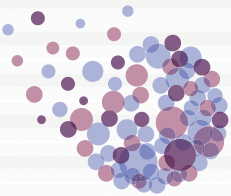
CML TREATMENT GUIDELINES

VERSION 2019



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INITIAL **INVESTIGATION**

- **Propose enrolment in the CML Registry of the CML-MPN Quebec Research Group (GQR LMC-NMP);**
- **Medical history:**
  - Question for vascular disease (neurologic, cardiologic or peripheral), high blood pressure, diabetes, dyslipidemia, pancreatitis, respiratory disorders, and tobacco use;
  - Information on siblings if patient is eligible for allogenic stem cell transplant;
  - Pharmacologic history to identify drugs metabolized by CYP3A4 and drugs that prolong QTc.
- **Physical examination including spleen size (in cm below the costal margin);**
- **Blood analysis*:**
  - CBC (with differential and smear), electrolytes, creatinine, LDH, uric acid, bilirubin, AST, ALT, Alk P., GGT, fasting glucose, amylase, lipase, cholesterol (total, LDL, HDL), HbA1c;
  - Molecular diagnosis: breakpoint identification and determination of the number of *BCR-ABL1* transcripts (% IS) by RT-PCR on blood;
  - Screening of HBV is recommended at the start of treatment (HBsAg, anti-HBc and anti-HBs).
- A **bone marrow aspiration, biopsy and a marrow karyotype** are mandatory at diagnosis to establish the phase of the disease and detect additional cytogenetic aberrations, other than the Philadelphia chromosome, with impact on prognosis (2nd Philadelphia chromosome, gain of chromosome 8 or 19, isochromosome 17q);
- An ECG for QT interval assessment is appropriate before initiating a tyrosine kinase inhibitor (TKI).
- An echocardiogram should be considered.

* CBC: complete blood count; LDH: lactate dehydrogenase; AST: aspartate aminotransferase; ALT: alanine aminotransferase; Alk P.: alkaline phosphatase; HBV: Hepatitis B virus; GGT: gamma glutamyltransferase;
LDL: low density lipoprotein; HDL: high density lipoprotein;
HbA1c: glycated hemoglobin; IS: International Scale;
RQ-PCR: real time quantitative polymerase chain reaction.

INITIAL **INVESTIGATION** (CONT'D)

- **Use the MD Anderson Cancer Center (MDACC) criteria to determine accelerated and blast phases;**
  - Accelerated phase if at least one of the following criteria is present:
  - Blasts in blood ≥ 15%;
  - Blasts and promyelocytes in blood ≥ 30%;
  - Basophils in blood ≥ 20%;
  - Persistent thrombocytopenia (< 100 X 10^9/L) unrelated to treatment;
  - Clonal evolution.
  - Blast phase if at least one of the following criteria is present:
  - Blasts in blood or marrow ≥ 30%;
  - Chloroma.
- **Sokal score** should be calculated and recorded in the patient's file at diagnosis, prior to treatment, based on the following parameters:
  - Age;
  - Spleen size (cm below costal margin);
  - Platelet count (x 10^9/L);
  - Blasts in blood (%).
  - Website to calculate:
  - https://www.leukemia-net.org/content/leukemias/cml/euro__and_sokal_score/index_eng.html
  - Risk category:
  - Low < 0,8;
  - Intermediate: 0,8-1,2;
  - High: >1,2.
- The EUTOS Long Term Survival Score (ELTS) can also be calculated (with the same parameters as the Sokal score)
  - https://www.leukemia-net.org/content/leukemias/cml/elts_score/index_eng.html
  - Risk category:
  - Low < 1,5680;
  - Intermediate: 1,5681-2,2185;
  - High: >2,2185.

INITIAL **INVESTIGATION** (CONT'D)

- **Evaluation of cardiovascular risk factors:**
  - The calculation of the Framingham Score is suggested by the GQR LMC-NMP and should be recorded in the patient's chart;
  - The Framingham Score allows the evaluation of patient's cardiovascular risk, based on the following parameters:
  - Age;
  - Cholesterol levels (total and HDL);
  - Blood pressure;
  - Tobacco use;
  - Diabetic status.

    It is important to determine this score and to consider it in the therapeutic management of patients with CML.
  - Website to calculate the score:

    → https://www.mdcalc.com/framingham-risk-score-hard-coronary-heart-disease
  - For more information, see the « Evaluation and management of cardiovascular risks » section on our website (gqr-lmc-nmp.ca)

TREATMENT **TARGETS**

- Disease control - for all patients
  - Reaching therapeutic milestones
  - Optimization of treatment tolerance
- Treatment free remission (TFR) - for selected patients in chronic phase.

CHRONIC PHASE (CP) CML **TREATMENT**

- **The following treatments are recommended in first line :**
  (in alphabetical order)
  - Bosutinib 400 mg QD;
  - Dasatinib* 100 mg QD;
  - Imatinib** 400 mg QD;
  - Nilotinib 300 mg BD;
  - Approved clinical trial.

  * **Dasatinib:**
  - Consider a reduced dose in elderly patients.

  ** **Imatinib:**
  - It is recommended to always administer the same generic drug. Document in the patient's chart the drug source (brand-name or generic drug – Teva, Apotex, Cobalt, PMS, etc...).
- The GQR LMC-NMP recognizes that 2nd generation tyrosine kinase inhibitors (TKI) lead to faster and deeper responses, are associated with less transformation and are globally better tolerated. Their superiority versus imatinib must be balanced with their specific associated toxicities;
- For patients in whom TFR is considered, a 2nd generation TKI is favored for a deeper and faster response, thus increasing the number of candidates eligible for discontinuation.
- For higher risk patients (Sokal, ELTS or Hasford score), 2nd generation TKI are preferred;
- **The selection of a TKI takes into account multiple factors such as :**
  1. The best anti-CML effect for the patient;
  2. Drug availability;
  3. Potential harmful effects on patient-specific co-morbidities (pulmonary, gastrointestinal, cardiovascular, etc).
  4. The treatment target

** **For more information :**
See the « Evaluation and management of cardiovascular risks » section on our website (gqr-lmc-nmp.ca).

CHRONIC PHASE (CP) CML **TREATMENT** (CONT'D)

- The benefits of using a 2nd generation TKI instead of imatinib must be weighed against the increased risk of cardiovascular events associated with a 2nd generation TKI. The risk of cardiovascular events is significantly greater with 2nd generation TKIs in patients with intermediate or high Framingham scores. Treatment decisions must be individualized. With cardiovascular comorbidities**, we believe that 2nd generation TKI should not be a first choice for certain patients such as:

  a) Individuals with symptomatic vascular disease (CVA, myocardial infarction or peripheral vascular disease) and who have other therapeutic options;

  b) Individuals with high Framingham Score (over 20% risk of cardiovascular disease at 10 years), that is unmodifiable and for whom other therapeutic options exist. However, 2nd generation TKI may be a first choice for older patients in whom the high Framingham Score is attributed only to age.

TREATMENT OF MDACC DEFINED ACCELERATED PHASE (AP) CML

- **Patient eligible for allogenic stem cell transplant:**
  - Refer to a center with expertise in evaluation of this therapeutic option.
  - HLA type of patient, siblings and search for an alternate donor if possible.
- **The following treatments are acceptable: (in alphabetical order)**
  - Bosutinib 500 mg QD ;
  - Dasatinib 140 mg QD ;
  - Imatinib 600 mg QD ;
  - Nilotinib 400 mg BID ;
  - Ponatinib 45 mg QD (consider dose reduction with a satisfactory response and discontinuation in the absence of response at 3 months) ;
  - Approved clinical trial.
- Allogenic stem cell transplant remains the therapeutic option of choice. Patients who are ineligible or waiting for a donor are treated with a TKI until disease progression;
- The GQR LMC-NMP favors 2nd or 3rd generation TKI (according to their availability).

TREATMENT
OF MDACC DEFINED BLAST PHASE (BP) CML

- **Patient eligible for allogenic stem cell transplant:**
  - Refer to a center with expertise in evaluation of this therapeutic option.
  - HLA type patient, siblings and search for an alternate donor if possible.
- **For the lymphoid form:**
  - TKI with chemotherapy is preferred.
- **For the myeloid form:**
  - TKI in monotherapy is reasonable, mainly as a bridge to allogenic stem cell transplant.
- **The following treatments are acceptable: (in alphabetical order)**
  - Bosutinib 500 mg QD ;
  - Dasatinib 140 mg QD ;
  - Imatinib 800 mg QD with or without chemotherapy (reduce to 400-600 mg during chemotherapy) ;
  - Nilotinib 400 mg BID ;
  - Ponatinib 45 mg QD (consider dose reduction with a satisfactory response and discontinuation in the absence of response at 3 months) ;
  - Approved clinical trial.
- Allogenic stem cell transplant remains the standard of care. Patients who are ineligible or waiting for a donor are treated with a TKI until disease progression;
- The GQR LMC-NMP recommands 2nd or 3rd generation TKI for their superiority in resistant or refractory disease
  as monotherapy;
- The central nervous system (CNS) should be evaluated and treated if positive. In lymphoid blast phase:
  - Prophylaxis must be added even if the CNS evaluation is negative;
  - If the CNS is positive, experts favor dasatinib.

MONITORING

- CBC every 2 weeks until complete hematological response (CHR) – every 3 months thereafter;
- Electrolytes, renal function, hepatic enzymes, Mg^{2+}, PO^{4}, Ca^{2+}, glucose, lipase every 2 weeks until CHR – every 3 months thereafter;
- Treatment of cardiovascular disease risk factors (cholesterol, diabetes, tobacco use, hypertension) and annual follow-up of these risk factors;
- Electrocardiography (ECG) before and 1-2 weeks after initiation of a 2nd generation TKI (QTc < 500 ms);
- Chest X-Ray only if symptomatic.
- **RT-PCR *BCR-ABL1* every 3 months:**
  - Ensure RT-PCR is done at 3 months (+/- 1 week) after TKI initiation. It is important to notify the laboratory that this is the 3 month test so that results are obtained rapidly (2-3 weeks);
  - Once major molecular response (MMR) (0.1% IS) is achieved and stable for 2 years, it is possible to extend monitoring interval to 6 months.
- **Verify adherence at each visit;**
- **Search for *ABL1* mutations if:**
  - Failure to achieve therapeutic milestones;
  - Expression of *BCR-ABL1* by RT-PCR increases by more than 0.5 log in 2 consecutive blood samples and > 0.1% IS;
  - Lack of response to the introduction of an alternative TKI or new loss of response.
- **Obtain bone marrow karyotype:**
  1. Milestone failure and RT-PCR BCR-ABL1 ≥ 1.0 % IS;
  2. Cytopenias with RT-PCR *BCR-ABL1* < 1.0 % IS to exclude new cases of MDS (rare) or acute leukemia in a Ph-negative clone.

THERAPEUTIC MILESTONES FOR PATIENTS IN CHRONIC PHASE CML

- Milestones established with data from first line imatinib treated patients;
- **Clinical milestones**
  - .Complete hematological response (CHR) at 3 months;
  - .Correction of splenomegaly;
  - .Normal blood count other than mild cytopenia associated with TKI.
- **Molecular milestones:**
  - Early molecular response (EMR) at 6 months:
  - RT-PCR *BCR-ABL1* < 10% IS* (1 log reduction)
  - 12 months:
  - RT-PCR *BCR-ABL1* < 1% IS* (2 log reduction)
  - MMR at 18 months:
  - RT-PCR *BCR-ABL1* < 0.1% IS (3 log reduction)

MANAGEMENT IN CASE OF **PRIMARY THERAPEUTIC MILESTONE FAILURE**

- Verify drug adherence;
- Verify the “halving time” if the data is available (It is possible to consider a patient in failure at 3 months, if the halving time is long and RT-PCR *BCR-ABL1*> 10% IS *);
- Search for *ABL1* mutations;
- Obtain karyotype if RT-PCR *BCR-ABL1*> 1% IS (except for the 6 month milestone).

If first line is imatinib:

- Change for a 2nd or 3rd generation TKI.

*** The result must come from a laboratory that obtained an IS correction factor or that uses an IS internal calibrator.**

MANAGEMENT IN CASE OF **PRIMARY THERAPEUTIC MILESTONE FAILURE** (CONT'D)

If first line is a 2nd generation TKI:

- In the context of EMR, consider a rapid confirmatory control and the halving time before making changes;
- Evaluate stem cell transplant options;
- The following approaches are acceptable:
  - Increase TKI dosage;
  - Change for an alternative TKI (according to *ABL1* mutation analysis results);
  - Approved clinical trial.

MANAGEMENT IN CASE OF **SUSTAINED SERIAL RESISTANCE**

- Sustained serial resistance (SSR) is defined as the failure of a therapeutic milestone after the initiation of a second line of treatment. The conduct in the event of SSR is to:
  - Consult with a center with expertise in CML management;
  - Switch to a 3rd generation TKI(bosutinib or ponatinib):
    - Note that ponatinib is more effective in the third line setting, however bosutinib has less cardiovascular toxicity;
  - Evaluate the patient's stem cell transplant options;
  - Approved clinical trial

CONSIDERATION FOR TREATMENT FREE REMISSION

Criteria required for a TFR attempt

- **A persistent deep molecular response**
  - With an analytical sensitivity of at least 4.5 log;
  - The success of the discontinuation is associated with the duration of the deep response. With imatinib, optimal results are obtained after 5 years. The use of 2nd or 3rd generation TKI could reduce this period;
  - RT-PCR *BCR-ABL1* every 4 weeks with rapid turn around time (2 weeks) for at least the first year of follow-up.

SECONDARY RESISTANCE

Transformation to AP or BP

- Management as AP or BP.

Loss of molecular milestones or a confirmed increase of 0.5 log and remains in CP:

- Verify drug adherence;
- Search for *ABL1* mutations (if RT-PCR *BCR-ABL1* > 0.1 % IS);
- Obtain bone marrow karyotype for assessment of clonal evolution. (if RT-PCR *BCR-ABL1* > 0.1 % IS)

If first line is imatinib:

- Change for a 2nd or 3rd generation TKI;
- Consider allogenic stem cell transplant according to patient's specific situation.

If first line is a 2nd generation TKI the following options are acceptable depending on the condition of the patient and the type of resistance:

- Approved clinical trial;
- Increase nilotinib dosage to 400 mg BID;
- Increase dasatinib dosage to 140 mg daily;
- Change for an alternative TKI (according to *ABL1* mutation analysis results);
- Refer to a center with expertise in allogenic stem cell transplant:
  - HLA type patient, siblings and search for an alternate donor if possible.

MANAGEMENT ACCORDING TO *ABL1* MUTATION TESTING

- The majority of mutations that appear while on imatinib are sensitive to 2nd generation TKI;
- ***ABL1* mutations with distinctive sensitivities:**
  - T315I :
  - Consider allogenic stem cell transplant;
  - Ponatinib;
  - Approved clinical trial.
  - F317L/V/I/C, Q252H, or V299H/L:
  - Nilotinib or bosutinib preferred (take into account comorbidities);
  - Ponatinib, if available, may be an option.
  - E255K/V, Y253H, or F359C/V/I:
  - Dasatinib or bosutinib is preferred (take into account comorbidities);
  - Ponatinib, if available, may be an option.
  - Any other mutation:
  - Nilotinib, dasatinib or bosutinib preferred;
  - Ponatinib, if available, may be an option.

MANAGEMENT OF MOST COMMON SIDE EFFECTS

Common TKI laboratory side effects:

- **Myelosuppression (thrombocytopenia, neutropenia, anemia):**
  - In CP, drug interruption is recommended for neutrophil counts < 1,0 x 10^9/L and platelets < 50 x 10^9/L;
  - Restart at the same dose if recovery < 2 weeks;
  - Reduce imatinib dose to 300 mg daily, dasatinib to 70 mg daily, nilotinib to 400 mg daily, bosutinib to 300 mg daily and ponatinib to 15 mg daily if recovery takes ≥ 2 weeks or meets stopping rules > twice;
  - Consider escalating the dose in the absence of toxicity > 4 weeks after restarting treatment;
  - With more advanced disease, drug interruption is generally avoided but is recommended for neutrophils < 0,5 x 10^9/L or platelets < 10 x 10^9/L :
  - Consider adding growth factors;
  - A bone marrow aspiration/biopsy to re-evaluate cellularity and blast count may help in deciding to continue or interrupt a TKI.
- **Increased transaminases and bilirubin:**
  - For bilirubin > 3 times normal or liver enzymes > 5 times normal (Grade 3 toxicity), a drug interruption is recommended;
  - Ponatinib: If enzymes > 3 times normal (grade 2 toxicity), discontinuation of the drug is recommended;
  - Once toxicity is < 1,5 times normal values, restart TKI at a reduced dose;
  - Consider escalating in 6-12 weeks if toxicity does not reappear;
  - Bosutinib and ponatinib: If enzymes > 3 times normal AND bilirubin > 2 times normal, permanent discontinuation of the drug is recommended.
- **Electrolyte level changes:**
  - Monitor K^+, Ca^{2+} and Mg^{2+} especially at TKI initiation, particularly for 2nd generation TKI, to avoid QTc prolongation;
  - Correct according to standard protocol.

Common TKI non-hematological side effects:

- **Gastrointestinal toxicity:**
  - Diarrhea:
  - Add the BRAT diet (bananas, rice, applesauce and toast)
  - Avoid food products containing lactose, alcohol, laxatives, spicy or fatty foods and caffeine. Eat and drink small amounts of clear foods and fluids frequently;
  - Optimize hydration status;
  - Loperamide (variable dosage depending on stool).
  - Constipation:
  - Avoid mannitol and sorbitol (sugar substitutes) in the diet:
  - Add psyllium/fibers (fruits and vegetables) and optimize hydration;
  - Mild laxative (Lax-a-day).
  - Nausea and emesis :
  - Modify, if possible, drug administration schedule (take at night);
  - With the exception of nilotinib, take with or after a meal;
  - Administer TKI dose in divided dose;
  - Add an anti-emetic (prochlorperazine, metoclopramide) if needed.
  - Dyspepsia :
  - Recommend smaller meals, limiting spices;
  - Raise the bed's headboard and/or maintain sitting or upright position for 1 hour after TKI administration before going to bed;
  - Proton pump inhibitors with imatinib, nilotinib and ponatinib. Long-term suppression of stomach acid with stomach ulcer drugs reduces systemic exposure to dasatinib and bosutinib. If antacids (e.g. aluminum or magnesium hydroxide) are needed, they should be taken 2 hours before or 2 hours after TKI administration.
- **Pruritus, skin rash, and hives:**
  - Hydration with cream, SPF 30+ solar protection, bath with baking soda for pruritus;
  - Hydrocortisone cream;
  - TKI interruption for problematic and/or severe rash and reintroduce TKI at lower dose with dose escalation once resolved;
  - Add oral corticosteroids and /or antihistamine if needed.

MANAGEMENT OF MOST COMMON **SIDE EFFECTS** (CONT'D)

Common TKI non-hematological side effects (cont'd):

- **Muscle, bone and joint pain:**
  - Ca^{2+} (citrate > carbonate) and Mg^{2+} supplementation;
  - NSAID to relieve muscle and bone pain, provided that the platelet count is normal. In patients treated with imatinib, take acetaminophen with caution and limit the dose to a maximum of 1300 mg per day, taken occasionally.
- **Fluid retention (edema):**
  - Reduce sodium load in the diet;
  - If periorbital: Elevate the head during sleep and hydrocortisone 1% topical or 0.25% phenylephrine;
  - Diuretic for severe case (HCTZ vs furosemide if needed);
  - TKI interruption with dose reduction is an option for more problematic cases in CP disease;
  - Ask patients to weigh themselves 1-2 times a week if possible.
- **Headaches:**
  - Avoid all known triggers (caffeine, chocolate, etc...);
  - Maintain good hydration and sleeping habits;
  - Acetaminophen at usual doses for short periods (max 1300 mg / day with imatinib).
- **Tiredness:**
  - Rest when needed and good sleeping habits;
  - Exercise and training program according to physical capacity;
  - Often related to laboratory perturbations; consider correcting anemia (erythropoietin stimulating agents, transfusions) and electrolyte disorders (PO^4, Ca^{2+} replacement).

TKI specific side-effects:

- **Nilotinib:**
  - Increased pancreatic enzymes (amylase, lipase):
  - Drug interruption for lipase increase of Grade 3 (2 to 5 times normal) or higher;
  - Once Grade 1 or better, restart at 400 mg daily with blood monitoring for relapse.
  - Indirect hyperbilirubinemia:
  - Drug interruption for bilirubin increase of Grade 3 (3 to 10 times normal) or higher;
  - Once Grade 1 or better, restart at 400 mg daily with blood monitoring.
  - Hyperglycemia:
  - Stop medication when blood sugar is uncontrolled despite all available treatments.
- **Dasatinib:**
  - Pleural and pericardial effusion:
  - Consider/eliminate alternative causes;
  - If asymptomatic, imaging is recommended (drug does not need to be interrupted);
  - If symptomatic:
    - Drug interruption;
    - Diuretic and/or corticosteroid can suffice if Grade 2;
    - Pleurocentesis and pleural fluid analysis is recommended for Grade > 2;
    - Once resolved, restart medication at reduced dose and re-evaluate dose according to clinical and laboratory evolution.
  - Bleeding:
  - More frequent in more advanced phases but platelet dysfunction has been documented in vitro;
  - Monitor for cytopenias, avoid regular use of antiplatelet agents, anticoagulants and / or NSAID if possible;
  - Hold medication;
  - Platelet transfusion with active bleeding.

MANAGEMENT OF MOST COMMON **SIDE EFFECTS** (CONT'D)

TKI specific side-effects (cont'd):

- **Dasatinib (cont'd):**
  - Shortness of breath:
  - Review detailed medical history for possible etiology;
  - Consider pulmonary hypertension;
  - Obtain chest X-Ray, proBNP dosage, and consider measuring pulmonary arterial pressure;
  - Stopping medication usually resolves pulmonary hypertension. Refer to specialist and formal pulmonary arterial pressure evaluation in the appropriate setting.
- **Bosutinib:**
  - Diarrhea:
  - Consider dose escalation (300 mg with weekly increases) as tolerated when starting in CP;
  - Follow the non-pharmacological measures mentioned on page 14;
  - Treat symptoms as soon as possible with loperamide;
  - If Grade 3/4, interrupt dose and restart medication at 300 to 400 mg daily once resolved (≤ Grade 1).
  - Pleural and pericardial effusion:
  - Diuretic and/or corticosteroids;
  - Interruption/dose reduction; once resolved, restart medication at reduced dose.

- **Ponatinib**
  - Arterial obstruction and venous thromboembolism:
  - Evaluate the patient's cardiovascular status before starting treatment and actively manage cardiovascular risk factors;
  - If vision decreases or becomes blurred, patients require formal ophthalmological examination (including ophthalmoscopy);
  - Stop treatment if arterial occlusion or venous thromboembolism is suspected;
  - Advise patients to go to the emergency room immediately should they experience any symptoms suggestive of a blood clot: chest pain, shortness of breath, weakness on one side of the body, slurred speech, leg pain or swelling in the legs.
  - Hemorrhage:
  - More frequent with advanced phase;
  - Monitoring for cytopenias, avoid regular use of antiplatelet agents and / or NSAID if possible.
  - Congestive heart failure and left ventricular dysfunction:
  - The ejection fraction of the left ventricle must be evaluated in all patients: before the start of treatment, three months after the start of treatment and whenever clinically justified;
  - Stop treatment in patients with new onset heart failure or worsening heart failure.
  - Treatment should be discontinued or the dose reduced in patients with no clinical evidence of congestive heart failure, but with an ejection fraction < 50% and > 10% below the levels measured at the baseline visit.

The current guidelines are intended as a reference for management strategies pertaining to CML. These guidelines are a consensus of the CML-MPN Quebec Research Group based on published data as well as expert opinion and were developed during consensus meetings. They do not in any way replace clinical judgment and are not intended to establish treatment protocol that would be applicable to all cases of CML.

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