

## Imatinib failed to eradicate chronic myeloid leukemia in a patient with minimal residual disease

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Imatinib induces complete cytogenetic remissions (CCR) in over 75% of patients with chronic myeloid leukemia (CML) treated at diagnosis, while in early chronic phase.<sup>1</sup> However, fewer than 10% of such patients achieve a molecular remission, defined as negative quantitative polymerase chain reaction (PCR) confirmed by nested PCR.<sup>2</sup> The significance of molecular responses is unknown at present, since most patients continue treatment.

We report here on an exceptional case in which imatinib treatment was started in a patient who had already achieved CCR with interferon- $\alpha$  (IFN- $\alpha$ ) in whom molecular remission was obtained very early after starting imatinib, and persisted unaltered for 16 months, but which was rapidly lost after forced drug discontinuation.

A 41-year old male patient was diagnosed with CML in 1999. The patient started treatment with at IFN- $\alpha$  3MU/day and obtained a CCR by April 2000. He started imatinib at 400 mg/day in June 2000 because of imatinib intolerance (hepatic toxicity). At that time his only sign of disease was a positivity for Bcr-Abl transcripts by nested PCR. By month 3 he became PCR negative (sensitivity  $10^{-5}$ ), and tested negative at months 6, 9, 12, 15, and 16 (December 2001).

The patient lived in the far East, and because of employment problems (he feared for his position because of too many sick leaves) he skipped a follow-up appointment in October 2001. In the following months, because of the international situation after september 11th, his home country did not allow the shipment of imatinib to him. For this reason, the patient had to stop imatinib for 4 months (from December 2001 to April 2002). In April 2002 he was finally able to return to Italy; at that time PCR analysis was positive and cytogenetics showed 3/20 Ph+ metaphases. Imatinib was resumed at the same dosage: CCR and molecular remission were again achieved after 3 and 6 months respectively, and are continuing (month 67).

Cortes recently published similar data in three CML patients.<sup>3</sup> Our case does, however differ significantly from those of Cortes. Who had more advanced disease (one in late chronic phase resistant to IFN- $\alpha$ , one in accelerated phase), and started imatinib with Ph+ cells being the dominant population in their marrow.

In contrast, our patient was in early phase disease, was responding to IFN- $\alpha$ , started imatinib treatment with less than 1/1000 Ph+ cells, and remained continuously negative by PCR for 16 months. In spite of this, a cytogenetic relapse was detected 4 months after treatment discontinuation.

This case must however, also be considered in the frame of the evolving data emerging from the long-term follow-up of the initial cohorts of patients<sup>7</sup> showed more recently than our case and the report by Cortes,<sup>3</sup> disease relapse no longer seems to be a universal and constant consequence of imatinib discontinuation, especially when there have been at least 2 years of continuous PCR negativity prior to drug discontinuation.

Further studies and techniques will be needed to define the patients in whom treatment discontinuation can be safely attempted.

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