of the Canadian Consensus Group on the Management of Chronic Myeloid Leukemia. *Current Oncology* 2006; 13(6):1-20

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