Should Treatment for CML Continue Indefinitely?

Since the advent of tyrosine kinase inhibitors (TKIs), chronic myeloid leukemia (CML) has been transformed from a disease that was usually fatal into one in which patients have a close-to-normal life expectancy. In some cases, the response to treatment is sufficiently prolonged and deep that patients may be able to discontinue their medication. Is this a good idea? In this month’s Counterpoints, Drs Nicholas Short and Elias Jabbour argue for the continued treatment of CML, whereas Drs Gabriel Etienne and François-Xavier Mahon make the case for treatment discontinuation.

Yes, Treatment for CML Should Continue Indefinitely

Nicholas J. Short, MD, is a hematology/medical oncology fellow in the cancer medicine division at the University of Texas MD Anderson Cancer Center in Houston, Texas.

Elias Jabbour, MD, is an associate professor in the leukemia department at the University of Texas MD Anderson Cancer Center in Houston, Texas.

The therapeutic landscape for CML changed dramatically with the development of small-molecule TKIs targeting BCR-ABL1. These agents have improved the 10-year survival rate from 20% to approximately 80% to 90%.1 TKIs have transformed CML from a disease in which outcomes were relatively dismal in the absence of allogeneic stem cell transplant into one in which adherence to daily oral therapy can lead to a life expectancy approximating that of the general population.2

Historically, the standard of care for CML has been indefinite TKI therapy. However, recent studies of TKI discontinuation in CML have suggested that some patients with prolonged deep molecular responses may be effectively cured. This finding has led to the concept of treatment-free remission (TFR), which is emerging as an important goal in CML therapy.3 TFR has the potential to become a valuable therapeutic endpoint because

No, Treatment for CML Should Not Continue Indefinitely

Gabriel Etienne, MD, PhD, is the head of the department of hematology at the Institut Bergonié Cancer Center in Bordeaux, France.

François-Xavier Mahon, MD, PhD, is a professor of hematology at the University of Bordeaux in Bordeaux, France.

Imatinib and second-generation TKIs have dramatically improved outcomes for patients with CML. Until recently, treatment recommendations stated that TKI therapy should continue indefinitely regardless of whether the target remained detectable. However, problems related to the tolerability of TKIs over time have emerged, particularly for young patients who are expected to have a long exposure to the drugs. Long-term treatment with these expensive drugs increases the risk for nonadherence, may adversely affect fertility and pregnancy, and creates an economic burden. As many of us have experienced in clinical practice, patients often ask whether continued treatment is necessary.

The issue of treatment cessation has gained importance, illustrated by the increasing number of ongoing clinical trials and publications on this topic. Because the length of follow-up after TKI discontinuation has increased and certain patients have not shown evidence

(continued on page 490)
indefinite TKI therapy places a considerable burden on both patients and the health care system; the drugs are expensive, and long-term side effects include cardiovascular events and pulmonary hypertension. However, several important questions regarding the safety of TKI discontinuation for patients with CML remain unanswered, currently precluding the adoption of this approach outside the context of clinical trials.

Data on TKI Discontinuation in CML

Several studies have evaluated whether TKIs can be safely discontinued in patients with long-term deep molecular responses. In the STIM (Stop Imatinib) study, 100 patients in complete molecular remission (>5-log reduction in BCR-ABL and ABL levels and undetectable transcripts on quantitative reverse transcription polymerase chain reaction [qRT-PCR]) after more than 2 years of imatinib treatment discontinued TKI therapy and were followed prospectively. Molecular relapse occurred in 42 of the 69 patients (61%) with at least 12 months of follow-up, and all but 2 relapses occurred within 6 months after TKI discontinuation. After the reintroduction of imatinib, 26 patients again achieved complete molecular remission, and the other 16 patients had decreases in their BCR-ABL1 levels. Similar results were observed in the comparably designed TWISTER study (A Phase II Study to Determine Relapse-Free Interval After Withdrawal of Imatinib Therapy in Adult Patients With Chronic Phase Chronic Myeloid Leukaemia in Stable Complete Molecular Remission). Among the 40 patients enrolled, the actuarial estimate of stable TFR was 47.1% at 2 years. All patients were sensitive to re-treatment with imatinib.

TFR rates are higher with second-generation TKIs such as nilotinib (Tasigna, Novartis) and dasatinib (Sprycel, Bristol-Myers Squibb) than with imatinib owing to the relatively deeper and more sustained molecular responses achieved with the former agents. In the ENESTFreedom study (Nilotinib Treatment-Free Remission Study in CML Patients), TKI discontinuation was evaluated in patients with chronic-phase CML who had at least a 4.5-log reduction from the original baseline value (MR4.5) after 2 or more years of frontline nilotinib therapy followed by 1 year of nilotinib consolidation. Nilotinib was reintiated in the patients who lost a major molecular response. Of 190 patients who entered the TFR phase, 98 patients (51.6%) remained in major molecular response or better at 2 years after stopping nilotinib. As in the experience with imatinib, the vast majority of patients regained a deep molecular response after the reinitiation of nilotinib, although it is notable that 11.6% of patients were unable to regain MR4.5 after resuming nilotinib. In the STOP 2G-TKI study (STOP Second Generation Tyrosine Kinase Inhibitor), patients receiving first-line or subsequent dasatinib or nilotinib for at least 3 years who also were in MR4.5 with undetectable BCR-ABL1 transcripts for the preceding 2 years were eligible for TKI discontinuation. The 2-year TFR rate was 53.6%, and in all of the patients in whom molecular relapse developed and TKI therapy had to be reinitiated, MR4.5 was achieved again.

Similar results were observed in Euro-Ski (European Stop Tyrosine Kinase Inhibitor Study), the largest study to date of TKI discontinuation in CML. In this study of 821 patients who had CML treated with frontline imatinib, nilotinib, or dasatinib, who achieved at least MR4 (BCR-ABL level <0.01% on the International Scale), and who subsequently stopped TKI therapy, the molecular recurrence-free survival rate at 2 years was 52%. Among the patients who received imatinib, a longer duration of therapy (optimal, >5.8 years) and a longer duration of MR4 before discontinuation were associated with an increased likelihood of sustained molecular response after treatment discontinuation.

The relatively higher TFR rates observed in patients initially treated with second-generation TKIs suggest that second-generation TKIs may be preferred as initial therapy for patients in whom eventual TKI discontinuation would be particularly valued (eg, younger patients with a longer life expectancy). However, when one factors in the number of patients with sufficiently deep molecular responses for them to be candidates for TKI therapy discontinuation, the incidence of molecular cure remains relatively low, ranging from approximately 15% with...
imatinib to 25% to 30% with second-generation TKIs. Although the use of second-generation TKIs certainly increases the likelihood of obtaining a sufficiently deep molecular response that TKI discontinuation can be considered, the use of these second-generation agents comes at significant financial cost. It has been estimated that frontline treatment with second-generation TKIs results in an increased cost of $800,000 per quality-adjusted life-year compared with generic imatinib treatment.12,13 The financial burden associated with the frontline use of second-generation TKIs should therefore be carefully weighed against the marginal improvement in cure fraction achieved with imatinib.

Potential Risks of TKI Discontinuation

Although there is certainly a high likelihood of TFR after TKI discontinuation in patients with CML in whom prolonged deep molecular responses have been achieved with frontline treatment, several questions remain regarding the feasibility of this approach in community practice. Although TKI discontinuation was safe in these studies, it is unclear whether results would be similar outside a closely monitored clinical trial setting. Adherence to consensus guidelines for molecular monitoring in CML is imperfect in the community setting, and poor adherence may correlate with inferior outcomes.14 Because most patients who discontinue TKI therapy have a molecular relapse in less than 6 months, close monitoring of BCR-ABL1 transcript levels is imperative for the rapid identification of relapse and the reintiation of TKI therapy. In all the previously mentioned studies of TKI discontinuation, highly experienced centralized laboratories were used for the purpose of molecular monitoring. However, many laboratories in the community are not able to produce accurate and reliable molecular results comparable with those obtained in these studies, which could lead to inappropriate patient selection for TKI discontinuation.

Although TKI discontinuation has several potential theoretical advantages, especially a decrease in TKI-related toxicity, additional data are needed to confirm the benefits associated with this approach. The optimal criteria for both discontinuing TKI and defining molecular relapse to prompt TKI reinitiation are yet to be established. Because of these unanswered questions, as well as the relatively short follow-up of the discontinuation studies, we continue to view TKI cessation for patients with CML as investigational. We therefore recommend that TKI therapy be stopped only in the context of a clinical trial.

Strategies to Increase CML Cure Rates

Although it is encouraging that some patients may be at least functionally cured with long-term TKI therapy, alternative strategies should be explored to increase the cure fraction of patients with CML. These approaches should focus on both inducing deeper molecular responses and targeting the CML stem cell. Despite the presence of a constitutively active BCR-ABL1 kinase, these leukemic stem cells may be quiescent, which renders them relatively resistant to TKI therapy.15 The presence of resistant leukemic stem cells partially explains why relapse occurs rapidly in a substantial proportion of patients when TKI therapy is stopped. It will be imperative in the future to develop TKI-independent therapeutic approaches that target the leukemic stem cell if the number of patients with CML who can be cured is to increase.

The addition of pegylated interferon alfa-2b to imatinib or dasatinib results in deep molecular responses that compare favorably with those observed with either TKI alone, suggesting that this approach may be useful to increase the potential for TFR.16,17 Emerging data also suggest that BCL-2 inhibitors such as venetoclax (Venclexta, AbbVie/Genentech) in combination with TKIs can enhance cytotoxicity and deplete CML stem cells.18,19 Studies of several other agents in combination with TKIs are currently ongoing; these include hypomethylating agents,20 JAK2 inhibitors,21 and immune-based therapies such as anti–programmed death 1 monoclonal antibodies and dendritic cell vaccines.22 The hope is that these novel strategies will lead to deeper and more durable responses than those achieved with TKI therapy alone and will therefore facilitate functional cure in a higher proportion of patients with CML.

Disclosures

The authors have no relevant conflicts to disclose.

References

No, Treatment for CML Should Not Continue Indefinitely (cont)

of relapse, the next step for the coming decade will be to address the question of CML cure.

CML as a Model Disease

CML is considered a representative model of cancer for several reasons. The disease is characterized by the clonal expansion of terminally differentiated myeloid cells originating from a leukemic stem cell. It presents as a chronic myeloid disorder that most commonly progresses from a chronic phase to an accelerated phase and then to a myeloid/lymphoid blast crisis. The notion that the initiation and progression of cancer involve a combination of stemlike cells together with a multistep acquisition of molecular oncogenic events over time is now considered key to oncogenesis.1,2 However, the main reason for choosing CML as a model relates to the discovery of a constitutively active BCR-ABL tyrosine kinase, the functional result of a reciprocal translocation between chromosomes 9 and 22 that generates the infamous Philadelphia chromosome.3,4 Not only is BCR-ABL a cancer marker, it is also the causative lesion in CML, a finding that led to the development of the first TKI—imatinib.5 Now, 15 years later, studies from different centers and countries have demonstrated that imatinib and second-generation TKIs significantly improve the prognosis of patients with the disease. Life expectancy for patients with CML is now close to that of the healthy population.5,7 This achievement in the treatment of CML is an example of what targeted therapy can accomplish in human malignancy, but it also increases the importance of quality-of-life and financial issues.

Cessation of Treatment in the Pre-TKI Era

Before the current millennium, allogeneic hematopoietic stem cell transplant (HSCT) was the best way to produce sustained remissions in eligible patients with CML owing to the graft-vs-leukemia effect.8 Rather surprisingly, long-term positive results on qRT-PCR testing for BCR-ABL after transplant were reported, a finding that did not automatically imply relapse inasmuch as no other signs of disease recurrence were observed.8,9 For patients who were ineligible for allogeneic HSCT, alternative treatments were limited to regimens based on interferon alfa and palliative chemotherapy with agents such as hydroxyurea.10 Of note, in some patients treated with interferon alfa, an optimal response was achieved at the cytogenetic level (ie, a complete cytogenetic response) and in very rare instances at a molecular level, defined as the absence of BCR-ABL transcripts detectable on the qRT-PCR available at that time.11 In these patients, discontinuation of interferon alfa may not lead to disease relapse, although leukemic cells with BCR-ABL expression remain detectable; furthermore, discontinuation lowers the incidence of late, sometimes unexpected drug-related adverse events.12,13 Despite the possibility of very rare late relapses, even in patients with undetectable residual disease after allogeneic HSCT and interferon alfa treatment, the concept of a functional cure or an operational cure has been proposed.14

In some patients with low levels of detectable BCR-ABL1, molecular remission can be maintained without treatment.

Cessation of TKIs: A New Goal in CML Trials

It is necessary to achieve a very low level of sustained residual disease before imatinib discontinuation can be proposed. Each attempt to discontinue imatinib without a deep and sustained response has been unsuccessful. More than 10 years ago, we first reported that discontinuation of imatinib in patients with a sustained deep molecular response did not lead to relapse in half of the selected patients.15 Then, STIM confirmed these preliminary data in more than 100 patients with CML who continued to have undetectable BCR-ABL. Molecular recurrence was defined as positive RT-PCR results showing a significant (10-fold or 1-log) increase on at least 2 consecutive assessments. With use of this definition, the molecular recurrence-free survival rate was 38% at 60 months and remained unchanged at a median follow-up of 77 months.16,17 On the other side of the world, TWISTER (also known as the Australasian Leukemia and Lymphoma CML8 trial) confirmed these results. This study, whose design was similar to that of STIM, found that the likelihood of a sustained deep molecular response after imatinib discontinuation was approximately 40%.18 Then, the A-STIM study (According to Stop Imatinib) demonstrated that loss of major molecular response—rather than molecularly detectable disease—was a valuable criterion for TKI resumption. This finding highlighted
the fact that in some patients with low levels of detectable BCR-ABL1, molecular remission can be maintained without treatment.19

Euro-Ski is a large trial of more than 800 patients representing a broader population. Patients in this study must have received TKI therapy for at least 3 years and maintained a deep (≥4-log) molecular response during 1 year before discontinuation. Preliminary reports have shown that after 1 and 2 years without treatment, roughly half of the patients are still in major molecular response. A prognostic modeling analysis of patients treated with imatinib showed that treatment duration has a significant effect on the success of imatinib discontinuation, as already suggested by STIM.17,20

Second-generation TKIs in frontline or second-line therapy are associated with deeper and faster molecular responses than imatinib. Second-generation TKIs are believed to allow a greater proportion of patients to be in an optimal situation to stop TKI therapy. The feasibility of TKI cessation following nilotinib or dasatinib discontinuation also has been evaluated.26 The results of several second-generation TKI discontinuation studies have been published recently and are very comparable with those reported after imatinib cessation.21,22

The convincing results of all these studies have validated the concept of TFR, which has become the main endpoint in clinical trials for CML. A consensus guideline and an algorithm have emerged from the published and unpublished results of ongoing studies that use TFR as a main criterion of evaluation. We are clearly entering the era of TFR, which CML advocacy groups consider to be of utmost importance.

Disclosures
Dri Etienne and Mahon have consulted for Ariad, Bristol-Myers Squibb, Novartis, and Pfizer, and have received research funding from Novartis.

References