HEMATOLOGY

Curing CML with imatinib—a dream come true?

Michael Deininger

Imatinib was discontinued in patients with chronic myeloid leukemia (CML) who gained a complete molecular response (CMR). Of those patients with at least 12 months follow-up, 61% experienced recurrence, all of whom responded to rechallenge. The remaining patients maintained CMR, suggesting that imatinib may 'cure' a small proportion of patients with CML.

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Can imatinib cure chronic myeloid leukemia (CML)? No other question in the field of CML has been debated with the same fervor since it was recognized that some patients with a complete molecular response (CMR, defined as consistently negative tests for *BCR-ABL* transcripts in the blood), maintain this response after discontinuation of therapy.[1] As almost all of the patients in this original report had previously been treated with interferon-α (IFN-α) it remained unclear whether or not this response could be accomplished with imatinib alone.[1]

Mahon and colleagues now report the first results of the Stop Imatinib (STIM) trial, which enrolled 100 patients who discontinued imatinib after achieving and maintaining CMR for 2 years or more, including 49 patients who had never received IFN-α.[2] Of the 69 patients with at least 12 months of follow-up (median 24 months), 42 (61%) experienced a re-emergence of *BCR-ABL* transcripts; the remaining patients maintained their CMR. Factors independently associated with recurrence were female sex, shorter duration of imatinib therapy and high Sokal risk disease at diagnosis, whereas previous exposure to IFN-α was not relevant. All but one of the recurrences occurred within 7 months of stopping imatinib, and all patients with recurrent disease responded to imatinib rechallenge. This finding suggests that stopping imatinib may be safe if done with close monitoring, and that the term 'recurrence' should be used to distinguish this situation from 'relapse', which implies progression despite continued therapy. As it is possible to determine relatively early those patients whose disease is destined to recur, one might be able to decrease the frequency of monitoring once a patient has maintained CMR for a yet to be determined length of follow-up.

Are patients with sustained CMR off imatinib truly cured of CML? At this point, the answer is a qualified 'maybe'. First we have to be sure that what we are seeing is indeed a genuine plateau and not a slow but inexorable attrition. A study reported in 2010 using a patient-specific DNA-based assay found residual leukemia in seven out of eight patients who maintained CMR after imatinib discontinuation;[3] it is quite possible that these seven patients will eventually proceed to negativity but it is also possible that the apparent inability to eradicate all residual *BCR-ABL*-positive cells is a sign that a patient's disease will eventually recur. The second consideration is more conceptual: how do we define 'cure'? A first thought would be to equate cure with the complete absence of *BCR-ABL*. This definition is radical but impractical, as it cannot be tested experimentally. Moreover, we know that highly sensitive assays can detect *BCR-ABL* transcripts even in healthy volunteers.[4] Thus, another concept of cure is needed that takes account of the ability to safely discontinue treatment but not the certainty of having annihilated all CML cells. In this frame of thinking, cure would be defined as a likelihood of developing clinical CML that is no different from the general population. The fact that occasional relapses have occurred almost two decades after allogeneic stem-cell transplant suggests that considerable observation time will be needed before making this call.[5] The major concern is that stopping imatinib in the absence of clonal extinction might lead to renewed exposure of CML stem cells to *BCR-ABL* kinase activity, promoting genomic instability and, ultimately, disease progression.[6]

The STIM study found no association between sustained CMR and previous exposure to IFN-α. These data are somewhat at odds with the French STI571 Prospective Randomized Interferon Trial (SPIRIT) that reported increased CMR rates in patients receiving a combination of imatinib plus pegylated IFN-α compared with imatinib alone.[7] It remains possible that simultaneous administration of imatinib and IFN-α is required rather than sequential administration. At some point this hypothesis may be tested by controlled discontinuation of therapy in a subset of the SPIRIT study.

Practice point

The stop imatinib (STIM) study suggests that CML patients who consistently tested negative for *BCR-ABL* by reverse transcription PCR for at least 2 years may safely stop imatinib, provided they are subjected to intense monitoring to detect disease recurrence. Given the limited experience with the approach and the short follow-up of the study this should be done only in the setting of a clinical trial.

Perhaps the most fascinating observation in the STIM study is the apparent dichotomy of outcomes: early recurrence versus no recurrence. What tentative conclusions can we draw from this phenomenon about the disease biology in the two groups? The behavior of the first cohort (those with early recurrence) is consistent with the current concept of residual disease in imatinib-treated CML. Leukemic progenitor cells, unlike stem cells, are sensitive to imatinib suggesting that the reconstitution of leukemic hematopoiesis at the expense of normal hematopoiesis may start immediately after imatinib treatment is stopped. The kinetics of recurrence in the STIM study—an increase in leukemia load of approximately one log per month—suggests that residual leukemia

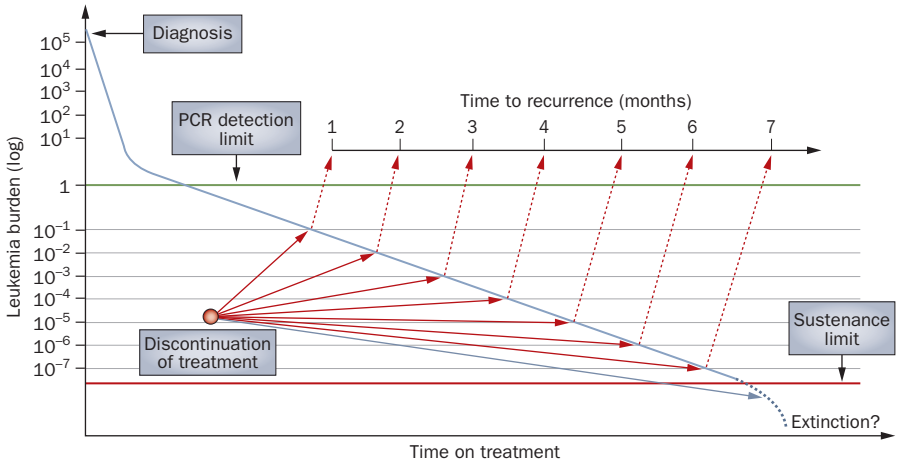

Figure 1 | Hypothetical model of chronic myeloid leukemia persistence and recurrence versus extinction. Whether the leukemic clone can be erradicated may depend on inherent feature of the disease or on the duration of therapy or both.

'smolders' at a level that is 10–10^7 times lower than the detection limit of the PCR assay (Figure 1). Importantly, a high Sokal risk is a reliable predictor of recurrence. This situation is strikingly different from patients with CMR who continue therapy and have a very low risk of relapse irrespective of their risk at presentation.[8] Thus, some cases of CML must have biological properties that are controlled only by continued therapy, irrespective of CMR. The second distinct feature of patients with a rapid recurrence is a shorter duration of imatinib therapy. At first glance, this finding seems to suggest a higher level of residual leukemia, consistent with the slow but steady reduction of *BCR-ABL* transcripts in imatinib responders treated on the International Randomized study of Interferon and STI571 (IRIS) trial.[9] However, in this case one would expect to see recurrences continue with time, rather than the dichotomy observed in the STIM study. To reconcile prediction and observation we postulate the existence of a threshold with a minimum residual number of leukemic cells required to reconstitute leukemic hematopoiesis (in analogy to minimum viable population sizes in animal species[10]). Once suppressed below this threshold, the *BCR-ABL*-positive clone may lose its reconstitution potential; certain immunological mechanisms may control it or it may finally become extinct by chance (Figure 1).

Mahon and colleagues estimate that 10% of patients with CML may be eligible for a trial of imatinib discontinuation.[2] Thus, with a 40% rate of sustained CMR, 4% of CML patients may be 'curable' with imatinib. The big question is whether the more potent *BCR-ABL* inhibitors nilotinib and dasatinib will increase this rate by a significant margin. At least two scenarios are possible. Firstly, a more potent inhibitor will drive disease burden below the 'threshold of no return' in a larger proportion of patients. The observation that a longer duration of imatinib therapy predicts a higher likelihood of maintaining CMR after stopping could support this scenario. Secondly, the capacity of the CML clone to undergo complete involution may represent an infrequent biological feature—extremely low risk—that is determined *a priori*, and not modified by *BCR-ABL* kinase inhibitors. In this case, the rates of non-recurrence would remain at a comparable level with more-potent tyrosine kinase inhibitors. Whatever the case, the most meaningful end point of any future interventional study in CML, as Mahon and colleagues propose, will be the ability to discontinue therapy after inducing CMR.

What are the practical implications for patients with CML in 2011? First and foremost: caution. At this point the STIM data are preliminary and follow-up is too short for changes in clinical practice. As with any experimental treatment, patients who wish to stop imatinib should enroll in a controlled trial. If this approach is not feasible and a patient insists on being taken off therapy, then intense monitoring with high-quality reverse transcription PCR (RT-PCR) is mandatory. Inclusion in the STIM study required at least five negative RT-PCR tests over a 2-year period using highly sensitive assays, and similarly stringent criteria must be applied in every other setting. The biggest concern is that the results of the STIM trial are misinterpreted as a carte blanche to stop therapy in unsuitable patients and with insufficient monitoring. The good news, however, is that CMR achieved with imatinib monotherapy may in some patients continue indefinitely after stopping therapy. If this finding really holds true we might start talking about a cure.

Division of Hematology and Hematologic Malignancies, University of Utah, Huntsman Cancer Institute, 2000 Circle of Hope, Room 4280, Salt Lake City, UT 84112-5550, USA.
michael.deininger@hci.utah.edu

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Competing interests
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1. Rousselot, P. *et al.* Imatinib mesylate discontinuation in patients with chronic myelogenous leukemia in complete molecular remission for more than 2 years. *Blood* **109**, 58–60 (2007).
2. Mahon, F. X. *et al.* Discontinuation of imatinib in patients with chronic myeloid leukaemia who have maintained complete molecular remission for at least 2 years: the prospective, multicentre Stop Imatinib (STIM) trial. *Lancet Oncol.* **11**, 1029–1035 (2010).
3. Ross, D. M. *et al.* Patients with chronic myeloid leukemia who maintain a complete molecular response after stopping imatinib treatment have evidence of persistent leukemia by DNA PCR. *Leukemia* **24**, 1719–1724 (2010).
4. Bose, S., Deininger, M., Gora–Tybor, J., Goldman, J. M. & Melo, J. V. The presence of BCR-ABL fusion genes in leukocytes of normal individuals: implications for the assessment of minimal residual disease. *Blood* **92**, 3362–3367 (1998).
5. Goldman, J. M. *et al.* Relapse and late mortality in 5-year survivors of myeloablative allogeneic hematopoietic cell transplantation for chronic myeloid leukemia in first chronic phase. *J. Clin. Oncol.* **28**, 1888–1895 (2010).
6. Koptyra, M. *et al.* BCR/ABL kinase induces self-mutagenesis via reactive oxygen species to encode imatinib resistance. *Blood* **108**, 319–327 (2006).
7. Guilhot, F. *et al.* Significant higher rates of undetectable molecular residual disease and molecular responses with pegylated form of interferon a2a in combination with imatinib (IM) for the treatment of newly diagnosed chronic phase (CP) chronic myeloid leukaemia (CML) patients (pts): confirmatory results at 18 months of part 1 of the Spirit phase III randomized trial of the French CML Group (FI LMC) [abstract]. *Blood* **114**, a340 (2009).
8. Druker, B. J. *et al.* Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. *N. Engl. J. Med.* **355**, 2408–2417 (2006).
9. Hughes, T. P. *et al.* Long-term prognostic significance of early molecular response to imatinib in newly diagnosed chronic myeloid leukemia: an analysis from the International Randomized Study of Interferon and STI571 (IRIS). *Blood* **116**, 3758–3765 (2010).
10. Traill, L. W., Bradshaw, C. J. & Brook, B. W. Minimum viable population size: A meta-analysis of 30 years of published estimates. *Biological Conservation* **139**, 159–166 (2007).