ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

Section Editor: Susan O'Brien, MD

Continued Therapeutic Response Monitoring in Optimal Responders With CML

Susan Branford, PhD, FFSc (RCPA)
Section Head, Leukaemia Unit
Department of Molecular Pathology
Affiliate Associate Professor, School of Medicine
Affiliate Associate Professor, School of Molecular and Biomedical Science
University of Adelaide
Adelaide, South Australia

H&O What components are involved in molecular monitoring?

SB Molecular monitoring in chronic myelogenous leukemia (CML) has 2 components. The first is the measurement of *BCR-ABL1* mRNA levels to assess response to therapy and measure minimal residual disease. Most laboratories use real-time quantitative polymerase chain reaction (PCR) techniques to measure *BCR-ABL1* levels of peripheral blood. The second component involves sequencing of the *BCR-ABL1* kinase domain to detect kinase inhibitor–resistant mutations. Mutation analysis is usually performed only in cases of suspected inhibitor therapy failure or when there is a rise in *BCR-ABL1* levels.

H&O How has monitoring of treatment response traditionally been performed?

SB Traditionally, the main components of response monitoring have been hematologic monitoring and cytogenetic assessment of bone marrow. Before the era of kinase inhibitor therapy, most patients had levels of leukemia that were detectable by cytogenetic analysis; however, molecular monitoring is more than 300 times more sensitive than cytogenetic analysis. This is important because the majority of patients treated with kinase inhibitors have levels of residual leukemia that are below the level of detection by bone marrow cytogenetic analysis.

H&O Although molecular response closely reflects cytogenetic response, why does cytogenetic assessment remain important?

SB Cytogenetic analysis remains important for patients who have not achieved a complete cytogenetic response. It is also important for patients with loss of any response, including a confirmed loss of a major molecular response (MMR) with at least a 5-fold *BCR-ABL1* rise. Only cytogenetic analysis can detect additional chromosomal abnormalities. These abnormalities in the Philadelphia chromosome–positive cells may be an indication that the disease is progressing, and it is recommended that their detection be considered kinase inhibitor failure.

H&O What is the recommended monitoring for patients with CML?

SB The European LeukemiaNet (ELN) and the National Comprehensive Cancer Network (NCCN) have published recommendations and clinical practice guidelines for monitoring patients (Table 1).[1,2] Monitoring includes cytogenetic assessment until a complete cytogenetic response is achieved and confirmed, and approximately every 12 months thereafter if access to regular molecular monitoring cannot be assured. Molecular monitoring every 3–6 months is appropriate for patients who maintain an MMR. There is a concerted effort to standardize

Table 1. National Comprehensive Cancer Network and European LeukemiaNet Recommendations for Monitoring CML Patients on Tyrosine Kinase Inhibitors

Test	Time Point
Metaphase cytogenetics	1. At diagnosis and 6, 12, and 18 months until CCyR is achieved. If CCyR is achieved at an earlier time point, then there is no need to perform metaphase cytogenetics in stable patients 2. A significant rise in *BCR-ABL1* transcript level without achieving MMR
QRT-PCR for *BCR-ABL1* transcript	1. At diagnosis to establish baseline transcript level and type 2. Every 3 months thereafter until patient is responding to TKIs, and every 3–6 months after achieving MMR 3. If level of *BCR-ABL1* transcript is rising after achieving MMR, then QRT-PCR should be performed every 1–3 months
Kinase domain mutation testing	1. At time of suboptimal response or failure 2. Before switching to another TKI

CCyR=complete cytogenetic response; MMR=major molecular response; QRT-PCR=quantitative reverse transcription polymerase chain reaction; TKI=tyrosine kinase inhibitor.

molecular methods to an international reporting scale in order to allow result reporting on a common scale.

H&O What are the causes of imatinib (Gleevec, Novartis) failure, and how can it be assessed?

SB *BCR-ABL1* kinase domain mutations remain a major mechanism of resistance to kinase inhibitors. These are detected in approximately 50% of patients with drug resistance. Most laboratories use Sanger sequencing techniques or high performance liquid chromatography (HPLC) for detection. Newer techniques allow for more sensitive mutation detection, which is important for the detection of subclonal resistant mutations, or to determine whether mutations are compound (more than 1 mutation on the same *BCR-ABL1* molecule) or single mutant clones. This is important since certain compound mutations may cause resistance to newer inhibitors. Other causes of resistance include duplication of the Philadelphia chromosome, additional chromosomal abnormalities in the Philadelphia-positive cells, poor intestinal drug absorption of drug interactions, or perturbed drug influx or efflux. Poor adherence to drug therapy may also be a major reason for imatinib failure. Drug level testing in these cases may identify nonadherence; a rise in *BCR-ABL1* levels is also associated with poor adherence.

H&O Why is MMR considered a very important response?

SB The achievement of an MMR is important because it is associated with a very favorable prognosis. Patients with this response at 12 or 18 months of kinase inhibitor therapy have an extremely low incidence of disease progression to accelerated phase or blast crisis. Furthermore, patients with an MMR have a significantly lower probability of loss of a complete cytogenetic response compared to patients without an MMR.[3] Loss of a complete cytogenetic response is considered treatment failure. Accurate measurement of an MMR using a molecular method that is validated for the international reporting scale allows for an appropriate assessment of this response, which is considered a safe haven. It also allows for comparison of responses among clinical trials.

H&O What is the significance of achieving an MMR for patients treated with new inhibitors?

SB For patients treated with new inhibitors as first-line therapy, the significance of achieving an MMR is just as important as it is for patients who are treated with imatinib. MMR at 12 or 18 months appears to offer protection from disease progression.

H&O What are the biggest remaining challenges in this field?

SB A number of challenges remain. A small number of patients acquire the T315I mutation, which is most commonly detected in patients with blast crisis. This mutation is problematic because it is resistant to the currently approved kinase inhibitors. However, trials are under way using ponatinib, a kinase inhibitor that has proved to be effective against this mutation for patients in chronic phase. Successful treatment of patients who progress to blast crisis remains a major challenge. Irrespective of the initial therapy, once a patient progresses to blast crisis, the outcome is very poor.

The ability to identify patients who are destined to fail therapy at the earliest point possible is very important, as it may allow for early therapeutic intervention. Additionally, despite many years of working toward international standardization and harmonization of molecular methods, the process is still ongoing. The procedure has proved technically challenging and many laboratories remain without a process for standardization. Determining the sensitivity of detection of *BCR-ABL1* is important for treatment discontinuation trials, but remains a major challenge. This is related to variations in the molecular procedures. Inadequate sensitivity may simply be related to the collection of an inappropriate volume of peripheral blood for analysis.

H&O Are there any promising developments on the horizon?

SB Research into targeting pathways or proteins in addition to *BCR-ABL1* is ongoing, and there are new drugs in development or beginning clinical trials, several of which are aimed at targeting leukemic stem cells. The elimination of stem cells may be important for the eventual successful discontinuation of therapy. Four pathways are important in CML progression and offer targeting opportunities: WNT, Hedgehog, AKT/PI3K, and JAK/STAT/PP2A. The advent of massively parallel sequencing may identify additional pathways that are activated as CML progresses and could identify new therapeutic targets. These initiatives may lead to the majority of patients with CML living disease- and therapy-free in the future.

References

1. Baccarani M, Cortes J, Pane F, et al. Chronic myeloid leukemia: an update of concepts and management recommendations of European LeukemiaNet. *J Clin Oncol*. 2009;27:6041-6051.
2. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Chronic Myelogenous Leukemia. Version 2.2012. http://www.nccn.org/professionals/physician_gls/pdf/cml.pdf. Updated July 22, 2011. Accessed November 26, 2012.
3. Hughes TP, Hochhaus A, Branford S, et al. Long-term prognostic significance of early molecular response to imatinib in newly diagnosed chronic myeloid leukemia: an analysis from the International Randomized Study of Interferon and STI571 (IRIS). *Blood*. 2010;116:3758-3765.