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Monosomy 7 in t(9;22)-Negative Cells during Nilotinib Therapy in an Imatinib-Resistant Chronic Myeloid Leukemia Case

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A 33-year-old white female was diagnosed with t(9;22)-positive chronic myeloid leukemia (CML) in December 2004 and was started on imatinib at 400 mg daily. She achieved only minor cytogenetic response after eight months of treatment and therefore imatinib was increased to 600 mg daily. The patient then developed grade III thrombocytopenia that persisted despite reducing the imatinib dose. She was therefore enrolled on a phase II dose-escalation study of oral nilotinib 400 mg twice daily on October 2005. The patient responded to nilotinib with mild thrombocytopenia but as she started to develop cytogenetic response, *de novo* abnormal clone with monosomy 7 (45,XX,-7) and dysplastic changes started to appear in the marrow (Figure). Therefore, in September 2006 the patient taken off nilotinib with plans to switch to dasatinib and evaluate for allogeneic stem cell transplantation.

To the best of our knowledge, this is the first case report of monosomy 7 arising in t(9;22)-negative cells in an imatinib-resistant CML patient during nilotinib therapy. The appearance of cytogenetic aberrations in t(9;22)-negative cells has been rarely reported following chemotherapy [1], interferon [2] and in approximately 2% to 17% of patients following imatinib therapy [3–7]. Few of these patients developed myelodysplastic syndromes (MDS) or acute myeloid leukemia (AML); especially those with monosomy 7 [reviewed in 7]. The mechanisms to explain the emergence of such abnormal clones are not clear. It was postulated that the t(9;22)-negative clone may have predated the acquisition of the t(9;22) translocation in a two-step mechanism for CML pathogenesis. Another closely-related explanation [5] is the presence of several abnormal clones after the patient's hematopoiesis has been subjected to genetic damage. One of these clones carries the t(9;22) and is at a proliferative advantage therefore masking the underlying clonal diversity. The selective pressure applied by imatinib, or nilotinib in our case, therapy could suppress the proliferation of cells with t(9;22) which allows the monosomy 7 clone to grow. This may explain the higher frequency of t(9;22)-negative clones arising in response to therapy with imatinib than with interferon, as imatinib is generally more effective in suppressing the t(9;22)-positive clone than interferon [6]. The

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Dr. Zeidan wrote the manuscript, Dr. Kakati performed the cytogenetic analyses, Ms. Anderson was the research nurse following the patient on the nilotinib protocol, Dr. Barcos was the pathologist who studied the case and Dr. Wetzler was the attending physician who cared for the patient. All authors reviewed the manuscript and approved its content.

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third theory is that the t(9;22)-negative clones arise as result of DNA damage inflicted by imatinib or nilotinib therapy. The c-Abl protein interacts with some of the proteins involved in the response to DNA damage and repair [8–9]. Therefore, permanent inhibition of c-Abl can result in genomic damage [3].

The clinical significance of these t(9;22)-negative clones that arise while on therapy with imatinib is not clear as the majority of these patients fare well with a similar prognosis to those who do not develop such clones. Whether nilotinib caused the abnormality in our patient or merely “unmasked” a pre-existing t(9;22)-negative clone carrying monosomy 7 as the patient responded to therapy is to be determined. However, given the serious consequences of monosomy 7 and its association with MDS/AML, all patients treated with imatinib, as well as nilotinib and most probably dasatinib, should be followed with regular cytogenetic analyses, even after achieving complete cytogenetic response.

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Figure 1.

Cytogenetic and morphological analyses of an imatinib-resistant CML patient during nilotinib therapy. A, percentages of 46,XX, monosomy 7 and t(9;22) cells; B, marrow biopsy from August 2006 representing advanced granulopoiesis and erythropoiesis and several dysplastic megakaryocytes with hypolobated or bizarre elongated hyperchromatic nuclei (Giemsa stained section, x25); C-E, different areas from the bone marrow biopsy from September 2006; C, advanced granulopoiesis and erythropoiesis and syncytial dysplastic megakaryopoiesis with hypolobated or vesicular nuclei (Giemsa stained section, x25); D, dysplastic megakaryocyte with large hypolobated nucleus with reticular chromatin (Wright-Giemsa stained imprint, x250); E, dysplastic mononuclear and binuclear pronormoblasts with prominent nucleoli (Wright-Giemsa stained smear, x100).