

## Hematopoietic Stem Cell Transplantation in Children with Genetic Defects

VELU NAIR, SATYARANJAN DAS AND AJAY SHARMA

From Department of Haematology and Bone Marrow Transplantation, Army Hospital Research and Referral, Delhi Cantonment, Delhi, India.

Correspondence to:  
Col (Dr) Velu Nair,  
Professor and Head,  
Department of Haematology and Bone  
Marrow Transplantation,  
Army Hospital (R&R),  
Delhi Cantonment, India.  
E-mail: [nairvelu2000@yahoo.com](mailto:nairvelu2000@yahoo.com).  
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Seventeen children (mean age: 7.2 years) with genetic defects involving hematopoietic cell production or function, underwent 19 allogeneic stem cell transplantations from HLA identical siblings. Twelve children were suffering from thalassemia major; 2 from Diamond Blackfan anemia; 2 from Fanconi anemia and 1 from congenital dyserythropoietic anemia. The disease free survival was 77% with a mean follow up of 36 months. The major complications were graft versus host disease, veno-occlusive disease, CMV infection and hemorrhage. One case each of thalassaemia major and Fanconi anemia rejected the graft after 1 year and 11 months, respectively. Both patients were successfully transplanted second time from the same donor with some modification in the conditioning regimen and stem cell source.

**Keywords:** Bone marrow transplant, Diamond Blackfan anemia, Fanconi anemia, Thalassaemia major.

Hematopoietic stem cell transplantation (HSCT) is being increasingly used to cure several inherited defects of hematopoietic cell production or function and metabolic diseases. Thalassaemia major is the most common indication for HSCT among the non-malignant diseases(1). Diamond-Blackfan anemia, congenital dyserythropoietic anemia and Fanconi anemia are some of the other genetic defects, for which HSCT has been accepted as the preferred form of treatment. We describe 17 cases who underwent 19 allogeneic HSCTs from matched sibling donors.

### METHODS

Seventeen children (12 males, 5 females) with genetic defects underwent 19 allogeneic HSCTs from matched sibling donors at our center between Jan 2002 to Jan 2007. Of these, 12 were cases of thalassaemia major; 2 of Fanconi's anemia; 2 of Diamond Blackfan anemia and 1 child had

congenital dyserythropoietic anemia (CDA type-1). One child with Diamond Blackfan anemia also had associated Duchenne muscular dystrophy. The mean age was 7.2 years ranging from 2 to 15 years. Five transplants were ABO mismatched, 3 major and 2 minor mismatches. The source of stem cells was bone marrow in 15 cases, peripheral blood (PBSC) in 2, cord blood in 1 and cord blood and bone marrow in another. For major ABO mismatches, RBC depletion of the bone marrow was carried out with hydroxy-ethyl-starch sedimentation and for minor mismatches plasma depletion was carried out with refrigerated high-speed centrifugation. The mean cell dose was  $4.7 \times 10^8$  mononuclear cells per kg body weight ranging from 1.5 to 7.6. The conditioning regimen in 14 out of 15 cases of thalassaemia major, Diamond Blackfan anemia and CDA comprised of busulphan, cyclophosphamide and anti-thymocyte globulin (ATG). In a 13 year old Hepatitis-C positive thalassaemic child, the conditioning regimen was modified to fludarabine, reduced dose busulphan

### WHAT THIS STUDY ADDS?

- Allogeneic hematopoietic stem cell transplantation offers a curative treatment for genetic defects and a second transplant can be done successfully in case of failed first transplant, using the same donor.

and cyclophosphamide. Both cases of Fanconi anemia were transplanted with modified conditioning regimen using fludarabine, reduced dose cyclophosphamide and ATG. GVHD prophylaxis constituted of methotrexate and cyclosporine. Post transplant cyclosporine levels were monitored to achieve a target level of 250 ng/mL for 6 months (or longer in cases with GVHD) and then tapered over the next 6 months. Phenytoin was used for seizure prophylaxis where busulphan was used for conditioning. All the cellular blood products were irradiated using Gamma cell irradiator.

### RESULTS

There was no case of primary graft failure and engraftment was 100%. The mean period for neutrophil engraftment i.e. absolute neutrophil count (ANC) of more than 500/ $\mu$ L, was 13 days (8-22 days). The mean period for platelet engraftment i.e. unsupported platelet count of 20,000/ $\mu$ L, was 15 days (8-26 days). Chimerism was done on day 30, 90 and 180 post transplant in 11 cases by DNA analysis and in 3 cases by FISH for X and Y chromosome in sex mismatched transplants. In 3 cases, chimerism studies could not be done. Two cases died prior to day 30, hence chimerism was not done. Day 30 post transplant chimerism was of 100% donor type in all cases where it was done. In one case of thalassaemia major, the child rejected the graft 1 year post umbilical cord blood transplant. She underwent a second transplant successfully 5 years later from the same donor with bone marrow as source of stem cell and is now transfusion free with 100% donor chimerism, 1 year post-transplant. Another case of Fanconi anemia rejected the graft 11 months post bone marrow transplant. She was successfully transplanted again with modification in conditioning regimen (replacing fludarabine with reduced dose busulfan) and stem cell source being PBSC. She has 100% donor chimerism, 16 months post transplant.

All patients were nursed in double high

efficiency particulate air (HEPA) filtered rooms from conditioning to engraftment. All patients except one had febrile neutropenia and were treated with broad spectrum antibiotics and antifungals as per protocol based on the recommendations of the hospital infection committee. Two patients developed sinusoidal occlusion syndrome (veno-occlusive disease) of which one died on 16th day post transplant. Three patients developed grade II-III acute GVHD. One thalassemic child developed grade IV GVHD of gut, liver and skin, and died on day 90 post-transplant. One patient had late engraftment on day 22 and died due to diffuse pulmonary hemorrhage on 28th day post transplant. The mean requirement of single donor platelets was 4.5 bags ranging from 1-18 bags. Mean packed RBC requirement was 3 units ranging from 0 to 6 units. Seven patients (36%) developed mucositis of grade I to III requiring total parenteral nutrition and 3 of them who had grade III mucositis required opioid analgesics. One patient had busulphan induced seizure, which was successfully managed with benzodiazepine in addition to phenytoin. Two patients developed hemorrhagic cystitis which was successfully managed with hydration. One patient had tricuspid valve bacterial endocarditis with vegetations which was managed successfully with open heart surgery and vegetectomy. The patient of Diamond Blackfan anemia and Duchenne muscular dystrophy is transfusion free and interestingly has not shown any deterioration after 14 months of follow up post allogeneic BMT. His CPK levels have reduced from 20,000 U/L pre BMT to 350 U/L at present.

Out of 17 HSCT patients, 4 died due to various complications. The survival among the thalassaemia major patients was 79% and for Fanconi anemia it was 100%. The sole patient of CDA died. The disease free survival in the whole group was 77% with a mean follow up of 34 months, ranging from 8-68 months post transplant. All cases of thalassaemia

were of Lucarelli Class-II or III. Patients were vaccinated one year post HSCT, provided there was no evidence of GVHD. All surviving patients are transfusion free and enjoying good general health.

### DISCUSSION

Allogeneic HSCT is curative and offers an alternative to life long transfusion and iron chelation for thalassemia major patients. This also is economical in the long run(2). The survival in our patients was comparable to previous reports(2,3). Diamond Blackfan anemia can also be cured by successful HSCT(4,5). Fanconi anemia, which has predisposition to malignancy can also be cured by allogeneic HSCT(6,7).

Our study has certain highlights. The child with Diamond Blackfan anemia with Duchenne muscular dystrophy, in addition to being transfusion free, has shown non progression of muscular dystrophy. Two children who rejected the graft first time could be transplanted successfully with change in conditioning, with stem cells sourced from the same donor as there was no alternate donor available. One of the children with thalassemia who developed bacterial endocarditis refractory to medical management could be successfully managed by open heart surgery with vegetectomy.

The major limitation of allogeneic HSCT is the non-availability of matched sibling donor. Alternate options like 1 to 2 antigen mismatched cord blood transplant, haploidentical transplantations and matched unrelated transplants are now increasingly being undertaken successfully(8,9).

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### REFERENCES

1. Thomas ED, Buckner CD, Sanders JE, Papayanopoulou T, Borgna-Pignatti C, De Stefano P, *et al.* Marrow transplantation for thalassaemia. *Lancet* 1982; 2: 621-623.
2. Chandy M, Srivastava A, Dennison D, Mathews V, George B. Allogeneic bone marrow transplantation in the developing world: experience from a centre in India. *Bone Marrow Transplant* 2001; 27: 785-790.
3. Lucarelli G, Galimberti M, Polchi P, Angelucci E, Baronciani D, Giardini C, *et al.* Bone marrow transplantation in patients with thalassemia. *N Engl J Med* 1990; 322: 417-421.
4. August CS, King E, Githens JH, McIntosh K, Humbert JR, Greensheer A, *et al.* Establishment of erythropoiesis following bone marrow transplantation in a patient with congenital hypoplastic anemia (Diamond-Blackfan syndrome). *Blood* 1976; 48: 491-498.
5. Vlachos A, Federman N, Reyes-Haley C, Abramson J, Lipton JM. Haematopoietic stem cell transplantation for Diamond Blackfan anemia: a report from the Diamond Blackfan Anemia Registry. *Bone Marrow Transplant* 2001; 27: 381-386.
6. Gluckman E. Bone marrow transplantation in Fanconi's anemia. *Stem Cells* 1993; 11: 180-183.
7. Farzia A, Davies SM, Smith FO, Filipovich A, Hansen M, Auerbach RD, *et al.* Matched sibling donor haematopoietic stem cell transplantation in Fanconi anaemia: an update of the Cincinnati Children's experience. *Br J Haematol* 2007; 136: 633-640.
8. Elhasid R, Arush M W, Katz T, Gan Y, Shechter Y, Sami I, *et al.* Successful haploidentical bone marrow transplantation in Fanconi anemia. *Bone Marrow Transplant* 2000; 26: 1221-1223.
9. Gaziev D, Galimberti M, Lucarelli G, Polchi P, Giardini C, Angelucci E, *et al.* Bone marrow transplantation from alternative donors for thalassemia: HLA-phenotypically identical relative and HLA-nonidentical sibling or parent transplantats. *Bone Marrow Transplant* 2000; 25: 815-821.