To the editor:

Initial experience with L-leucine therapy in myelodysplastic syndromes with associated chromosome 5q deletion

In murine and zebrafish preclinical models of Diamond-Blackfan anemia (DBA), supplementation with the essential amino acid L-leucine ameliorates defective erythropoiesis and alleviates anemia, probably via upregulation of the mammalian target of rapamycin signaling pathway.[1-3] In addition, at least a single European patient with DBA experienced improved hemoglobin levels during L-leucine supplementation.[4] Because dysregulated ribosome biogenesis similar to that underlying DBA is present in cells from patients with myelodysplastic syndromes (MDSs) associated with deletion of chromosome 5q, it has been proposed that L-leucine might also improve MDS-associated anemia, especially in patients with the so-called 5q- syndrome, a lower-risk form of MDS associated with haploinsufficiency of ribosomal component ribosomal protein S14.[1,5] To date, no clinical experience with L-leucine in MDS has been reported, although the low cost, widespread availability, and excellent tolerability of this dietary supplement suggest that clinical trials should be undertaken.

Three consenting patients with World Health Organization–defined MDS with isolated del(5q) (a 71-year-old man, a 65-year-old woman, and a 58-year-old woman; 2 of whom were red cell transfusion–dependent and 1 of whom had no response to erythropoiesis-stimulating agent therapy) who were reluctant to initiate treatment with lenalidomide took L-leucine capsules obtained from a nutritional supplement store at a dose of 1500 mg orally 3 times daily for 2 to 3 months, approximating the 700 mg/m^2 dose chosen for a planned trial of L-leucine in transfusion-dependent patients with DBA. The DBA trial is registered at www.clinicaltrials.gov as #NCT01362595.

Although no adverse events were observed during L-leucine therapy, none of the patients experienced any improvement in their cytopenias or transfusion needs. Two of the 3 patients subsequently agreed to take lenalidomide, and both became transfusion-independent during that therapy.

DBA is a congenital disorder with germline associated with mutations in ribosomal genes. The goal of therapy is to improve red blood cell production from erythroid progenitor cells with dysfunctional ribosomes. In MDS with del(5q), patients have somatically acquired *ribosomal protein S14* haploinsufficiency, as well as haploinsufficiency for multiple additional genes on chromosome 5q and additional somatic mutations. The goal of therapy in MDS is to eliminate the del(5q) clone or, potentially, to improve red blood cell production from the neoplastic clone or residual normal hematopoietic clones. Of note, an improvement in ribosome function could potentially improve the clonal advantage of the del(5q) MDS clone. An absence of response could be a result of an insufficient dose of L-leucine, a more general lack of response in patients with ribosomal dysfunction, or that L-leucine does not improve erythropoiesis more specifically in del(5q) MDS. We eagerly await results of the formal DBA clinical trial and additional clinical experience with L-leucine in the MDS setting.

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To the editor:

Transient proliferation of donor-derived ATL cell–like lymphocytes early after allogeneic stem cell transplantation in an adult T-cell leukemia/lymphoma patient

A 46-year-old man was admitted to our hospital because of systemic lymphadenopathy and generalized erythema. White blood cell (WBC) count was 8.3 × 10^9/L with 8% morphologically abnormal lymphocytes that were positive for CD3, CD4, and CD25. Antibody against human T-cell lymphotropic virus type I (HTLV-1) was positive, and Southern blot analysis (SBA) using his peripheral blood (PB) and a biopsy specimen of erythema revealed monoclonal integration of HTLV-1 provirus. With an elevated serum lactate dehydrogenase level (642 IU/L), he was diagnosed as having acute-type adult T-cell leukemia/lymphoma (ATL).[1] His ATL was resistant

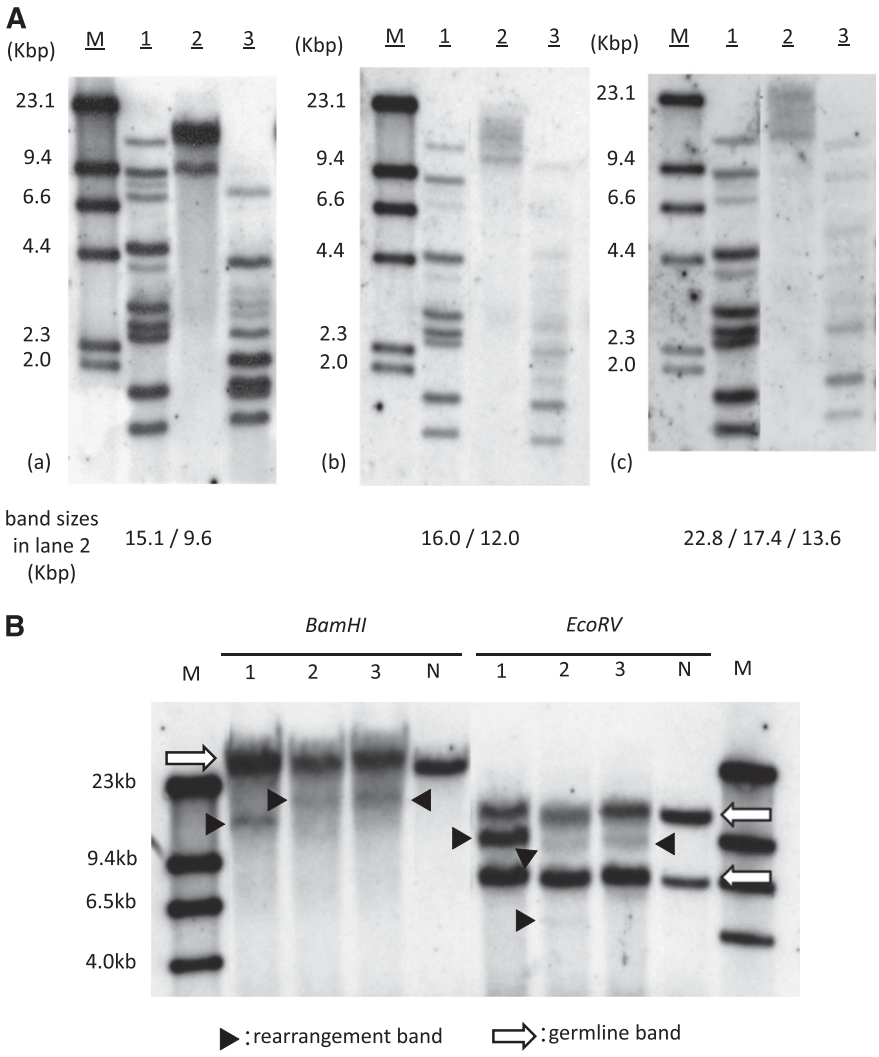

Figure 1. Clonality analysis of expanded lymphocytes. (A) SBA of HTLV-1. (a) PB of pretransplantation, (b) day 18 of transplantation, and (c) day 71 of transplantation. Band sizes in lane 2 in each panel are shown at the bottom. M, size marker (λDNA/*Hin*dIII); lane 1, positive control; lane 2, DNA digested with *Eco R1*; lane 3, DNA digested with *Pst1*. (B) SBA of T-cell receptor Cβ1 genes. Lane 1, PB of pretransplantation; lane 2, day 18 of transplantation; lane 3, day 71. Arrows indicate germ-line bands; arrowheads indicate rearranged bands. M, molecular weight marker II; N, negative control (placenta DNA).

to chemotherapy, so he then received allogeneic PB stem cell transplantation after administration of high-dose cytarabine and 12 Gy of total body irradiation. Cyclosporine and a short course of methotrexate were given as prophylaxis for graft-versus-host disease. The donor was his HLA-identical brother, an asymptomatic carrier of HTLV-1. Donor PB had no abnormal lymphocytes, and its SBA demonstrated no monoclonal proliferation of HTLV-1–infected cells.

The patient showed neutrophil engraftment on day 14 of transplantation. Simultaneously, his peripheral lymphocyte count started to increase and reached 4.6×10^9/L (45% of WBC count) by day 18. The morphological feature of proliferated lymphocytes resembled that of typical ATL cells, and the surface antigens were positive for CD3, CD4, and CD25. Increased HTLV-1 proviral load of 119.2 copies/100 PB mononuclear cells was detected by quantitative polymerase chain reaction. At this point, we thought this was an early relapse of ATL, but within a week, lymphocytosis rapidly disappeared without additional treatment. The ATL-like lymphocyte count became less than 0.5×10^9/L (5% of WBC count) by day 31, and the proviral load decreased to 14.3 copies/100 PB mononuclear cells on day 71. This phenomenon prompted us to investigate the clonality of expanded lymphocytes. SBA did reveal monoclonal integration of an HTLV-1 provirus; however, band sizes were different from those of pretransplantation (Figure 1A). SBA of T-cell receptor Cβ1 genes also demonstrated different patterns of bands between pre- and posttransplantation (Figure 1B), suggesting the expanded lymphocytes were not from original ATL cells. The result of short tandem repeat polymerase chain reaction using PB showed mixed chimerism, with only 6.3% recipient cells on day 18, and complete donor chimerism on days 31 and 71, implying the expanded lymphocytes were of donor origin.

Allogeneic hematopoietic stem cell transplantation (allo-SCT) is increasingly used as a curative option for ATL.[2,3] Although HLA-matched related siblings are generally preferred as donors in allo-SCT, 2/3 of the siblings of ATL patients are asymptomatic carriers of HTLV-1[4] and there are reports demonstrating that transplantations from such donors actually lead to the development of donor-derived ATL.[5,6] Our case suggests that allo-SCT from asymptomatic carriers of HTLV-1 may lead to the development of transient, donor-derived, benign HTLV-1–associated monoclonal lymphocytosis very early after transplantation. Such lymphocytosis should not be misdiagnosed as a relapse or a development of donor-derived ATL. To fully understand this phenomenon, further collection of similar cases is necessary.

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