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Molecular Monitoring of Quantitative BCR-ABL1 of Chronic Myeloid Leukemia (CML) Patients Treated with Imatinib: When should the Test be Done?

Harryanto Reksodiputro A*, Hillmans Tadjoedin, Ikhwan Rinaldi, Djumhana Atmakusuma and Fuji Yanto

*Division of Medical Oncology-Hematology, Department of Internal Medicine, Universitas Indonesia, Jakarta, Indonesia.

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ABSTRACT

Hematological and molecular responses, especially BCR-ABL1 transcripts in peripheral blood, are prognostic and treatment planning parameters used to assess the level of reduction of leukemic cells in Chronic Myeloid Leukemia (CML). Molecular response is assessed with standardized quantitative PCR at 3, 6 and 12 months. Achieving Major Molecular Response (MMR) with BCR-ABL1 transcripts ≤ 0.1% is the goal of treatment with Imatinib. Once TKI therapy has been initiated, BCR-ABL should be done every 3 months until MMR has been achieved and at the interval of 3 to 6 months thereafter. After 12 months, if MMR is achieved, the response can be assessed every 3 to 6 months. Although some inaccurate BCR-ABL findings have been reported, long-term molecular follow-up studies would make it possible to evaluate MMR rates and the prognostic effect of different levels of BCR-ABL transcript reduction given the same complete cytogenetic results.

BACKGROUND

The first generation of Tyrosine Kinase Inhibitor (TKI), Imatinib, has revolutionized the treatment of Chronic Myeloid Leukemia (CML) leading to a significant reduction of the Breakpoint Cluster Region-Abelson murine Leukemia 1 (BCR-ABL1) transcript levels in peripheral blood [1]. Hematological and molecular responses, especially BCR-ABL1 transcripts in peripheral blood, are prognostic and treatment planning parameters used to assess the level of reduction of leukemic cells [2-4] BCR-ABL RQ-PCR represents the scientific paradigm for successful molecular diagnostic monitoring of the targeted cancer therapy. Furthermore, achieving Major Molecular Response (MMR), defined as BCR-ABL1 transcripts ≤ 0.1%, is the goal of treatment with Imatinib due to the association between this level of response and the greater likelihood of disease-free progression [5,6]. However, patients with CML can exhibit various treatment responses including the resistance to Imatinib and they have a higher risk of disease progression [7,8]. The optimal frequency of molecular monitoring after the first generation of TKI of patients with CML has been established [3]. The standardization is needed to properly use for success in therapy.

HEMATOLOGICAL AND MOLECULAR RESPONSE

The simplest treatment monitoring is a hematological response. To achieve Complete Hematological Response (CHR), peripheral blood counts and spleen size must be normal. Blood counts and differentials are required biweekly until CHR has been achieved and confirmed at least every three months thereafter. The treatment goal is to achieve CHR within one to three months after the start of treatment [7].

CLINICAL MOLECULAR MONITORING

Quantitative reverse transcription PCR is the most sensitive tool for assessing disease burden in patients with CML. Quantitative BCR-ABL results are usually expressed as a percentage ratio related to an internal control transcript. RT Q-PCR BCR-ABL with its increased sensitivity and dynamic range has become the main tool used to monitor

Corresponding author: Ary Harryanto Reksodiputro, Division of Hematology and Medical Oncology, Department of Internal Medicine, Faculty of Medicine, Universitas Indonesia/Cipto Mangunkusumo, Jl. Diponegoro No. 71, Jakarta 10430, Indonesia, Tel: 0628161877583; E-mail: arryrek@gmail.com

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CML patients. The long-term molecular follow-up studies of these patients would make it possible to evaluate the major molecular response rates and the prognostic effect of different levels of BCR-ABL transcript reduction given the same complete cytogenetic result [8].

As emerging evidence suggests that the slope of the initial BCR-ABL1 decline may add prognostic information, some studies routinely send blood for RT Q-PCR in all newly diagnosed patients [9,10]. Once TKI therapy has been initiated, RT Q-PCR should be done every 3 months until MMR has been achieved and at the interval of 3 to 6 months thereafter [3,11]. Clinical judgment is needed to determine the appropriate testing interval. For example, it is good practice to monitor patients with adherence issues every 3 months even if they have achieved MMR or a deep molecular response [12].

The European Leukemia Network (ELN) established response goals to be achieved in different intervals of drug exposure, particularly in the chronic phase of CML. Molecular response is assessed with standardized RT Q-PCR at 3, 6 and 12 months. BCR-ABL1 transcript levels ≤ 10% at 3 months, <1% at 6 months calls and ≤ 0.1% from 12 months onward define optimal response, whereas >10% at 6 months and >1% from 12 months onward define failure, mandating a change in treatment. Between optimal and failure, there is an intermediate warning zone requiring more frequent monitoring **(Table 1)** [3]. Because cutoff values are subjected to fluctuation in case of molecular data close to the indicated values, repetition of the tests is recommended.

Table 1. Molecular response based on European leukemia net (ELN).

Months	Optimal	Warning	Failure
3	BCR-ABL1 ≤ 10%	BCR-ABL1>10%	No CHR
6	BCR-ABL1<1%	BCR-ABL1 1-10%	BCR-ABL1>10%
12	BCR-ABL1 ≤ 0.1%	BCR-ABL1 0.1-1%	BCR-ABL1>1%
Then, and at any time	BCR-ABL1 ≤ 0.1%	NA	Loss CHR Loss MMR

Molecular testing must be performed by RQ-PCR on buffy coat of more than 10 mL of blood to measure BCR-ABL1 transcript level expressed as BCR-ABL1% on International Scale (IS) [6]. IS refers to a system based on the conversion of laboratory-specific numerical values to conform to a universal scale [12]. IS as the ratio of BCR-ABL1 transcripts to ABL1 transcripts or other internationally recognized controls transcripts and it is expressed and reported as BCR-ABL1% on a log scale, where 10%, 1%, 0.1%, 0.01%, 0.0032% and 0.001% correspond to the decrease of 1, 2, 3, 4, 4.5 and 5 logs, respectively [3].

The first MR (Molecular Response) level shown to be associated with subsequent outcome was a 3 log reduction of BCR-ABL1 transcripts (MR3.0) or BCR-ABL1 ≤ 0.1%. This is termed Major Molecular Response (MMR). MR4.0, MR4.5 and MR5.0 refer to 4.0 log, 4.5 log and 5.0 log transcript reductions expressed on IS. Good laboratories are able to measure MR4.5or even MR5.0 using conventional technology [12]. The five-year follow-up in the IRIS study showed that no patients progressed to the accelerated or blast phase after 12 months if MMR was achieved [7]. Failure to achieve MMR during Imatinib therapy was associated with inferior outcomes including a significantly shorter PFS.

Complete Molecular Response (CMR) occurs when there is no detectable BCR-ABL mRNA level in the blood, or term as molecularly undetectable leukemia. These definitions depend on the ability of laboratories, as well as their ability to PCR sensitivity required for BCR-ABL1 detection.

RT Q-PCR methodology is complex and requires considerable attention of details to ensure reproducible results. Hence, variation among methods, methodological shortcomings such as suboptimal procedures, performance problems, and operator error may impact on the accuracy and reproducibility of BCR-ABL testing. Although BCR-ABL monitoring is recommended for monitoring signs of relapse and therapy resistance, test accuracy and variability issues are a potential reason why molecular monitoring is not recommended for more extensive use in treatment decisions.

After 12 months, if MMR is achieved, the response can be assessed by RQ-PCR every 3 to 6 months and cytogenetics is required only in case of failure or if standardized molecular testing is not available. MMR is optimal for survival but that deeper response is likely to be required for successful treatment [3].

Patients who discontinue TKIs are usually monitored prospectively on an intended schedule of monthly blood quantitative PCR BCR-ABL1 for 3 months, quarterly for 12 months and every 6 months thereafter until the loss of MMR. However, less frequent monitoring of BCR-ABL1 does not appear to affect outcomes and that discontinuation of TKIs used as first-line treatment or beyond after

resistance or intolerance to first-line treatment appears feasible [13].

CONCLUSION

Molecular response is assessed with standardized quantitative PCR at 3, 6 and 12 months. RT Q-PCR should be done every 3 months until MMR has been achieved and at the interval of 3 to 6 months thereafter. MMR is a 3 log reduction of BCR-ABL1 transcripts ($MR^{3.0}$) or BCR-ABL1 ≤ 0.1%. After 12 months, if MMR is achieved, the response can be assessed by every 3 to 6 months.

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