Discontinuation of Imatinib May Be Possible in Chronic Myelogenous Leukemia

A new study shows that it may be safe to stop imatinib in patients with chronic myelogenous leukemia (CML) who have been in a complete molecular remission for at least 2 years.

Investigators in the French CML Intergroup conducted the Stop Imatinib (STIM) study, a multi-institutional, prospective, nonrandomized study that showed a subset of patients did not relapse after stopping imatinib. The study raised the possibility that some patients with CML may be cured with tyrosine kinase inhibitors. A substantial proportion of patients did develop disease recurrence, but were effectively retreated with imatinib (Lancet Oncol. 2010;11:1029-1035).

Lead author Francois-Xavier Mahon, MD, PhD, professor of medicine in the blood disease service division of the Centre Hospitalier Universitaire de Bordeaux in France, says the results may help improve on the marked successes already achieved in the management of CML. “We need to do studies like these to improve and individualize treatment in order to offer the best quality of life along with the increased survival we have in CML,” he says.

The group chose to pursue the current study after a pilot study they conducted showed that 50% of patients who stopped imatinib had a molecular relapse (Blood. 2007;109:58-60).

Current Standard
The current standard of care for the frontline treatment of CML is imatinib, an oral tyrosine kinase inhibitor. The landmark International Randomized Study of Interferon vs STI571 (IRIS) protocol (Blood. 2009;114:Abstract 1126.) of imatinib in patients with CML showed the overall survival rate to be 85% at 8 years for patients treated initially with imatinib and 93% when only counting CML-specific deaths. Subsequently, the standard of care has become treating CML patients with tyrosine kinase inhibitors indefinitely. More recently, 2 other tyrosine kinase inhibitors, dasatinib and nilotinib, have also been shown to be very effective as a first-line therapy for CML. These second-generation tyrosine kinase inhibitors were initially approved by the US Food and Drug Administration for the treatment of patients who are refractory or intolerant to imatinib. They are now approved for initial therapy as well. Imatinib, however, remains the most commonly used drug upfront.

Study Results
The research team enrolled 100 patients with chronic or accelerated phase CML with a sustained complete molecular response (CMR), defined as a greater than 5 log reduction in BCR-ABL and ABL levels as well as undetectable transcripts on reverse transcriptase-polymerase chain reaction, for at least 2 years. Fifty-one patients were previously treated with interferon. After stopping imatinib, molecular relapse was noted in 54 patients after a median follow-up of 17 months. The remaining 46 patients remained in CMR at a median follow-up of 14 months, with an overall probability of maintaining a CMR at 12 months of 43%.

In the subset of 69 patients with follow-up over one year (median, 24 months), molecular relapse occurred in 42 patients, usually within 6 months. The molecular relapse-free survival rate in this group was 41% at one year and 38% at 2 years. Patients treated with interferon before imatinib showed no differences in relapse rates compared with those treated with imatinib first. Molecular relapse at or before 18 months occurred in 70% of men and 46% of women. Among patients with high, intermediate, and low Sokal risk scores (calculated based on patient age, spleen size, platelet count, and percentage of peripheral blood myeloblasts), molecular relapses were
detected in 88%, 65%, and 49% of patients, respectively. Further, patients with a duration of imatinib therapy of at least 50 months had a 53% likelihood of molecular relapse, whereas 78% of patients with a shorter duration of treatment relapsed. When these 3 factors (gender, Sokal risk group, and duration of treatment) were entered into a Cox regression model, they all significantly and independently predicted the likelihood of molecular relapse.

All patients who relapsed were retreated with imatinib and all patients remained sensitive. No loss of hematologic response was noted, nor was progression to advanced phase disease. Of the 42 patients who relapsed, 26 achieved a CMR with imatinib retreatment.

Dr. Mahon says treating with a second-generation tyrosine kinase inhibitor may improve the response noted at relapse in these patients, but a trial would be needed to show that, a point the study authors noted in their conclusion.

Elias Jabbour, MD, assistant professor in the department of leukemia at The University of Texas M. D. Anderson Cancer Center in Houston, says trials using second-generation tyrosine kinase inhibitors to treat patients with early, chronic phase CML have shown a higher efficacy than imatinib in inducing molecular responses (major and CMRs), which may lead in the future to the cure of more CML patients.

**Future Directions**

The authors concluded that future studies should seek to more accurately identify patients who would benefit from stopping imatinib, and that more research is needed to confirm the predictive value of Sokal risk score, gender, and duration of imatinib treatment. In addition, more sensitive molecular techniques to identify leukemic clones may help to better identify patients, they write.

These results raise the possibility that some patients may be cured of their CML with tyrosine kinase inhibitors, but the authors say that for now, indefinite therapy remains the standard of care, and discontinuation of therapy should only be done in the context of a clinical trial.

“The key message is that discontinuation of treatment is possible,” Dr. Mahon says.

He says the next step is to study combinations of treatments. “In CML we have not very often tried combining the different targeted therapy because we proceed step by step, in contrast to other diseases such as HIV [human immunodeficiency virus] infections,” he adds.

The recent STI571 Prospective Randomized Trial (SPIRIT) study, which examined using interferon with imatinib versus imatinib alone, is one such combination trial. Results show that interferon with imatinib induces more CMRs than imatinib alone. Dr. Mahon says combination studies such as SPIRIT may increase the number of people who are candidates for stopping therapy beyond the approximately 10% of patients found in the STIM study.

Dr. Jabbour concurs that discontinuation of imatinib may be possible, and even cure may be within reach for more patients in the future. “Combination trials with tyrosine kinase inhibitors and interferon, vaccines, or other targeted therapies are ongoing,” he says. These trials may help define criteria to identify patients who may discontinue treatment.