ADVANCES IN LLM

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

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Switching Drugs Midstream for Patients With Chronic Myeloid Leukemia

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H&O Have concrete prognostic factors been identified for patients with chronic myeloid leukemia?

DDA Traditionally it has been difficult to identify factors that predict long-term outcomes for patients diagnosed with chronic myeloid leukemia (CML). Most patients with chronic-stage disease have excellent outcomes with the currently available therapies. But specific prognostic factors associated with progression-free survival (PFS), transformation-free survival, or overall survival were not known until recently.

H&O Tyrosine kinase inhibitors have been available for the treatment of CML for more than 10 years. Were there any factors associated with outcome identified early on?

DDA One of the earliest indicators of outcome is a rapid molecular reduction in the number of cells housing the *BCR/ABL* mutation that drives CML. A 1-log reduction in the *BCR-ABL/ABL* ratio on a quantitative polymerase chain reaction test—from 100% at the time of diagnosis to 10% soon after starting treatment with imatinib—distinguished patients who were likely to have a longer PFS from those who would likely have a shorter PFS.

H&O Has this difference been apparent with second- and third-generation tyrosine kinase inhibitors?

DDA Yes. Studies of patients receiving nilotinib (Tasigna, Novartis) and dasatinib (Sprycel, Bristol-Myers Squibb) have confirmed that a 1-log reduction from baseline is associated with a better outcome. So we can conclude that this prognostic factor holds true regardless of which tyrosine kinase inhibitor (TKI) is selected. The rapid molecular reduction stems from some inherent biologic factor.

In 2 randomized trials, one comparing imatinib (Gleevec, Novartis) and nilotinib (the ENESTnd [Evaluating Nilotinib Efficacy and Safety in Clinical Trials – Newly Diagnosed Patients] trial, which was published in the *New England Journal of Medicine* in 2010) and another comparing imatinib to dasatinib (the DASISION [Dasatinib Versus Imatinib Study in Treatment-Naive CML] trial, which was published in the *New England Journal of Medicine* in 2010), a 1-log reduction by 3 months after commencing treatment occurred in a proportion of patients in both groups. However, the imatinib arms of both trials had 2 to 3 times as many patients who did not achieve that early 1-log reduction compared with those receiving a second-generation TKI.

H&O But of course, patients who do not have this 1-log reduction at 3 months may still respond to the prescribed treatment.

DDA Yes. The 1-log reduction is one type of response, but there are different levels of responses. When we do a statistical analysis of responses, we tend to try to draw a line in the sand: the line is some level of response, and patients either reach it or not. In reality, there is a gradation of response that cannot be measured in this yes-or-no way. That being said, patients who achieve a 1-log reduction by 3 months tend to have a better prognosis than those who do not.

H&O Can that poorer prognosis be overcome by changing therapy?

DDA That is the important question. If a patient taking imatinib does not achieve this level of response early on, can the 50 mg outcome be improved by increasing the dose or switching to an alternative TKI? Studies investigating this question have not been done, so we do not yet know for sure whether such intervention is warranted.

H&O Could you describe how you approach the care of patients who do not have that early, strong response?

DDA For patients who achieve a 1-log reduction by 3 months, obviously I do not suggest any change. For patients who are close—they are responding, but perhaps the response is not quite as strong as it could be—I tend to not recommend any change. However, I do reinforce the importance of adhering to treatment. I then reevaluate the response at 6 months.

Some patients do not have a 1-log reduction early on owing to toxicity or hematologic issues. These individuals may have to pause or even discontinue treatment. Whether the clock resets, so to speak, after a break is not clear. If a patient has not had a response to a TKI by 3 months and I am as certain as possible that he or she has adhered to treatment, then I will consider changing the drug.

H&O Improvements in technology have altered the definition of complete response over the years. How has this changed the early-response analysis?

DDA There are multiple definitions of response. We are always looking for patients to achieve the deepest response possible. However, it is unclear whether a complete molecular remission should be our goal. With current technology, we can detect an approximately 4.5-log reduction from baseline—approximately 0.01% or lower by SI units.

Right now, the standard definition of a major molecular response is a 3-log reduction in the *BCR-ABL/ABL* ratio. There are no data suggesting that a different level of molecular remission is better in terms of outcomes. Going from 100% at diagnosis to 0.1% has been the ultimate goal for most patients with CML for many years, with some achieving an even deeper molecular remission. But there is no evidence, at least currently, that a deeper molecular remission is linked to a better overall prognosis.

H&O Could there be an advantage to that deeper remission?

DDA It is possible that some patients who reach that level of remission may consider discontinuing therapy. However, that possibility has only been shown in a clinical trial setting and there are no long-term data showing that patients who achieve a molecular remission can safely discontinue therapy. Major molecular response remains the gold standard, and the discontinuation of TKIs should be done only in the context of a clinical trial.

H&O What are some other considerations when recommending that a patient switch to another TKI?

DDA Resistance mechanisms are always a concern, of course. For patients who do not have a deep level of response to a second TKI, there is a risk of developing resistance to the original agent or others. Metabolism issues are also a consideration. Patients tolerate TKIs differently, and it is difficult, sometimes impossible, to predict how a particular patient will tolerate a new TKI. Other innate characteristics, extending beyond molecular pathways of resistance, may also differ among patients. Why do some patients respond better than others? It is still unclear.

Many issues related to resistance are also unresolved. At least 50% of patients who become resistant to TKIs have molecular changes within the ABL tyrosine kinase domain. But for the other half of patients, it is not clear why resistance develops and why these patients have a suboptimal response to the medication.

H&O Do you think that further genomic research will elucidate additional mechanisms of resistance?

DDA It is difficult to say what avenue of research might bring clarification. Is this resistance disease-based? Is it patient-based? Whole-genome sequencing may lead to better understanding.

H&O When you recommend that a patient switch from one TKI to another, is there a particular order you follow in terms of choosing which one to try next?

DDA Approximately 50% of academic physicians recommend that CML patients begin treatment with a second-generation TKI. The other 50% recommend starting with imatinib. Experience, comfort level, and the disease itself are major factors in this decision. Cost also may be factored in. But overall, the choice of what sequence to follow really needs to be shaped around the individual patient.

If a patient is taking imatinib and either the disease does not respond or the drug is hard to tolerate, then I usually recommend switching to one of the 3 second-generation TKIs (nilotinib, dasatinib, or bosutinib [Bosulif, Pfizer]).

The decision to move to one of these 3 agents is based on patient characteristics and also the specific toxicities that the patient experienced while on the TKI. If the disease progressed, then is there a genetic mutation that may have precluded the response? The presence of a mutation might dictate the next treatment option. The presence of certain side effects may influence the choice in the same way. If a patient seems to have a proclivity to a particular side effect, then that might rule out certain TKIs.

In general, I recommend a second-generation TKI as the first treatment for CML, though I will still consider the use of imatinib in patients with low-risk disease. If a switch is necessary, then I tend to recommend another second-generation TKI. Ponatinib (Iclusig, Ariad) is usually reserved for a third-line approach. Usually I do not utilize imatinib if the second-generation TKI does not work well, unless the issue is solely to do with toxicity.

If there is a toxicity issue, then the decision is based on what drug the patient might tolerate best. In that situation, the second- or third-line treatment could be any of the available TKIs.

This approach holds true at the 3-month mark and also later on. As I mentioned earlier, however, I tend to be reluctant to make any changes at 3 months unless there is concrete evidence that the treatment is not working.

Suggested Readings

Branford S, Kim DW, Soverini S, et al. Initial molecular response at 3 months may predict both response and event-free survival at 24 months in imatinib-resistant or -intolerant patients with Philadelphia chromosome-positive chronic myeloid leukemia in chronic phase treated with nilotinib. *J Clin Oncol*. 2012;30(35):4323-4329.

Hughes TP, Saglio G, Kantarjian HM, et al. Early molecular response predicts outcomes in patients with chronic myeloid leukemia in chronic phase treated with frontline nilotinib or imatinib. *Blood*. 2014;123(9):1353-1360.

Kantarjian H, Shah NP, Hochhaus A, et al. Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med*. 2010;362(24):2260-2270.

Kantarjian HM, Shah NP, Cortes JE, et al. Dasatinib or imatinib in newly diagnosed chronic-phase chronic myeloid leukemia: 2-year follow-up from a randomized phase 3 trial (DASISION). *Blood*. 2012;119(5):1123-1129.

Larson RA, Hochhaus A, Hughes TP, et al. Nilotinib vs imatinib in patients with newly diagnosed Philadelphia chromosome-positive chronic myeloid leukemia in chronic phase: ENESTnd 3-year follow-up. *Leukemia*. 2012;26(10):2197-2203.

Marin D, Hedgley C, Clark RE, et al. Predictive value of early molecular response in patients with chronic myeloid leukemia treated with first-line dasatinib. *Blood*. 2012;120(2):291-294.

Saglio G, Kim DW, Issaragrisil S, et al; ENESTnd Investigators. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. *N Engl J Med*. 2010;362(24):2251-2259.