

Monitoring Molecular Response to Tyrosine Kinase Therapy in Chronic Myelogenous Leukemia

Presented by Jerald P. Radich, MD

Abstract

The dramatic decline in mortality rates in chronic myelogenous leukemia (CML) is a direct result of the advent of tyrosine kinase inhibitors (TKIs) and the dawning of the targeted era. Although many patients experience long-term benefits from imatinib or related agents, problems with resistance and tolerance dampen the outcomes for many others. During his presentation at the NCCN 19th Annual Conference, Dr. Jerald Radich reviewed the ever-expanding menu of TKIs for CML and shared his thoughts on resolving the clinical questions regarding when to start which drugs, how to sequence the drugs, and how best to decide when to change the therapeutic tack. (*J Natl Compr Canc Netw* 2014;12:817–820)

“Chronic myelogenous leukemia is where all the other leukemias and solid tumors would like to go,” declared Jerald P. Radich, MD, Director, Molecular Oncology Lab, Fred Hutchinson Cancer Research Center, Seattle, and a member of the NCCN Guidelines Panel for Chronic Myelogenous Leukemia. Chronic myelogenous leukemia (CML) is the first disease with a specific molecular target that has made an impact in the natural course of the disease, and the success story with the tyrosine kinase inhibitor (TKI) imatinib is well-known. The embarrassment of riches in CML continues, with the emergence of both second- and third-generation TKIs; however, not every patient with CML tolerates therapy, has a response to

initial treatment, or avoids relapse. Thus, improvements in both therapeutic options and in decision-making skills are needed in the care of patients with CML.

Ever-Expanding Menu of TKIs for CML: Yet Reasons to Improve

The change in survival in early chronic phase CML as a result of TKI therapy has been nothing short of remarkable. “This shows how the power of a really good drug with a defined target can impact the natural history of disease,” explained Dr. Radich. The long-term outcomes from the well-known International Randomized Study of Interferon vs STI571 (IRIS) trial,¹ which are now out to 10 years, show an overall survival rate of nearly 90%, which Dr. Radich coined “absolutely phenomenal.”

However, a closer look at sustained responses with imatinib suggests problems with relapse and an event-free survival of closer to 60%, according to the Hammersmith Hospital experience in the United Kingdom.² In the IRIS trial, Dr. Radich noted that the event-free survival is about 50%. “Imatinib is still great but maybe not as great as at first blush,” he acknowledged. Although many patients who respond to imatinib are likely to experience long-term benefits, about one-third of patients do not.² Reasons for a suboptimal response include an inability to tolerate imatinib therapy, no initial response, and a response followed by relapse.

And so the later-generation TKIs emerged. Now, newly diagnosed patients with chronic phase CML may be offered the second-generation agents nilotinib or dasatinib, and for those who are intolerant to imatinib or who have resistant disease, the newest-generation agents bosutinib or ponatinib may offer promise.

Dr. Radich briefly reviewed the clinical trial data behind the use of nilotinib and dasatinib in CML,³⁻⁶

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suggesting that they appear to be better than imatinib in the short term. The initial report from the ENESTnd study showed that the major molecular response (MMR) rate—a “safe harbor” according to Dr. Radich—for nilotinib was nearly twice that for imatinib at 12 months.³ At 4-year follow-up, nilotinib continued to show a benefit over imatinib, with higher rates of early molecular response and a lower risk of disease progression.⁴

Similar results were obtained with dasatinib in the DASISION trial.^{5,6} At 12-month follow-up, dasatinib induced significantly higher and faster rates of complete cytogenetic response and MMR compared with imatinib.⁵ And 4-year follow-up continued to support dasatinib as first-line treatment for patients with newly diagnosed chronic phase CML.⁶

There was a remarkably similar MMR at 12 months between the 2 studies, admitted Dr. Radich, and a 10% gain in complete cytogenetic response with second-generation agents in both trials. In addition, imatinib appears to be inferior to these newer agents in preventing transformation of disease to accelerated phase/blast crisis, he added.

However, in terms of long-term outcomes such as overall and progression-free survivals, Dr. Radich revealed that none of the second-generation agents has proved to be better than imatinib thus far. For example, in the DASISION trial, 4-year progression-free survival rates were about 90% for both imatinib and dasatinib, and overall survival rates were between 92% and 93% for both agents.⁶

Treatment Considerations Guided by Response Milestones

Dr. Radich explored the clinical decision-making regarding the selection of therapies for CML and emphasized that response milestones as listed in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for CML should guide the way. For upfront therapy, Dr. Radich noted that one could start with either imatinib or one of the newer agents, based on clinical features (such as the Sokal score), comorbidities, and treatment goals. Regardless of the first agent used, it is important to give initial therapy a fair trial before considering it ineffective, he added.

The first milestone is the 3-month BCR-ABL/ABL percentage. According to the NCCN Guidelines, if the BCR-ABL/ABL is less than 10% (indica-

tive of a lack of response), it may be time to consider a second-generation agent. However, the European LeukemiaNet (ELN) guidelines are a bit more patient: if the BCR-ABL/ABL is less than 10% at 6 months, they suggest considering a switch to another agent, noted Dr. Radich.

“Frankly, there are no data [that show] that switching at 6 months makes any difference either,” admitted Dr. Radich. However, “we do know that some patients who don’t reach 10% by 3 months will progress to accelerated phase or blast crisis before 6 months, so you lose some of those people if you are too patient.”

Moreover, early MMR appears to have long-term prognostic significance.⁷ The IRIS trial showed a strong association between the degree to which BCR-ABL transcript numbers are reduced by therapy and long-term clinical outcomes, supporting the use of time-dependent molecular measures to determine optimal response to therapy. According to Marin et al,⁸ patients who experienced a molecular response at 3 months had a higher probability of overall survival than did those who had transcript levels greater than 10% (93% vs 57%). In fact, for patients treated with either first-line imatinib or dasatinib, BCR-ABL reduction to at least 10% at 3 months was linked to an increased likelihood of experiencing cytogenetic complete response by 12 months and MMR by 24 months.⁹

Another consideration in predicting response is treatment adherence. Response to initial treatment with a TKI may be clouded by compliance, especially with oral agents, said Dr. Radich. “If the BCR/ABL level goes up, it is possible that the patient quit taking the drug,” he noted.

If a patient does not experience a BCR-ABL/ABL of 10% or less or partial cytogenetic response to imatinib by 3 to 6 months, Dr. Radich recommended switching therapy to one of the newer-generation TKIs. In such cases, patients may reach complete cytogenetic response with nilotinib, for instance, at 12 months; then by 18 months, their BCR-ABL/ABL may climb back up to greater than 10%. At this point, for patients with an inadequate response or a loss of response, Dr. Radich would consider mutational analysis.

Both NCCN and ELN offer similar recommendations on the timing of mutational analysis. Genetic testing to identify a possible mutation is indicated

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for patients in chronic phase whose BCR-ABL/ABL transcript levels are greater than 10% or who have less than a partial cytogenetic response at 3 and 6 months, stated Dr. Radich. Patients who have a 1-log increase in BCR-ABL/ABL transcript levels and loss of MMR or have disease progression to accelerated or blast phase should also undergo mutational analysis.

“Once you start getting a mutation, there is a worry among us that resistance is forever,” warned Dr. Radich. “The most worrisome mutations, which affect what kind of drugs you can use, are the T315I and all of those in the so-called T-loop.” Ponatinib is the only drug with activity against the T315I mutation.¹⁰

A good time to discuss the option of transplantation with patients and family members and to line up a donor search is during consideration of second-line agents, noted Dr. Radich, because it may take about 3 to 4 months to secure a donor. Then, if patients respond to second-line therapy, the transplant can be put on hold, he added. If patients do not respond to second-line therapy, transplant would be the next option. It is important to move patients at this stage in a timely fashion, because accelerated blast crises cannot be helped by TKIs or chemotherapy but only by transplantation, cautioned Dr. Radich.

Cardiovascular Class Effect of Newer Agents for Resistant Disease

Over the past few years, newer TKIs such as ponatinib and bosutinib have been approved by the FDA for imatinib-resistant chronic phase CML. Accord-

ing to the 2014 NCCN Guidelines for CML, recommended treatment options such as these are based on BCR-ABL kinase domain mutation status (Table 1). For instance, ponatinib is the preferred choice for patients who have a T315I mutation, although omacetaxine, transplantation, and clinical trial are other alternatives. As for bosutinib, a dual Src/Abl TKI, it represents a novel treatment option for patients who have chronic phase CML after treatment with multiple TKIs.¹¹

Dr. Radich called ponatinib a “remarkable story,” although its horizon has changed a lot over the past 6 months. According to the results of the PACE study,¹⁰ 56% of 267 patients with chronic phase CML had a major cytogenetic response to ponatinib, and 70% of these patients had a T315I mutation. The responses appeared to be durable, with a 91% estimated rate of sustained major cytogenetic response of at least 12 months.¹⁰

However, at 2-year follow-up in December 2013, the FDA issued a boxed warning for ponatinib regarding the risk of cardiovascular effects. Up to 27% of patients treated with this agent experienced vascular occlusion and arterial events, some serious, including myocardial infarction, stroke, stenosis of larger arterial vessels of the brain, and severe peripheral vascular disease, noted Dr. Radich. However, no such action was taken in Europe regarding these cardiac effects, he remarked.

Cardiovascular events seem to be a class effect with the newer-generation TKIs,⁴ said Dr. Radich, although not with imatinib. For instance, in the ENESTnd trial,⁴ selected cardiovascular events were

Table 1 NCCN-Recommended Treatment Options Based On BCR-ABL Kinase Domain Mutation Status	
Mutation	Treatment Options
T315I	Ponatinib, omacetaxine, HSCT, or clinical trial
V299L	Consider nilotinib, ponatinib, or omacetaxine
T315A	Consider nilotinib, imatinib, bosutinib, ponatinib, or omacetaxine
F317L/V/I/C	Consider nilitinib, bosutinib, ponatinib, or omacetaxine
Y253H, E255K/V, F359V/C/I	Consider dasatinib, bosutinib, ponatinib, or omacetaxine
Any other mutation	Consider dasatinib, nilotinib, bosutinib, ponatinib, high-dose imatinib, or omacetaxine

Abbreviation: HSCT, hematopoietic stem cell transplant.

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noted by 5 years with nilotinib, he added. However, about 85% of patients with such an event had at least one risk factor and were not optimally managed for hyperglycemia and hypercholesterolemia. When considering the use of ponatinib, Dr. Radich recommended performing a good screen for cardiovascular risk factors. “For those with aggressive disease, the risk of going into accelerated phase or blast crisis that will kill them is probably greater than their odds of having an arterial problem,” he concluded.

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