

Durable molecular response to imatinib mesylate following non-myeloablative allogeneic stem-cell transplantation for persisting myeloid blast crisis in chronic myeloid leukemia

We report a chronic myeloid leukemia (CML) patient in chronic phase (CP) who developed blast crisis (BC) under imatinib mesylate administered in a dose reduced and non-continuous fashion because of hematologic intolerance. The patient underwent non-myeloablative stem-cell transplant from a matched unrelated donor, but failed to achieve full donor chimerism and antileukemic response resulting in persistence of advanced disease. Complete hematologic, cytogenetic and molecular responses were attained 5 weeks after readministration of regularly dosed imatinib and two-step nested RT-PCR confirmed molecular remission throughout a 6 month follow-up period. This is the first case demonstrating that imatinib mesylate is a highly effective and safe treatment option to induce durable molecular remission in patients with CML who remain in myeloid blast crisis after non-myeloablative allogeneic stem-cell transplantation.

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Introduction. Allogeneic hematopoietic stem-cell transplantation (allo SCT) is the only approach capable of curing patients with chronic myeloid leukemia (CML).¹ The course of CML is generally triphasic displaying an initial chronic phase, changing spontaneously after a variable interval to an accelerated phase, and finally proceeding to blast crisis (BC) with a median survival of only 3 to 6 months.² There is no standard therapy for patients in BC and allogeneic stem cell transplantation for chronic myeloid leukemia in BC is associated with poor outcome due to treatment-related complications and relapse.^{3,4} Nonmyeloablative allo SCT lacks the toxicities of a myeloablative regimen and still harbours the potential to cure.⁵ However, relapse after non-myeloablative allo SCT remains a major obstacle of treatment. Approaches to treat patients with CML in relapse after allo SCT include interferon alpha, chemotherapy and donor lymphocyte infusions (DLI). The use of DLI induces remissions in a substantial number of patients but may be associated with fatal aplasia and severe graft-versus-host disease (GvHD).^{6,7} Imatinib (Glivec, formerly STI 571) - a rationally developed inhibitor of the Bcr-Abl tyrosine kinase - induces high rates of major cytogenetic (69%) and hematologic (95%) responses in patients with chronic phase CML.⁸ Thus far, a limited number of patients in relapse after allo SCT have been treated with imatinib mesylate.⁹ No reports have appeared describing such treatment for myeloid BC persisting after non-myeloablative allo SCT. Here we describe a case of advanced CML after failed unrelated hematopoietic stem cell transplantation. Under imatinib treatment stable complete donor chimerism, improved graft function and a durable molecular remission were achieved. **Case report.** A 54-year-old female Caucasian was diagnosed with Philadelphia chromosome

positive (Ph+) CML in chronic phase (CP) in 1990. Initial treatment consisted of interferon alpha (INF- α) combined with Ara-C and subsequently of hydroxyurea monotherapy due to INF- α associated side effects. Ten years after diagnosis she commenced treatment with imatinib mesylate at a daily dose of 400 mg but due to hematologic intolerance (neutropenia, WHO grade 3) imatinib therapy was administered in a non-continuous schedule at a reduced dose level of 300 mg daily. Twenty three months after initiation of imatinib, bone marrow biopsy revealed myeloid blast crisis with 80% blastic infiltration and 100% Ph+ positivity. At this advanced disease stage, imatinib was stopped and the patient underwent non-myeloablative stem cell transplantation (SCT) from an HLA-matched unrelated female donor. Dose-reduced conditioning included fludarabine (150mg/m²) and total body irradiation with 2 Gy. The peripheral stem cell dose was 6.37 x 10⁶ CD34+ cells/kg body weight (bw). Graft-versus-host disease prophylaxis consisted of cyclosporine, mycophenolate mofetil, and anti-thymocyte globulin. The post transplant course was uneventful and no signs of acute or chronic GvHD were present. However, chimerism analysis of peripheral blood mononuclear cells revealed a decrease of donor chimerism from 49% (median; range: 42-57%) at day 28 and 65% (median; range: 55-73%) at day 39 to 21% at day 104 (median; range: 14-27%). Bone marrow examination on days 28 and 100 showed a hypercellular marrow with infiltration of 50% and 60% blasts fulfilling cytological and histological criteria of persisting blast crisis. Karyotype of marrow aspirates uniformly demonstrated Ph positivity (day 60) or only a minor percentage of Ph-negative metaphases (day 100). Accordingly, two-step nested RT-PCR for Bcr-abl transcripts in peripheral blood remained positive during this period. Imatinib mesylate was restarted on day 106 after transplantation, commencing at a dose of 200 mg/day and gradually escalating to 400 mg by day 115. From day 124 imatinib mesylate was temporarily stopped due to treatment related neutropenia down to 0.32 x10⁹/L. It was suspected that the neutropenia arose from an immune-mediated mechanism so imatinib mesylate was reinstated 2 weeks later together with dexamethasone. Since no hematologic impairment was present in the further course - even after steroid tapering - imatinib mesylate could be fully escalated to a dose level of 600 mg/d. Bone marrow examination on day 143 revealed clearance of myeloid blast (< 5%) in bone marrow and cytogenetics, and fluorescence *in situ* hybridization (FISH) analyses were negative for t(9;22). Bcr-abl transcripts measured by two-step nested RT-PCR were repeatedly negative, indicating a complete cytogenetic and molecular remission. Analysis of peripheral blood leukocytes on day 182 revealed full donor chimerism. Up to the date of this report, 6 months after treatment with imatinib had been started, our patient remains in complete hematologic, cytologic, and molecular remission.

Discussion. The clinical course of this patient demon-

strates the potential value of imatinib as treatment of persisting myeloid BC after non-myeloablative SCT. To date, no long term molecular responses have been described in this setting and only limited experience is available with imatinib in the treatment of advanced CML after conventional allogeneic hematopoietic stem cell transplantation.⁹⁻¹¹ With respect to the dose-reduced conditioning regimen, a stable molecular remission within 9 weeks of therapy with imatinib has been described in a patient relapsing to lymphoid blast crisis after allogeneic SCT for CML in 2nd CP. The complete hematologic, cytogenetic and molecular response was maintained for 27 months.¹² A second case of CML persisting after a failed unrelated bone marrow transplantation in 2nd CP was reported by Vandenberghe.¹³ Stable complete donor chimerism, improved graft function and a complete molecular response was achieved 294 days after imatinib treatment was started. An outstanding feature of this case is the rapid induction of a complete cytogenetic and molecular response, which was documented 37 days after starting imatinib. We confirmed the molecular response by repeated analyses with two-step nested RT-PCR and it has been maintained over an observation period of 6 months. The PCR data were consistent with the results obtained by FISH and conventional cytogenetics. Interestingly, the hematologic intolerance (neutropenia, WHO grade 3) occurring during the 1st and 2nd imatinib administration was no longer observed after full donor chimerism had been obtained suggesting the newly established donor myelopoiesis might not have been susceptible to the direct myelosuppressive effect of imatinib. Hence, the therapeutic potential of imatinib could be fully exploited by successful escalation to a final dose of 600 mg. It is well known that imatinib can induce complete hematologic response in a subset of patients with chronic phases and advanced phases of CML. However, molecular remissions are rare, particularly in the latter group. The rapid induction of Bcr-abl negativity in conjunction with swift re-establishment of full donor chimerism in blood leukocytes after imatinib administration might indicate that imatinib confers a selective advantage to the normal donor stem cells and immune effector cells, which might have augmented a graft-versus-leukemia (GvL) effect. In addition, the course of disease suggests that imatinib pre-SCT and non-myeloablative SCT alone are insufficient to eradicate the malignant clone. However, imatinib combined with the GvL effect was able to elicit a complete molecular response, further substantiating the concept of a synergistic antileukemic effect. This is consistent with the notion that imatinib significantly enhances antigen presentation by bone marrow derived antigen-presenting cells (APC), thereby facilitating GvL reactivity.¹⁴ In summary this case demonstrates that imatinib mesylate is a highly effective and safe treatment option capable of inducing durable molecular remissions in the treatment of advanced persisting CML after non-myeloablative allogeneic stem-cell transplantation. Further, we provide clin-

ical evidence that imatinib mesylate may promote or synergize the graft-versus-leukemia effect associated with allogeneic stem cell transplantation.

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