Monitoring Response to Tyrosine Kinase Inhibitor Therapy, Mutational Analysis, and New Treatment Options in Chronic Myelogenous Leukemia

Presented by Jerald P. Radich, MD

Abstract

Unlike in other leukemias, survival rates have climbed dramatically in early-phase chronic myelogenous leukemia (CML). This improvement in long-term prognosis is primarily the result of the tyrosine kinase inhibitor (TKI) imatinib and its second-generation cousins nilotinib and dasatinib. In his presentation at the NCCN 18th Annual Conference, Dr. Jerald P. Radich reviewed the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) recommendations for monitoring response to treatment with the TKIs, which center on complete cytogenetic response, and the role of mutational analysis for guiding treatment decisions in the setting of imatinib resistance. He also offered a brief mention of 2 new agents recently approved for resistant CML—ponatinib and bosutinib. (JNCCN 2013;11:663–666)

No disease has been more educational about how to move from basic understanding of molecular genetics to actual clinical care than chronic myelogenous leukemia [CML],” announced Jerald P. Radich, MD, Director of the Molecular Oncology Lab at the Fred Hutchinson Cancer Research Center in Seattle, Washington, and a member of the CML Panel of the NCCN. A “spectacular” difference has been seen in survival in early-phase CML with the targeted agents. In his presentation at the NCCN 18th Annual Conference, Dr. Radich took stock of CML in 2013, noting improvements that include multiple tyrosine kinase inhibitors (TKIs) and sensitive measures of disease burden and thus response to therapy. Transplant also remains an effective salvage regimen that is independent of BCR-ABL activity, he added.

Monitoring Response to Treatment With TKIs

“Cytogenetics has always been the gold standard,” Dr. Radich explained. “We really want a complete cytogenetic response [CCyR], which is 0% Philadelphia chromosome-positive (Ph+) marrow metaphases,” as they correspond to long-term outcomes such as progression-free and overall survival (OS).

The treatment options recommended by the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for chronic-phase CML include imatinib, nilotinib, and dasatinib. These second-generation agents tend to be preferred over higher doses of imatinib, as that approach is more toxic, explained Dr. Radich.

The data supporting imatinib for chronic-phase CML came from the well-known IRIS study. The trial was stopped at 12 months because the difference in cytogenetic response rates was so large, according to Dr. Radich, with a 70% CCyR rate with imatinib versus a 7% CCyR with interferon. “By 3 months, most people are going to get a complete hematologic response, with normal counts,” he added. The benefits of imatinib were also seen in the more recent 8-year follow-up study, with responders having a low overall risk of progression to acute-phase disease or blast crisis and “remarkable” OS.

The data supporting nilotinib and dasatinib were from the ENESTnd and DASISION trials, respectively. Compared with imatinib, both nilotinib and da-
satinitib have shown lower transformation rates and superior responses in newly diagnosed patients with chronic-phase CML. "The ability to achieve a major molecular response is better with the second-generation drugs," declared Dr. Radich. However, so far, the newer agents show no difference in OS.

The NCCN Guidelines also include recommendations for monitoring response to treatment for chronic-phase Philadelphia chromosome-positive (Ph+) CML (Figure 1). A patient is considered to be a "responder" if he or she shows a major cytogenetic response (optimally CCyR) at 12 months. A patient is considered to be a "nonresponder" if he or she has less than a partial cytogenetic response at 12 months. For example, "If there is a lousy response, your chance of ever getting a major molecular response [MMR] is low," explained Dr. Radich. And the opposite is true: "If you respond at 3 months, your chance of getting an MMR is spectacularly high." These NCCN general criteria are similar to those from the European Leukemia Network.6–8

The NCCN Guidelines also incorporate a 3-month response algorithm. "At 3 months out of the gate, we can tell a lot," added Dr. Radich. For responders, the same dose of the drug should be continued, and monitoring with quantitative polymerase chain reaction should be performed every 3 months. For patients without a response, compliance and drug-drug interactions should be evaluated, and mutational analysis should be performed. "If there is no response at 3 months, you have to start thinking about other options," suggested Dr. Radich. Moreover, compliance is an issue in CML, with adherence to oral TKIs often suboptimal. "The best strategy for a patient to achieve complete molecular response is to take the medicine," he said.

For those who do not show response to imatinib by 3 months, other options include nilotinib, dasatinib, transplant, or a clinical trial. Patients who fail to respond to "salvage" TKI can undergo transplant before they progress to advanced phase disease. He also suggested discussing the possibility of transplant with these patients. It can take 4 months or so to find a donor, and patients in blast crisis have a short life expectancy. Thus, it is important to anticipate accelerated blast crisis, he noted, "and don’t let patients get into it."

Dr. Radich also briefly discussed the duration of TKI therapy, which originally was thought to be forever. The STIM trial was the first discontinuation of imatinib trial.9 Of the 100 patients in the study who had been in CCyR for several years, 60% experienced relapse within 3 to 4 months of stopping imatinib. Although the remaining 40% remarkably did not experience relapse, "these patients are not out of the woods yet," warned Dr. Radich. This approach should only be considered within the context of a clinical trial, he added. "But if I were tolerating these drugs well, I would stay on them."

**Mutational Analysis for Imatinib Resistance**

The NCCN Guidelines offers recommendations for performing mutational analysis, particularly in the context of imatinib resistance. Quantitative

<table>
<thead>
<tr>
<th>Month</th>
<th>Optimal</th>
<th>Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>BCR-ABL ≤ 10% by QPCR or PCyR</td>
<td>BCR-ABL &gt; 10% by QPCR or &lt; PCyR</td>
</tr>
<tr>
<td>6</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>12</td>
<td>CCyR</td>
<td>&lt; PCyR</td>
</tr>
<tr>
<td>18</td>
<td>CCyR</td>
<td>&lt; CCyR</td>
</tr>
<tr>
<td>Any</td>
<td>Stable or improving MMR</td>
<td>Loss of CHR or CCyR, IM-insensitive mutation</td>
</tr>
</tbody>
</table>

**Figure 1** NCCN Guidelines response for chronic phase Philadelphia chromosome-positive chronic myelogenous leukemia. From Cortes et al.; with permission. 
Abbreviations: CCyR, complete cytogenetic response; CHR, complete hematologic response; IM, imatinib mesylate; MMR, major molecular response; PCyR, partial cytogenetic response; QPCR, quantitative polymerase chain reaction.
polymerase chain reaction should be performed every 3 months. In addition, if neither CCyR nor MMR is seen at 12 months, bone marrow cytogenetics should be performed. Molecular testing should be performed after good polymerase chain reaction results, Dr. Radich suggested. “If things don’t go the way you expect, then do cytogenetics,” he said. BCR-ABL kinase domain mutation analysis is recommended if patients in chronic phase have an inadequate initial response or disease progresses to accelerated or blast phase.

According to Dr. Radich, there are now more than 200 point mutations, which may account for anywhere between 25% and 60% of the cases of resistance. To assist in deciding when to switch drugs for resistant disease, the NCCN Guidelines suggest basing the choice on mutations: consider nilotinib over dasatinib for V299L and F317L mutations; consider dasatinib over nilotinib for Y253H and E255K/V mutations. Until recently, the T315I mutation has been resistant to all available TKIs, with transplant or a clinical trial being the only options for these patients. However, with the preliminary data on the new BCR-ABL inhibitor ponatinib, this agent appears to be effective against the T315I mutation.

**Newly Approved Agents for Resistant CML**

Two new drugs were recently approved by the US Food and Drug Administration for Ph+ CML (chronic, acute, or blast phase) that no longer respond to other therapies: ponatinib and bosutinib (Figure 2). Ponatinib has received a great deal of press attention. With substantial preliminary results available for more than 400 heavily pretreated patients in the PACE trial, its major claim to fame thus far is its activity against the T315I mutation. About 70% of the patients with chronic-phase CML and the T315I mutation showed a response to ponatinib, findings Dr. Radich called remarkable. “This essentially would be 0% with other drugs,” he added. Furthermore, in resistant acute-phase CML, 57% of this group of sicker patients showed a response to the new agent. “As more people use it, ponatinib should move up the ladder,” predicted Dr. Radich.

In the BELA trial, more than 500 patients with newly diagnosed chronic-phase CML were treated with either bosutinib or imatinib. Nearly 60% of patients showed a response to bosutinib, compared with about 50% with imatinib, with fewer in the bosutinib group experiencing conversion to accelerated/blast phase than in the imatinib group. However, a much higher rate of gastrointestinal toxicity was seen with bosutinib. As a result, bosutinib appears to be less useful in the first-line setting, but remains a promising alternative in the relapsed or refractory setting.

**References**

Highlights of the NCCN 18th Annual Conference


