

Chromosomal abnormalities in Philadelphia (Ph)-negative cells of patients with chronic myeloid leukemia treated with imatinib (STI571)

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Chronic myeloid leukemia (CML) is a malignant clonal disorder of hematopoietic stem cells. After a chronic phase characterized by the isolated presence of the translocation t(9;22), the natural history of the disease includes progression from a benign chronic phase to a rapidly fatal blast crisis, generally accompanied by a range of non-random clonal changes in the malignant clone. This clonal evolution of Ph-positive cells in CML has been associated with a bad prognosis in nearly all cases.¹⁻³ However, the emergence of chromosomal abnormalities on Ph-negative hematopoietic progenitor cells is a very unusual fact in patients with CML treated with conventional pre-Imatinib therapies.^{4,6}

We present and discuss two cases of patients with Ph-positive CML treated with the tyrosine kinase inhibitor, imatinib, who developed new chromosomal abnormalities in their Ph-negative cells. At diagnosis both patients (45 and 38 year-old women respectively for cases 1 and 2) were in chronic phase, with 100% Ph-positive cells and no other chromosomal abnormality. They began treatment with imatinib after being resistant to interferon- α with an initial dose of 400 mg/day, but case 1 suffered grade III neutropenia that prompted us to reduce dose to 300 mg/day. Initial evaluations showed a minor (20%) and a major (80%) cytogenetic response at three months respectively for cases 1 and 2. At six months case 1 had a complete cytogenetic response with the presence of two different cell lines: 7 of 26 were normal, and 19 of 26 were 45,XX,-7 (FISH negative for t(9;22) but BCR/ABL positive by RT-PCR). Case 2 maintained her major cytogenetic response and at 17 months three different cell lines were found: 1 of 18 metaphases was 46,XX,t(9;22), 6 of 18 were 46,XX and 11 of 18 were 46,XX,t(2;15)(q37.3;q21.3). After a total follow-up of 11 and 21 months, both patients continue in major cytogenetic response with bone marrow studies showing slight signs of dyserythropoiesis and less than 4% of blasts for case 1 and normal morphology for case 2.

The first question to address is whether the treatment with imatinib may have induced these cytogenetic findings. The incidence was 2 cases from a cohort of 50 patients with CML treated with imatinib, being intolerant or refractory to interferon- α . A recent communication in the 2001 ASH meeting from investigators of Hammersmith Hospital in London, described the emergence of two different new chromosomal abnormalities (del(5)(q15q33) and trisomy 8) in Ph-negative cells from a cohort of 43 CML patients treated with Imatinib. As in our cases, these patients were in major cytogenetic response and showed no clinical progression during their short follow-up. Moreover, we performed a retrospective review of the cytogenetic follow-up of our previous CML patients treated with hydroxyurea, interferon- α , interferon- α plus cytarabine or allogeneic stem cell transplantation finding no chromosomal abnormalities in any Ph-negative cell line, even after patients had achieved complete cytogenetic or molecular responses. We can conclude from these preliminary data that the incidence of cytogenetic abnormalities in Ph-negative cells may be around 4% (4% in our data and 4.6% in the Hammersmith Hospital communication) after treatment with imatinib, while being very unusual or inexistent after other CML therapeutic procedures. So a clear rela-

tionship between the tyrosine kinase inhibitor and these findings should exist.

A second, more difficult point to discuss, is the mechanism of generation of these genomic abnormalities in Ph-negative cells and their clinical relevance. Imatinib inactivates the tyrosine kinase component of the BCR-ABL oncoprotein but also the kinase action of at least normal ABL, c-kit and platelet derived growth factor receptor γ tyrosine kinases.^{8,9} In vitro studies have demonstrated a selective killing of CML hematopoietic cells, presumably resulting from BCR-ABL kinase inhibition, with a minimal role in normal colony formation.¹⁰ However, the inhibition of several normal tyrosine kinases could generate other medium or long-term effects on normal cells. For example, normal ABL tyrosine kinase has been implicated in p53-mediated growth arrest and apoptosis after DNA damage.¹¹⁻¹² So, one could speculate that long-term inhibition of this ABL tyrosine kinase could make normal cells more tolerant to cytogenetic abnormalities derived from DNA damage. Until now, with a short follow-up of less than a year, we do not know the clinical relevance of these findings nor even if these genomic abnormalities could disappear after imatinib discontinuation or could imply a change in the therapeutic strategy. However, this report generates enough evidence to be aware while treating patients with tyrosine kinase inhibitors and warrants further investigation on the effects of normal tyrosine kinases inhibition on normal cells and after long-term administration.

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