Clinical significance of development of Philadelphia-chromosome negative clones in patients with chronic myeloid leukemia treated with imatinib mesylate

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To The Editor,

Since the introduction of imatinib mesylate as treatment for chronic myeloid leukemia (CML) there have been increasing reports of patients developing Philadelphia (Ph) chromosome negative cytogentic clones, a rare phenomenon in the pre-imatinib era.[1] We wish to report our experience of patients who developed Ph negative clones whilst on imatinib therapy, and briefly review the potential clinical implications of this phenomenon. Between 2000 and 2004, a total of 69 patients with CML treated with imatinib had had karyotyping performed at our institution. Of these, 3 (4%) were identified with Ph negative clones on routine cytogenetic analysis. The absence of a silent t(9;22) was confirmed in all 3 cases by interphase FISH analysis utilizing a *BCR-ABL* dual fusion probe (Vysis) as well as a probe specific for the identified non-Ph abnormality.

Case 1

A 77yr male was diagnosed with CML in first chronic phase in May 2001. He was treated initially with hydroxyurea and interferon alpha (IFN). Imatinib was commenced in August 2001 at a dose of 300 mg/day, with a complete cytogenetic response achieved by August 2002. Qualitative PCR testing for the bcr-abl fusion transcript was also negative at this time. In December 2003 a routine bone marrow (BM) examination demonstrated new cytogenetic findings, with the development of a Ph negative clone (46 XY,del5(q13q31)) in 2 of 50 metaphases. Morphologically, the marrow sample was considered mildly hypocellular, with no specific dysplastic features and no excess of blasts noted. Qualitative PCR testing for the bcr-abl fusion transcript remained negative. Imatinib was continued at 300 mg daily. In April 2004 progressive transfusion-dependent anaemia developed and repeat BM examination revealed acute myeloid leukemia (AML), with increased cellularity and 35% myeloblasts. Again, no specific morphological features of myelodysplasia were present. The karyotype showed complex abnormalities with progression of the previously noted Ph negative clone (44,XY,del(5)(q13q31),der(6),t(6,17)(p25;q11.2),-7,17,der(20),t(7,20)(q11.2;p13), +mar). Qualitative PCR testing for the bcr-abl fusion transcript remained negative. Despite receiving treatment for AML, the patient died of progressive AML 8 months later.

Case 2

A 63yr male was diagnosed with CML in first chronic phase in September 2002. He was initially treated with hydroxyurea, then IFN for approximately 4 months. Imatinib was commenced in March 2003 at 400 mg / day. In November 2003, although morphologically normal (with normal cellularity, no excess of blasts and no specific dysplastic features), a routine BM aspirate demonstrated the presence of a Ph negative clone (45 XY,-7) in 4 of 20 metaphases. Qualitative PCR for the BCR-ABL fusion transcript was not performed on this sample, though had previously always remained positive. No change in therapy was initiated at this time. In April 2004 the patient presented with a macular-papular rash secondary to leukaemia cutis. Repeat BM examination was hypercellular with >20% myeloblasts. Again, no specific morphological features of myelodysplasia were noted. Cytogenetic and interphase FISH analysis confirmed the persistence of the previously identified Ph negative monosomy 7 clone. Qualitative PCR for the BCR-ABL fusion transcript was positive. The patient underwent a failed induction with FLAG chemotherapy and died of presumed fungal sepsis 6 weeks later. Retrospective interphase FISH analysis performed on BM samples taken prior to commencement of imatinib showed that the monosomy 7 clone was not demonstrable at that time.

Case 3

A 63yr female was diagnosed with CML in first chronic phase in early 1997. She initially obtained a complete cytogenetic response to IFN. However, due to chronic fatigue, IFN was withdrawn and imatinib commenced in December 2003 A BM examination 4 months later demonstrated new cytogenetic findings, with the development of a Ph negative clone (47 XX,+X) in 2 of 50 metaphases. Morphologically the marrow sample was considered normal, without any specific myelodysplastic features. Qualitative PCR testing for the bcr-abl fusion transcript was positive. Imatinib was continued unchanged and the Ph negative +X clone had disappeared on repeat BM examination in September 2004. The reported incidence of development of Ph negative clones in imatinib treated CML patients varies from 2% to 17%, with >130 cases now reported in the literature.[1-8] In most cases, the clinical significance of development of Ph negative clones is unclear. However, (limited) follow-up of identified cases has only been reported in 56% (77) of cases.[1-4] As seen in our cases, development of secondary AML may not occur for several months after initial recognition of the Ph negative clone on routine BM samples. This suggests that little comfort can be taken in the relatively low incidence of adverse outcomes in reported series to date. Including our 2 cases, we identified 14 reported cases of Ph negative myelodysplastic syndrome (MDS) or AML developing in imatinib treated CML patients.[1,2,6,7] In these cases, the Ph negative clone involved monosomy 7 in 8 patients (alone in 4 and in combination with other changes in 4), deletions of 5q in 2, trisomy 8 alone in 1, deletion 20q in 1, and other changes in 2. These cases represent 29%, 40%, 2%, 13% and 9% of all cases of monosomy 7, deletion 5q, trisomy 8 (as a sole abnormality), deletion 20q and other translocations respectively to have been reported in Ph negative clones developing in patients on imatinib therapy.[1-8] Thus, the risk of developing MDS or AML following the identification of Ph negative clones appears greatest with development of monosomy 7 or deletion of 5q. We believe that because of this risk, in younger patients with identified allogeneic donors, development of Ph negative clones including monosomy 7 or deletion of 5q is an indication to proceed directly to allogeneic stem cell transplantation. Longer follow-up is required to determine the clinical significance of other Ph negative clonal abnormalities developing during imatinib therapy.

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