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LETTER TO THE EDITOR

A prompt graft-versus-thalassemia effect upon withdrawal of cyclosporine A in a child who received allogeneic peripheral blood stem cell transplantation

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Stable mixed chimerism is a common event in children with thalassemia major who have undergone bone marrow transplantation (BMT). However, persistence of unstable mixed chimerism in these children is associated with a greater risk of rejection and/or relapse of the disease. Andreani *et al.*[1] has reported that rejection and/or disease recurrence occurs in approximately one third of patients with early mixed chimerism in thalassemia major.

Here, we report a child with thalassemia major who developed unstable mixed chimerism associated with rapidly decreasing hemoglobin levels at day +90. Full donor chimerism was achieved promptly after withdrawal of cyclosporine. To the best of our knowledge, this is the first report of a child with thalassemia major in whom unstable mixed chimerism was reversed by only cyclosporine withdrawal.

Briefly, a 4-year-old girl underwent peripheral blood stem cell (PBSC) transplantation from her human lymphocyte antigen (HLA)-6/6 identical mother for class II β-thalassemia major in June 2005. The conditioning treatment included cyclophosphamide (200 mg/kg) that was administered on days −5, −4, −3, −2 and busulfex (12.8 mg/kg), administered on days −10, −9, −8, −7 and graft-versus-host disease (GVHD) prophylaxis consisted of cyclosporine and methotrexate. The patient received the G-CSF mobilized peripheral blood graft that included 4×10^6/kg CD34(+) cells from her mother. Neutrophil engraftment was achieved at day +16 and platelet engraftment, at day +20. Full donor chimerism by molecular testing (STR-PCR) was attained at day +30. The patient's late post transplant period was complicated by decreasing chimerism and it reached to 26% donor chimerism at day +90 associated with a drop in Hb level from 12 to 7.7 g/dl. Following cessation of cyclosporine, there was a rapid increase in Hb levels reaching to 9.7 g/dl in 10 days and 11 g/dl in 20 days without transfusion (Figure 1). The graft-versus-thalassemia effect was confirmed by achievement of 100% donor chimerism and development of grade III acute GVHD (biopsy proven) involving the skin and the gut. Cyclosporine, mycophenolate mofetil, and methylprednisolone were used for the treatment of acute GVHD. Methylprednisolone starting dose was 10 mg/kg for 3 days and 5 mg/kg for 3 days and was tapered off very slowly in 3 months. Cyclosporine treatment was restarted intravenously at a dosage to maintain serum cyclosporine level above 250 ng/ml and mycophenolate mofetil was used for 6 weeks which was also tapered off slowly. The patient developed limited chronic GVHD in the oral mucosa at +9 months of transplantation, whereas she did not need additional therapy. She remains in well clinical condition with limited chronic GVHD and full donor chimerism (molecular method) at +12 months of PBSC transplantation with a Karnofsky score above 90%.

Unstable mixed chimerism has rarely been turned back to full donor chimerism without donor lymphocyte infusion (DLI). Donor lymphocyte infusion has been used for dissolution of unstable mixed chimerism in recipients of many malignant and nonmalignant hematopoietic diseases after BMT.[2–5] However, this effect of DLI has rarely been successful in thalassemia major. Aker *et al.*[2] reported that a patient with thalassemia and unstable mixed chimerism after BMT was successfully treated with DLI to attain complete donor-derived reconstitution of the residual hematopoietic host cells. However, DLI was not used in our patient and withdrawal of cyclosporine treatment alone as an immunotherapeutic strategy was effective to obtain full donor chimerism associated with a sudden rise in hemoglobin levels.

Bader *et al.*[6] presented two children diagnosed as myelodysplastic syndrome and acute myelogenous leukemia with mixed donor chimerism in whom withdrawal of post transplant immunosupression or DLI had been effective to prevent relapse. Similarly, Gorczynska *et al.*[7] reported that in 12 out of 14 children with hematological

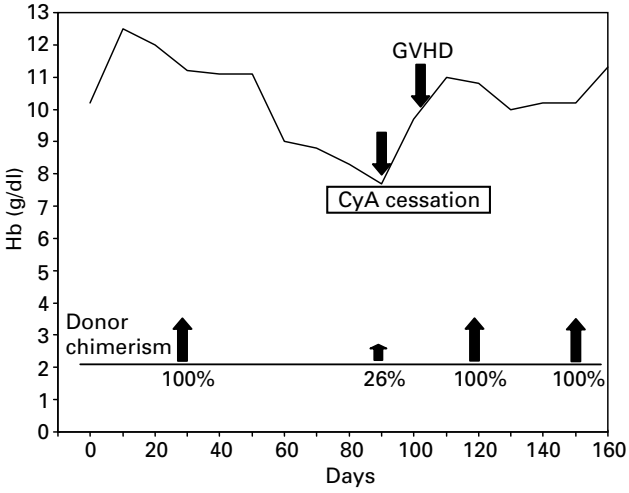

Figure 1 Shows the hemoglobin values and chimerism status of the patient.

malignancy, immunotherapy consisting of withdrawal of immunosuppression and/or DLI resulted in improvement of the mixed chimeric status and prevention of hematological relapse. Similarly, withdrawal of post transplant immunosupression was also effective in our thalassemic patient and unstable mixed chimerism was turned back to full donor chimerism.

Thus, if a child has unstable mixed donor chimerism after BMT, immunotherapy is an option to prevent rejection and/or relapse of the disease in children with malignant and also nonmalignant diseases including thalassemia. Thalassemic children with early unstable mixed donor chimerism may be rescued from rejection and/or relapse of the disease by withdrawal of cyclosporine alone. Our observation is encouraging and further studies are needed.

B Tavil[1], M Kazık[2], B Kuşkonmaz[1], M Çetin[1] and D Uçkan[3]
[1]*Pediatric Hematology Unit, Hacettepe University School of Medicine, Sıhhiye Ankara, Turkey;*
[2]*Hacettepe University School of Medicine, Ihsan Dogramacı Children's Hospital, Sıhhiye Ankara, Turkey and*
[3]*Pediatric Hematology, Bone Marrow Transplantation Unit, Hacettepe University School of Medicine, Sıhhiye Ankara, Turkey*
E-mail: duckan@hacettepe.edu.tr

References

1 Andreani M, Manna M, Lucarelli G, Tonucci P, Agostinelli F, Ripalti M *et al*. Persistence of mixed chimerism in patients transplanted for the treatment of thalassemia. *Blood* 1996; **87**: 3494–3499.
2 Aker M, Kapelushnik J, Pugatsch T, Naparstek E, Ben-Neria S, Yehuda O *et al*. Donor lymphocyte infusions to displace residual host hematopoietic cells after allogeneic bone marrow transplantation for beta-thalassemia major. *J Pediatr Hematol Oncol* 1998; **20**: 145–148.
3 Akioka S, Itoh H, Ueda I, Matsumoto Y, Iwami H, Tsunamoto K *et al*. Donor lymphocyte infusion at unstable mixed chimerism in an allogeneic BMT recipient for chronic granulomatous disease. *Bone Marrow Transplant* 1998; **22**: 609–611.
4 Godder KT, Abhyankar SH, Lamb LS, Best RG, Geier SS, Pati AR *et al*. Donor leukocyte infusion for treatment of graft rejection post partially mismatched related donor bone marrow transplant. *Bone Marrow Transplant* 1998; **22**: 111–113.
5 Raiola AM, Van Lint MT, Valbonesi M, Lamparelli T, Gualandi F, Occhini D *et al*. Factors predicting response and graft-versus-host disease after donor lymphocyte infusions: a study on 593 infusions. *Bone Marrow Transplant* 2003; **31**: 687–693.
6 Bader P, Beck J, Schlegel PG, Handgretinger R, Niethammer D, Klingebiel T. Additional immunotherapy on the basis of increasing mixed hematopoietic chimerism after allogeneic BMT in children with acute leukemia: is there an option to prevent relapse? *Bone Marrow Transplant* 1997; **20**: 79–81.
7 Gorczynska E, Turkiewicz D, Toporski J, Kalwak K, Rybka B, Ryczan R *et al*. Prompt initiation of immunotherapy in children with an increasing number of autologous cells after allogeneic HCT can induce complete donor-type chimerism: a report of 14 children. *Bone Marrow Transplant* 2004; **33**: 211–217.