Review Article-II

Hematopoietic Stem Cell Transplantation for Hemoglobinopathies: Progress and Prospects

LAKSHMANAN KRISHNAMURTI AND D GUPTA

SUMMARY

Allogeneic bone marrow transplantation from an HLA-identical donor is currently the only means of curing thalassemia . Transplant outcome depends upon the presence of risk factors (hepatomegaly, portal fibrosis and poor quality of chelation). patients are defined to have class I - if no risk factor, class II with one or two and class III - if all three risk factors are present. For patients under 16 years of age, for class I, class II and III the probabilities of survival are approximately 95%, >80% and 60-70%, respectively. The risk of transplant related morbidity & mortality is low when transplant is done at an early age. Currently, busulfan, cyclophospahmide and antithymocyte globulin based combination is used for conditioning.

More than 200 patients with sickle cell disease (SCD) have undergone allogeneic SCT with long term survival in >80% of patients. Results are better if donor is an HLA-identical sibling and if transplant is done early in the course of disease. Presently, experience with reduced intensity SCT and matched unrelated donor transplant is limited to recommend their routine use.

SICKLE CELL DISEASE

Advances in the care of children with Sickle cell disease (SCD) including newborn screening, early introduction of penicillin, the pneumococcal vaccines and comprehensive care[1-3] have resulted in a marked improvement in the life expectancy of patients with SCD. However, mean age of death for patients with SCD is 42 years for males and 48 years females[2] which is 25-30 years less than average life expectancy for African-American. Stroke, organ failure, acute chest syndrome and recurrent pain crises are major complications that shorten life expectancy and impair overall health related quality of life (HRQOL). While hydroxyurea (HU) and chronic transfusion regimens can ameliorate several of the complications of SCD, allogeneic hematopoietic cell transplantation (HSCT) is the only therapeutic option with curative intent.

INDICATIONS

Indications for HSCT have been empirically determined from prognostic factors derived from studies of natural history of SCD. Table-1 describes criteria for transplantation used in the national collaborative study of HSCT for SCD.[4]

RESULTS

Allogeneic HSCT after myeloablative therapy has been performed in approximately >250 young patients (<16 years of age) with SCD (Table 2). The preparative regimens usually consists of Busulfan (BU) 14-16mg/Kg and Cyclophosphamide (CY) 200mg/kg. Additional immunosuppressive agents. Antithymocyte Globulin(ATG), rabbit ATG (rATG),[5] Ant lymphocyte Globulin (ALG)[6] or Total Lymphoid Irradiation (TLI)[7] are also used. Cyclosporine A (CsA) alone or with Methylprednisolone (MP) or Methotrexate (MTX) has been utilized for post-transplant GVHD prophylaxis.

The outcomes of HSCT from matched siblings is excellent with overall survival of 93-97% and event free survival (EFS) of 85%.[2,6, 8-22] Stabilization or reversal of organ damage from SCD has been documented after HSCT.[10] Patients who have stable donor engraftment, complications related to SCD resolve, and there are no further episodes of pain, stroke, or acute chest syndrome. Patients who are successfully allografted do not experience sickle-related CNS complications and have evidence of stabilization of CNS disease by cerebral MRI.[23,24] However, the impact of successful HSCT on

Department of Comprehensive Hemoglobinopathies Program Division of Hematology/Oncology/BMT Children's Hospital of Pittsburgh 3705 Fifth Avenue, Pittsburgh, PA 15213
Correspondence to: **LAKSHMANAN KRISHNAMURTI**
E-mail: Lakshmanan.Krishnamurti@chp.edu

Table 1 Indications for HCT in SCD (modified from Walters et al 1996)[4]

Patients with SCD 16 years of age or less years with an HLA-identical sibling bone marrow donor with one or more of the following:
Stroke, CNS hemorrhage or a neurologic event lasting longer than 24 hours, or abnormal cerebral MRI or cerebral arteriogram or MRI angiographic study and impaired neuropsychological testing,
Acute chest syndrome with a history of recurrent hospitalizations or exchange transfusions,
Recurrent vaso-occlusive pain 3 or more episodes per year for 3 years or more years or recurrent priapism,
Impaired neuropsychological function and abnormal cerebral MRI scan,
Stage I or II sickle lung disease,
Sickle nephropathy (moderate or severe proteinuria or a glomerular filtration rate [GFR] 30-50% of the predicted normal value),
Bilateral proliferative retinopathy and major visual impairment in at least one eye,
Osteonecrosis of multiple joints with documented destructive changes,
Requirement for chronic transfusions but with RBC alloimmunization >2 antibodies during long term transfusion therapy.

reversal of cerebral vasculopathy has been variable.[25-28] HSCT for SCD generally does not cause growth impairment in young children; however, diminished growth may occur if HSCT is carried out near or during the adolescent growth spurt.[29] An adverse effect of Busulfan conditioning on ovarian function was demonstrated in five of seven evaluable females who are currently at least 13 years of age. None of the four males tested had elevated serum gonadotropin levels.[10] Radiological improvement of a patient with osteonecrosis of humeral head[30] and correction of splenic reticuloendothelial dysfunction have been reported.[16,31] There may be differences in recommendations of health care providers and risk accepted by patients or parents.[32] Majority of parents and patients are willing to accept some risk of mortality.

THALASSEMIA

Thalassemia results from mutations in one or more globin genes or other regulatory elements that result in the decreased or absent synthesis of *a* or β globins. Nearly 200 different mutations have been described in patients with β Thalassemia and related disorders.[34] It is estimated that there are 200 million carriers of the disease, of which 20 percent are in South East Asia and 10 percent in India alone. More than 9,000 children with Thalassemia major are born every year in India, which signifies the huge disease burden.[35, 36]

SURVIVAL

The prospect of improved survival without cardiac disease has greatly increased, especially for children with Thalassemia born since the current treatment became widely available.[37, 38] Nonetheless, there are still cases of iron-related illness and death, even in patients who apparently complied with desferrioxamine therapy. A sustained reduction in iron, as measured by the proportion of serum ferritin measurements that did not exceed 2500 ng per milliliter, is the most consistent predictive factor of survival without cardiac disease.[37] Desferrioxamine treatment is cumbersome and expensive; compliance is a major obstacle especially in children.[39, 40] Deferiprone is also used widely as an oral chelator albeit with limited clinical data in

Table 2: Results of HSCT for Sickle cell disease (SCD)

Reference	Preparative Regimen	GVHD Prophylaxis	N	Median Age (Range)	Overall Survival	Event free survival/ Follow-up	Complications
Walters et al. [10] 2000	BU 14 mg/kg Cy 200 mg/kg ATG 90 mg/kg	CsA CsA + MP CsA + MTX	50	9.9 years (3.3-15.9)	94%	84% 2.2 years (0.1-5.6)	Rejection (n=4) GVHD (n=1) ICH (n=1)
Vermylen et al (1998).[16]	BU 14-16 mg/kg CY 200 mg/kg ATG/TLI	CsA alone (n=15) CsA + MTX (n=25)	50	9.5 years (0.9-23.0)	96%	85% 3.1 years (0.3-65)	Rejection (n=3) GVHD (n=1)
Bernaudin, Socie et al [24] (2007)	BU 14-22 mg/kg CY 200-260 mg/kg + rATG	CsA alone (n=25) CsA + MTX (n=62)	87 87	9.5 years (2-22)	93.1%	86% 6 years (1.6-17.5)	Rajection (n=6) ICH (n=1) Fatal GVHD (n=4) Fatal Sepsis (n=1)
Giardini et al.[12] (1993)	BU 14-16 mg/kg CY 120-200 mg/kg ALG	Not described	8	8.0 years (4.0-26.0)	5/8	5/8	GVHD (n=2) ARDS (n=1)+
Abboud et al.[18] (1997)	BU 14 mg/kg CY 200 mg/kg	CsA + MTX (n=8) CsA + MP (n=2)	10	12.4 years	9/10	9/10	Infection (n=1)
Ferster et al.[6] (1995)	BU 14 mg/kg CY 50 mg/kg ALG (in 6 pts)	CsA + MTX	9	8 (2-11)	9/9	6/9	Rejection (n=3)
Panepinto et al[33] (2007)	BU 16 mg/kg CY 200 mg/kg Fludarabine, Bleomycin, TBI, ATG in combinations	CsA+MTX Tacrolimus=2	67	10 (2-27)	97%	85% 61(3-178)	ICH=1 Multi organ failure=1

Table 3: Results of HSCT for Thalassemia

Reference	Preparative Regimen	GVHD Prophylaxis	N	Median Age in (Range)	Overall Survival	Event free survival/ Follow-up	Cause of death
Mentzer at al {55}	BU 14 mg/kg CY 200 mg/kg ATG 90 MG/KG	CsA + MTX	17	9.9 years (3.3-15.3)	94%	71% 2.2 years (0.1-5.6)	Rejection (n=4) GVHD ICH (N=1)
Lucarelli et al {56} {57, 58}	BU 14-16 mg/kg CY 200 mg/kg Bu 16+Cy 160+Flu AZA, HU (Class III) Bul 16+Cy 90+Flu, AZA, HU (Adult)	CsA + MTX	886	9.5 (1-23.0) Class III 79% Adult 66%	Class I 93% Class Ii 87% Class III 58% Adult 62% 3.1 years (0.3-6.5)	Class I 91% Class II 83%	Rejection (n=3) GVDH (n=1)
Boulad et al {47} {59}	CY 120+TBI or BU 14-16 mg/kg+ CY 200 mg/kg or BU 14 mg/kg FLU 150mg/m^2 ATG	MTX CsA+MP CsA+ MTX	17		94%	76% 5.5 years (1-8)	Grade IV GVHD (n=1)
Mathews et al (45)	BU 14-22 mg/kg CY 200-260 mg/kg	CsA + MTX	190	7 years	Class II (Low risk) 78.3% Class III(High risk) 39.01%	Class II 78.53% Class III (Low risk) 70.3% Class III (High risk 23.93%	
Lee et al (60)	BU 14-16 mg/kg CY 120-200 mg/kg ALG	Not described	8	8.0 years (4.0-26.0)	5/8	5/8	GVHD (n=2) ARDS n=1)+
Khojasteh et al{61}	BU 14 mg/kg CY 200 mg/kg	CsA+ MTX (n=8) CsA + MP	10	12.4 years (3.8-19.3)	9/10	9/10	infection (n=1)
Zhu W{62}	BU 16 mg/kg CY 200 mg/kg ATG 90mg/kg	CsA+MTX	4				
Li CK et al {63}	BU `16 mg/kg CY 150-200mg/kg ATG 10-30mg/kg	CsA+MTX Ganciclovir	44	10.7 yrs (1.8-21)	Class 100% Class II 88% Class III 57% 86% at 5 yrs	Class I 100% Class II 80% Class III 57% 825 at 5 yrs 65 months 920-105)	TRM (n=4) Pneumonia (n=1)
Lee et al (64)	BU 16mg/kg CY 200 mg/kg ATG in 1 120 mg/kg	CsA+MTX	4	6.2 (4-11)			3 of 4 free of transfusion

prospective trials.[41] Deferasirox, a tridentate iron chelator allows once daily dose orally and has shown promising results in decreasing the liver iron concentration[42] and has been recently licensed for use. However oral iron chelation remains expensive. At present HSCT is the only therapy with curative intent.

INDICATIONS

Patients with Thalassemia major who are transfusion dependent have been offered HSCT. Selected patients with severe forms of Thalassemia intermedia such as E/β Thalassemia as well as αThalssemia with hydrops [43] have been offered HSCT. Success of HSCT can be predicted by the (Lucarelli Class I, II, III) on basis of hepatomegaly >2cm, liver fibrosis and inadequate chelation. Sodani et al demonstrated that Class III children less than 17 years have a good outcome after HSCT.[44] A prospective trial on 190 patients has shown that in India has demonstrated a good prognosis in children less than 7 years who come in Class III.[45]

RESULTS

Allogeneic HSCT after myeloablative therapy has been performed in more than 1500 patients[46] (Table -3). BU 14-16mg/Kg and Cyclophosphamide (CY) 200mg/kg with or without ATG is the backbone of preparative regimens used, although CY/TBI regimens have been used.[47] CsA alone or with MP or MTX has been utilized for post-transplant GVHD prophylaxis. The outcome of HSCT in over 800 patients with Thalassemia is excellent especially in those who are young and do not have advanced disease.[48] The overall survival (OS) and EFS are 95% and 90% for Pesaro class I, 87% and 84% for class II for patients 79% and 58% for Class III patients and 66 % and 62 % for adult patients. Recently, modification of the conditioning regimen for young patients with Class III disease has improved outcomes in these patients.[49] These patients received HU 30mg/Kg and azathioprine(AZA) 3mg/Kg given daily day -45 to day -11, fludarabine (FLU) 20 mg/m2 /day, from day -17 to day -11 and BU14 mg/Kg. Class 3 patients aged less than 17 years received CY 160 mg/Kg while patients 17 years or older, received CY90 mg/Kg. In this group of 31 Class 3 young Thalassemic patients, OS and EFS were 97% and 90%, respectively.

Following HSCT, 40% of patients attained puberty normally despite clinical and hormonal evidence of gonadal dysfunction in majority.[50] Hormonal dysfunction could be attributed to the cytotoxic effects of alkylating agents, gonadotropin insufficiency or secondary to previous iron overload. In 41 patients treated with phlebotomy after successful HSCT, liver iron concentration decreased from 20.8 (15.5-28.1) to 3 (0.9-14.6) mg/g dry weight ($p < 0.0001$), suggesting that phlebotomy is a safe and effective method to decrease iron overload in the "ex-thalassemic".[51] Six patients who developed liver cirrhosis before or after their Thalassemia was cured by bone marrow transplantation received iron depletion and antiviral therapies. Follow-up biopsies showed regression of incomplete or definite cirrhosis in all patients.[52] Post HSCT phlebotomy has also helped reverse subclinical cardiac dysfunction.[53] Short stature is present in a significant percentage of transplanted Thalassemic children.[54] While there is a close effect of the age at time of transplant (before or after 7 years) on subsequent growth rate, the growth impairment in these subjects is probably multifactorial.

NOVEL APPROACHES TO HSCT FOR HEMOGLOBINOPATHIES

Paucity of donors, inadequate management early in life, regimen related effects have limited the acceptability of the curative therapy for majority of patients with hemoglobinopathies. Various approaches are being evaluated to increase engraftment and minimize the side effects at the same time. Complete substitution of Cyclophosphamide was done by Fludarabine ($30mg/m^2/day \times 6$) and rATG ($10mg/kg/day \times 4$) with Busulfan orally ($3.5mg/kg/day \times 4$) and all the five patients attained engraftment with no case of GVHD more than Grade I.[65] Alemtuzumab with Busulfan at dose of 8mg/kg has also been used in the preparative regimen. Sodani et al report that likelihood of engraftment is increased and graft rejection decreased with use of azathioprine, fludarabine, hydroxyurea coupled with a hypertransfusion and adequate chelation regime prior to HSCT.[66] Short term ATG has also shown to decrease the chances of acute and chronic GVHD.[67] Hydroxyurea has good compliance without severe side effects in patients with SCD and improves the outcome of HSCT when administered before HSCT.[68]

Table 4: Results for Unrelated Donor Transplantation

Reference	Preparative Regimen	GVHD Prophylaxis	N	Median Age in (Range)	Overall Survival	Event free survival/ Follow-up	Complications/ comment
La Nasa et al {87}	BU 14 mg/kg CY 120-200mg/kg TT 10mg/kg	CsA+MTX ATG	68	15 (2-37)	79.3% Class II 96.7% Class III 65.2%	65.8% Class II 80% Class III 54.5% 3.4 (8mo n-12yr)	Rejection 11% Mortality 18%
Contu et al {94)	BU 14 mg/kg CY 160 mg/kg	Not described	1	16 years	1/1	1/1 7 months	N GVHD
Werner et al. {21}	CY 6 gm/m^2 VP 16 1.8 gm/m^2 TBI 1200 cGY	Not described	1	19.0	1/1	1/1	unrelated donor UCB for SCD with AML
Yeager et al {100}	BU 16 mg/kg CY 200 mg/kg ATG 90 mg/kg	CsA	2	6 years, 12 years		2/2 (2 years & 4 years)	1 extensive unrelated donor UCB for SCD
Hongeng et al {101}	BU 8-16mg/kg ATG 20-40 mg/kg Fludarabine 35 mg/m^2x5d TLI 500cGy	CsA + MP	49	Related 7.2 (0.5-18.7) Unrelated (0.7-12)	Related 92% Unrelated 82%	Related 82% 51 (6-157)	Unrelated 71% 35 (6-55)
Feng et al {90}	BU 16 mg/kg CY 200 mg/kg ATG 30 mg/kg Flu 40 mg/m^{2x} 3 days	CsA+MTX	9	6.5 (1.5-9)	8/9 engraftment	78% (patients)	Pulm hemorrhage=1 Unrelated marrowdonors
Jaing et al {88}	BU 14 mg/kg CY 200 mg/kg	CsA+MP	5	11.1 -13.1 yr)	100% engraftment by UCB		1 Late graft failure 4 patients with 2-4 loci mismatch 1 patient with 6/6 match
Adamkiewicz et al {89}	BU 640 mg/m^2 CY 200 mg/kg ATG 30 mg/kg 3 patients got various combinations RIC	CsA+MP (n=2) CsA+MMF (1) CsA+MMF+MP Tac+MP (n=2) Tac+MMF (n=1)	7		3/7 curative (43%)		Unrelated UCB for SCD HLA 4/6 (n=5) HLA 5/6 (n=2)
Zhu WG {102}	BU 16 mg/kg CY 200 mg/kg ATG 90mg/kg Fludarabine	CsA+MTX	2				

NONMYELOABLATIVE HSCT AND REDUCED INTENSITY CONDITIONING

Myeloablation for the eradication of host hematopoiesis and host immunosuppression has been considered to "create space" in the host marrow and the prevention of immunologic rejection of the graft, respectively. Allogeneic marrow can create its own "space" by a local graft versus host reaction after a Nonmyeloablative preparative regime.[69-83] But the regime related toxicity (RRT) has been the major limiting factor in the trend for a less toxic preparative regime. Nonmyeloablative regimes do not cause eradication of host erythropoiesis and allow hematopoietic recovery without infusion of donor stem cells whereas regimes causing some myeloablation and requiring donor stem cells for recovery are termed as reduced intensity conditioning.[79] Fludarabine, a purine analog is the backbone of most of the nonmyeloablative preparative regimens used. Sauer et al have showed 100 percent engraftment and minimal RRT using Fludarabine, ATG, Busulfan.[65]

MATCHED UMBILICAL CORD BLOOD FROM SIBLING AS STEM CELL SOURCE FOR HSCT

Recently, 44 patients with hemoglobinopathies (33 Thalassemia, 11 SCD) received an umbilical cord blood (UCB) transplantation from a sibling.[22] Forty one UCB donors were HLA matched, and 3 had 1 HLA-A difference. The 2 year OS and EFS were 100% and 81%, respectively. Remote-site collection and directed-donor banking of UCB for sibling recipients with malignancy, SCD, Thalassemia major, non-malignant hematological conditions, and metabolic errors has been accomplished with a high success rate. Sixteen of 17 UCB allograft recipients had stable engraftment of donor cells.[84] The Sibling Donor Cord Blood (SDCB) Program has helped in transplantation of 14 patients of Thalassemia major with HLA matched UCB, of which 11 are free of disease.[85] Thus it is important to emphasize the role of cord blood banking which offers an alternative source of hematopoietic stem cells.

HSCT FROM UNRELATED DONORS

While young patients without advanced disease who have received HCT from a matched sibling, have an excellent outcome, the applicability of HSCT for these conditions is limited by the fact that fewer than one third of these patients will find a suitable human leukocyte antigen (HLA) matched related or family donor.[86] Worldwide experience (Table 4) in unrelated donor transplantation for Hemoglobinopathies is limited because in the past, HSCT from unrelated donors (URD) has not been offered to patients with hemoglobinopathies. LaNasa et al have reported results in 68 patients indicating an OS of 79.3% and DFS of 65.8%[87] while Hongeng et al have reported 21 patients indicating an OS of 71% and DFS of 71%. Unrelated UCBT can lead to stable engraftement and amelioration of clinical phenotype but engraftment, GVHD and infections remain the challenges.[88-90]

Since these diseases may be associated with prolonged survival, the increased regimen related toxicity (RRT) of URD HCT was considered unacceptable. The world-wide number of alternative donor transplants for hemoglobinopathies remains limited to date.[15, 91-95] The advent of novel strategies for reduction of RRT, including the use of nonmyeloablative preparative regimens[96, 97] and the improvement in outcomes of URD HCT[98] has sparked fresh interest in the consideration of URD HCT for patients with Hemoglobinopathies. A study in north Indian population shows that they have unique HLA haplotypes and possibility of finding a matched sibling is further decreased.[99] Efforts are ongoing to establish bone marrow donor registries in India.

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