Brief report

Myelodysplastic syndromes and acute leukemia developing after imatinib mesylate therapy for chronic myeloid leukemia

Craig Kovitz, Hagop Kantarjian, Guillermo García-Manero, Lynne V. Abruzzo, and Jorge Cortes

During therapy with imatinib, some patients with chronic myeloid leukemia (CML) develop chromosomal abnormalities in Philadelphia chromosome (Ph)–negative cells. These abnormalities are frequently transient and their clinical consequence is unclear. Although some reports have suggested that the abnormalities might be associated with secondary myelodysplastic syndrome (MDS), the diagnosis has not always been established using standard criteria. We report 3 cases of patients treated with imatinib for CML who were subsequently found to have chromosomal abnormalities in Ph-negative cells. One of them developed acute myelogenous leukemia (AML) and the other 2 developed high-risk MDS that rapidly transformed to AML. These cases were identified in a total study group of 1701 patients. Although these occurrences are rare, the findings highlight the need for close monitoring of patients with CML treated with imatinib. (Blood. 2006;108:2811-2813)

Introduction

During treatment for chronic myeloid leukemia (CML), a subset of patients develops chromosomal abnormalities in the Philadelphia chromosome (Ph)–negative cells that emerge as they respond to therapy. This phenomenon was first described in rare cases of patients treated with chemotherapy, interferon-alpha (IFN), and recently with imatinib. Although it has been suggested that this phenomenon may be associated with the development of myelodysplastic syndromes (MDSs), the criteria to diagnose MDS have not always been standard. Isolated instances of high-risk MDS or acute myeloid leukemia (AML) have been reported. We reviewed our experience with this phenomenon and identified 3 patients undergoing treatment for CML with imatinib who developed AML according to World Health Organization (WHO) criteria.

Study design

Medical records of all patients with Ph-positive CML treated with imatinib at the M. D. Anderson Cancer Center (MDACC) (Houston, TX) since December 1999 were reviewed to identify patients with chromosomal abnormalities in Ph-negative metaphases during imatinib therapy. All pathologic material was reviewed to identify patients with MDS or AML according to the WHO classification. Among 1701 patients analyzed, 3 patients were identified as meeting such criteria (0.1%; 95 CI, 0%-1%). All patients were registered in protocols approved by the M. D. Anderson institutional review board (IRB), and informed consent was obtained in accordance with the Declaration of Helsinki in all, per institutional guidelines.

Patient 1

A 51-year-old woman diagnosed with CML in October 1999 received IFN without achieving cytogenetic response. In June 2001, she started 400 mg imatinib daily and later increased to 600 mg, achieving a complete cytogenetic response. After 3 years, she developed progressive pancytopenia. A bone marrow (BM) aspiration performed in January 2005 showed 4% blasts and dysplasia consistent with MDS (refractory cytopenia with multilineage dysplasia [RCMD] with ringed sideroblasts). Conventional cytogenetic analysis demonstrated monosomy 7 as the sole abnormality in all 20 metaphases. Interphase fluorescence in situ hybridization (FISH) for BCR/ABL1 was borderline positive (2.5% of interphases; normal, 0%-1.5%). Imatinib was withheld without improvement of pancytopenias. Three weeks later, BM aspirate showed trilineage dysplasia with 14% blasts, consistent with refractory anemia with excess blasts (RAEB-2). Cytogenetic analysis demonstrated monosomy 7 as the sole abnormality in 18 of 20 metaphases and 2 diploid metaphases. Interphase FISH for BCR/ABL1 was borderline positive (2.0%) with BCR-ABL/ABL ratio by polymerase chain reaction (PCR) of 0.16. The patient started treatment with 5-azacitidine. After 2 months, her disease transformed to AML and she died.

Patient 2

A 64-year-old man diagnosed in January 2001 with Ph-positive chronic-phase CML started IFN and cytarabine, but because of intolerance, treatment was changed to 400 mg imatinib daily in
April 2002. He achieved partial cytogenetic response and in April 2003 the dose was increased to 600 mg. In November 2004, a marrow evaluation showed 12% blasts. Cytogenetic studies demonstrated 2 clones: 45,X,—Y, t(9;22)(q32;q11.2) in 25 metaphases and 45,XY,—Y,—7 in 4. Treatment with nilotinib was begun, but the BM blast count increased to 62%. Cytogenetic analysis demonstrated that the Ph-negative clone with monosomy 7 was predominant in 18 of 20 metaphases and that 2 other metaphases showed t(9;22). FISH showed 11% of the 100 interphases positive for BCR/ABL1, and a BCR-ABL/ABL ratio of 3.49, suggesting Ph-negative AML. Nilotinib was discontinued, and induction chemotherapy with idarubicin and cytarabine was begun. The patient achieved a complete remission and received an allogeneic peripheral blood stem cell transplant. He remains in complete cytogenetic remission after 14 months, with no evidence of the Ph or monosomy 7.

**Patient 3**

A 55-year-old man diagnosed with chronic-phase CML in February 2000 received peglated IFN and cytarabine and achieved a complete cytogenetic remission, but he discontinued therapy because of peripheral neuropathy. In July 2003, he relapsed and started 800 mg imatinib daily, achieving complete cytogenetic remission. BM examination in February 2004 demonstrated megaloblastoid erythropoiesis, and conventional cytogenetic analysis showed 18 of 20 normal metaphases, 1 hyperdiploid metaphase (54,XY,+Y,+1,+4,+6,+8,+11,+14,+19,+2mar), and 1 pseudo-diploid (46,XY,del(5)(q12)). FISH for BCR/ABL1 rearrangement was negative. In December 2005, the patient developed thrombocytopenia. BM examination was morphologically consistent with MDS with 10% blasts. Conventional cytogenetic studies demonstrated 5 of 20 Ph-negative hyperdiploid metaphases, 50-52,XY,+Y,+1, dup(2)(q11.2q21), del(5)(q13q33), +6,+8,+11,—21,+r,+3-5mar, and 15 diploid. FISH for BCR/ABL1 rearrangement was negative. In January 2006, BM blasts increased to 20% with persistent complex cytogenetic abnormalities and no BCR/ABL1 rearrangement by PCR. The patient failed induction and salvage chemotherapy, and he died.

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### Results and discussion

The incidence of chromosomal abnormalities in Ph-negative metaphases after imatinib has been reported in approximately 2% to 17% of patients treated. In a study of 272 evaluable patients treated with imatinib, this event occurred in 21 (8%; 95% CI, 0.05-0.12) patients. Most abnormalities are similar to those associated with MDS, including trisomy 8, monosomy 5 or 7, and 20q—. Thus, the clinical consequences of such events are of major concern. We report 3 patients who developed acute leukemia, 2 of them after rapid progression through MDS according to standard definitions by the WHO. To our knowledge, 17 cases of Ph-negative MDS or acute leukemia (6 with AML, including the 3 presented here) have been reported among CML patients treated with imatinib (Table 1). However, the criteria used to diagnose MDS were not always standard; in some, the diagnosis was based only on the presence of the cytogenetic abnormality together with cytopenias and/or megaloblastoid changes in the BM. Since cytopenias are relatively common during therapy with imatinib, and megaloblastoid changes in the BM occur in patients responding to imatinib even in the absence of other cytogenetic abnormalities, the presence of these abnormalities should not be the sole criteria used to diagnose MDS. O’Dwyer et al compared the BM and peripheral blood of patients responding to imatinib with or without chromosomal abnormalities in Ph-negative cells and found similar megaloblastoid changes with varying degrees of dysplasia in both groups. This suggests that the changes were nonspecific and possibly related to a reversible drug effect of imatinib.

In the 3 patients reported here, the diagnosis of MDS or AML was unequivocal, including a significant increase in blasts, and both patients with MDS rapidly progressed to AML. Of importance, in all 3 cases FISH studies confirmed minimal expression of BCR/ABL1, making the possibility that any of these constituted transformation of CML into the accelerated or blast phases unlikely. This phenomenon is rare, as we identified it in only 0.1% of 1701 patients treated with imatinib at our institution and in less than 2% of those who developed chromosomal abnormalities in Ph-negative metaphases.

### Table 1. Reported cases of MDS/acute leukemia by WHO criteria in patients with Ph-negative clones treated with imatinib

<table>
<thead>
<tr>
<th>Reference</th>
<th>Ph-cytogenetics</th>
<th>Diagnosis</th>
<th>Characteristics</th>
<th>Previous treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current report, patient 2</td>
<td>7</td>
<td>AML</td>
<td>—</td>
<td>IFN/cytarabine, HU, imatinib, AMN-107</td>
</tr>
<tr>
<td>Perel et al20</td>
<td>Complex*†</td>
<td>AML</td>
<td>No dysplastic features</td>
<td>IFN/imatinib</td>
</tr>
<tr>
<td>Chee et al19</td>
<td>Complex*†</td>
<td>AML</td>
<td>—</td>
<td>HU, IFN, BMT, DLI, imatinib</td>
</tr>
<tr>
<td>Current report, patient 1</td>
<td>7</td>
<td>MDS (RAEB-2) → AML</td>
<td>—</td>
<td>HU, imatinib</td>
</tr>
<tr>
<td>Current report, patient 3</td>
<td>Complex</td>
<td>MDS (RAEB-2) → AML</td>
<td>—</td>
<td>IFN/cytarabine, imatinib</td>
</tr>
<tr>
<td>Perel et al20</td>
<td>7</td>
<td>MDS/AML (&gt; 20% blasts)</td>
<td>No dysplastic features</td>
<td>IFN/imatinib</td>
</tr>
<tr>
<td>Bacher et al21</td>
<td>7</td>
<td>MDS (RAEB-2)</td>
<td>—</td>
<td>IFN/cytarabine, HU, imatinib</td>
</tr>
<tr>
<td>Patchenko et al15</td>
<td>i8</td>
<td>MDS (RAEB-2)</td>
<td>Spontaneous improvement in dysplastic changes?</td>
<td>HU, imatinib</td>
</tr>
<tr>
<td>Bacher et al21</td>
<td>7</td>
<td>MDS (RAES)</td>
<td>—</td>
<td>Busulfan, IFN, HU, imatinib</td>
</tr>
<tr>
<td>Meuss et al22</td>
<td>7, +8</td>
<td>MDS</td>
<td>RA</td>
<td>IFN, auto BMT, imatinib</td>
</tr>
<tr>
<td>Bumm et al14</td>
<td>7</td>
<td>MDS</td>
<td>Severe dysplasia</td>
<td>HU, IFN, imatinib</td>
</tr>
<tr>
<td>Bumm et al14</td>
<td>i(3,21)</td>
<td>MDS</td>
<td>10% blasts</td>
<td>Ida/cytarabine, HU, IFN, imatinib</td>
</tr>
<tr>
<td>Mozziocca et al21</td>
<td>5q—/7q—</td>
<td>MDS</td>
<td>—</td>
<td>IFN, ROAP, auto BMT, imatinib</td>
</tr>
<tr>
<td>O’Dwyer et al24</td>
<td>inv(1)(p32.3p31.2), del(10)(q22q22)</td>
<td>MDS</td>
<td>7% blasts</td>
<td>IFN, imatinib</td>
</tr>
<tr>
<td>Alimena et al17</td>
<td>i8</td>
<td>MDS</td>
<td>—</td>
<td>HU, imatinib</td>
</tr>
<tr>
<td>Jin Huh et al25</td>
<td>Diploid</td>
<td>ALL</td>
<td>—</td>
<td>HU, IFN, imatinib</td>
</tr>
<tr>
<td>Cherrier-De Wilde et al10</td>
<td>Diploid</td>
<td>ALL</td>
<td>—</td>
<td>HU, IFN, imatinib</td>
</tr>
</tbody>
</table>

— indicates none; IFN, interferon-α; HU, hydroxyurea; BMT, bone marrow transplantation; Ida, idarubicin; and ROAP, rubidomycine, vincristine, cytosine arabinoside, prednisone.

*Included monosomy 7 among the chromosomal aberrations.
†Including del(5)(q13q31).
Of interest, among patients with confirmed MDS or AML with chromosomal aberrations in Ph-negative metaphases, chromosome 7 abnormalities are particularly common. Of the 17 cases listed in Table 1, 10 had chromosome 7 abnormalities, with 5 having monosomy 7 as the only cytogenetic abnormality. This abnormality is common in secondary AML or MDS, evolving after exposure to alkylating agents, and patients with AML or MDS with this abnormality have poor outcomes similar to those described in our 2 patients with RAEB—namely, poor response to chemotherapy and rapid progression to AML.

The cause of this phenomenon remains to be determined. It is unlikely that this is a direct effect of imatinib as these changes have not been reported in other diseases treated with imatinib. It could be speculated that CML requires a 2-step pathogenesis, where a monoclonal Ph-negative state antecedes the acquisition of BCR-ABL. Alternatively, these abnormalities may represent evidence of genomic damage to the bone marrow that may be predisposed to multiple genetic changes, including BCR-ABL.14

In conclusion, high-risk MDS and AML after treatment with imatinib occur in a small subset of patients. The occurrence of this rare phenomenon emphasizes the need for continued monitoring with bone marrow aspirations and cytogenetic analysis of CML patients receiving imatinib.

References

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