Treatment Milestones in Chronic Myelogenous Leukemia: Stay the Course or Change Therapy?

Presented by Jerald P. Radich, MD

Abstract

The success of various generations of tyrosine kinase inhibitors in chronic myelogenous leukemia (CML) is well-known, with many patients experiencing long-term benefits from treatment. However, not every patient with CML can tolerate this therapy, shows response to initial treatment, or avoids disease progression or drug resistance. During his presentation at the NCCN 20th Annual Conference, Jerald Radich, MD, shared his thoughts and some supportive data on the critical role of monitoring response at 3 months, the often-neglected yet key issue of patient adherence to therapy, the recommended timing for mutational analysis, and the pressing need to prevent patients from going from chronic-phase disease into accelerated phase/blast crisis. (*J Natl Compr Canc Netw* 2015;13:697–699)

“Early molecular response is a harbinger of good things to come,” declared Jerald P. Radich, MD, Director of the Molecular Oncology Laboratory at Fred Hutchinson Cancer Research Center, Professor of Medicine at University of Washington School of Medicine; and Chair of the NCCN Guidelines Panel for Chronic Myelogenous Leukemia (CML). “The milestone of major molecular response is a safe harbor, and very few bad things happen once you go south of that,” he added.

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Milestones for Monitoring Response

Several milestones can be used to judge response to treatment, and decisions about staying the course or switching therapy should be based on these milestones. The first major milestone, according to Dr. Radich, is complete cytogenetic remission, and the second major milestone is major molecular response.

Early molecular response has predicted a higher probability of experiencing a future major molecular response, revealed Dr. Radich. In fact, data from the IRIS,^{1,2} DASISION,³ and ENESTnd trials have shown that early molecular response is associated with a longer duration of complete cytogenetic response and improved progression-free and overall survival outcomes. Additionally, the finding that not experiencing or losing a major molecular response has been associated with shortened progression-free survival, added Dr. Radich.

Marin et al⁴ reported similar trends, with an overall survival rate after imatinib therapy of more than 90% in those who experienced a molecular response at 3 months compared with less than 60% in those who did not. Dr. Radich called this “quite a dramatic difference at 3 months.” Furthermore, Dr. Radich revealed that the same is true in the second-line setting (with nilotinib or dasatinib). There is a highly significant difference in outcomes at 3 months favoring response over nonresponse, he added.

Importance of Testing at 3 Months

The first valid reason to test patients at 3 months is to assess response to treatment—or in essence nonresponse to treatment. There are 2 very different possible reasons for a poor early response, explained Dr. Radich: poor adherence and poor biology.

Response to initial treatment with a tyrosine kinase inhibitor may be clouded by nonadherence, especially

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with oral agents. Thus, Dr. Radich stressed the importance of patient adherence to treatment, and that the NCCN Guidelines recommend evaluating adherence whenever a milestone is not reached.

Furthermore, investigators in the ADAGIO study evaluated nonadherence to imatinib therapy in patients with CML,⁵ and revealed some disturbing findings. Although physicians, patients, and family members believed that adherence rates were very high, this small study demonstrated an actual adherence rate of only 14.2%.⁵ With a “spectacular” difference in molecular response based on adherence, Dr. Radich called this problem “a failure of both oncologists and patients.”

If adherence is not the cause of poor response, poor biology may be, he noted. According to Marin et al,⁴ a single measurement of *BCR-ABL1* transcripts performed at 3 months may be the best way to identify patients destined to fare poorly, thereby allowing early clinical intervention. “If a patient has poor biology and no cytogenetic response by 6 months, it might be time to think about changing therapy and going to plan B,” suggested Dr. Radich.

And the NCCN Guidelines concur: if the *BCR-ABL/ABL* is less than 10% International standard (IS) at 3 months, it may be time to consider a second-generation agent. The European LeukemiaNet guidelines are a bit more conservative, however: if the *BCR-ABL/ABL* is less than 10% IS at 6 months, they suggest considering switching to another agent.

In addition, when considering a change in therapy, clinicians must consider comorbidities and patient goals, added Dr. Radich. The treatment goals of an 80-year-old patient are usually not the same as those of a 30-year-old patient, he added.

A final reason to assess response at 3 months is the need to begin to think about disease progression and what is associated with it. “If a patient has a poor early response, it should set off a bell that he or she may need more than a tyrosine kinase inhibitor in the future,” advised Dr. Radich.

Disease progression comes early in patients with poor response, and so clinicians may want to consider hematopoietic stem cell transplantation (HSCT) while contemplating a switch to second-line agents. Because the process of securing a donor, performing HLA typing, and assessing insurance parameters may take 3 to 4 months, Dr. Radich suggested that talking to patients at this stage about considering HSCT in a timely fashion may be important.

Although Dr. Radich acknowledged that no data have confirmed the benefit of changing treatment at 3 or 6 months, he briefly mentioned a recent Australian study that supports the efficacy of an early switch to nilotinib after an imatinib-based approach.⁶ This clinical trial, TIDEL-II, reported “some suggestion” of benefit, Dr. Radich noted, and perhaps we may get “some mileage out of changing agents.”

However, cutoffs for response can be problematic, admitted Dr. Radich, and he urged a common sense approach. For instance, “if you have a patient who starts with a high *BCR-ABL* and does not quite make the 10% mark, that is probably very different biologically than someone who does not move at all.”

In fact, Branford et al⁷ recently explored the rate of *BCR-ABL1* decline as a factor in response at 3 months. They contend that how quickly the disease “goes away,” which they call “halving time,” may affect outcomes. “I wouldn’t be surprised if we soon end up moving this molecular testing into starting to make decisions earlier, at 1 to 2 months, but [it is] not yet ready for prime time,” Dr. Radich commented.

Finally, Dr. Radich supported the logic behind not waiting to change therapy. First, he noted that it is unlikely that the risk associated with switching therapies would be greater than the potential benefit. Second, he said it is difficult to fathom biology whereby a patient with poor response at 3 months would magically have a better response at 6 months (unless adherence was an issue).

When to Consider Mutational Analysis

Mutational analysis may provide additional information for patients with an inadequate response. Both the NCCN and European LeukemiaNet offer similar recommendations on the timing of mutational analysis. Genetic testing to identify a possible mutation is indicated for patients in chronic phase whose *BCR-ABL/ABL* transcript levels are greater than 10% IS or who have less than a partial cytogenetic response at 3 and 6 months, stated Dr. Radich. In addition, he said, if patients do not reach milestones or reach them and then lose them, that would be the time to perform mutational testing.

The NCCN Guidelines for CML note that decisions on different treatment options should be based

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on BCR-ABL kinase domain mutation status. For instance, ponatinib would be preferred for *T315I* mutation; and for a *F317L* mutation, dasatinib should not be considered, as it has shown no activity against this mutation, said Dr. Radich.

The Ticking Biologic Clock

Dr. Radich closed with a brief mention of the importance of preventing patients with chronic-phase disease from progressing to accelerated phase/blast crisis. “There is a point of no return in CML biology,” he declared (Figure 1). In fact, most cases of progression to accelerated phase/blast crisis in the IRIS trial occurred early.^{1,2}

“The biologic clock is ticking,” he stressed. “The problem is when you see a patient in your office, you

can’t tell how long he or she has had CML: 1 month or 10 years before diagnosis.” Some patients are diagnosed with relatively advanced disease and progress more quickly. Furthermore, the molecular biology of disease progression and poor response appear to be correlated, concluded Dr. Radich.

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Figure 1 Length bias and progression: is there a point of no return?