Bone Marrow Transplantation (2006) 37, 801–802

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LETTER TO THE EDITOR

Development of donor cell derived acute myeloid leukemia after stem cell transplantation for chronic myeloid leukemia

Bone Marrow Transplantation (2006) **37,** 801–802. doi:10.1038/sj.bmt.1705332; published online 27 February 2006

Relapse of the underlying disease is the most frequent cause of treatment failure after allogeneic stem cell transplantation (SCT).[1] However, at least 34 cases of leukemia or myelodysplasia originating in donor cells have been described[2–9] with an estimated incidence of 124 per 100 000 transplants.[4]

A 45-year old man underwent a marrow allograft from his HLA-identical brother in March 2001 for CML in the chronic phase; 15 months after diagnosis. The conditioning regimen was oral busulfan 16 mg/kg and cyclophosphamide 120 mg/kg. The cell dose was 3.59×10^8 nucleated bone marrow cells, and methotrexate and cyclosporine were administered for GVHD prophylaxis. Engraftment was prompt. Mild acute GVHD was seen. Cytogenetic studies and RT-PCR were negative for residual/recurrent disease on days 100, 180, 365, 540, 730, 915 and 1279 after SCT. On day 1279, peripheral blood was normal, bone marrow showed 2% blasts, and VNTR analysis of chimerism showed full donor-type chimerism.

In July 2005, 1584 days after SCT, the patient presented with painful enlargement of inguinal lymph nodes and thrombocytopenia. Bone marrow showed 46% MPO+ blasts with Auer rods. The immunophenotype was $CD34^+13^+33^+117^+HLA\text{-}DR^+$. The karyotype was del(6)(q23q25), inv(16)(p13q22). The Ph chromosome was not seen (Figure 1). RT-PCR was negative for BCR-ABL (Figure 2) but amplified for the CBFB/MYH11 fusion gene. PCR amplification of the VNTR loci D4S43, TH11 and TPOX, in DNA from $CD34^+$-selected cells, isolated at relapse, when compared with the donor's pre-SCT marrow sample confirmed donor origin of the leukemia (Figure 3). The patient is in remission after induction with daunorubicin-cytarabine, and a second transplant from another HLA-identical brother is being considered. The original donor is alive without evidence of leukemia almost 5 years after the marrow donation.

The original disease for which transplants were performed was CML in 11 of the 34 reported cases of donor

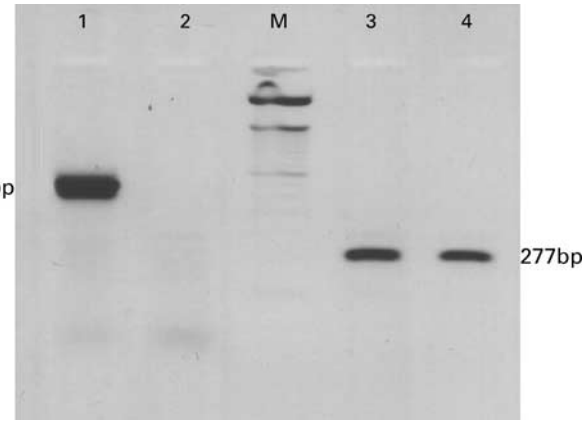

Figure 2 RT-PCR for BCR-ABL. Lane 1: Pretransplant recipient; lane 2: Day +1584 post transplant recipient; lane 3: positive control lane 1 (normal ABL gene); lane 4: positive control lane 2 (normal ABL gene); M: molecular weight marker.

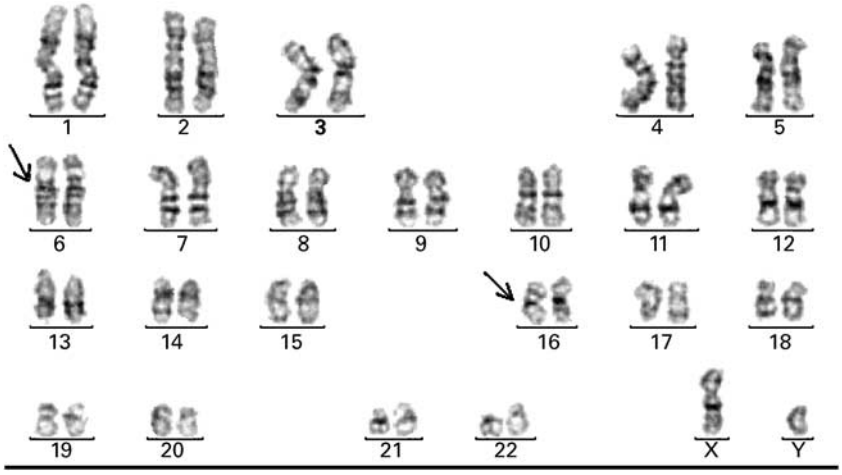

Figure 1 46,XY,del(6)(q23q25)[17],inv(16)(p13q22)[5][cp16]/46,XY[21].

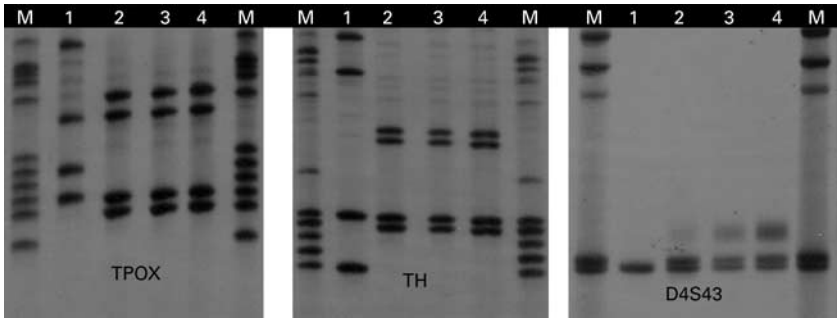

Figure 3 VNTR analysis for D4S43, TPOX and TH. Lane 1: Pretransplant recipient; lane 2: Pretransplant donor; lane 3: Post transplant recipient on blast cells isolated form the marrow; lane 4: Post transplant recipient peripheral blood; M: molecular weight marker.

cell leukemia,[3–9] including ours; seven AML, three ALL and one CML blast crisis. The median time between SCT and the occurrence of donor cell leukemia was 36 months (range, 4–132 months). Molecular techniques were used to demonstrate donor cell origin in eight cases. In three cases only cytogenetic methods were used. In two cases (including ours), the absence of BCR-ABL mRNA in the leukemia cells provided additional evidence of donor-derived disease.

Several hypotheses have been suggested to explain the mechanism of donor cell leukemia: occult leukemia in the donor, transfer of oncogenic material from the host to donor, impaired immune surveillance after SCT, abnormal recipient marrow microenvironment (primary defect), and exposure to residual chemotherapy or immunosuppressants after SCT.[5,7] Since the actual donors themselves did not develop leukemia in most cases including ours, the likely mechanism probably does involve the host in some way.

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