LETTER TO THE EDITOR

What is the minimum level of donor chimerism necessary to sustain transfusion independence in thalassaemia?

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Allogeneic haemopoietic SCT is an established procedure for achieving transfusion independence in patients with β -thalassaemia major.¹ Transfusion independence is not contingent on achieving or sustaining full donor chimerism (DC). Up to one-third of patients have mixed chimerism (MC) at 2 months, with the number decreasing to around 10% at 2 years post transplant.² Patients with persistent MC can become transfusion independent, suggesting that a low level of engrafted donor cells can maintain this clinical state.^{2,3} However, the minimum level of stable DC necessary for transfusion independence is uncertain. We report a 5-year-old girl with β -thalassaemia major who remains transfusion independent with a stable marrow DC of 10% at 3 years following a matched sibling allogeneic BMT.

The patient was one of two twins of a dichorionic diamniotic pregnancy. Both parents were carriers of β -thalassaemia trait. Following delivery, cord blood was successfully harvested and banked from both twins. The patient's diagnosis was confirmed at birth (April 2004) with compound heterozygosity for β -0 thalassaemia mutations Cd8/9(+G) and Cd15(G-A). Her male twin sibling was found to be unaffected and to be a full HLA match. She commenced on regular monthly blood transfusions for symptomatic anaemia from July 2004. Regular monitoring showed no evidence of iron overload-related end-organ damage with normal growth and development. After extensive discussion, the family decided to proceed to allogeneic transplant using her fully matched twin brother as the donor in April 2006. The patient was Lucarelli Class 1 at the time of transplant. Both the patient and her donor were blood group O + ve. The donor has thalassaemia trait with a baseline Hb of 11.7 g per 100 ml. As the cord blood nucleated cell dose was insufficient, it was topped up with BM harvested on the day of transplant. She received treosulphan 12 g/m² i.v once daily for 3 consecutive days (total dose 36 g/m²), CY 50 mg/kg i.v once daily for 4 consecutive days (total dose 200 mg/kg) and antithymocyte globulin (Genzyme, Cambridge, UK) 1 mg/kg once daily for 4 consecutive days (total dose 4 mg/kg) conditioning, with CYA starting at 5 mg/kg and short-course MTX 10 mg/m² on days +3 and +6 (total dose 20 mg/m²) for GvHD prophylaxis. After an uneventful post transplant course, she showed neutrophil and platelet recovery at days 13 and 11, respectively, and required local treatment for stage I acute skin GVHD. However, at 2 months post transplant with her marrow DC at only 28%, CYA was

discontinued. Despite this, her DC continued to decrease reaching a low of 20% in September 2006 with a falling Hb. She received a marrow top-up in November 2006 following Campath 2.7 mg daily i.v for 5 consecutive days (total five doses) and Fludarabine 30 mg/m² i.v daily for 5 consecutive days (total dose 150 mg/m²) conditioning, but her DC continued to fall before reaching a plateau of around 10% at 10 months following the initial transplant. However, her Hb showed a gradual rise over the same period and she remains transfusion independent at last follow-up 3 years post transplant (Figure 1). Following her second transplant, CYA doses were tapered from 3 months onward and eventually stopped at 5 months. There was no obvious correlation between CYA exposure and percentage DC. Hb electrophoresis at the point of transfusion independency with 10% DC showed HbF 19%. We have been unable to undertake lineage-specific chimerism, but her peripheral blood DC (27%) is higher than a contemporaneous marrow DC of 10%.

In contrast to the malignant disease setting, the presence of transient MC does not inevitably lead to graft failure in thalassaemics.^{2,4} In a study of 295 patients undergoing BMT with a minimum of 2 years follow-up, about one-third of patients were observed to have MC at 2 months after BMT and over time this decreased to 9% at 2 years after the transplant.² In an analysis of 27 consecutive cord blood transplants from related donors, all cord blood recipients engrafted and displayed MC early after transplantation, 13 patients converted to full DC over time, whereas 14 maintained stable MC after a median follow-up of 42 (range 15–76) months with all patients being alive and transfusion independent.⁴ In these studies, the lowest reported DC was 10% in two patients who remained transfusion independent at 1 year post transplant. Although patients with stable MC can sustain long-term transfusion independence, the level of MC within the first 2 months after BMT is highly predictive of secondary graft failure. Patients with >25% MC have a 96% risk of becoming transfusion dependent and those with an MC between 10 and 25% have a 41% risk of doing so.² It would appear, therefore, that the outcome for patients with MC is related to achieving a state of stable long-term MC. About 10% of patients achieve this state wherein the number of donor marrow cells is sufficient to sustain erythroid cell production and maintain transfusion independence.⁵ However, graft failure has been known to occur after a long period of stable MC.⁶ The reasons as to why patients with persistent MC remain transfusion independent are uncertain. A possible explanation could be the presence of high proportions of IL-10-producing type 1 regulatory cells (Tr1) in such patients, possibly as a result of MC providing

Figure 1 Kinetics of donor chimerism in relation to timing of transplant and Hb levels.

chronic allogeneic stimulus.⁷ Endogenous IL-10 inhibits alloreactivity against both host and donor cells and may be responsible for the induction and maintenance of long-term tolerance. Such patients are reported to have a lower incidence of GVHD.⁸ It has also been reported that transfusion independency can be maintained by an increase in autologous HbF production post transplant in the event of graft failure.⁹ This explanation may partly apply to our case as HbF production was increased when the DC reached its nadir, although, in the absence of erythroid chimerism, we do not know whether it was produced by donor or autologous erythropoiesis.

In conclusion, rare patients with marrow DC as low as 10% can sustain long-term transfusion independence following allogeneic transplant for thalassaemia. Understanding the mechanisms underlying persistent MC and its relation to erythroid cell production may enable the development of novel transplant regimens favouring a state of MC without the need to achieve complete DC.

Conflict of interest

The authors declare no conflict of interest.

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