CML TREATMENT GUIDELINES
2019 short version

INITIAL INVESTIGATION

1) Enrolment in the CML Registry

2) Medical history: Question for vascular disease (neurologic, cardiologic or peripheral), AHT, diabetes, dyslipidemia, pancreatitis, respiratory disorders, tobacco use and pharmacologic history (CYP3A4 and QTc)

3) Physical examination including spleen size

4) Blood analysis: CBC (diff. and smears); electrolytes; biochemistry incl. hepatic, renal, pancreatic, lipid and glucose (incl. HbA1c) profiles; molecular diagnostic incl. breakpoint identification and quantification of BCR-ABL transcripts (% IS) by RQ-PCR; HBV screening.

5) A bone marrow aspiration, a biopsy and a marrow karyotype are mandatory at diagnosis to establish the phase of the disease and detect additional cytogenetic aberrations with impact on prognosis.

6) The Sokal or ELTS score must be calculated at diagnosis and recorded in the patient's file:

→ https://www.leukemia-net.org/content/leukemias/cml/euro__and_sokal_score/index_eng.html

→ https://www.leukemia-net.org/content/leukemias/cml/elts_score/index_eng.html

7) Evaluation of cardiovascular risk factors using the Framingham Score:

→ https://www.mdcalc.com/framingham-risk-score-hard-coronary-heart-disease

CML TREATMENT ACCORDING TO DISEASE PHASE
(by alphabetical order)

Chronic Phase (CP)

Bosutinib	400 mg QD
Dasatinib*	100 mg QD
Imatinib**	400 mg QD
Nilotinib	300 mg BID
Approved clinical trial	

* Dasatinib: Consider a reduced dose in elderly patients.

** Imatinib: Administer the same generic drug and document in the patient's chart the drug source (brand-name or generic drug).

- For high risk patients, 2nd generation TKI are preferred

Accelerated Phase (AP)

- Refer to a center with expertise in allogenic stem cell transplant

Bosutinib	500 mg QD
Dasatinib	140 mg QD
Imatinib	600 mg QD
Nilotinib	400 mg BID
Ponatinib	45 mg QD ***
Approved clinical trial	

- 2nd generation TKI are preferred to imatinib.

Blast Phase (BP)

- Refer to a center with expertise in allogenic stem cell transplant

Bosutinib	500 mg QD
Dasatinib	140 mg QD
Imatinib	800 mg QD +/- chemotherapy (reduce to 400-600 mg during chemotherapy)
Nilotinib	400 mg BID
Ponatinib	45 mg QD***
Approved clinical trial	

- Patients that are ineligible for transplant or waiting for a donor are treated with a TKI
- For the **lymphoid form**, a TKI with chemotherapy is preferred
- For the **myeloid form**, a TKI in monotherapy is reasonable, mainly as a bridge to a stem cell transplant
- The CNS should be evaluated and treated if positive. In lymphoid blast phase :
  - Prophylaxis must be added even if the CNS is negative
  - If the CNS is positive, experts favor dasatinib

*** consider dose reduction with a satisfactory response and discontinuation in the absence of response at 3 months

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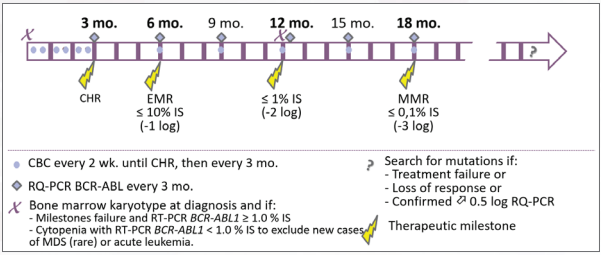
MONITORING AND THERAPEUTIC MILESTONES



- **Ensure RQ-PCR is done at 3 months (+/- 1 week) after TKI initiation.**
- ECG before and 1-2 weeks after initiation of a 2nd generation TKI
- Chest X-Ray only if symptomatic
- Follow-up and treatment of cardiovascular risk factors (cholesterol, diabetes, tobacco use, AHT)

PRIMARY THERAPEUTIC MILESTONE FAILURE

- Verify adherence
- Search for *ABL1* mutations

If 1st line is imatinib:

- Change for 2nd generation TKI

If 1st line is a 2nd generation TKI:

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

SECONDARY RESISTANCE

AP or BP transformation:

- Management as above

Loss of CHR, loss of CCR, loss of MMR or confirmed ↗ 0.5 log and remains in CP:

- Verify adherence
- Search for *ABL1* mutations
- Bone marrow karyotype to search for clonal evolution

  If 1st line is imatinib:
  - Change for 2nd generation TKI
  - Consider transplant option

  If 1st line is a 2nd generation TKI:
  - Refer to a center with expertise in transplantation
  - ↗ dosage
  - Approved clinical trial
  - Change for an alternative TKI according to *ABL1* mutation analysis results

ABL MUTATIONS

T315I	• Allograft • Ponatinib • Approved clinical trial
F317L/V/I/C, Q252H, V299H/L	• Nilotinib or bosutinib preferred (take into account comorbidities) • Ponatinib, if available, may be an option
E255K/V, Y253H, F359C/V/I	• Dasatinib or bosutinib 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

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