To the editor:

Molecular response to imatinib mesylate following relapse after allogeneic SCT for CML

We read with interest the article by Kantarjian et al.[1] With the advent of allogeneic matched sibling stem cell transplantation (allo-SCT), it is clear that long-term disease-free survival can be achieved in patients with chronic phase (CP) chronic myelogenous leukemia (CML).[2] Measurement of BCR/ABL transcript numbers has enhanced the accuracy of assessment of posttransplantation disease activity.[3] Failure to detect transcripts or detection of low numbers is associated with prolonged disease-free survival, and this has become the "gold standard" following allo-SCT. In spite of the success of allo-SCT relapse will occur in a small but steadily increasing number of patients over time.[4] The use of donor lymphocyte transfusions (DLTs) induces a remission in a substantial number of patients but has been associated with fatal aplasia and severe graft-versus-host disease (GvHD) and relies upon the availability of the original donor.[5,6]

Kantarjian et al have demonstrated a complete cytogenetic response to imatinib mesylate in patients relapsing after allograft and failing DLTs.[1] But a cytogenetic responder may still harbor significant levels of BCR-ABL transcripts. We describe 3 patients who had a molecular response to imatinib mesylate after relapse of CML following allograft, in first CP. One patient relapsed, with clonal evolution, 10 years following matched sibling bone marrow transplantation (BMT; his donor had died from a myocardial infarct 5 years after the transplantion). He had a complete cytogenetic response to imatinib mesylate, 600 mg/d after 3 months, and was a complete donor chimera by polymerase chain reaction (PCR) of short tandem repeats (STRs; sensitivity 10^{-4}).[7] He remains in complete cytogenetic remission one year later on imatinib mesylate (400 mg/d). The second patient had a cytogenetic relapse, t(9:22), 5 years following a sibling allograft uncomplicated by GvHD. He had a complete cytogenetic response to imatinib mesylate (400 mg/d) at 3 months and was a donor chimera. He remains in complete cytogenetic remission at 21 months. The third patient had a sibling allograft in July 1998. He had a cytogenetic t(9;22) relapse 6 months later and was a mixed chimera. He received DLTs from the original donor in March and June 2000 without response. He received a nonmyeloablative SCT in February 2001 from the original donor, which was followed by a transient response. He had a complete cytogenetic response at 6 months to imatinib mesylate (400 mg/d). No patient had granulocytopenia or GvHD.

BCR/ABL transcripts were measured in a serial fashion in all patients using real-time quantitative PCR (RQ-PCR) using TaqMan probes (sensitivity 10^{-6}). Standard curves were generated following application of a dilution series of the bcr-abl–expressing plasmids pNC210 (a gift of Nick Cross, University of Southampton) for the b3a2 assay and pb2a2 (generated in house) for the b2a2 assay. Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) was also tested in serial samples to allow quantitative assessment of BCR-ABL/GAPDH ratios.

The results are shown in Figure 1. Imatinib mesylate was associated with a molecular remission in 2 patients who were treated for relapsed CML 10 and 5 years following BMT for CP CML, and in 1 patient, who failed allografting, DLTs, and a nonmyeloablative SCT, Bcr/Abl transcripts were almost undetectable. There was no evidence of toxicity in this small group of patients. O'Dwyer et al[8] have demonstrated that clonal evolution per se does not impair the response to imatinib mesylate, which concurs with our experience with our first patient. Serial monitoring using both chimerism analysis and RQ-PCR provides evidence that imatinib mesylate can induce molecular remissions in patients who relapse following allo-SCT for CML.

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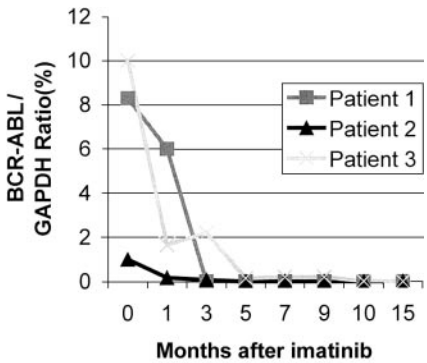

Figure 1. BCR-ABL/GAPDH ratios in serial analysis of imatinib-treated relapsed CML transplantation patients. The BCR-ABL/GAPDH ratio is expressed as a percentage following RQ-PCR analysis of reverse transcribed cDNA samples. Both patients 1 and 3 were 100% Ph-positive at time 0, whereas patient 2 exhibited 40% Ph-positivity. Both patients 1 and 2 achieved complete BCR-ABL negativity, whereas patient 3 exhibited extremely low BCR-ABL/GAPDH ratio (1×10^{-5}) at 14 months.

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To the editor:

Graft versus myeloma may overcome the unfavorable effect of deletion of chromosome 13 in multiple myeloma

Partial or complete deletion of chromosome 13 (del13) is considered one of the most important prognostic factors for multiple myeloma (MM).[1-4] The impact of del13 on the outcome of allogeneic stem cell transplantation is unknown. We describe 2 patients with unfavorable MM who benefited from a graft-versus-myeloma effect, resulting in sustained molecular remissions.[5] Retrospectively a del13 was found in the diagnostic bone marrow (BM) aspirates of both patients.

The first patient progressed from monoclonal gammopathy of undetermined significance (MGUS; diagnosed in 1982) to MM (1991, IgA λ, stage IIIA). She was refractory to melphalan+ prednisone, and in March 1992 at age 48 she received a partial T-cell–depleted (1×10^5 T cells/kg) BM transplant from her HLA-identical sister after conditioning with cyclophosphamide (120 mg/kg) and total body irradiation (12 Gy). This was complicated by transient acute graft-versus-host disease (GVHD), grade I. At the time of transplantation, her BM contained 55% myeloma cells. After achieving a partial remission (PR; disappearance of M protein, 8% residual BM cells), she relapsed 8 months after transplantation: reappearance of M protein, increasing 10 months later to 20g/L, 30% BM infiltration. She then received donor lymphocyte infusions (DLIs), 3.3×10^8 T cells/kg. DLIs were complicated by severe extensive chronic GVHD of skin and joints.

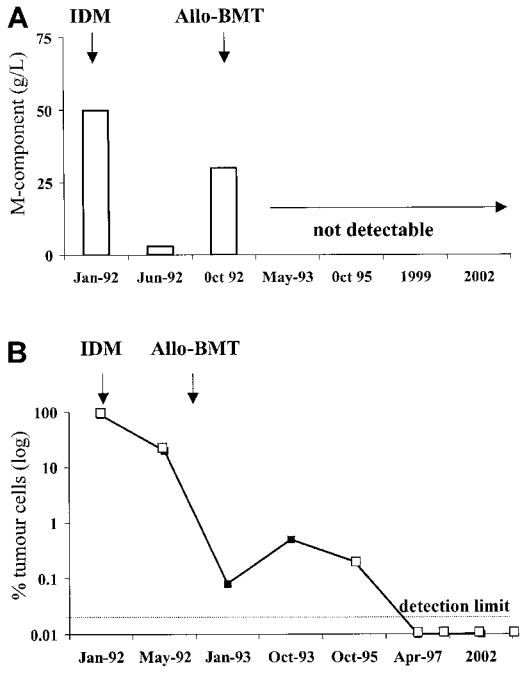

Figure 1. Longitudinal measurement of disease activity in a MM patient with del13. The patient presented with a combination a unfavorable prognostic features including del13. After allogeneic bone marrow transplantation performed during relapse, he went into sustained clinical (A) and molecular (B) remission. Remarkable residual MM cells were detected by quantitative PCR more than 3 years after disappearance of myeloma proteins (B).

Since May 1994 she is in complete clinical and molecular remission as demonstrated by absence of M protein, normalization of BM, and quantitative allele-specific oligonucleotide (ASO)–PCR[6] (sensitivity to detect 1 tumor of 1×10^5 normal cells). Molecular remission was demonstrated in 8 subsequent BM aspirates.

The second patient (stage IIIA, IgG κ) presented with bone pain and diplopia. His BM showed a 99% infiltration, labeling index 3%, and β_2-microglobulin level of 5 mg/mL. The liquor was infiltrated with plasmablastic cells. He achieved a PR after induction with intermediate-dose melphalan[7] but relapsed just before allogeneic (allo)–BMT. In the liquor a persistent M protein of 1 g/L was found after treatment with methotrexate and cytarabine intrathecally. Evaluation 6 months after transplantation showed a complete clinical remission. Residual myeloma cells however could be detected by quantitative ASO-PCR until 36 months after transplantation (Figure 1). Double-color FISH was performed on thawed cytocentrifuged BM cells, which had been prepared from diagnostic samples and had been stored at −20°C. A del13 was found in 99 of 100 myeloma cells of patient 1 and in 35 of 100 myeloma cells of patient 2.

The 2 patient histories demonstrate that alloreactivity may overcome the prognostic unfavorable impact of del13 in myeloma. The first patient is in molecular remission more than 10 years after allo-BMT and 8 years after DLIs. The second patient presented with a combination of adverse prognostic factors including a high β_2-microglobulin level, high labeling index, and meningeal infiltration. He received a transplant in relapse after a very short period of remission. Remarkable, quantitative PCR became negative not until 3 years after transplantation.

Our results suggest that in patients with del13 a search for an HLA-identical family or unrelated donor is justified. The promising results of nonmyeloablative allo-SCT in MM[8,9] justify inclusion of patients in such protocols as soon as unfavorable factors are identified after diagnosis.

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