

Switch From Beta-Thalassemia Major to Beta-Thalassemia Intermedia After Secondary Graft Failure

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Abstract

In this article, we report a switch of β -thalassemia major to intermedia β -thalassemia after allogeneic bone marrow transplant of a 6-year-old girl from her HLA-matched brother.

After stable mixed chimerism, the patient had a secondary graft rejection and returned to total recipient chimerism as assessed by real-time polymerase chain reaction assay. Nonetheless, with a medium hemoglobin rate of 89 g/L, she did not need further transfusions for 60 months after rejection.

We conclude that complete loss of donor cells after bone marrow transplant for β -thalassemia major is compatible with a stable clinical state, probably due to a γ -globin gene demethylation that enhances γ -globin chain production and further allows constitution of a fetal hemoglobin rate compatible with free transfusion survival.

Key words: Transplant, Chimerism, Graft rejection

Introduction

Beta-thalassemia is a genetic disease that results from mutations of the globin genes that in its major form, causes absence or extremely reduced production of the β chain of hemoglobin. As consequence, an ineffective erythropoiesis, a bone marrow massive erythroid hyperplasia, and a hemolytic anemia occur

(1). So, affected patients are maintained on a regular transfusion schedule, receive folate supplementation, and chelation therapy. Until now, allogeneic hematopoietic stem cell transplant remains the only curative therapy (2).

Case report

We report a switch of a β -thalassemia major to an intermedia β -thalassemia after allogeneic bone marrow transplant of 6-year-old girl from her HLA-matched brother.

Our patient was born from β -thalassemia major, heterozygous, second-degree consanguineous parents. At 8 months of life, she was diagnosed with a homozygous β -thalassemia major, with (hemoglobin F = 96.88%, hemoglobin A2 = 3.12%, and hemoglobin A = 0%) on hemoglobin electrophoresis. She was splenectomized at 4 years because she developed hypersplenism. Her transfusions requirements, which were about 580 mL/kg/y fell to 200 mL/kg/y with residual hemoglobin rate of 60 g/L before bone marrow transplant.

At 6 years of age, she was class 2 Pesaro, she was allografted with 3.9×10^8 nucleated cells/kg from her HLA-identical ABO-compatible brother. The myeloablative regimen consisted of total dose of busulphan 14 mg/kg and Endoxan 200 mg/kg. Prophylactic graft-versus-host disease therapy consisted of intravenous cyclosporine 3 mg/kg/d, and a short course of methotrexate (at day +1, +3, and +6 after bone marrow transplant). Three weeks later, intravenous cyclosporine was switched to oral cyclosporine (8 mg/kg/d) until 9 months after bone marrow transplant.

After bone marrow transplant, her outcome was complication free. No graft-versus-host disease or major infections occurred. Partial donor engraftment

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was documented by real-time polymerase chain reaction assessment on day 31 postbone marrow transplant, and found a 26% donor chimerism that did not exceed 44%. Later, at day 570 after bone marrow transplant, molecular donor chimerism fell to 0.4% and completely disappeared at day 647 after bone marrow transplant (Figure 1). Donor erythrocyte chimerism reached 100% at day 66 after bone marrow transplant and completely disappeared

on day 758 after bone marrow transplant (Figure 2). Evolution of hemoglobin electrophoresis showed a β normal pattern at day 53 after bone marrow transplant with hemoglobin A = 98.7% and hemoglobin A2 = 1.29%, followed by a β -thalassemia minor at day 165 after bone marrow transplant. At a year and a half (day 548 after bone marrow transplant), we observed a switch toward a β -thalassemia intermedia characterized by hemoglobin

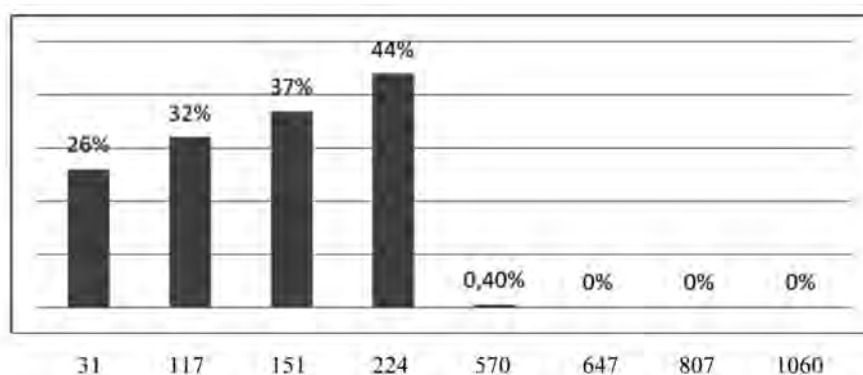


Figure 1. Evolution of molecular donor chimerism in recipient after bone marrow transplantation.

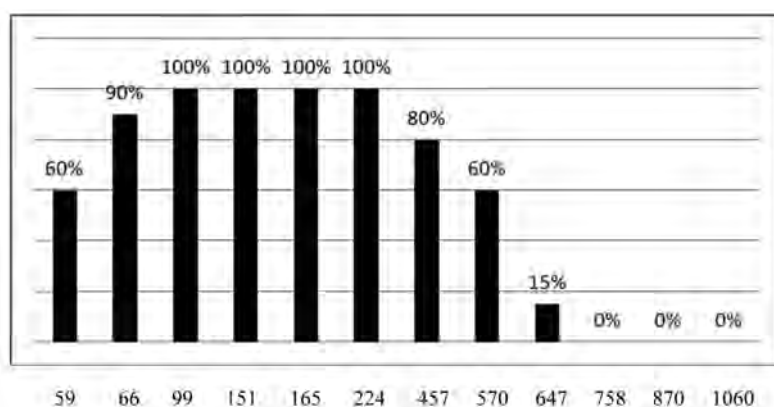


Figure 2. Evolution of erythrocyte donor chimerism in recipient after bone marrow transplantation.

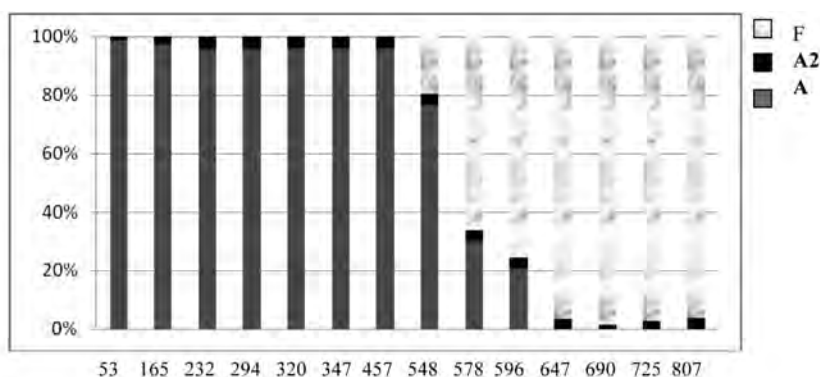


Figure 3. Evolution of recipient hemoglobin electrophoresis after bone marrow transplantation.

Abbreviations: A, Hemoglobin A; A2, Hemoglobin A2; F, Hemoglobin F.

F reappearance (with hemoglobin F = 75.6%, hemoglobin A2 = 3.6%, and hemoglobin A = 20.68%). From day 647 until day 807 after bone marrow transplant, hemoglobin A disappeared and hemoglobin F was always over 95% (Figure 3). After bone marrow transplant, the patient had a medium hemoglobin rate of 89 g/L and did not need further transfusions.

Discussion

Detection of hematopoietic and immune cells of host origin, commonly referred to as donor/recipient mixed chimerism, is not uncommon in patients undergoing bone marrow transplant for β -thalassemia major and is rather associated with a low incidence of graft-versus-host disease (3, 4), as for our patient. Our patient experienced a 26% donor mixed molecular chimerism at day 31 after bone marrow transplant, which probably accounts for the graft failure, because soon after bone marrow transplant, the status of mixed chimerism (particularly when there are more than 25% residual host cells in the early phase after a transplant (3) is associated with an increased risk of graft failure (2, 4). This secondary graft failure was assessed by the progressive fall of donor erythrocyte chimerism from 100% to 0% at day 758 after bone marrow transplant (Figure 2) and the switch of donor molecular chimerism from 44% to 0% from day 224 to day 647 after bone marrow transplant (Figure 1).

According to the proportion of residual host cells (based on molecular chimerism analysis) present in the recipient, Andreani and associates (5) classified mixed chimerism into 3 levels. The mixed chimerism level 3, with host cells percentage over 25% during the first 2 months after bone marrow transplant, which correspond to our patient status, was associated with a higher incidence of rejection. Nevertheless, she had a prolonged mixed chimerism (which constitutes a graft failure protecting factor) (6), and she experienced this failure more than a year and half after the bone marrow transplant. According to Lisini and associates (7), our patient experienced a worsening mixed chimerism defined as the condition in which chimerism kinetics indicated a progressive increase in the proportion of recipient cells over at least a 6-month period.

Even complete donor hematopoiesis is not essential for sustained engraftment after a bone

marrow transplant in a thalassemic patient, and enrichment of donor cells in the mature red blood cell compartment is sufficient to make patients transfusion independent (6). We cannot sustain such a hypothesis when complete molecular and erythrocyte chimerism disappear, as was the case in our patient.

Two hypotheses can explain our patient case: First, the state of transitory mixed molecular chimerism with coexistence of recipient and donor cells may induce a tolerance status that allows a partial engraftment of donor erythroblast stem cells and a subsequent switch in β -thalassemia type (2). Second, several studies have shown that the symptoms in β -thalassemia can be partly alleviated by treatment with DNA demethylation (8) or histone acetylation agents (9). Therefore, the conditioning regimen may provide a γ -globin gene demethylation tool that enhances γ -globin chain production compatible with free transfusion survival.

The definition of secondary graft failure as an association of biological (confirmed loss of donor cells after transient engraftment of donor-origin hematopoiesis) and clinical (return to erythrocyte transfusion dependence) (7) must be revisited. Because, as in our patient, complete loss of donor cells is compatible with making patients transfusion independent.

References

1. Lo L, Singer ST. Thalassemia: current approach to an old disease. *Pediatr Clin North Am.* 2002;49(6):1165-1191.
2. Lucarelli G, Gaziev J. Advances in the allogeneic transplantation for thalassemia. *Blood Rev.* 2008;22(2):53-63.
3. Andreani M, Nesci S, Lucarelli G, et al. Long-term survival of ex-thalassemic patients with persistent mixed chimerism after bone marrow transplantation. *Bone Marrow Transplant.* 2000;25(4):401-404.
4. Li CK, Chik KW, Tsang KS, Pong H, Shing MM, Yuen PM. Mixed chimerism after bone marrow transplantation for thalassemia major. *Haematologica.* 2002;87(7):781-782.
5. Andreani M, Testi M, Battarra M, et al. Relationship between mixed chimerism and rejection after bone marrow transplantation in thalassaemia. *Blood Transfus.* 2008;6(3):143-149.
6. Wu CJ, Hochberg EP, Rogers SA, et al. Molecular assessment of erythroid lineage chimerism following nonmyeloablative allogeneic stem cell transplantation. *Exp Hematol.* 2003;31(10):924-933.
7. Lisini D, Zecca M, Giorgiani G, et al. Donor/recipient mixed chimerism does not predict graft failure in children with beta-thalassemia given an allogeneic cord blood transplant from an HLA-identical sibling. *Haematologica.* 2008;93(12):1859-1867.
8. Ley TJ, DeSimone J, Anagnou NP, et al. 5-azacytidine selectively increases gamma-globin synthesis in a patient with beta+ thalassemia. *N Engl J Med.* 1982;307(24):1469-1475.
9. Perrine SP, Ginder GD, Faller DV, et al. A short-term trial of butyrate to stimulate fetal-globin-gene expression in the beta-globin disorders. *N Engl J Med.* 1993; 328(2):81-86.