ORIGINAL ARTICLE

Providing a Cure for β Thalassaemia Major

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Summary

The current treatment options for β thalassaemia major patients include conservative treatment with red blood cell transfusions and iron chelation or stem cell transplantation. Regular blood transfusions inevitably lead to multi-organ haemosiderosis and are attended by risks of blood-borne infections. Results from stem cell transplantation are good and suggest that this should be offered as first line therapy when a matched sibling donor is available because the patient is often cured and able to live a normal life. Of 38 Malaysian children who underwent bone marrow or cord blood transplantations using matched sibling donors, 29 (76%) are now cured.

Key Words: β thalassaemia major; Stem cell transplantation

Introduction

The β thalassaemia gene is one of the most common haemoglobinopathy gene carried by Malaysians[1]. The incidence is reported to be approximately 5% for the Chinese and Malays and less for Indians. There are at least 2200 patients who have transfusion dependent β thalassaemia major in Malaysia. The management of these patients requires adequate packed red cell transfusions with the aim of correcting the state of chronic anaemia and switching off endogenous production of erythropoietin. Regular transfusions carry the risk of blood-borne infections and result in haemosiderosis. Patients need regular hospital attendance which disrupts personal and family lifestyles. Survival of these patients may be prolonged with iron chelation[2,3] an arm of therapy which demands compliance, discipline and expense.

Without any preventive strategies or screening programmes, the burden of care for thalassaemia patients is considerable. Bone marrow transplantation for thalassaemia was first reported in 1982[4]. Since, then, stem cell transplantation (SCT) using either bone marrow or umbilical cord blood has been proven to cure this disease and is cost effective[5,6,7]. Initial fears related to transplant mortality are diminished as transplant outcome continues to improve. We report the outcome of stem cell transplantation for β thalassaemia in Malaysia.

Materials and Methods

We retrospectively reviewed the hospital records of 43 consecutive SCTs on 38 patients with transfusion dependent thalassaemia who underwent allogeneic transplantation at University Malaya Medical Centre between August 1987 till June 2000. The patients came from various towns in Malaysia and their initial management varied. All donors were human leucocyte antigen (HLA) matched siblings except for 1 patient who used a partially matched (5 out of 6 HLA antigens) parent and had his first bone

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marrow transplantation in Sydney, Australia. Six of the 43 transplantations were second transplantations for graft rejection and used the same donors.

Pre-SCT assessment

Patients were assessed for size of liver and spleen, use and adequacy of iron chelation, presence of fibrosis in liver biopsies and serum ferritin levels. Hepatomegaly, inadequate iron chelation and hepatic fibrosis were the three factors used to classify patients according to the Pesaro Risk Groups. Patients without hepatomegaly who had adequate iron chelation and no hepatic fibrosis were classified as low risk patients (Pesaro Risk Class 1) while those with 1 or 2 risks factors were intermediate risk (Pesaro Risk Class 2) and patients with all three features mentioned were high risk patients (Pesaro Risk Class 3). The clinical features of the patients are shown in Table I.

Conditioning or Preparative regimen

All patients received combinations of busulphan and cyclophosphamide (43 SCT) with addition of anti-thymocyte globulin ATG (29) or melphalan (5). Patients who underwent a 2nd transplantation were conditioned with total lymphoid irradiation, busulphan, cyclophosphamide and ATG. Prophylaxis against graft-versus-host disease was with standard doses of methotrexate and cyclosporin A.

Surportive treatment

All patients were nursed in simple isolation rooms. Regular doses of intravenous immunoglobulins were given. Episodes of febrile neutropaenia were treated empirically with broad spectrum antibiotics with addition of anti-fungals for prolonged fever. All packed cell and platelet transfusions were irradiated to prevent graft-versus-host disease.

Table I
Clinical Characteristics of 43 Stem Cell Transplantations

Characteristic		n
Indication for transplant:	β thal. major	38
	HbE-β thal	5
Gender:	Male	26
	Female	17
Race:	Chinese	29
	Malay	13
	Indian	1
Age at transplant:	Median	4 years
	Range	1 - 13 years
Serum ferritin levels:	Median	2187ng/ml
	Range	167 - 15000ng/ml
Iron Chelation status:	Adequate	0
	Some	8
	None	35
Hepatomegaly	Absent	1
	Present	42
Hepatic fibrosis:	Present	9
	Absent	27
	Unknown	7
Pesaro Risk:	Class 1	0
	Class 2	33
	Class 3	10
Donor Stem cell source:	Bone Marrow	40 (matched sibling 39, partially matched parental 1)
	Cord Blood	3 (all matched sibling)
Hepatitis B antigen:	Positive	0
	Negative	43
Hepatitis C Antibody:	Positive	2
	Negative	41

Graft/Donor

Stem cells were obtained from bone marrow (BM) or cord blood (CB). Bone marrow was harvested from the iliac bones of the donor under general anaesthesia. Cord blood was collected when prenatal diagnosis through molecular beta-globin gene mutation studies had confirmed that the sibling donor (foetus) did not suffer from β thalassaemia major.

Statistical Method

Chi square test was used to compare survival outcome with age, Pesaro Risk Group, hepatomegaly, hepatic fibrosis, iron chelation, serum ferritin level, gender, race, blood group and donor thalassaemia status.

Results

The clinical characteristics of the 43 stem cell transplantations are shown in Table I. Survival outcome is shown in Figure 1.

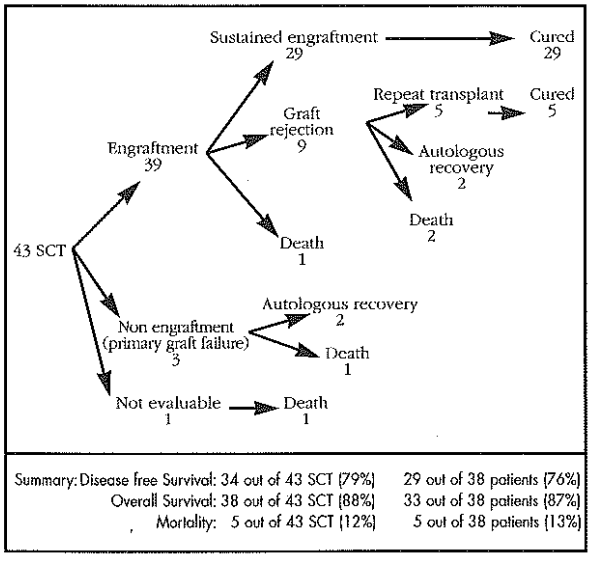

Fig. 1: Survival Outcome of 43 Stem Cell Transplantations.

Primary graft failure occurred in 3 patients while 1 was not evaluable as the patient died of septicaemia on Day 17 of transplant. Out of the 3 patients who failed to engraft, 2 had autologous recovery of marrow function and reverted to transfusion dependent thalassaemia status. The remaining patient died of intracranial haemorrhage on Day 107 of transplant.

Thirty-nine transplantations engrafted successfully with the mean day of engraftment on Day 19 (range 12 - 67 days). Unfortunately 9 of these transplantations suffered graft rejection. Of these, 2 experienced autologous recovery while another 2 suffered marrow aplasia which resulted in death from intracerebral haemorrhage and fungal infection respectively. The remaining 5 patients went on to successful second transplantations using the same donors. Overall transplant mortality was 5 out of 38 patients (13%). All deaths occurred before 1997. Of the remaining 33 survivors, 4 are alive with disease (11%) while 29 patients (76%) are cured.

Significant risk factors to successful transplantation are age (greater than 5 years) and Pesaro Risk Class 3 (which incorporates hepatomegaly, high iron load and hepatic fibrosis). Gender, race, blood group of recipient and donor thalassaemia status did not affect the outcome of transplantation. See Table II.

Discussion

The burden of care for β thalassaemia patients in Malaysia is aggravated by the lack of preventive strategies. While doctors and the Ministry of Health deliberate on screening programmes, babies with β thalassaemia major will continue to be born. Recommended conservative treatment involves regular blood transfusions with concurrent iron chelation using desferrioxamine[8,9]. Although this has increased the life-span for many thalassaemics, the quality of life is difficult and likely to deteriorate over time[10,11]. Alternative treatment with stem cell transplantation (SCT) is no longer controversial because of increasingly good results

Table II
Characteristics of Stem Cell Transplantations and Survival Outcome

Characteristic		Number of SCT	Alive	Dead	X^2 test p value
Age:	< 5 years	23	23	0	
	5 - 10 years	19	15	4	0.001
	> 10 years	1	0	1	
Pesaro Risk:	Class 1	0	0	0	
	Class 2	33	31	2	0.038
	Class 3	10	7	3	
Hepatomegaly:	Yes	41	36	5	0.030
	No	2	2	0	
Hepatic fibrosis:	Yes	9	6	3	
	No	27	25	2	0.063
	Unknown	7	7	0	
Iron Chelation:	Adequate	0	0	0	
	Some	8	8	0	0.255
	None	35	30	5	
Serum Ferritin level (ng/ml):					
	<1000	8	8	0	
	1000 - 5000	19	19	0	0.000
	5000 - 10000	8	7	1	
	10000 - 15000	2	0	2	
	Not available	6	5	1	
Gender:	Male	26	23	3	0.985
	Female	17	15	2	
Race:	Chinese	29	29	2	
	Malay	13	10	3	0.298
	Indian	1	1	0	
Blood Group:	A Rhesus pos.	17	15	2	
	B Rhesus pos.	9	8	1	0.958
	AB Rhesus pos.	2	2	0	
	O Rhesus pos.	15	13	2	
Donor Thalassaemia Status:					
	Trait	26	23	3	0.930
	Normal	17	15	2	

and the chance of a cure[5,12,13,14]. The quality of life of a patient who has successfully undergone SCT is completely normal. Gene therapy is still a long way off because of the huge obstacles related to transfer of a gene as large as the β globin gene[15].

With present expertise and results, SCT should be recommended for all β thalassaemia patients who have an HLA matched sibling donor. With such donors, the chances of cure are dependent on recipient factors like age, hepatomegaly, degree

of iron overload and presence of hepatic fibrosis. Lucarelli *et al* from Pesaro, Italy who have performed the most number of SCT on β thalassaemia patients, identified 3 risk factors which are hepatomegaly (defined as >2cm below costal margin), adequacy of iron chelation (defined as chelation which starts within 18 months of the first transfusion and given subcutaneously over 8 - 10 hours for at least 5 times per week) and hepatic fibrosis[5,16]. Low risk patients have none, intermediate risk patients have 1 - 2 while high risk patients have all 3 risk factors. With this Pesaro Risk classification, a disease free survival rate of 90%, 82% and 53% has been reported for low, intermediate and high risk patients respectively[17].

Our own results show concurrence with an overall cure rate of 76% which breaks down to 79% and 67% for intermediate and high risk patients respectively. None of our patients qualified for the low risk group. Most of our patients did not receive iron chelation therapy prior to transplantation and for the 8 patients who did, therapy was not optimised. Patients younger than 5 years of age who had received fewer blood transfusions and were less iron overloaded had a cure rate of 100%. These patients live normal lives free from the burden of subcutaneous infusions or blood transfusions. Older patients fared less well. Three patients died from infection while 2 died of haemorrhage. Mortality from haemorrhage is expected to decrease with our present facilities where the patient's own bone marrow is cryopreserved as a back-up in the event of primary graft failure or graft rejection with marrow aplasia. Should we therefore offer SCT to all patients with β thalassaemia major seeing that this is the only therapeutic modality which offers cure? Malaysian patients who are older than 10 years of age, who have poor or no iron chelation, very high serum ferritin levels or hepatic fibrosis would generally fare badly. The availability of an appropriate donor remains the single most important factor to consider. Although outcome of transplantation using matched sibling donors is no longer questioned, the results using partially matched family or parental donors are far less satisfactory. Data from a limited number of centres suggest a disease free survival of 20 - 50%[18,19]. The same could be said for matched unrelated donor transplantation[20]. Obstacles to such transplants are primary graft failure or graft versus host disease (GVHD)[21,22]. The use of less allo-reactive stem cells from cord blood could theoretically overcome the problem of GVHD[23] but there are no published reports on unrelated cord blood transplants for thalassaemia and most centres have disappointing results (verbal communication). With current expertise and experience, transplantation using matched unrelated or partially matched related bone marrow or cord blood is not routinely recommended[24].

Conclusions

The chance of cure for β thalassaemia major patients with SCT should always be exercised when a matched sibling donor is available. Such transplants should be performed as soon as possible before poor prognostic factors like increasing age of recipient, hepatomegaly, increasing iron overload and hepatic fibrosis occur. Those patients who do not have an appropriate sibling donor should avail themselves to the current best known treatment i.e. adequate blood transfusions using leucocyte filters, good blood screening facilities, optimal iron chelation and good nutrition. As transplant related mortality and morbidity continue to decrease, there is every likelihood that unrelated cord blood transplants will become more available and acceptable in the future.

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