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Allogeneic stem cell transplantation for thalassemia major in India

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ABSTRACT

Allogeneic stem cell transplantation (allo-SCT) is the only currently available curative treatment for thalassemia major. Since it was first done in 1981, several thousand patients have benefited from it and it is now possible to offer this treatment in different parts of the world with good results. With better risk stratification and supportive care, the results of allo-SCT are now very good even in high risk patients who have significant iron overload related organ dysfunction. The improvements have mainly been in the conditioning strategies with less toxic myeloablation and management of the complications of SCT. However, several challenges remain. Transplant related complications still cause significant morbidity and mortality. There is data to show that the results of transplantation as best if done in well transfused and chelated patients <7 years of age. As only a third of the patients will have a matched related donor, there is need for investigating SCT with alternative donors. Experience with SCT for thalassemia major from matched unrelated donors or haplo-identical donors is still limited but needs further exploration. Adequate management needs to be provided post-SCT for all pre-existing complications particularly iron chelation to prevent further organ dysfunction. Systematic follow-up is needed to measure long term outcomes. The biggest challenges in India are the cost of this treatment and access to centres capable of providing this treatment. With greater support from the government, health insurance and philanthropic programs, there has been a rapid increase in the number of SCTs for thalassemia major in India. The number centres providing this treatment are also increasing making this curative treatment more widely available in India.

1. Introduction

Recent advances in gene therapy for hemoglobinopathies could potentially be a paradigm change in the management of these disorders. Currently however, an allogeneic stem cell transplant (allo-SCT) remains the only curative option for the majority of patients with β thalassemia major. The use of allo-SCT is rapidly increasing in India and other developing countries and is hence the most widely available and accessible curative therapeutic strategy for this condition. The central concept revolves around the ability to replace the hematopoietic stem cells (HSC) from a donor to a recipient resulting in a new donor derived hematopoietic system in the recipient. Significant advances over the last two decades have resulted in a steady improvement in clinical outcomes for patients with this disorder undergoing such a procedure. Currently in patients with good risk features it is reasonable to anticipate a greater than 90% chance of a successful transplant outcome [1]. Even among those with high risk features, success rates are approaching 80%. These improvements have resulted from use of better risk stratified conditioning regimen and more effective supportive care [1,2].

With thalassemia being a significant public health problem in the country, there is great need for effective transplant programs. Absence of suitable donors, cost of treatment and lack of enough centers capable of offering this therapy are major challenges preventing wider use of this therapy. With increase in the donor pool by the use of matched unrelated donors, cord blood stem cells and haplo-identical donors, more patients can access this curative therapy. Experience with alternate donor transplants for

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thalassemia major is gradually increasing and their results are also getting better. However, more experience is required with these transplants before they can be considered standard of care. Better understanding of graft characteristics and immune re-constitution post-transplant has the potential to identify interventions to further improve the short and long term clinical outcomes. There is limited data on the role of splenectomy prior to transplant or optimal post-transplant chelation and care of these patients. These are some of the issues that will be briefly addressed in this review along with a description of the situation with HSCT for thalassemia in India.

2. Risk of graft rejection and regimen related toxicity (RRT) in high risk populations

Risk stratification of patients with β thalassemia major undergoing a myelo-ablative allogeneic (SCT) classifies them into three risk groups (Pesaro Class I, II and III) based on liver size (>2 cm), presence of liver fibrosis and inadequate iron chelation [3,4]. Patients with none of the above risk factors are classified as Class I, those with one or two of these risk factors are Class II while those patients who have all three adverse risk factors are classified as Class III. Patients in Class I and II our considered to be low risk and have an excellent long term outcome following an allogeneic SCT [3,4]. Class III patients on the other hand are considered high risk and have inferior outcomes following a SCT. However, in a population with poor medical treatment prior to SCT, the above risk stratification is limited by its failure to recognize [2] the significant heterogeneity among patients in Class III. The Pesaro risk stratification [3,4] does not recognize a very high risk subset of Class III in these populations perhaps because such patients hardly exist in Western countries. With allo-SCT being increasingly offered in many developing countries where this category of patients exist in large numbers, recognizing this high risk group is extremely important to suitably modify their HSCT protocols [2,5,6].

Retrospective analysis of factors impacting clinical outcome on large data set from our center done in 2007, helped us to identify age ≥7 years old and had a liver size ≥5 cm in a patient pre-transplant to constitute what has been shown to be a very high risk subset of a conventional Class III group (Class III Vellore high risk or Class III VHR) [2]. The adverse impact of age (≥7 years) and liver size (>2 cms) was further validated by an international collaborative analysis in 2010 [7]. The significance of this differentiation has been emphasized by the fact that outcomes of HSCT were clearly different in these two groups when treated with the same protocols. Class III and more specifically Class III Vellore high risk [8] subset have a high risk of graft rejection and regimen related toxicity (RRT), especially sinusoidal obstruction syndrome (SOS) leading to multi-organ failure and death. These complications are perhaps related to the high degree of allo-immunization and iron over load related end organ damage in this cohort. The poor clinical outcome in this subset of older patients with very poor pre-transplant medical therapy, as reported previously, is not reflected in the Western literature as such patients are distinctly uncommon there. However, when such a population is transplanted even in a developed country with expertise in such transplants the rejection rate is as high as 34% [9].

3. Challenges to select conditioning regimen: reducing graft rejection and RRT

At our center we evaluated two different regimens of busulfan to see their effect on graft rejection, we also added anti-lymphocyte globulin in one of them to see its effect on graft rejection and GVHD [10]. While we did succeed in demonstrating an association with graft rejection and busulfan pharmacokinetics we were not able to see any effect of anti-lymphocyte globulin in this study on graft rejection or GVHD (data not shown for GVHD), we were also not able to address the relatively high incidence of RRT in this population [10]. The increased incidence of RRT, particularly in the high risk patients with thalassemia major, has led to the evaluation of a number of novel conditioning regimens to improve the clinical outcome among these patients [3,4,11–16] (summarized in Table 1). Early efforts to reduce the RRT among Class III patients involved reducing the cumulative dose of cyclophosphamide from 200 mg/kg to 160 mg/kg[13]. While this approach did significantly reduce the RRT associated mortality it was also associated with an increased incidence of graft rejections (from 13% to 35%) [13]. An increased risk of graft rejections was noted in all subsequent attempts at reduced intensity conditioning regimens to reduce RRT [17,18] and hence for the most part such an approach has been abandoned as an option in patients with transfusion dependent hemoglobinopathies such as Thalassemia major. The first successful attempt at improving clinical outcomes in Class III patients by modifying the conditioning regimen was reported by Sodani et al. [12]. They used the same template of reducing the cyclophosphamide dosing to 160 mg/kg but based on their initial adverse experience with this approach augmented the immune-suppression by adding fludarabine and azathioprine to the conditioning regimen. Additional elements starting from day −45 included intensive chelation and hyper-transfusion therapy along with hydroxyurea and growth factors. They achieved <10% graft rejection with a >85% event free survival in a relatively small series of 33 consecutive Class III patients. There have been no subsequent series from the same or other centers that have replicated these results. Intravenous busulfan along with therapeutic dose monitoring and dose modifications was a promising strategy to reduce RRT and potentially reduce the risk of graft rejection as illustrated in the study by Gaziev et al. [19]. However, as demonstrated in the study by Chiesa et al. this approach while effective in reducing RRT was not able to reduce the risk of graft rejection in patients with very high risk thalassemia major [9]. More recently, Anurathapan et al. reported a novel approach of administration of one or two courses of immune-suppressive therapy with a combination of fludarabine and dexamethasone one to two months prior to start of conditioning and followed this up with a reduced toxicity myelo-ablative conditioning regimen consisting of fludarabine, intravenous busulfan and anti-thymocyte globulin with promising results in another small series of 18 patients with Class III VHR thalassemia major [20]. The caveat to interpretation of the above studies is that the proportion of Class III patients varies and the subset of patients who would fulfill the criteria for Class III VHR is often not available. These variables, especially the proportion in Class III VHR would significantly impact the clinical outcome and make comparison across different studies difficult unless they are clearly identified in all reports.

4. Novel conditioning regimen

Treosulfan (dihydroxy-busulfan), in the recent past, has attracted a lot of attention as an agent to replace busulfan in view of its favorable toxicity profile [21]. While treosulfan is structurally similar to busulfan, unlike busulfan it is water soluble and easy to reconstitute and administer intravenously. It also has a linear pharmacokinetic profile but with large intra and inter individual variability in pharmacokinetic profile of nearly 30 fold [22,23]. However, again unlike busulfan, it has a huge therapeutic window because in Phase I studies at even at cumulative doses of 56 gm/m^2 (a dose not usually reached when used as an agent in conditioning regimens) there were no dose limiting hepatic, renal, neurological

Table 1
Major reported clinical studies that have attempted to improve the outcome of patients with Class III thalassemia major.

	Year	N	Median Age (yrs)/ (range)	Proportion in Class III (%)	Proportion in Class III VHR[d] (%)	Major defining feature of change in protocol	Treatment related mortality (%)	Graft rejection (%)	EFS (%)	OS (%)
Lucarelli et al. [13][a]	1996	115	11(3–16)	100	NA	Reduction in cumulative cyclophosphamide from 200 mg/kg to 160 mg/kg	24	35	49	74
Sodani et al. [12]	2004	33	11(5–16)	100	NA	Reduction in cyclophosphamide dose to ≤160 mg/kg. Addition of azathioprine and fludarabine and intensification of immunosupression. Suppression of erythropoesis by hyeprtransfusion, chelation and hydroxyurea starting from day −45	6	6	85	93
Gaziev et al. [19]	2010	71	9(1.6–27)	57.3	NA	Intravenous busulfan, dose adjustments with therapeutic drug monitoring	7	5	87	91
Chiesa et al. [9]	2010	53	8(1–17)	47	NA	Intravenous busulfan, dose adjustments with therapeutic drug monitoring	4	15	79	96
Chiesa et al. [9][c]	2010	25	NA	100	NA	Intravenous busulfan, dose adjustments with therapeutic drug monitoring	4	34	66	96
Bernardo et al. [30]	2012	60	7(1–37)	27[e]	NA	Treosulfan based conditioning regimen	7	9	84	93
Li et al[ne] [15]	2012	82	6 (0.5–15)	NA	NA	Conditioning with age adjusted PK based IV Bu, Cy (110 mg/kg), high dose Flu (200 mg/kg), Thiotepa. Additional therapy from day −45 with immunosuppression with Azt and suppression of erythropoiesis withHU	8.5[e]	4[e]	88[e]	91[e]
Choudhary et al. [31]	2013	28	9.6(2–18)	75	39	Treosulfan based conditioning regimen	21	7	71	79
Anurathapan et al. [20]	2013	18	14(10 –18)	100	NA	Pre-conditioning immunosuppression therapy with Fludarabine and dexamethasone; one or two courses one to two months prior to transplant. Conditioning regimen of fludarabine with intravenous busulfan	5	0	89	89
Mathews et al. [28]	2013	50	11(2–21)	100	48	Treosulfan based conditioning regimen with PBSC graft in 74%	12	8	79	87
Mathews et al. [28][b]	2013[b]	24	12(3–21)	100	100	Treosulfan based conditioning regimen with PBSC graft in 74%	13	8	78	87
Gaziev et al. [16]	2016	37	10 (5–17)	100	NA	As in Sodani et al. [22] but with higher dose of Fludarabine (150 mg/kg) and addition of Thiotepa(10 mg/kg)	8	0	92	92

[a] Only patients <17 years included in this table.
[b] Subset of high risk cases from same paper.
[c] Subset of high risk cases from same paper.
[d] As defined previously [2].
[e] Includes all adult cases as well (assumed to be Class III).

or cardiac toxicity [24]. Hepatic sinusoidal obstruction syndrome (SOS) which is a common problem with a conventional busulfan based myelo-ablative regimens with an incidence ranging from 5 to 40% [25] occurs only infrequently with treosulfan. Use of a busulfan based conditioning regimens was associated with an increased incidence of SOS on a multivariate analysis in a prospective study [26]. Similarly the link between iron overload pre-transplant and SOS is well recognized [27]. Targeted busulfan levels and prophylaxis with defibrotide have significantly reduced this complication in patients with thalassemia major [9,25]. These interventions are expensive or not available to the majority of centers doing allo-SCT for thalassemia major in developing countries. In the absence of such interventions, the cumulative incidence of SOS in the very high risk subset (Class III VHR) of patients has been reported to be as high as 78% and in 24% of such cases it lead to multi-organ failure and death [28]. For these reasons treosulfan, with its large therapeutic window, is especially attractive in the context of an allo-SCT for high risk β thalassemia major because of its reported low hepatic toxicity profile even at myeloablative doses which was a significant problem with conventional busulfan in this population [2,10,29]. It is important to recognize that the pharmacokinetic profile treosulfan based regimens both in patients with thalassemia major and when it is combined with other high dose chemotherapeutic agents as part of the conditioning regimen have not been studied extensively.

4.1. Current data using treosulfan based conditioning regimen

The first report on the use of treosulfan being used as part of the conditioning regimen for thalassemia, in a small series of 20 patients of which 45% were Class III and 18 were matched unrelated stem cell transplants, was by Bernado et al. [14]. Only two patients in this series developed transient liver enzyme elevation. The conditioning consisted in addition thiotepa and fludarabine and was very well tolerated and 17 cases had complete chimerism. Recently, the same group reported on their expanded experience with this reduced toxicity myelo-ablative regimen [30]. In this expanded series of 60 cases with thalassemia major the median age was 7 years, though only 7% of the 48 children were Class III and the remaining 12 were adults. 40 (67%) of the patients received an unrelated donor transplant and in 47 (79%) the stem cell source was a bone marrow. The regimen as previously reported was very well tolerated with a low (<10% graft failure) and a thalassemia free survival of 84%. In contrast to this favorable experience a small series reported a comparable outcome between a similar treosulfan based (n = 28) and a historical busulfan based regimen (n = 12)[31]. However, the median age in the busulfan group was 7 years versus 9.6 years in the treosulfan group and the treosulfan group had 75% Class III patient of whom 52.4% were Class III VHR as defined previously. In the busulfan arm 58% were Class III and the number that fulfilled the criteria of Class III VHR is not available. The age and risk group of the patients in the treosulfan arm that died due to RRT (n = 4) and those that had a graft rejection (n = 2) is not available. As reported previously the outcome of Class III VHR can be significantly different from Class III as a whole [2]. Interpreting this data and comparing the two groups without this information must be done with caution, more so because of the small numbers in both groups. It is possible that the inferior outcome in the treosulfan arm

is related more to the biology of Class III in which a greater proportion of cases were Class IIIVHR rather than the impact of conditioning regimen.

4.2. High risk population: balancing early vs. late complications

In a larger series, from the authors center, a clear advantage of a treosulfan based regimen on the clinical outcome of Class III as a whole and the subset of Class III VHR was recently reported [28]. A significant reduction in non-relapse mortality and RRT, especially SOS was demonstrated in the Class III VHR in comparison to a historical control arm that had used a conventional busulfan based conditioning regimen [28]. It was also noted that in this very high risk group there was a significantly increased risk of mixed chimerism which could be overcome with the use of a peripheral blood stem cell graft (PBSC). The use of this regimen with a PBSC graft translated to a significantly superior overall and event free survival in the Class III VHR subset without a significant increased risk of graft versus host disease (GVHD) [28].

In summary a treosulfan based conditioning regimen is ideally suited for patients with thalassemia major including very high risk patients. The low hepatic and other toxicity profile over a wide range of AUCs obviates the need for drug dose monitoring and makes this an attractive agent to use in the conditioning regimen. It is highly likely that treosulfan will replace busulfan as the drug of choice in the conditioning regimen for transfusion dependent hemoglobinopathies in the future. With only one manufacturer in the world at present of treosulfan, its cost amounting to nearly a quarter of the total cost of the HSCT, is a major restrictive factor in its widespread use in our country and possibly other developing nations with a similar costing stricture for allo-SCT. With a new generic product receiving market authorization in India, this limitation should soon be addressed to a significant extent. As SCT becomes more widely used in patients with thalassemia major, there will be a great need for controlled trials to evaluate the effectiveness of specific treatment regimens for specific groups of patients.

5. Bone marrow versus peripheral blood stem cell grafts

Bone marrow (BM) has been the preferred choice of stem cells in non-malignant hematological disorders to reduce the risk of GVHD, though the incidence of both acute and chronic GVHD in this predominantly pediatric population is low [10,32]. Peripheral blood stem cell grafts (PBSC) when used have been reported to be associated with faster engraftment and lower requirement of blood product support in the peri-transplant period [28,33,34] and have also been associated with a low incidence of graft rejection [11,34]. However, the risk of chronic GVHD is increased [28,33,34]. Our experience of using a PBSC graft with a treosulfan based regimen to overcome early mixed chimerism and potential graft failure remains to be validated in larger studies. Larger prospective studies are required to confirm the benefit of PBSC over BM in thalassemia major in Class III patients receiving treosulfan based conditioning. The current consensus, however, is that a BM graft should be used as far as possible for non-malignant conditions to reduce the risk of GVHD.

6. Alternate donor sources

6.1. Matched unrelated stem cell transplants

Unfortunately, only about a third of patients with thalassemia major have a HLA matched sibling donor which limits the utility of an allo-SCT. Use of a matched unrelated donor (MUD) SCT has the potential to overcome this. The initial results with this approach, prior to the advent of high resolution HLA typing, were dismal with a 55% graft rejection [35]. Since then, there has been significant improvement in MUD SCT with high resolution molecular HLA typing becoming standard in MUD selection. Outcome in malignant disorders with MUD is now comparable to that of HLA matched sibling transplants. More recent data suggests that OS of 79% can be achieved with this approach with TFS of 66% and a 25% chance of TRM [36]. This study also suggested that an extended haplotype match was associated with a superior outcome. The overall data would suggest that MUD SCT should only be considered in centers that have reasonable experience with this approach and is best limited to low risk patients at present. High resolution HLA typing with a full (10 of 10) match is the preferred donor and in addition they should ideally not have HLA-DP1 mismatches in the direction favoring graft rejection [37].

6.2. Cord blood transplants

Cord blood transplants over the last decade have been the most rapidly growing source of stem cells for allogeneic SCT. However, for patients with thalassemia major there is limited data. Using cord blood stem cells for allogeneic SCT in thalassemia major must be considered under two categories, which are distinctly different in terms of clinical outcome:

1. Related cord blood transplant: when a HLA matched or partly mismatched sibling is the source of stem cells
2. Unrelated cord blood transplant: when an unrelated cord blood product is procured from a cord blood bank as part of donor search for an allogeneic SCT. There could be varying degrees of HLA mismatch.

Using related cord blood the Eurocord Transplant Group reported a 2 year probability of EFS of 79% in 33 patients with thalassemia. There was a 21% (7 rejections) risk of rejection of the graft, in spite of none of the patients being Class III, in fact 20(61%) of the patients were Class I [38]. A few smaller series have reported lower rejection rates but the numbers are small [39,40]. A large series recently reported by Eurocord and EBMT demonstrated comparative clinical outcomes with bone marrow and a fully HLA matched related cord [41]. However, in this report it is important to note that of the 96 related HLA cord blood transplants only 2 patients were Class III while the rest (96%) were Class I (61%) or II (35%) and in spite of this statistically significantly higher proportion of Class I cases in the related cord blood arm the graft rejections were higher at 10.4%. This data cannot and should not be extrapolated to populations where the majority of patients are Class III where we would err on waiting for two years and do a regular bone marrow harvest and stem cell transplant from the same donor without this increased risk of graft rejection. The proposed reduction in acute GVHD from approximately 20%–10% with the related cord blood transplant must be tempered by the fact that only 2% of patients in the bone marrow arm developed Grade 4 GVHD [41]. There is a theoretically reduced risk of GVHD and more importantly less donor discomfort if one were to do a related donor cord blood transplant.

Unrelated cord blood transplant genuinely increases the potential pool of donors for patients with thalassemia major. Unfortunately the published data is limited. In a recent review over 6 studies a total of 19 patients were reported [42]. After combining data from three different registries, Ruggeri et al. reported in 2011, that the cumulative graft failure rate was an unacceptable 52% [43]. At this time point one cannot recommend an unrelated cord blood transplant outside the setting of a clinical trial particularly with

increasing possibilities of haplo-identical related donor transplants. The cost of unrelated cord blood grafts can also be a significant limitation.

6.3. Haplo-identical stem cell transplants

There is a lot of interest in haplo-identical stem cell transplants in the world over the last few years. Novel conditioning and GVHD prophylaxis regimens have resulted in dramatic improvements in clinical outcome even without T cell depletion of the graft. There is however very limited data in thalassemia major. In one small series ($n = 22$) using T cell depletion grafts the graft rejection rate was 27% and the TFS about 67%. More recently the use of grafts with depletion of CD3αβ T cells looks promising with a few successful reports [44]. In a disease where several management options exist and newer ones are on the horizon, whether a treatment option that gives less than ~80% TFS can or should be recommended needs further discussion. Haplo-identical SCT therefore cannot be recommended at this time outside the setting of a clinical trial.

7. Stem cell dose and immune re-constitution post-transplant and its impact on clinical outcomes

Given the high rate of rejection in all HSCT for thalassemia major, at our center we had prospectively evaluated bone marrow graft cellular subsets and patterns of immune reconstitution in cohort of 63 consecutive thalassemia major patients who underwent a HLA matched sibling allogeneic SCT [32]. Data from this analysis suggests that in this cohort of patients, increasing the stem cell dose reduces the risk of post-transplant bacterial and fungal infections. We hypothesize that faster immunologic recovery occurs with higher CD34 cell doses and, consequently, diminishes the risk of bacterial and fungal infections as observed in a previous report [45]. We were however not able to demonstrate a correlation in speed of recovery of any specific cellular subset in relationship to the stem cell dose. We also noted that patients in the highest quartile of the stem cell dose did not have an increased risk of acute or chronic GVHD (data not shown). While the number of events is few and the cohort studied small, it would still be reasonable in future, based on the available data, to target a CD34 cell dose of $7–9 \times 10^6$/Kg. At these doses, our data would suggest that there should be a significant reduction in post-transplant without an increased risk of GVHD [32]. We also noted an association with the day 28 NK cell count recovery and graft rejection. Patients who achieved less than the median level on day 28 post-transplant were significantly more likely to have secondary graft rejection [31]. More data is required on these aspects of the graft and subsequent immune reconstitution before any definitive conclusions can be drawn but these are certainly areas to be explored further to incrementally improve outcome of allo HSCT for thalassemia major. We also had a subset of cases that had a G-CSF primed bone marrow product, this approach was used for a period of time at our center based on some preliminary data that suggested the potential benefit of such an approach, however as illustrated in our analysis we could not demonstrate any benefit for such an approach over a standard non-primed bone marrow product [32].

8. Role of pre-transplant splenectomy

Massive splenomegaly in patients with β thalassemia major is often a reflection of inadequate medical care and/or advanced disease and is often seen in Class III patients [46]. It is associated with increased blood transfusion requirement [47]. Splenectomy is conventionally indicated when the transfusion requirement exceeds 220 ml PRBC/kg/year [47]. Splenectomy is also indicated if there is significant abdominal discomfort, splenic infarction or symptomatic hypersplenism [47].

Presence of splenomegaly prior to a SCT raises the theoretical concern of sequestration of infused stem cells which could potentially have an adverse impact on engraftment. Splenectomy prior to a SCT could alter engraftment kinetics which in turn could have an impact on graft tolerance and development of GVHD [48]. Splenectomy prior to an allogeneic SCT has the theoretical potential of reducing peri-transplant transfusion requirement and hastening engraftment [49].

Splenectomy in patients with β thalassemia major is also considered a surrogate marker of high risk disease, since it is often performed in older patients or in those who have had inadequate medical care. Splenectomy is reported to be associated with increased risk of pulmonary hypertension [8], progressive restrictive pulmonary disease [8] and alteration in hemostatic parameters that favor thrombosis [50–52]. It has also been reported to be associated with an increased risk of infections [53]. All the above factors could contribute to an adverse outcome following an allogeneic SCT.

In a retrospective analysis done at our center we evaluated the impact of pre-transplant splenectomy on clinical outcomes [54]. Our analysis would suggest that though pre-transplant splenectomy among patients with thalassemia major was associated with faster engraftment and reduced transfusion support it did not translate to an improved TFS or OS due to the higher RRT and peri-transplant infection related deaths in the splenectomized group. On multivariate analysis splenectomy was not an independent adverse factor and its perceived adverse effect on survival was probably due to its association with other adverse features such as older age group and inadequate medical therapy prior to transplant. We could not demonstrate any significant beneficial effect that would warrant considering this procedure routinely prior to transplant [54,55].

9. Post-transplant care and management of iron overload

The iron overload state continues to require attention post transplantation. Post a successful transplant, provided the patients is stable and the Hb is above 100 g/L, the preferred method of iron removal is phlebotomy. It can be repeated once in 14–28 days and a volume of 6–8 ml/kg can be removed in one sitting [56]. If the child is too small with difficult venous access or the hemoglobin level is not adequate or if phlebotomy is not possible even in older children then the patient should be started on chelation therapy. It should be continued (maybe required for years) till the ferritin level is < 100 ng/ml. The optimal pharmacological agent(s) and chelation regimen post-transplant remains to be defined. In addition to iron chelation, these patients need close attention to immunization, endocrine and organ dysfunction secondary to iron overload. All these need to be adequately evaluated and managed through a multidisciplinary team post allo- SCT. This is also a good reason why allo-SCTs should be done at younger age, between 2 and 5 years, well before any end organ damage occurs in these patients so that there are no sequelae of the disease after a successful allo-SCT and these children can then grow up to live normally.

10. HSCT for thalassemia major in India

Since the first allo HSCT for thalassemia major in India in 1991, data from the Indian Stem Cell Transplant Registry shows that the number of centers that offer this treatment has increased significantly to about 35. However, most of these centers perform only a small number of these transplants so that the annual number transplants being done in the country remains relatively small at

about 250. Given that nearly 10,000 children are still born with thalassemia major every year in the absence of an effective control program, there is need to enhance this number rapidly while also taking steps to initiate a thalassemia prevention program. Economic reasons are a major barrier to larger numbers of these transplants being done. Recently, the Ministry of Health of the Union Government has initiated a program to fund an additional 200–300 allo-SCTs for thalassemia major in the country. This funds are provided by one of the public sector undertakings of the Union Government, the Coal India Limited, under its corporate social responsibility program. Currently, this program is limited to four HSCT centres in the country – Christian Medical College, Vellore; All India Institute of Medical Sciences, New Delhi; Tata Medical Centre, Kolkata and the Rajiv Gandhi Cancer Hospital, New Delhi. If successful, this will be expanded to include several more centres and that would be a major boost to increasing access to this treatment in the country. It could become a new model for supporting management of other such treatable genetic disorders.

11. Conclusion

Significant progress has been made in the understanding of allogeneic stem cell transplant for thalassemia major with regards to risk stratification, optimal conditioning regimens, alternative stem cell sources and this has translated to improved outcomes for patients. These have translated to a steady improvement in clinical outcomes. However, there are limitations as to which of these advances can be readily translated to the larger worldwide community. The major constraints are the lack of awareness, trained personnel and the infrastructure for allo-SCTs as well as the cost of therapy. As a result, allo-SCT is an option available to only to a small fraction of patients. Therefore, apart from efforts to improve transplant protocols and expand donor options, major attention also needs to be given to factors which limit access of more patients to this well-established therapy.

References

[1] Mathews V, Srivastava A, Chandy M. Allogeneic stem cell transplantation for thalassemia major. Hematol Oncol Clin N Am 2014;28(6):1187–200. https://doi.org/10.1016/j.hoc.2014.08.009.

[2] Mathews V, George B, Deotare U, Lakshmi KM, Viswabandya A, Daniel D, et al. A new stratification strategy that identifies a subset of class III patients with an adverse prognosis among children with beta thalassemia major undergoing a matched related allogeneic stem cell transplantation. Biol Blood Marrow Transplant 2007;13(8):889–94. https://doi.org/10.1016/j.bbmt.2007.05.004. e-pub ahead of print 2007/07/21; S1083-8791(07)00276-5 [pii].

[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(7):417–21. https://doi.org/10.1056/NEJM199002153220701. e-pub ahead of print 1990/02/15.

[4] Lucarelli G, Galimberti M, Polchi P, Angelucci E, Baronciani D, Durazzi SM, et al. Bone marrow transplantation in adult thalassemia. Blood 1992;80(6):1603–7. e-pub ahead of print 1992/09/15.

[5] Hongeng S, Pakakasama S, Chuansumrit A, Sirachainan N, Kitpoka P, Udomsubpayakul U, et al. Outcomes of transplantation with related- and unrelated-donor stem cells in children with severe thalassemia. Biol Blood Marrow Transplant 2006;12(6):683–7. https://doi.org/10.1016/j.bbmt.2006.02.008. e-pub ahead of print 2006/06/02; S1083-8791(06)00181-9 [pii].

[6] Fang JP, Xu LH. Hematopoietic stem cell transplantation for children with thalassemia major in China. Pediatr Blood Canc 2010;55(6):1062–5. https://doi.org/10.1002/pbc.22742. e-pub ahead of print 2010/10/28.

[7] Sabloff M, Chandy M, Wang Z, Logan BR, Ghavamzadeh A, Li CK, et al. HLA-matched sibling bone marrow transplantation for beta-thalassemia major. Blood 2010;117(5):1745–50. https://doi.org/10.1182/blood-2010-09-306829. e-pub ahead of print 2010/12/02; blood-2010-09-306829 [pii].

[8] Phrommintikul A, Sukonthasarn A, Kanjanavanit R, Nawarawong W. Splenectomy: a strong risk factor for pulmonary hypertension in patients with thalassaemia. Heart 2006;92(10):1467–72. https://doi.org/10.1136/hrt.2005.079970.

[9] Chiesa R, Cappelli B, Crocchiolo R, Frugnoli I, Biral E, Noe A, et al. Unpredictability of intravenous busulfan pharmacokinetics in children undergoing hematopoietic stem cell transplantation for advanced beta thalassemia: limited toxicity with a dose-adjustment policy. Biol Blood Marrow Transplant 2010;16(5):622–8. https://doi.org/10.1016/j.bbmt.2009.11.024. e-pub ahead of print 2009/12/08; S1083-8791(09)00584-9 [pii].

[10] Chandy M, Balasubramanian P, Ramachandran SV, Mathews V, George B, Dennison D, et al. Randomized trial of two different conditioning regimens for bone marrow transplantation in thalassemia–the role of busulfan pharmacokinetics in determining outcome. Bone Marrow Transplant 2005;36(10):839–45. https://doi.org/10.1038/sj.bmt.1705151. e-pub ahead of print 2005/09/10; 1705151 [pii].

[11] Lawson SE, Roberts IA, Amrolia P, Dokal I, Szydlo R, Darbyshire PJ. Bone marrow transplantation for beta-thalassaemia major: the UK experience in two paediatric centres. Br J Haematol 2003;120(2):289–95. e-pub ahead of print 2003/01/25; doi: 4065 [pii].

[12] Sodani P, Gaziev D, Polchi P, Erer B, Giardini C, Angelucci E, et al. New approach for bone marrow transplantation in patients with class 3 thalassemia aged younger than 17 years. Blood 2004;104(4):1201–3. https://doi.org/10.1182/blood-2003-08-2800. e-pub ahead of print 2004/03/25; 2003-08-2800 [pii].

[13] Lucarelli G, Clift RA, Galimberti M, Polchi P, Angelucci E, Baronciani D, et al. Marrow transplantation for patients with thalassemia: results in class 3 patients. Blood 1996;87(5). 2082-2088. e-pub ahead of print 1996/03/01.

[14] Bernardo ME, Zecca M, Piras E, Vacca A, Giorgiani G, Cugno C, et al. Treosulfan-based conditioning regimen for allogeneic haematopoietic stem cell transplantation in patients with thalassaemia major. Br J Haematol 2008;143(4):548–51. https://doi.org/10.1111/j.1365-2141.2008.07385.x. e-pub ahead of print 2008/11/07; BJH7385 [pii].

[15] Li C, Wu X, Feng X, He Y, Liu H, Pei F, et al. A novel conditioning regimen improves outcomes in beta-thalassemia major patients using unrelated donor peripheral blood stem cell transplantation. Blood 2012;120(19):3875–81. https://doi.org/10.1182/blood-2012-03-417998.

[16] Gaziev J, Isgro A, Sodani P, Marziali M, Paciaroni K, Gallucci C, et al. Optimal outcomes in young class 3 patients with thalassemia undergoing HLA-identical sibling bone marrow transplantation. Transplantation 2016;100(4):925–32. https://doi.org/10.1097/TP.0000000000000928.

[17] Iannone R, Casella JF, Fuchs EJ, Chen AR, Jones RJ, Woolfrey A, et al. Results of minimally toxic nonmyeloablative transplantation in patients with sickle cell anemia and beta-thalassemia. Biol Blood Marrow Transplant 2003;9(8):519–28. e-pub ahead of print 2003/08/22; doi: S1083879103001927 [pii].

[18] Horan JT, Liesveld JL, Fenton P, Blumberg N, Walters MC. Hematopoietic stem cell transplantation for multiply transfused patients with sickle cell disease and thalassemia after low-dose total body irradiation, fludarabine, and rabbit anti-thymocyte globulin. Bone Marrow Transplant 2005;35(2):171–7. https://doi.org/10.1038/sj.bmt.1704745. e-pub ahead of print 2004/11/09; 1704745 [pii].

[19] Gaziev J, Nguyen L, Puozzo C, Mozzi AF, Casella M, Perrone Donnorso M, et al. Novel pharmacokinetic behavior of intravenous busulfan in children with thalassemia undergoing hematopoietic stem cell transplantation: a prospective evaluation of pharmacokinetic and pharmacodynamic profile with therapeutic drug monitoring. Blood 2010;115(22):4597–604. https://doi.org/10.1182/blood-2010-01-265405. e-pub ahead of print 2010/03/20; blood-2010-01-265405 [pii].

[20] Anurathapan U, Pakakasama S, Rujkijyanont P, Sirachainan N, Songdej D, Chuansumrit A, et al. Pretransplant immunosuppression followed by reduced-toxicity conditioning and stem cell transplantation in high-risk thalassemia: a safe approach to disease control. Biol Blood Marrow Transplant 2013;19(8):1259–62. https://doi.org/10.1016/j.bbmt.2013.04.023. e-pub ahead of print 2013/05/08; S1083-8791(13)00191-2 [pii].

[21] Danylesko I, Shimoni A, Nagler A. Treosulfan-based conditioning before hematopoietic SCT: more than a BU look-alike. Bone Marrow Transplant 2012;47(1):5–14. https://doi.org/10.1038/bmt.2011.88.

[22] Hilger RA, Harstrick A, Eberhardt W, Oberhoff C, Skorzec M, Baumgart J, et al. Clinical pharmacokinetics of intravenous treosulfan in patients with advanced solid tumors. Cancer Chemother Pharmacol 1998;42(2):99–104. e-pub ahead of print 1998/07/08.

[23] Glowka FK, Karazniewicz-Lada M, Grund G, Wrobel T, Wachowiak J. Pharmacokinetics of high-dose i.v. treosulfan in children undergoing treosulfan-based preparative regimen for allogeneic haematopoietic SCT. Bone Marrow Transplant 2008;42(Suppl 2):S67–70. https://doi.org/10.1038/bmt.2008.287. e-pub ahead of print 2008/11/26; bmt2008287 [pii].

[24] Scheulen ME, Hilger RA, Oberhoff C, Casper J, Freund M, Josten KM, et al. Clinical phase I dose escalation and pharmacokinetic study of high-dose chemotherapy with treosulfan and autologous peripheral blood stem cell transplantation in patients with advanced malignancies. Clin Cancer Res 2000;6(11):4209–16. e-pub ahead of print 2000/12/06.

[25] Cappelli B, Chiesa R, Evangelio C, Biffi A, Roccia T, Frugnoli I, et al. Absence of VOD in paediatric thalassaemic HSCT recipients using defibrotide prophylaxis and intravenous Busulphan. Br J Haematol 2009;147(4):554–60. https://doi.org/10.1111/j.1365-2141.2009.07871.x. e-pub ahead of print 2009/09/15; BJH7871 [pii].

[26] Cesaro S, Pillon M, Talenti E, Toffolutti T, Calore E, Tridello G, et al. A prospective survey on incidence, risk factors and therapy of hepatic veno-occlusive disease in children after hematopoietic stem cell transplantation. Haematologica 2005;90(10):1396–404. e-pub ahead of print 2005/10/13.

[27] de Witte T. The role of iron in patients after bone marrow transplantation.

Blood Rev 2008;22(Suppl 2):S22–8. https://doi.org/10.1016/S0268-960X(08)70005-5. e-pub ahead of print 2008/12/17; S0268-960X(08)70005-5 [pii].
[28] Mathews V, George B, Viswabandya A, Abraham A, Ahmed R, Ganapule A, et al. Improved clinical outcomes of high risk beta thalassemia major patients undergoing a HLA matched related allogeneic stem cell transplant with a treosulfan based conditioning regimen and peripheral blood stem cell grafts. PLoS One 2013;8(4):e61637. https://doi.org/10.1371/journal.pone.0061637.
[29] Srivastava A, Poonkuzhali B, Shaji RV, George B, Mathews V, Chandy M, et al. Glutathione S-transferase M1 polymorphism: a risk factor for hepatic venoocclusive disease in bone marrow transplantation. Blood 2004;104(5):1574–7. https://doi.org/10.1182/blood-2003-11-3778. e-pub ahead of print 2004/05/15; 2003-11-3778 [pii].
[30] Bernardo ME, Piras E, Vacca A, Giorgiani G, Zecca M, Bertaina A, et al. Allogeneic hematopoietic stem cell transplantation in thalassemia major: results of a reduced-toxicity conditioning regimen based on the use of treosulfan. Blood 2012;120(2):473–6. https://doi.org/10.1182/blood-2012-04-423822.
[31] Choudhary D, Sharma SK, Gupta N, Kharya G, Pavecha P, Handoo A, et al. Treosulfan-thiotepa-fludarabine-based conditioning regimen for allogeneic transplantation in patients with thalassemia major: a single-center experience from north India. Biol Blood Marrow Transplant 2012;19(3):492–5. https://doi.org/10.1016/j.bbmt.2012.11.007. e-pub ahead of print 2012/11/20; S1083-8791(12)00480-6 [pii].
[32] Rajasekar R, Mathews V, Lakshmi KM, George B, Viswabandya A, Chandy M, et al. Cellular immune reconstitution and its impact on clinical outcome in children with beta thalassemia major undergoing a matched related myeloablative allogeneic bone marrow transplant. Biol Blood Marrow Transplant 2009;15(5):597–609. https://doi.org/10.1016/j.bbmt.2009.01.016. e-pub ahead of print 2009/04/14; S1083-8791(09)00061-5 [pii].
[33] Iravani M, Tavakoli E, Babaie MH, Ashouri A, Khatami F, Ghavamzadeh A. Comparison of peripheral blood stem cell transplant with bone marrow transplant in class 3 thalassemic patients. Exp Clin Transplant 2010;8(1):66–73. e-pub ahead of print 2010/03/05.
[34] Ghavamzadeh A, Iravani M, Ashouri A, Mousavi SA, Mahdavi N, Shamshiri A, et al. Peripheral blood versus bone marrow as a source of hematopoietic stem cells for allogeneic transplantation in children with class I and II beta thalassemia major. Biol Blood Marrow Transplant 2008;14(3):301–8. https://doi.org/10.1016/j.bbmt.2007.12.491. e-pub ahead of print 2008/02/16; S1083-8791(07)01170-6 [pii].
[35] 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 transplants. Bone Marrow Transplant 2000;25(8):815–21. https://doi.org/10.1038/sj.bmt.1702242. e-pub ahead of print 2000/05/16.
[36] La Nasa G, Giardini C, Argiolu F, Locatelli F, Arras M, De Stefano P, et al. Unrelated donor bone marrow transplantation for thalassemia: the effect of extended haplotypes. Blood 2002;99(12):4350–6. e-pub ahead of print 2002/05/31.
[37] Fleischhauer K, Locatelli F, Zecca M, Orofino MG, Giardini C, De Stefano P, et al. Graft rejection after unrelated donor hematopoietic stem cell transplantation for thalassemia is associated with nonpermissive HLA-DPB1 disparity in host-versus-graft direction. Blood 2006;107(7):2984–92. https://doi.org/10.1182/blood-2005-08-3374. e-pub ahead of print 2005/12/01; 2005-08-3374 [pii].
[38] Locatelli F, Rocha V, Reed W, Bernaudin F, Ertem M, Grafakos S, et al. Related umbilical cord blood transplantation in patients with thalassemia and sickle cell disease. Blood 2003;101(6):2137–43. https://doi.org/10.1182/blood-2002-07-2090.
[39] Lisini D, Zecca M, Giorgiani G, Montagna D, Cristantielli R, Labirio M, et al. Donor/recipient mixed chimerism does not predict graft failure in children with beta-thalassemia given an allogeneic cord blood transplant from an HLA-identical sibling. Haematologica 2008;93(12):1859–67. https://doi.org/10.3324/haematol.13248. e-pub ahead of print 2008/10/24; haematol.13248 [pii].
[40] Walters MC, Quirolo L, Trachtenberg ET, Edwards S, Hale L, Lee J, et al. Sibling donor cord blood transplantation for thalassemia major: experience of the sibling donor cord blood program. Ann N Y Acad Sci 2005;1054:206–13. https://doi.org/10.1196/annals.1345.025. e-pub ahead of print 2005/12/13; 1054/1/206 [pii].
[41] Locatelli F, Kabbara N, Ruggeri A, Ghavamzadeh A, Roberts I, Li CK, et al. Outcome of patients with hemoglobinopathies given either cord blood or bone marrow transplantation from an HLA-identical sibling. Blood 2013;122(6):1072–8. https://doi.org/10.1182/blood-2013-03-489112.
[42] Pinto FO, Roberts I. Cord blood stem cell transplantation for haemoglobinopathies. Br J Haematol 2008;141(3):309–24. https://doi.org/10.1111/j.1365-2141.2008.07016.x. e-pub ahead of print 2008/03/01; BJH7016 [pii].
[43] Ruggeri A, Eapen M, Scaravadou A, Cairo MS, Bhatia M, Kurtzberg J, et al. Umbilical cord blood transplantation for children with thalassemia and sickle cell disease. Biol Blood Marrow Transplant : j Am Soc Blood Marrow Transpl 2011;17(9):1375–82. https://doi.org/10.1016/j.bbmt.2011.01.012.
[44] Bertaina A, Merli P, Rutella S, Pagliara D, Bernardo ME, Masetti R, et al. HLA-haploidentical stem cell transplantation after removal of alphabeta+ T and B-cells in children with non-malignant disorders. Blood 2014. https://doi.org/10.1182/blood-2014-03-563817. e-pub ahead of print 2014/05/30; blood-2014-03-563817 [pii].
[45] Bittencourt H, Rocha V, Chevret S, Socie G, Esperou H, Devergie A, et al. Association of CD34 cell dose with hematopoietic recovery, infections, and other outcomes after HLA-identical sibling bone marrow transplantation. Blood 2002;99(8):2726–33.
[46] Rund D, Rachmilewitz E. Beta-thalassemia. N Engl J Med 2005;353(11):1135–46. https://doi.org/10.1056/NEJMra050436. e-pub ahead of print 2005/09/16; 353/11/1135 [pii].
[47] Panigrahi I, Marwaha RK. Common queries in thalassemia care. Indian Pediatr 2006;43(6):513–8. e-pub ahead of print 2006/07/06.
[48] Shatry AM, Jones M, Levy RB. The effect of the spleen on compartmental levels and distribution of donor progenitor cells after syngeneic and allogeneic bone marrow transplants. Stem Cells Dev. 2004;13(1):51–62. https://doi.org/10.1089/15473280477309925 4.
[49] Li Z, Gooley T, Applebaum FR, Deeg HJ. Splenectomy and hemopoietic stem cell transplantation for myelofibrosis. Blood 2001;97(7):2180–1.
[50] Tripatara A, Jetsrisuparb A, Teeratakulpisarn J, Kuaha K. Hemostatic alterations in splenectomized and non-splenectomized patients with beta-thalassemia/hemoglobin E disease. Thromb Res 2007;120(6):805–10. https://doi.org/10.1016/j.thromres.2007.02.006.
[51] Pattanapanyasat K, Gonwong S, Chaichompoo P, Noulsri E, Lerdwana S, Sukapirom K, et al. Activated platelet-derived microparticles in thalassaemia. Br J Haematol 2007;136(3):462–71.
[52] Singer ST, Kuypers FA, Styles L, Vichinsky EP, Foote D, Rosenfeld H. Pulmonary hypertension in thalassemia: association with platelet activation and hypercoagulable state. Am J Hematol 2006;81(9):670–5. https://doi.org/10.1002/ajh.20640.
[53] Robin M, Guardiola P, Devergie A, Yeshurun M, Shapiro S, Esperou H, et al. A 10-year median follow-up study after allogeneic stem cell transplantation for chronic myeloid leukemia in chronic phase from HLA-identical sibling donors. Leukemia 2005;19(9):1613–20. https://doi.org/10.1038/sj.leu.2403821.
[54] Mathews V, George B, Lakshmi KM, Viswabandya A, John JM, Sitaram U, et al. Impact of pretransplant splenectomy on patients with beta-thalassemia major undergoing a matched-related allogeneic stem cell transplantation. Pediatr Transplant 2009;13(2):171–6. https://doi.org/10.1111/j.1399-3046.2008.00953.x. e-pub ahead of print 2008/05/17: PTR953 [pii].
[55] Bhatia M, Cairo MS. Splenectomy or no splenectomy prior to allogeneic stem-cell transplantation in patients with severe thalassemia: this is the question. Pediatr Transplant 2009;13(2):143–5. https://doi.org/10.1111/j.1399-3046.2008.01058.x. e-pub ahead of print 2008/12/11: PTR1058 [pii].
[56] Angelucci E, Muretto P, Lucarelli G, Ripalti M, Baronciani D, Erer B, et al. Phlebotomy to reduce iron overload in patients cured of thalassemia by bone marrow transplantation. Italian cooperative group for phlebotomy treatment of transplanted thalassemia patients. Blood 1997;90(3):994–8. e-pub ahead of print 1997/08/01.