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LETTER TO THE EDITOR

Rejection of paternal vs maternal fully matched bone marrow grafts in children with thalassemia

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The bidirectional passage of cells across the placenta during fetal life is a well-described phenomenon which may result in a state of reciprocal persistent tolerance towards unshared histocompatibiity antigens.[1–3] On the other hand sera of multiparous women were pivotal in the initial discovery of new HLA antigens and donor parity may increase the risk of GvHD.[4] In the partially matched related (haploidentical) context many centers may prefer the mother as a donor for T-cell depleted grafts[5,6] and for non-malignant conditions,[6,7] while for T-replete grafts for malignancies the mother might be the last choice.[8] This could be related to the much lower likelihood of observing rejection in the latter context while a graft vs malignancy effect may confer a survival advantage. We are not aware of any recommendations as to who might be the preferable fully matched related non-sibling donor. In fact, in regions with high consanguinity or close-ethnicity rates, 10–20% of cases may find a fully matched donor among family members other than siblings, particularly parents.[9,10]

We have reviewed the occurrence of both rejection and GvHD in a group of 12 patients with severe thalassemia transplanted from fully matched parents, 7 from the father and 5 from the mother. BMTs where performed between August 2015 and July 2016 in 4 collaborating institutions, 3 in India (People Tree Hospital in Bangalore, South East Asia Institute for Thalassemia in Jaipur and Kokilaben Dhirubhai Ambani Hospital in Mumbai) and one in Sri Lanka (Nawaloka Hospital in Colombo). Liver biopsy for degree of fibrosis was not performed but none of these patients had a liver palpable more than 2 cm below the costal margin and would thus be considered Pesaro class I–II. The spleen was also below 2 cm in all patients A uniform regime was employed consisting of anti-thymocyte globulin (ATG; rabbit-thymoglobulin) 4 mg/kg total dose on day −12 to −10, oral busulfan 3.5 mg/kg day in 4 divided doses on days −9 to −6 (total dose 14 mg/kg, not adjusted to blood levels) and cyclophosphamide 50 mg/kg/day once daily on days −5 to −2 (total dose 200 mg/kg) followed by the infusion of freshly harvested HLA-compatible marrow on day 0. Bone marrow was G-CSF-primed in all cases by treating the donor with filgrastim 5 μg/kg/dose twice daily for either 3 or 5 days prior to harvest. GvHD prophylaxis consisted of cyclosporin A combined with methotrexate or mycophenolate mofetil.[11] All patients and parental donors had sequence-based high-resolution extended 6-loci HLA typing (DKMS Life Science Lab, Dresden, Germany, www.dkms-lab.de) which was confirmed in a second independent laboratory (Jeevan's HLA Laboratory, Chennai, India, http://www.jeevan.org/ngs-hla-lab/).[10] Patients' characteristics are summarized in Table 1. Sibling number and gender were included since the mother may have developed immunization against inherited paternal minor histocompatibility antigens during previous pregnancies.[12] This retrospective study was approved by institutional review boards.

With all the limitations of a very small patient series, we noticed a striking outcome difference, albeit of borderline significance by log-rank statistics, between maternal and paternal grafts with an actuarial rejection rate of 20 and 86%, respectively (Figure 1). The only patient who did not reject the graft from the father developed severe GvHD.

Previous reports of HLA-compatible grafts from a non-sibling related donor have included very small numbers of parental transplants: Gaziev *et al.*[13] described 6 paternal and 2 maternal pheno-identical transplants in thalassemia patients with no rejections observed after conditioning with fludarabine, busulfan, thiotepa, cyclophosphamide and ATG (Protocol 26.1). Hamidieh *et al.*[9] reported a total of 109 non-sibling HLA-compatible BMTs, of which 37 were maternal and 25 were paternal grafts, in patients with different malignant and non-malignant disorders conditioned with standard intensity regimens, mostly busulfan cyclophosphamide and ATG, and infused peripheral blood or marrow grafts; the authors found no appreciable differences between maternal and paternal graft outcomes but a separate subset analysis of non-malignant conditions was not included in the report.

A number of factors might have contributed to our observation of a possible difference in rejection rate between maternal and paternal HLA-compatible grafts such as the relatively non-aggressive myeloablative regime employed and the use of G-CSF-primed marrow which is known to be associated with a

Table 1. Patient characteristics

Age at BMT (years)	*Sex*	*Siblings*	*Donor age (years)*	*Donor*	*Consanguinity*	*Donor/recipient blood type*	*Cell dose (TNCx 10^8/Kg)*	*GvHD*	*Status*
1.1	M	1S	25	Father	Yes	B+/B+	14.6	No	Rej
1.0	F	1S	34.7	Father	Yes	B+/B+	8.6	No	Rej
4.1	M	1S	42.1	Father	Yes	0+/A+	5.4	No	Rej
2.8	M	1B	32.9	Father	Yes	AB+/AB+	9.0	No	Rej
1.0	F	2B	32.9	Father	Yes	AB+/A+	9.6	No	Rej
1.9	M	1S	29.1	Father	Yes	B−/B+	7.2	No	Rej
9.0	F	1S	41.2	Father	Yes	0+/0+	8.5	Grade III	A&C
11.2	M	1B	37.2	Mother	Yes	A+/A+	4.1	No	Rej
13.2	M	1B	32.6	Mother	Yes	A+/0+	5.2	Grade I	A&C
2.5	F	1S	29.5	Mother	Yes	B+/B+	9.4	Grade IV	TRM
1.1	F	1S	31.4	Mother	No	O+/O+	9.9	No	A&C
1.7	M	2S	37.4	Mother	Yes	B+ /B+	6.1	No	A&C

Abbreviations: A&C = alive and cured; B = brother; F = female; M = male; Rej = rejection; S = sister.

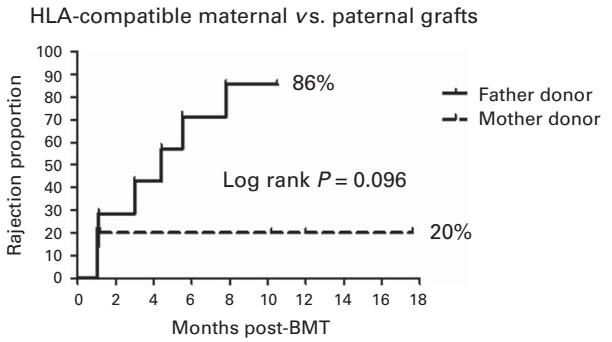

Figure 1. Kaplan–Meier plot of rejection proportions of paternal vs maternal transplants.

decreased GVH effect.[14] In the Indian subcontinent the great majority of donors are male and red cell concentrates are rarely leukodepleted, both factors might have contributed to preferential sensitization against unshared Y-chromosome-associated minor histocompatibility antigens; while this might account for higher rejection of paternal grafts by female recipients it does not explain why all four male patients in our series also rejected paternal grafts sharing the same Y-chromosome. Major ABO mismatch also did not seem to play a role since there was one in each group (Table 1). We have not directly analyzed feto-maternal microchimerism prior to BMT in our patients but we believe that feto-maternal tolerance might be the only plausible explanation for the strikingly lower rejection rates of HLA-compatible maternal grafts apparently independent from gender of the recipient.

In conclusion, this small experience underscores that the mother might be the preferable donor in the non-malignancy and multi-transfused context. Our observation also suggests that grafts from fully matched fathers should be used keeping in mind the high potential for rejection so that more aggressive preparative regimes might be warranted. Fully compatible maternal grafts may not require intensified conditioning.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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