[News * Analysis * Commentary * Controversy]

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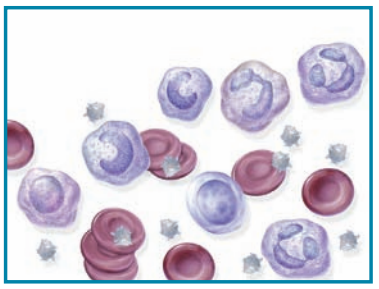

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PERIODICALS

Complete Cytogenetic Response Defines Long-term Outcome in CML Patients Treated with Second-Generation TKIs

BY MARK FUERST

"Molecular response is important, but is not as strong a predictor of risk reduction as cytogenetic response....Oncologists have to be more patient about their patients achieving a molecular response. The patient may need 12 or 18 months to show a molecular response."
—Michael Mauro, MD

The achievement of a major molecular response (MMR) offers no advantage over complete cytogenetic response (CCyR) in defining long-term outcome in patients with newly diagnosed CML treated with second-generation tyrosine-kinase inhibitors (TKIs), according to a study in the November 10 issue of the *Journal of Clinical Oncology (2011;29:4260-4265)*.

The use of second-generation TKIs as initial therapy in CML induces high rates of CCyR at early time points: "The European LeukemiaNet [ELN] definitions of response, which are based on front-line therapy with imatinib, are not applicable in this setting," said lead author Elias Jabbour, MD, Assistant Professor of Medicine in the Leukemia Department at the University of Texas MD Anderson Cancer Center.

"We propose that achievement of CCyR at six months should be considered an optimal response and a partial cytogenetic response at three months should be considered a suboptimal response."

Dr. Jabbour and his coauthors—Hagop M. Kantarjian, Susan O'Brien, Jianqin Shan, Alfonso Quintás-Cardama, Guillermo Garcia-Manero, Mary Beth Rios, and Jorge E. Cortes—treated 167 patients with newly diagnosed CML in chronic phase with second-generation TKIs in Phase II trials; 81 patients received nilotinib and 86 received dasatinib.

The patients were followed for a median of 33 months. Event-free survival (EFS) was measured from the start of treatment to the date of loss of complete hematologic response, loss of complete or major cytogenetic response, discontinuation of therapy for toxicity or lack of efficacy, progression to accelerated or blastic phases, or death at any time.

Overall, 155 patients (93%) achieved a complete cytogenetic response, including 146 patients (87%) who achieved a major molecular response. About one-quarter of the patients (28%) achieved a complete major response. Dr. Jabbour noted that according to the ELN definitions, the rates of suboptimal response were 2% or less up to 12 months of therapy. "There was no difference in event-free survival and CCyR duration between patients who achieved CCyR with and without MMR across all landmark times of three, six, 12, and 18 months."

Early Responses Important

Early responses seem to predict better outcomes. "Early response is important. We need to wait only six months, not 12, to see which patients are responding. What matters is that the patients who respond do really well."

He suggested starting all newly diagnosed chronic-phase CML patients on second-generation TKIs. "At six months, the large majority will respond and do better over the long-term. We can select good responders early on."

If bone marrow tests at three months indicate a partial response, the procedure should be to repeat the test again at six months, he said, cautioning though, that these new criteria have not yet been validated by others.

"If the patient achieves CCyR at six months, the outcome is good. If at six months the patient does not achieve a complete response, we don't have options at the moment," Dr. Jabbour said. He suggested monitoring these patients carefully, and if they still do not achieve a good response at 12 months, refer them to a clinical trial. "In the future, we may have new drugs coming to market for these patients."

The clinical message, said Dr. Jabbour, is "if patients do not achieve CCyR at six months, you have to follow them closely. If they do show CCyR, don't concern yourself so much with molecular testing. As long as they have CCyR, their outcome will be great. Once they hit CCyR, whether they have MMR or not, their outcome will be the same."

Michael Mauro: One of First Reports to...

Asked for his opinion for this article, Michael Mauro, MD, Associate Professor of Hematology at the Knight Cancer Institute, Center for Hematologic Malignancies, at Oregon Health & Science University, called the study further evidence that supports that cytogenetic response is still the best predictor of clinical response, even with new therapeutic agents.

"The ELN definitions of response, which are based on front-line therapy, are not applicable in this setting. We propose that achievement of CCyR at six months should be considered an optimal response and a partial cytogenetic response at three months should be considered a suboptimal response."

ELIAS JABBOUR, MD: "The clinical message is that if patients do not achieve CCyR at six months, you have to follow them closely. If they do show CCyR, don't concern yourself so much with molecular testing. As long as they have CCyR, their outcome will be great. Once they hit CCyR, whether they have MMR or not, their outcome will be the same."

He noted that the role of early cytogenetic response as a delineator of subsequent outcomes is fairly firm. "This is one of the first reports synthesizing the data on faster cytogenetic responses with nilotinib and dasatinib into earlier predictive time points," said Dr. Mauro.

Patients treated with second-generation TKIs declare themselves as responders even faster than with imatinib therapy, Dr Mauro said. "Early cytogenetic response shows the optimal subset of treated patients, and it appears that delineation occurs earlier with second-generation TKIs.

The current CML literature "does not guide us much regarding suboptimal molecular responses. The follow-up may need to be longer to clarify the benefit of prompt molecular response in this data set [with second-generation TKIs].

"Molecular response is important, but is not as strong a predictor of risk reduction as cytogenetic response," Dr. Mauro continued.

"A patient with a three-month and six-month cytogenetic response is more likely to go to complete remission and stay in remission, and suboptimal cytogenetic response at early time points often leads to subsequent re-classification as treatment failure. Oncologists have to be more patient about their patients achieving a molecular response. The patient may need 12 or 18 months to show a molecular response."