Long-term molecular response after discontinuation of interferon-alpha in two patients with chronic myeloid leukaemia

Endri Mauro

Section of Haematology and Bone Marrow Transplantation Unit, Cremona Hospital, Cremona, Italy

Dear Sir,

We would like to take part in the debate about the discontinuation of treatment of chronic myeloid leukaemia (CML), with particular reference to the Letter to the Editor by Veneri *et al.*[1], published in this Journal. Here we describe a patient with CML who received imatinib therapy. In February 2002 a 76-year old woman was diagnosed has having CML in accelerated phase. Cytogenetic analysis showed translocation of the Philadelphia chromosome (Ph) without others aberrations; therapy with imatinib mesylate at dose of 600 mg daily was started. We observed haematological, cytogenetic and molecular remission after 12 months (in 2003). However, during follow-up and imatinib treatment, after achieving of molecular remission, a cell line with trisomy of chromosome 8 appeared. In 2005, after 2 years of molecular remission, the patient began to experience abdominal pain, nausea, vomiting and weight loss. She refused an endoscopic examination and decided to stop imatinib treatment. Her symptoms briefly regressed and she obtained a state of very good health. At present, BCR-ABL mRNA is not detectable by a quantitative polymerase chain reaction (PCR)-based assay, thus showing a complete molecular response; on cytogenetic evaluation trisomy of chromosome 8 is still present.

This case report allows some considerations. In their Letter to the Editor, Veneri *et al.*[1] describe two cases of long-time persistence of molecular remission after cessation of interferon-α treatment; as supposed by authors, because our patient achieved molecular remission through treatment with a tyrosine kinase inhibitor, we could confirm that the long-time persistence of molecular response is not dependent on the type of treatment used. Moreover, Veneri *et al.*[1] considered assessment of BCR/ABL transcripts by PCR analysis not fully reliable for evaluating disease status. Our case illustrates the unreliability of molecular analysis well, showing that a sustained trisomy +8 appeared after a complete molecular response. Despite long-free survival without treatment, it is interesting to note that trisomy +8 may appear as an additional chromosomal aberration after therapy with tyrosine kinase inhibitors and may reflect genetic instability and intrinsic aggressiveness of Ph-positive cells[2,3]. In our case, as supposed by Cortes *et al.*[3], we assume the presence of a Ph-negative progenitor cell which is susceptible to the development of additional chromosomal abnormalities that are unmasked by the rapid suppression of the Ph-positive cells by imatinib therapy. On other hand, despite our patient's BCR/ABL molecular remission and sustained trisomy +8, her long, disease-free survival may highlight the key role of BCR/ABL not only in the development of CML from Ph-negative progenitor cells but also as a trigger to progression in accelerated phase with appearance of new cytogenetic aberrations that have prognostic significance only in combination with BCR/ABL molecular expression[2]. However, besides BCR/ABL molecular evaluation and the kind of treatment (tyrosine kinase inhibitors, interferon-α, etc.), others biological markers should be identified not only to explain the pathogenesis and evolution of CML better, but also to understand whether there is a genetic precursor lesion, as discussed for Ph-negative myeloproliferative diseases, and, if so, its role in the progression of CML and in the CML stem cell[4].

The Author declares no conflicts of interest.

References

1) Veneri D, Tecchio G, De Matteis G, et al. Long-term molecular response after discontinuation of interferon-alpha in two patients with chronic myeloid leukemia. Blood Transfus 2012; **10**: 233-4.
2) Kim TD, Turkmen S, Schwarz M, et al. Impact of additional chromosomal aberrations and BCR-ABL kinase domain mutations on the response to nilotinib in Philadelphia chromosome-positive chronic myeloid leukemia. Haematologica 2010; **95**: 582-8.
3) Cortes JE, Talpaz M, Giles F, et al. Prognostic significance of cytogenetic clonal evolution in patients with chronic myelogenous leukemia on imatinib mesylate therapy. Blood 2003; **101**: 3794-800.
4) Rumpold H, Webersinke G. Molecular pathogenesis of Philadelphia-positive chronic myeloid leukemia - is it all BCR-ABL? Curr Cancer Drug Targets 2010; **11**: 3-19.

Arrived: 5 November 2011 - Accepted: 29 November 2011
Correspondence: Endri Mauro
Section of Haematology & BMT Unit
Hospital of Cremona
Via Concordia 1
26100 Cremona, Italy
e-mail: endri76@libero.it