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Molecular Monitoring of Chronic Myeloid Leukemia (CML): A Current Perspective

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Editorial

Chronic myelomonocytic leukemia (CMML) is a clonal hematopoietic stem cell disorder characterized by the fusion of the Abelson murine leukemia (ABL) gene on chromosome 9 with the breakpoint cluster region (BCR) gene on chromosome 2 which results in expression of an oncoprotein, termed BCR-ABL tyrosine kinase that plays a causal role in the pathogenesis of the disease [1].

Until a little more than a decade ago, drug therapy for CML was limited to nonspecific agents such as busulfan, hydroxyurea, and interferon-alfa (INF-a). The landscape changed dramatically with the development of small molecule tyrosine kinase inhibitors (TKIs) that share the same therapeutic target, BCR-ABL and act by inhibiting its kinase activity [2].

Evidence now is rising that the achievement of a reduced disease burden early in treatment with TKIs predicts a favorable long-term outcome, and that patients who show suboptimal responses to TKI therapy may benefit from treatment modifications [3]. Therefore, the consistent use of accurate and reproducible techniques to adequately monitor treatment responses and minimal residual disease becomes a critical component of care in the management of patients with CML [4].

In CML, treatment response is measured on several levels: hematologic response, cytogenetic response, and molecular response. Due to the ability of TKIs to induce deep responses that are measurable only with sensitive detection technologies, monitoring molecular responses to TKI therapy in patients with CML in chronic phase (CML-CP) has become a critical component of patient management. Thus, molecular monitoring by measuring BRC-ABL1 expression offers the highest degree of sensitivity compared with monitoring hematologic or cytogenetic responses [5].

Molecular measurements are made by reverse transcriptase quantitative polymerase chain reaction (RT-qPCR) to estimate the amount of BCR-ABL1 mRNA relative to an internal reference gene, most commonly ABL GUSB, or BCR [6,7].

The results are expressed on an International Scale (IS) as a percentage, with 100% BCR-ABLIS corresponding to the International Randomized Study of Interferon and STI571 (IRIS) study standardized baseline and 0.1% BCR-ABLIS being defined as a major molecular response (MMR) [6].

Several studies have found that achievement of specific BRC-ABL1 levels, generally ≤10% (IS), after 3 months of TKIs therapy was a highly significant predictor of long-term outcomes, such as the 12-month probability of MMR and CMR [8].

Recently, considerable interest has focused on the achievement of undetectable BCR-ABL1 (complete molecular response, CMR) because it is now known that a proportion of patients can stop TKIs therapy and maintain remission after a prolonged period of CMR. Thus, more precautions are necessary since the factors leading to molecular relapse and its consequences are not known. Furthermore, accurate definition of deep molecular responses (MR) is therefore increasingly important for optimal patient management and comparison of independent data sets [9].

In summary, monitoring the molecular response to TKI therapy in CML patients is an essential component of modern disease management with achievement of early molecular responses playing an increasingly important role in therapeutic decision making.

Unfortunately, substantial variation of reported BCR-ABL1 values still exists between RQ-PCR methods, despite concerted efforts towards standardization over the past 5 years.

Efforts are now focused on the standardization of monitoring techniques and methods, as standardization is expected to affect both the use of health care resources and long-term patient outcome [10].

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