Can we stop imatinib?

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SUMMARY

The introduction of tyrosine kinase inhibitors (TKIs) has revolutionized the management of chronic myeloid leukaemia (CML). The median survival for CML patients is predicted to increase to 25 years from 8–9 years in the pre-TKI era. Latest data suggest that life expectancy of patients with CML is approaching the life expectancy of the general population.[1] Presently patients with CML receive imatinib mesylate (first generation TKI introduced in 2001) or newer TKIs—dasatinib or nilotinib (second generation TKI, introduced in 2006); both dasatinib and nilotinib are associated with faster and deeper molecular remission. The current recommendation is to continue either of these drugs indefinitely. However, with prolonged treatment side-effects such as fatigue, musculoskeletal symptoms (arthralgia/myalgia/cramps), poor quality of life and financial burden are important issues and can lead to non-adherence to therapy in up to one-third of patients treated with imatinib.[2] In addition, for young patients interference with conception and pregnancy are other important limitations. In the past few years, there have been attempts to discontinue TKI in specific subgroups of patients based on duration of TKI intake and response at the molecular level. Nonetheless some of these studies have methodological limitations such as small sample size, lack of standardized definition of molecular response and heterogeneous criteria for stopping as well as re-initiation of therapy.[3]

The current study by the French Group is the long-term follow-up of their earlier attempt 'to stop Imatinib' (STIM) in patients with CML. In this prospective cohort study conducted at 19 French centres, 100 Ph +ve CML-CP chronic phase (CP) patients (age >18 years) were recruited. These patients had received imatinib for more than 3 years with undetectable molecular residual disease (U-MRD) on six occasions in 2 years. Allogeneic stem cell transplant recipients, patients with second malignancy and those who had received other immunomodulatory drugs except interferon alpha were excluded. Once imatinib was stopped the patients were followed monthly in the first year, once in 2 months in the second year and once in 3 months in the third year. Molecular relapse (MR) was defined as at least two positive reverse transcriptase-polymerase chain reaction (RT-PCR) results showing a significant increase (by 10 times), at two consecutive assessments or loss of major molecular response (MMR). The median follow up was 77 months. Of the 100 patients, 39 patients had U-MRD and 61 patients had MR. Four of 61 patients refused re-initiation of TKI; 3 of 4 were alive at the time of reporting and 1 patient died of a second malignancy. The remaining 57 patients were restarted on TKI. Fifty-five patients achieved a second U-MRD and 2 achieved MMR. There were 4 deaths unrelated to CML in this group of patients. The median time for achieving a second deep molecular response was 4.1 months. Molecular recurrence-free survival was 43% and 38% at 24 and 60 months, respectively. The Sokal risk score and duration of imatinib treatment were predictive of molecular response in multivariate analysis.

The authors concluded that discontinuation of imatinib was safe. All patients achieved second molecular remission on re-initiation of TKI. They recommended that the Sokal score and duration of imatinib need to be given importance before stopping TKI. This trial gave further evidence that treatment-free remission is a valid concept in long-term management of patients with CML.

COMMENT

CML is a clonal disorder of pluripotent stem cells and results from translocation of the *ABL* gene on chromosome 9 to the region of the *BCR* gene on chromosome 22 (t9;22). This leads to the formation of the *BCR–ABL* fusion gene which encodes an abnormal chimeric protein (BCR–ABL p210) with constitutively activated tyrosine kinase activity. The latter is responsible for the activation of signal transduction pathways leading to abnormal marrow proliferation and the clinical and laboratory manifestations of CML.[4] Imatinib mesylate (STI 571, Gleevec, Glivec), the tyrosine kinase central to the pathogenesis of CML is a potent and a specific inhibitor of *BCR–ABL*.[1] Measurement of *BCR–ABL* transcripts by quantitative RT-PCR (RQ PCR) at periodic intervals is recommended and has helped to categorize patients in molecular remission as major (MMR) or complete (CMR) and is one of the desirable goals. In general, deeper molecular remission (4–4.5 log reduction in *BCR–ABL* transcript levels) early in the course of treatment is associated with improved outcome and lower probability of progression on discontinuation. Factors associated with a higher probability of treatment-free remission include low-risk Sokal score, prior interferon treatment, longer total duration of imatinib treatment and higher number of natural killer cells at the time of discontinuation of imatinib.[3]

A few important findings from the French study need to be highlighted. These are: (i) the authors used a sensitive RQ-PCR assay to detect *BCR–ABL* (detection threshold was below 5 log reduction). Eligible patients for imatinib cessation had undetectable transcripts for 2 years with at least six measurements. After stopping TKI the patients were closely monitored with scheduled visits. (ii) This was the first large study to test the concept of discontinuation of TKI. Studies of cessation of imatinib in patients with CMR ranging from 1.5 to 2 years have shown MR rates of 36%–50%.[5–8] Most imatinib failures occurred within the first 6 months and all patients responded to re-introduction of imatinib. It is unlikely that a longer follow-up will yield more information.[5–8] (iii) This study has been able to establish the criteria for cessation of TKI. However, at what molecular level of transcripts TKI should be re-initiated is not clear. The present study took loss of U-MRD as TKI re-initiating criteria but other trials took loss of major molecular remission as re-initiating criteria.[3] (iv) Imatinib has been shown to affect the quality of life in patients <60 years but not in those >60 years.[9] However,

improvement in the quality of life after stopping imatinib has not been studied yet. Results from imatinib cessation trials for quality of life are awaited. In ENESTop trial there was no difference in the quality of life before and after stopping nilotinib.[10] About 15%–30% of patients have TKI withdrawal syndrome on cessation of TKI which might contribute to impairment of quality of life.[3] Also, psychological aspects of cessation of TKI have not been studied. Lastly, it is important to know the number of patients who will benefit by stopping imatinib. In this study, 40% of patients attained deep molecular response. Of these, 40% were relapse-free at 5 years. Thus, approximately 16% will benefit from this approach. Finally, patients' preference also needs to be considered before discontinuation of the drug. In an Italian survey about 50% of patients were comfortable with the idea of discontinuation of TKI.[11]

Hughes and Ross have proposed guidelines for stopping TKI.[12] Patients above 18 years but less than 60 years of age, who were in CP at the time of diagnosis, with low or intermediate Sokal risk score and those who had received TKI more than 8 years and have attained deep molecular response (4.5 log reduction in *BCR–ABL* transcripts) with the duration of response lasting for more than 2 years are suitable candidates. It is assumed that treatment centres have a high quality, internationally standardized, accurate and sensitive RQ-PCR laboratory. The results should be available in 4 weeks and structured follow-up should be done and intervention must be planned in case of rising levels of *BCR–ABL* transcripts after cessation.

What could be the application of these results for our patients in India? Most patients at least at major cancer centres receive imatinib supported either by the Gleevec International Patients Assistance programme or by the hospital or by the patients themselves.[4] A small number receive second-generation TKI as first-line therapy. Currently, facilities for molecular monitoring are limited to a few centres.[2] Thus, even though applicability of these results is likely to be limited to a small number of patients, at least it can be considered for young patients and patients who are planning pregnancy.

Conflicts of interest. None declared

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