COMMENTARY

Discontinuing imatinib in chronic myeloid leukemia: don’t try this at home

RYAN MATTISON & RICHARD A. LARSON

Department of Medicine, Section of Hematology/Oncology, The University of Chicago, Chicago, IL, USA

The use of the tyrosine kinase inhibitors (TKIs) imatinib, dasatinib, and nilotinib has revolutionised the care of patients with chronic myeloid leukemia (CML) [1–3]. We now have more than 6 years of follow-up data on the IRIS study, and the frontline use of imatinib has been shown to be both highly efficacious and generally well-tolerated [4]. The large majority of newly diagnosed patients treated for CML in chronic phase achieve a complete cytogenetic remission (CCyR), and over time, most of these eventually achieve major molecular responses (MMR) and even complete molecular responses (CMR). However, cure has not yet been proven, and life-long therapy with imatinib is still the consensus recommendation [5].

Nevertheless, there are situations when cessation or temporary interruption of TKI therapy for patients who have had a good clinical response would be desirable. For instance, even relatively minor grade 1 or 2 side effects such as fluid retention, rash, muscle cramps or mild fatigue can, over the period of many months to years, become more than annoying and sometimes even debilitating to a patient who requires lifelong therapy. A brief drug holiday can provide a welcome respite, but this is often balanced against the anxiety of a quick relapse. The cost of continuous therapy can also prove to be a burden. Finally, there are situations such as pregnancy, elective surgical procedures or intercurrent illnesses for which interrupting treatment for a short period could be considered. The paper by Goh et al. in this issue of Leukemia and Lymphoma adds to the growing body of data about the clinical outcomes for patients with CML in remission who, for various reasons, have discontinued TKI therapy while in remission [6].

We place these new results in the context of prospective imatinib discontinuation studies reported on recently by Australian [7] and French investigators [8,9].

Goh et al. in Korea followed the clinical outcomes of 26 patients with Philadelphia chromosome positive CML who discontinued imatinib after achieving a CCyR or CMR [6]. The patients in this study stopped imatinib for a variety of reasons that included toxicity, pregnancy, cost or other patient-specific factors. In contrast to the studies described below, the design of the Korean study did not include a pre-planned discontinuation schema. A heterogeneous group of 26 patients were studied, including 11 who had previously had an allogeneic stem cell transplant and seven who had been in accelerated phase at the time imatinib was started. Twelve had previously received interferon, and only seven had received imatinib as their initial therapy for CML.

Of the 26 patients included, 11 stopped imatinib after achieving CCyR and 15 stopped treatment after achieving CMR. Importantly, the median remission duration prior to drug discontinuation was only 7 months for each cohort. Several discontinued imatinib within 1–4 months after achieving a response. Patients were monitored every month for hematologic relapse and every 3 months for cytogenetic or molecular relapse. Twenty-four patients experienced a relapse from their deepest remission state within a median of 7 months (range, 4–48 months) after discontinuing imatinib. When imatinib was resumed, 23 patients regained their best previous response, but one patient, previously in CCyR, died from progression of CML. Up to 28 months were required after resuming imatinib for some patients to regain...
their previous best response, but no additional progression events were reported. Median follow-up after resumption of imatinib therapy has been 44 months.

In contrast, Australian investigators are conducting a prospective imatinib discontinuation trial for patients who were previously in CMR for greater than 24 months [7]. Interim results presented at the 2008 American Society of Hematology (ASH) meeting reported on 13 patients who had received imatinib after prior interferon treatment and five patients who had received only imatinib. Ten of 13 interferon/imatinib patients and three of five imatinib only patients remained in CMR at last follow up. All five of the molecular relapses occurred within 5 months of discontinuing treatment, and all five patients regained CMR after restarting imatinib. No patients experienced hematologic relapse or were found to have acquired an ABL kinase domain mutation.

The most mature data have been published by the French group led by F-X Mahon. They first conducted a pilot study to evaluate the feasibility of imatinib discontinuation in patients who had been in CMR for more than 24 months [8]. After imatinib was discontinued, patients were monitored by quantitative RT-PCR (Q-PCR) monthly for the first 6 months and then every other month thereafter. The investigators enrolled 12 patients who had been in CMR for a median of 32 months after receiving imatinib for a median of 45 months. Ten of 12 patients had had previous treatment with interferon. After stopping imatinib, six patients experienced molecular relapse; all events occurred within 5 months of drug discontinuation. After restarting imatinib, two patients regained CMR, and the other four had decreasing transcript levels at the time of publication. Six patients remained in CMR with a median follow-up of 18 months at the time of reporting, and some for as long as 24 months.

Guided by these results, the French group initiated the multicenter Stop Imatinib (STIM) study in July 2007 [9]. Study enrollment required at least 36 months of imatinib therapy and at least 24 months with CMR documented on several occasions. This trial enrolled 50 patients, 25 of whom had received prior interferon. At the time of the abstract presentation at the 2008 ASH meeting, 34 patients had been followed for longer than 6 months after imatinib was stopped. Nineteen patients (56%) had already experienced a molecular relapse, with all but one relapse occurring within 6 months of imatinib discontinuation. Fifteen patients (44%) remained in CMR with monthly monitoring by Q-PCR, but only three patients had been followed for longer than 12 months. Of note, the observed relapse rate was similar for patients who had previously received interferon when compared with those who had received only imatinib.

Thus, a small but growing body of evidence suggests that a subset of patients treated for CML in chronic phase who are in a prolonged CMR on imatinib therapy may be able to discontinue their TKI therapy safely. However, this strategy requires further validation and much longer follow-up. As yet, there appear to be no patient or disease characteristics that would identify in advance those who can safely discontinue their imatinib. Thus, such patients should be observed extremely closely and within the context of a well-designed clinical trial. Monthly monitoring with a sensitive and reliable Q-PCR method appears mandatory as well as a commitment for restarting imatinib at the first sign of molecular relapse. Fortunately, most patients can be rescued after relapse. It remains to be determined whether patients who received interferon prior to imatinib have lower relapse rates than those patients who receive imatinib alone. Future studies may consider using both agents, either sequentially as in the past or concurrently, as a strategy for CML eradication with the ultimate goal of avoiding long-term TKI exposure.

For now, clinical practice should be guided by a conservative approach. Continuous daily imatinib therapy and the timely achievement of therapeutic milestones such as early hematologic response, CCyR and MMR are critical for ensuring that the excellent published outcomes in CML are replicated in widespread practice. No patient in a prolonged molecular remission, or with any depth of remission, should attempt to stop therapy on his or her own. In addition, treating clinicians should not apply these early findings to individual patients by stopping an effective therapy before the evidence base is larger and more mature.

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References


