

Recommendations from the European LeukemiaNet for the Management of chronic myeloid leukemia (CML)

Definitions of optimal response, suboptimal response, failure and warnings for previously untreated patients with early chronic phase CML who are treated with Imatinib 400 mg daily.

New recommendations are marked in yellow.

Time	Optimal response	Suboptimal response	Failure	Warnings
Diagnosis	N/A	N/A	N/A	High Risk CCA/Ph+ ³
3 mon.	CHR, at least Minor CgR	No CgR	Less than CHR	N/A
6 mon.	At least PCgR	Less than PCgR	No CgR	N/A
12 mon.	CCgR	PCgR	Less than PCgR	Less than MMR
18 mon.	MMR	Less than MMR	Less than CCgR	N/A
Any time (during treatment)	Stable or improving MMR	Loss of MMR Mutations ¹	Loss of CHR, Loss of CCgR, Mutations ² CCA/Ph+ ³	Increase in transcript levels CCA/Ph-

mon.: Months after diagnosis N/A: Not applicable CCA: Clonal chromosome abnormalities

¹ BCR-ABL1 kinase domain mutations still sensitive to imatinib, ² BCR-ABL1 kinase domain mutations poorly sensitive to imatinib or other TKIs, ³ CCA/Ph+ is a "warning" factor at diagnosis, although its occurrence during treatment (i.e., clonal progression) is a marker of treatment failure. Two consecutive cytogenetic tests are required and must show the same CCA in at least two Ph+ cells.

Treatment recommendations

Chronic phase (CP)		
1st line	All patients	Imatinib 400mg daily
2nd line (after imatinib)	Toxicity and intolerance	Dasatinib or nilotinib
	Suboptimal response	Continue imatinib same dose; or test high dose imatinib, dasatinib, or nilotinib
3rd line	Failure	Dasatinib or nilotinib AlloHSCT in patients who have experienced progression to AP/BP and in patients who carry the T315I mutation
	Dasatinib or nilotinib sub-optimal response	Continue dasatinib or nilotinib, with an option for alloHSCT in patients with warning features (i. e., prior hematologic resistance to imatinib, mutations), and in patients with an EBMT risk score ≤2
	Dasatinib or nilotinib failure	AlloHSCT
Accelerated and Blastic Phase (AP, BP)		
1st line	Patients who are TKI naïve	AlloHSCT, preceded by imatinib 600 or 800 mg, dasatinib, or nilotinib, in case of mutations poorly sensitive to imatinib
2nd line	Patients with prior treatment of imatinib	AlloHSCT, preceded by dasatinib or nilotinib

- **Optimal Response** means that there is no indication that a change of therapy may improve a survival that is currently projected as close to 100% after 6 to 7 years.
- **Suboptimal Response** means that the patient may still have a substantial long-term benefit from continuing a specific treatment, but the chances of an optimal outcome are reduced, so that suboptimal responders may be eligible for alternative approaches. However, the condition of suboptimal response is transitory by nature.
- **Failure** means that a favourable outcome is unlikely, and that the patient should receive a different treatment, whenever available and applicable. The relevance of these definitions - optimal, suboptimal, and failure - is modulated by the coexistence of warning prognostic factors.
- **Warnings** mean that the characteristics of the disease may adversely affect the response to that therapy and may require a more stringent and careful monitoring.

Provisional definition of the response to second-generation TKIs, dasatinib and nilotinib, as second-line therapy of patients with imatinib-resistant disease in chronic phase

Time	Failure	Warnings
Diagnosis	N/A	Hematologic resistance to imatinib, CCA/Ph+ (i. e., clonal progression), Mutations ²
3 mon.	No CgR, new mutations ²	Minimal CgR
6 mon.	Minimal CgR, new mutations ²	Minor CgR
12 mon.	Less than PCgR, new mutations ²	N/A

Remission definitions and monitoring

	Definition	Monitoring
Hematologic Complete (CHR)	Platelet count < 450 x 10 ⁹ /L WBC count < 10 x 10 ⁹ /L Differential: no immature granulocytes, basophils < 5% Non palpable spleen	Check at diagnosis , then every 15 days until CHR has been achieved and confirmed, then at least every 3 months or as required
Cytogenetic Complete (CCgR)⁴ Partial (PCgR) Minor Minimal None	No Ph+ metaphases 1-35% Ph+ metaphases 36-65% Ph+ metaphases 66-95% Ph+ metaphases > 95% Ph+ metaphases	Check at diagnosis, at 3 months , and at 6 months , then every 6 months until a CCyR has been achieved and confirmed, then every 12 months if regular molecular monitoring cannot be assured. Check always for occurrences of treatment failure (primary or secondary resistances), and for occurrences of unexplained anemia, leukopenia, or thrombocytopenia
Molecular Complete (CMR) Major (MMR)	Undetectable BCR-ABL mRNA transcripts by real time quantitative and/or nested PCR in two consecutive blood samples of adequate quality (sensitivity > 10 ⁻⁴) Ratio of BCR-ABL to ABL (or other housekeeping genes) ≤ 0.1% on the international scale	RT-Q-PCR: Every 3 months , until MMR has been achieved and confirmed, then at least every 6 months Mutational analysis: In occurrences of suboptimal response or failure, always required before changing to other TKIs or other therapies.

⁴ If marrow cell metaphases cannot be obtained or evaluated by chromosome banding analysis, the definition of CCgR may be based on interphase fluorescence in situ hybridization (FISH) of blood cells, provided that it is performed with BCR-ABL1 extrajunctional, dual color, dual fusion, or in situ hybridization probes, and that at least 200 nuclei are scored. CCgR: < 1% BCR-ABL positive nuclei. In many studies, PCgR and CCgR are counted together and reported as major CgR.

References

1. Baccarani M, Cortes J, Pane F, et al. Chronic myeloid leukemia. An update of concepts and management Recommendations of the European LeukemiaNet. J Clin Oncol. 2009, in press.
2. Baccarani M, Saglio G, Goldman J, et al: Evolving concepts in the management of chronic myeloid leukemia: recommendations from an expert panel on behalf of the European LeukemiaNet. Blood 108:1809-1820, 2006.