

ADVANCES IN LLM

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

Section Editor: Susan O'Brien, MD

Monitoring Treatment Results in Patients With Chronic Myelogenous Leukemia

Jerald P. Radich, MD

Member, Clinical Research Division

Fred Hutchinson Cancer Research Center

Professor of Oncology

University of Washington School of Medicine

Seattle, Wash.

H&O What is the need for monitoring treatment results in patients with chronic myelogenous leukemia?

JR There are several effective ways to treat chronic myelogenous leukemia (CML). Upfront therapy consists of the standard of imatinib (Gleevec, Novartis). There are now alternatives to imatinib for patients who relapse or do not respond to imatinib, the second-generation tyrosine kinase inhibitors dasatinib (Sprycel, Bristol-Myers Squibb) and nilotinib (Tasigna, Novartis). In addition, allogeneic hematopoietic stem cell transplantation is highly effective in chronic-phase disease and can salvage patients with advanced-phase CML. Given that there are several treatment options, it behooves the treating clinician to track treatment response and identify patients who are not responding to frontline therapy and who may benefit from a secondary tyrosine kinase inhibitor or transplantation. It is important to note that patients who do not respond to imatinib or become resistant are at greater risk of developing advanced-phase disease. Given that no treatment modality works as well in advanced-phase as in chronic-phase disease, careful monitoring of treatment results is important in order to institute alternative therapies before this transition to far less treatable disease.

H&O How are treatment results monitored in this setting?

JR The first treatment goal is normalization of the peripheral blood counts, which should occur relatively

quickly. The next goal is cytogenetic response; the standard approach is to use a bone-marrow cytogenetic examination that looks for the Philadelphia chromosome among at least 20 metaphase samples. The treatment goal is complete cytogenetic remission (CCyR), wherein there is no evidence of the Philadelphia chromosome. In chronic-phase disease, at least one half of patients destined to achieve CCyR have done so by 1 year. Remission is expected by 18 months of therapy, or else the patient is considered a treatment failure. Thus, routine monitoring calls for bone-marrow cytogenetic assessment at 6, 12, and 18 months. However, once CCyR is achieved, the clinician can forgo further bone marrow examination unless relapse is suspected. Therefore, a patient who has achieved CCyR at 12 months does not need an 18-month marrow examination.

After a patient has achieved CCyR, there are other, more sensitive, methods of response assessment. The two most commonly used additional methods are fluorescence in situ hybridization (FISH), looking for the *BCR-ABL* breakpoint at a chromosomal structural level in the bone marrow or in peripheral blood, and quantitative polymerase chain reaction (qPCR), which examines *BCR-ABL* mRNA. The sensitivity of FISH varies among different laboratories, but it is approximately 1% (meaning it will detect 1 Philadelphia chromosome-bearing cell per 100 normal cells). A disease burden lower than that level is undetectable via FISH. The sensitivity of qPCR, is approximately 1 CML cell per 100,000 normal cells, far more sensitive than FISH. There is a good deal of documented evidence showing that the assessment of the burden of disease reduction by qPCR yields a great deal of prognostic information; this assay can be used, therefore, for early detection of impending relapse.

H&O When is the use of one assay but not the other indicated?

JR Generally, peripheral blood FISH is recommended in cases in which it is difficult to obtain a sample of bone

marrow for traditional cytogenetic assessment (eg, due to marrow fibrosis). FISH of peripheral blood can be used for monitoring in cases in which a physician cannot find a laboratory to perform qPCR, though this situation is now unusual. The disadvantage of FISH, as noted above, is that it is not as sensitive as qPCR. In addition, the substantial number of reports addressing monitoring described qPCR; as a result, there are no good data with which to guide the physician who wants to use FISH as the monitoring method. Thus, qPCR is considered the monitoring method of choice by both the European and National Comprehensive Cancer Network (NCCN) guidelines.

H&O How does the level of *BCR-ABL* transcripts correlate with prognosis?

JR Several publications have addressed the issue of the correlation of the level of *BCR-ABL* transcripts with prognosis. In particular, data from the International Randomized Study of Interferon vs STI571 (IRIS) suggest that a 3-log reduction in the level of *BCR-ABL* (called major molecular response [MMR]) correlates well with overall survival. The significance of the MMR was established in IRIS as a 3-log reduction from a baseline average of a set of diagnostic samples (ie, not from the reduction of an individual patient's diagnostic value to subsequent values). In the IRIS study, patients who did not achieve CCyR within 12 months had progression-free survival (PFS) of approximately 70%. Of patients who did achieve CCyR within 12 months, greater than a 3-log reduction in *BCR-ABL* was associated with PFS of 97%, whereas those patients with CCyR but less than a 3-log reduction had PFS of 90%. Several studies have shown that a rising qPCR, or the loss of MMR, is associated with a high risk of relapse. Therefore, qPCR can be used to monitor patients and evaluate whether they are maintaining a good response or they are at risk of relapsing on therapy.

H&O What are the treatment options after a patient relapses?

JR If a patient relapses on frontline therapy, the next therapeutic option is typically another tyrosine kinase inhibitor. If a patient has the T315I mutation, however, the approved second-generation tyrosine kinase inhibitors (dasatinib or nilotinib) will not be effective. Such a patient who relapses is a candidate for either investigational therapy or transplantation. Chronic-phase patients who relapse without a T315I mutation can be started on second-generation therapy, and approximately 40–50% will

likely achieve CCyR. Patients who do not demonstrate an improvement after 3 months should be considered for transplantation. It should be noted that any patient who relapses and progresses to advanced-phase disease is a candidate for transplantation.

H&O Is there a need for more advanced assays?

JR There are two unmet needs in the setting of monitoring treatment results in patients with CML. First, there needs to be standardization of the reporting of the results of qPCR. Some laboratories report transcript numbers, whereas some report the ratio of the transcripts to a control gene (and because the control gene used varies among laboratories, so does the ratio). This lack of standardization makes it difficult for a physician to interpret the results of tests reported by different laboratories. Second, a need exists for the development of more sensitive and faster assays. The community—and patients—would benefit from greater mechanization of testing because the molecular assays currently in use are highly labor-intensive, involving a good deal of time, preparation, and training. As a result, many laboratories do not perform molecular assays. If these tests could be automated, which would likely aid in the standardization of reporting results, I believe they would become more widely available.

H&O What efforts are ongoing to improve assays, as well as the understanding of the relationship between transcript levels and prognosis, in this setting?

JR There is an international group that is working toward standardizing qPCR assays and reporting. Moreover, several companies are working on developing assays that will be more automated than those that are currently available.

As a result of IRIS, researchers are now using transcript burden as an endpoint in trials. The current intergroup CML trial is the first such study to use a molecular endpoint as the trial outcome, which is revolutionary in the oncology field. Subsequently, many trials organized by pharmaceutical companies have begun to use molecular endpoints as markers of outcome. Furthermore, there are many ongoing trials evaluating whether intervention at the detection of early molecular relapse has an effect on overall survival. The European and NCCN CML guidelines currently do not call for immediate change of therapy when molecular disease burden is observed to be increasing. It has not been proven that intervention before cytogenetic relapse, at the time of increasing disease burden, affects outcome. Many researchers believe

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intervention at this point should affect outcome, but further data are needed.

H&O Is remission with no detectable transcripts by quantitative PCR necessary?

JR This question is tricky to answer, as a patient can be deemed to be in “molecular remission” by using a suboptimal assay with poor sensitivity. However, it does not appear that a complete lack of detectable transcripts is necessary for patients to achieve durable outcomes. In fact, most patients who achieve MMR do not achieve a complete molecular response, yet, as noted above, they have a spectacular PFS.

Suggested Readings

Hughes T. ABL kinase inhibitor therapy for CML: baseline assessments and response monitoring. *Hematology Am Soc Hematol Educ Program*. 2006:211-218.

Hughes T, Deininger M, Hochhaus A, et al. Monitoring CML patients responding to treatment with tyrosine kinase inhibitors: review and recommendations for harmonizing current methodology for detecting BCR-ABL transcripts and kinase domain mutations and for expressing results. *Blood*. 2006;108:28–37.

Hughes TP, Kaeda J, Branford S, et al. International Randomised Study of Interferon versus STI571 (IRIS) Study Group. Frequency of major molecular responses to imatinib or interferon alfa plus cytarabine in newly diagnosed chronic myeloid leukemia. *N Engl J Med*. 2003;349:1423-1432.

Press RD, Galderisi C, Yang R, et al. A half-log increase in BCR-ABL RNA predicts a higher risk of relapse in patients with chronic myeloid leukemia with an imatinib-induced complete cytogenetic response. *Clin Cancer Res*. 2007;13:6136-6143.

Radich JP, Oehler V. Monitoring chronic myelogenous leukemia in the age of tyrosine kinase inhibitors. *J Natl Compr Canc Netw*. 2007;5:497-504.