When Can Tyrosine Kinase Inhibitors Be Discontinued in Patients With Chronic Myeloid Leukemia?

Francois-Xavier Mahon, MD, PhD
Professor and Senior House Physician
University of Bordeaux
Bordeaux, France

H&O What are the treatment goals for patients with chronic myeloid leukemia?

FM With the use of tyrosine kinase inhibitors (TKIs), life expectancy in chronic myeloid leukemia (CML) is very close to that of the healthy population. Therefore, the main treatment objective is to improve quality of life. CML is considered a model for other types of cancer, since the discovery of the Philadelphia chromosomal abnormality as a marker in bone marrow cells. This abnormality is a driver of the disease, and it leads to the formation of the BCR-ABL oncogene. This gene encodes for the BCR-ABL protein, which is a tyrosine kinase that is specific to leukemic cells. By targeting tyrosine kinase activity, it is possible to target the leukemic cells. This discovery led to the development of the first TKI, imatinib. The proof of concept of using targeted therapy for leukemia was illustrated by this disease model.

CML is also a model for the management of patients with chronic cancers, who must receive long-term treatment and follow-up. In addition to improved quality of life, another treatment goal is to manage the pharmacoeconomic aspects of therapy. An interest in improving both of these issues—quality of life and pharmacoeconomics—led to clinical trials evaluating the discontinuation of TKIs.

H&O What was the design of the EURO-SKI trial?

FM The EURO-SKI trial (European Stop Tyrosine Kinase Inhibitor Study) enrolled patients with CML in chronic phase who had received treatment with any TKI for at least 3 years and had achieved a deep molecular response. The primary endpoint was molecular relapse–free survival. Deep molecular response was defined by a 4-log reduction in the level of BCR-ABL (on the International Scale) that lasted for at least 1 year. Loss of major molecular response was defined as a BCR-ABL1 level of more than 0.1%. The inclusion criteria were less strict as compared with similar studies, such as STIM1 (Stop Imatinib) and STIM2. Most of the enrolled patients had received treatment with imatinib, but some had received a second-generation TKI.

A goal of the EURO-SKI trial was to enroll a large enough population to permit a strong statistical analysis, and more than 800 patients were enrolled. The EURO-SKI trial was the largest study to evaluate cessation of TKIs in patients with CML, and I offer my gratitude to all of the patients who participated.

H&O What were the results?

Results improved with the duration of treatment, reaching a plateau after more than 15 years.
Data were available for 755 evaluable patients. The rates of molecular relapse–free survival were 61% (95% CI%, 57%-64%) at 6 months and 50% (95% CI, 46%-54%) at 24 months after stopping therapy. All patients who stopped treatment with TKIs were still sensitive to treatment when it started again.

An important finding was the connection between the duration of treatment and the duration of molecular response. Results improved with the duration of treatment, reaching a plateau after more than 15 years. This does not mean that treatment should necessarily be continued for 15 years. However, in a case where the TKI is well-tolerated, it is important to inform the patient that treatment for several years will increase the probability of success after discontinuation.

What have other studies of this strategy shown?

Studies such as STIM1, STIM2, STOP 2G-TKI (STOP Second Generation Tyrosine Kinase Inhibitor), and DADI (Dasatinib Discontinuation), as well as the ENEST trials (Evaluating Nilotinib Efficacy and Safety in Clinical Trials) ENESTfreedom and ENEStop, also demonstrated that it is possible to stop treatment with TKIs. The results of these studies have been roughly the same. Most of the molecular relapses occurred during the first 6 months after discontinuation, and then there was a plateau. After 2 years, approximately 50% of patients who discontinued treatment were still in a major molecular response.

The first studies, such as STIM1 and STIM2, were started 10 years ago and used very strict enrollment criteria. In EURO-SKI, the enrollment criteria, including the definition of molecular recurrence, were less strict as compared with the STIM studies. The treatment was re-challenged in patients with a molecular recurrence as defined by an increase of 1 log of BCR-ABL between 2 separated points, and not only by the loss of major molecular response. An important point is that the trials assessing cessation of TKIs used different definitions of molecular recurrence.

What are the benefits to stopping treatment with TKIs?

There are several important benefits. TKIs cannot be used during pregnancy. These studies have shown that it is possible for a woman with CML to discontinue TKI therapy when she is trying to conceive or learns she is pregnant. Another important benefit concerns children and teenagers. TKIs can affect growth, so it is good to know that they can be discontinued. It should be noted, however, that enrollment of young people in these trials was limited.

TKIs inhibit tyrosine kinases other than their target, which can lead to off-target effects. First- and second-generation TKIs can be associated with severe adverse events, such as plural effusion and vascular effects. All of the side effects are not yet well-known. As mentioned previously, improvement in quality of life is an important goal in CML. It was important to demonstrate that treatment with TKIs does not have to be lifelong because the risk of side effects might increase with duration of use.

The economic benefit is also considerable. In the EURO-SKI trial, treatment discontinuation saved approximately 22 million Euros. This saving continues to increase with follow-up analysis.

Do you have any recommendations on how to safely discontinue TKIs?

Recommendations from the French Chronic Myeloid Leukemia Study Group were published in July 2018. In a presentation at the 2017 American Society of Hematology Annual Meeting, I proposed similar recommendations. It is possible to stop treatment outside of a clinical trial, but it is necessary to ensure that the patient will undergo close follow-up with molecular biology investigations. Appropriate candidates are patients who have received a TKI for at least 5 years and who are in deep molecular response, as defined by a 4.5-log reduction in BCR-ABL sustained for 2 years. The most important point is strict monitoring of molecular biology.

What kind of monitoring is needed after discontinuation of TKIs?

When the treatment is stopped, it is necessary to follow the patient very strictly with complete blood counts and reverse transcription polymerase chain reaction testing. These tests should be administered monthly until month 6, every 2 months from months 7 to 12, every 3 months from months 13 to 24, and then every 3 to 4 months thereafter. The laboratory must provide results based on the International Scale and show very good sensitivity, at least around the 4.5-log reduction.

When will a TKI need to be started again?

Treatment with a TKI will need to be started again when molecular biology investigations show a loss of major molecular response, so when the BCR-ABL level exceeds 0.1% on the International Scale.

What other research is needed in this area?
We need to accumulate more results from additional patients to better understand the mechanisms. Patients can develop relapsed disease quickly—during the first 6 months after discontinuation—or at a later time. In patients who experience a molecular recurrence during the first 6 months, the kinetics (the speed at which BCR-ABL increases) are faster compared with those who relapse later, and are more likely to be linked to the residual kinetic cells. Among patients with a late relapse, the kinetics are low and probably linked to immune control of the disease.

Disclosure
Dr Mahon is on the advisory boards and has received honoraria and research funding from Novartis Pharma, BMS, Pfizer, and Incyte.

Suggested Readings


