

# ADVANCES IN LLM

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

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## Use of PCR Testing in Chronic Myeloid Leukemia



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### **H&O** Approximately how many patients have chronic myeloid leukemia (CML)?

**EJ** CML belongs to a group of disorders called chronic myeloproliferative neoplasms. Approximately 6000 cases are diagnosed each year in the United States, and the prevalence is approximately 70,000 cases. CML is slightly more common in men than women. Previously, the outcome was poor, with a survival of 6 to 7 years. Today, the expected survival is 25 years or longer. Mortality from CML is 1% per year. Long-term survival has led to a rising prevalence, but a plateau is expected in 2050, at which point the number of new cases will equal the number of deaths per year. It is estimated that more than 200,000 patients will be living with CML at that time.

Improvements in the management of CML have been limited to patients with chronic-phase disease, which is the first of 3 phases. Approximately 85% of patients are diagnosed in the chronic phase. The middle phase is known as accelerated disease. The ultimate stage, blast disease, can be lymphoid, myeloid, or biphenotypic. Patients with myeloid blast, advanced-stage disease usually die of their disease within a year. Patients may progress to blast phase without transitioning through the accelerated phase.

### **H&O** What is the genetic characterization of CML?

**EJ** CML is characterized by the 9;22 translocation. Two genes, *BCR* and *ABL1*, combine to create the *BCR-ABL1*

oncogene, a driver event in CML. This abnormality is known as the Philadelphia chromosome. In animal models, transfusion of an animal with *BCR-ABL1* stem cells can create a myeloproliferative disorder. Discovery of the *BCR-ABL1* oncoprotein led to development of the first targeted therapy, imatinib (Gleevec, Novartis), which changed the outcome of the disease. In 2015, a CML patient who is responding well to treatment can expect to live a normal lifespan.

### **H&O** How is CML diagnosed?

**EJ** Occasionally, patients with CML have symptoms such as fever, fatigue, sweats, and early satiety due to splenomegaly. However, many patients are asymptomatic at diagnosis. Often, the diagnosis is made when a blood test is run (for other reasons or as part of a routine physical) and shows leukocytosis with a left shift (immature cells in the blood). If no infection is present, further tests usually include bone marrow aspirate, biopsy, and karyotyping.

Karyotyping is performed to identify the 9;22 translocation or any other abnormalities that can be followed during therapy. If the karyotype does not indicate an abnormality, another option is to perform fluorescence in situ hybridization (FISH) with a probe to detect the *BCR-ABL1* rearrangement.

An important test is the polymerase chain reaction (PCR), which can detect the presence of *BCR-ABL1*. It can be performed on the blood or bone marrow. PCR is more sensitive than karyotyping, and it is capable of

detecting a very low level of *BCR-ABL1* (although at diagnosis, this level is usually high). PCR testing can establish the level of *BCR-ABL1* at baseline, and this initial measurement is compared to later ones to evaluate a patient's response to therapy. A rising PCR level can indicate that the patient is not responding to treatment or has stopped treatment.

### H&O How are PCR test results reported?

**EJ** The results are expressed as a reduction in the mRNA transcripts from the baseline measurement. Previously, results were reported as a log reduction. Currently, a percentage reduction is provided.

A concern with PCR testing is that each laboratory uses its own scale. An International Scale was therefore developed so that results could be compared from laboratory to laboratory (see the table). This scale has standardized the test and allowed comparisons among different laboratories. On the International Scale, a major molecular response is defined as 0.1%. A complete cytogenetic response corresponds to a value of 1% on the International Scale.

I perform PCR using a blood test, not a bone marrow test. I recommend that PCR be performed at a standardized laboratory using the International Scale. One should use the same laboratory for each test.

### H&O How should PCR test results be interpreted?

**EJ** When the disease burden is very low, PCR is usually very sensitive, more so than at the beginning of treatment. Minor fluctuations, from 5-fold to 10-fold, are normal, and patients should not be concerned by them. A minor fluctuation does not indicate loss of response. At my institution, a small increase, such as from 0.04% to 0.08%, will not trigger a change in treatment. Instead, we confirm that the patient is taking his or her medication, and then we repeat the test within 3 months. We do not change therapy when the PCR is below 1%. A consistent increase in PCR, with a loss of more than 1%, should trigger other tests to determine whether the patient is losing his or her response to treatment.

Among patients with CML receiving therapy, PCR levels will drop below 0.1%, indicating a strong response to treatment, in approximately one-third. In another third, the level is between 0.1% and 1%, which indicates a complete cytogenetic response (CCyR), which is also a good outcome. In another third of patients, the PCR keeps changing—rising and falling. If it rises above 1%, then something is wrong. Either the patient is not taking his or her medication, or there is true resistance.

**Table.** Explanation of the International Scale

Log Reduction	Response Achieved	<i>BCR-ABL1</i> /Control Gene Ratio (according to the International Scale)
Baseline		100
-1	Complete hematologic response	10
-2	Complete cytogenetic response	1.0
-3	Major molecular response	0.1
-4	Major molecular response	0.01
-4.5	Complete molecular response—undetectable amount of <i>BCR-ABL1</i> cells	0.001
-5	Complete molecular response—undetectable amount of <i>BCR-ABL1</i> cells	0.0001

### H&O How important is PCR negativity in CML?

**EJ** PCR negativity, also known as a complete molecular response, is defined by *BCR-ABL1* levels that are undetectable or more than 4.5 log reductions from the original baseline value (labeled as MR4.5). It should be noted that patients who achieve a very deep molecular response do not have a survival advantage over those who achieve a CCyR (a PCR of 1% on the International Scale). In clinical trials, a complete molecular response, or MR4.5, might be an indication to discontinue treatment. Several studies are assessing when therapy can be stopped. This approach should be tried only in the context of a clinical trial.

Overall, PCR negativity will be reached by approximately 18% of patients with CML receiving therapy. Several trials, mainly in Europe and Australia, showed that it was possible to eventually stop therapy and manage with close monitoring. Approximately 50% of patients never relapse, meaning they remain in long-term remission. The likelihood that a patient will remain PCR negative is higher among those with low-risk disease treated with tyrosine kinase inhibitors for more than 8 years.

### H&O How do you address concerns from patients about a change in PCR levels?

**EJ** At my institution, we often see patients for a second opinion because their doctor at home recommended a change in therapy as a response to an increase in PCR.

Patients often ask whether they should be concerned about a change in their PCR level. Changes in PCR levels can be confusing. I do not react to a single change in a major way. Before I make any modifications to therapy, I continue to monitor the patient with repeat tests.

### **Disclosure**

*Dr Jabbour is a consultant for BMS, Ariad, and Pfizer. He has received research grants from Ariad, Teva, Pfizer, and Novartis.*

### **Suggested Readings**

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**Editor's Note: This article was corrected in March 2016.**