



Annotated Bibliography

XII. Sickle Cell Disease and Thalassemia ii. Thalassemia



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B. Bone Marrow and PBSC Transplantation

1. **Decision-making in adult thalassemia patients undergoing unrelated bone marrow transplantation: quality of life, communication and ethical issues.** Caocci G, Pisu S, Argioli F, Giardini C, Locatelli F, Vacca A, Orofino MG, Piras E, De Stefano P, Addari MC, Ledda A, La Nasa G. Bone Marrow Transplant. 2006;37:165-9. [Abstract](#)

In thalassemia major, lifelong need for medical care can have a major impact on physical and physical and psychosocial well-being and quality of life (QoL) of patients and their families. The authors emphasize that patients with thalassemia major are faced with a difficult decision. They can either continue traditional transfusion and chelation therapy, with no chance of complete recovery, or they can accept the high risk of TRM in the hope of obtaining a definitive elimination of the disease with prevention/reversion of its complications.

In this study the authors investigated the communication strategies and the post transplantation QoL in 19 adult thalassemia patients surviving after an unrelated donor BMT. The patients were given two questionnaires: a questionnaire to evaluate pre-transplantation communication factors and the EORTC QLQ-C30 questionnaire to assess global QoL.

All patients were satisfied with the communication modalities employed by the physicians. **The global post-transplantation QoL in this cohort was found to be good.** The mean global QoL was good (76.4). Twelve of the 19 patients (63%) enjoyed a very good global QoL (81-100), two had a good score (61-80) and four had an intermediate score (41-60). Only one patient had a poor global score. Very good scores were obtained for the physical, emotional, cognitive, role function and social function scales.

In the group of patients who developed chronic GVHD, the global QoL was good (mean score 65.3), whereas in those who did not develop GVHD, the score was very good (mean 81.9). However, the difference in global health status between the two groups was not statistically significant.

Ethical issues: The question that every adult patient must answer after a careful evaluation is whether the 30% mortality following BMT in adult class-3 patients is outweighed by the 70% chance of becoming independent from transfusions and iron-chelation therapy. **Any decisions in medicine should be based on respect for patient's autonomy, which must be seen within the larger relational context of the physician-patient relationship. This relationship bears the phenomenological marks of a convenantal exchange rather than a contract: it draws on the physician's virtues and his ability to recognize that the patient he encounters in an obvious position of power maintains the dignity of a person. Although the decision is ultimately the patient's (emphasis added), the physician has the responsibility to assess whether the patient is suitable for BMT.**

[Comment: This publication is unusual in stressing the necessity of considering the patient's desires after being informed of the pros and cons of transplantation. This concept is missing from most publications on the subject which omit any such discussion and, by inference, imply that it is solely the physician's role to make the decision.]

*The mortality rate of 30% stated by Caocci et al for adult patients is much higher than that found when transplanting young transfusion-dependent β -thalassemia patients (generally Lucarelli Class I). Indeed, Dr. Mark Walters reviewed data at the Fourth Annual International Umbilical Cord Blood Transplantation Symposium in May, 2006 indicating that in Lucarelli class 1 and class 2 patients transplanted with **marrow from sibling donors**, the survival and thalassemia-free survival rates were 87% and 84%, respectively. For class 3 patients <17 years of age who were treated with a conditioning regime providing more intensive chemosuppression, the DFS was 85% and OS was 93%. **Unrelated BMT** in children with class 1 or 2 thalassemia have an OS of 92% and DFS of 82%, results that are similar to those obtained with sibling BMT. In a multi-center series of patients with hemoglobinopathies treated by **HLA-identical sibling umbilical cord blood transplantation (UCBT)**, 26 of 29 (90%) survive, and 25 (86%) survive disease-free. Overall, the Kaplan-Meier probabilities of survival and event-free survival after sibling UCBT are 89% and 86%, respectively with a median follow-up of 1.3 (range, 0.1 – 7.6) years. Thus, a school of thought suggests that the decision regarding whether or not to transplant should be made at a young age.*

*The major question facing β -thalassemia major patients is whether matched unrelated donors should be used for transplants when a sibling donor is not available. Only a minority of patients in need of transplant (about 30%) are fortunate enough to have sibling donors. At the Symposium, Jaing et al presented data on **unrelated cord blood transplantation** indicating OS of 87±7% and thalassemia-free survival of 77±9% at experienced centers that did not perform post-thaw wash of the cord blood units.*

For a CD with audio and slides used by the lecturers and/or a reprint of the proceedings, send your postal mailing address to symposiumCD@cordbloodforum.org]

2. **Outcomes of transplantation with related- and unrelated-donor stem cells in children with severe thalassemia.** Hongeng S, Pakakasama S, Chuansumrit A, Sirachainan N, Kitpoka P, Udomsubpayakul U, Ungkanont A, Jootar S. Biol Blood Marrow Transplant. 2006;12:683-7. [Abstract](#)

In recent years there has been a steady increase in the number of unrelated-donor BMTs in a variety of disorders. There are only 2 case-series reports regarding unrelated BMT in thalassemia and both series have indicated favorable outcomes. (See [citation #8](#) and [citation #13](#)) [However, one should also note reports of unrelated umbilical cord blood transplants in thalassemia major - see *ii. Thalassemia C. Umbilical Cord Blood Transplantation, citations #2, #3, and #4*]

The present study investigated outcomes of related and unrelated stem cell transplantations (HSTs) and whether these compare favorably in children with severe thalassemia. Recently published reports indicate that the outcome of unrelated donor transplantations in patients with leukemia is currently comparable to that of transplantation from identical family donors.

The authors reviewed transplantation outcome in 49 consecutive children with severe thalassemia who underwent allogeneic stem cell transplantation with related-donor (n=28) and unrelated-donor (n=21) stem cells between September 1992 and May 2005 in Thailand. **Analysis of engraftment, frequency of procedure-related complications, and thalassemia-free survival showed no advantage from use of related-donor stem cells.** The 2-year thalassemia-free survival estimate for recipients of related-donor stem cells was 82% compared with 71% in the unrelated-donor stem cell group (P=.42).

The authors concluded that their study provides evidence to support the view that it is quite reasonable to consider unrelated-donor stem cell transplantation an acceptable therapeutic approach in severe thalassemia, at least for patients who are not fully compliant with conventional treatment and do not yet show irreversible severe complications of iron overload.

3. **Unrelated bone marrow transplantation for beta-thalassemia patients: The experience of the Italian Bone Marrow Transplant Group.** La Nasa G, Argioli F, Giardini C, Pession A, Fagioli F, Caocci G, Vacca A, De Stefano P, Piras E, Ledda A, Piroddi A, Littera R, Nesci S, Locatelli F. *Ann N Y Acad Sci.* 2005;1054:186-95. [Abstract](#)

Bone marrow transplantation (BMT) remains the only potentially curative treatment for patients with thalassemia major. However, most candidates for BMT do not have a suitable family donor. In order to evaluate whether BMT from an HLA-matched unrelated volunteer donor can offer a probability of cure comparable to that obtained when the donor is a compatible sibling, we carried out a study involving 68 thalassemia patients transplanted in six Italian BMT Centers. Thirty-three males and 35 females (age range, 2-37 years; median age, 15) were transplanted from **unrelated volunteer donors, all selected using high-resolution molecular typing of both HLA class I and II loci.** Fourteen patients were classified in risk class 1; 16 in risk class 2; and 38 in risk class III of the Pesaro classification system. Nine patients (13%) had either primary or secondary graft failure. Fourteen patients (20%) died from transplant-related causes. Grade II-IV acute graft-versus-host disease (GVHD) developed in 24 cases (40%), and chronic GVHD in 10 cases (18%). Overall survival (OS) in the cohort of 68 patients was 79.3% (CI 67-88%), whereas the Kaplan-Meier estimates of disease-free survival (DFS) with transfusion independence was 65.8% (CI 54-77%). In the group of 30 thalassemic patients in risk classes 1 and 2, the probability of OS and DFS were 96.7% (CI 90-100%) and 80.0% (CI 65-94%), respectively, whereas in the 38 patients in class 3 OS was 65.2% (CI 49-80%) and DFS was 54.5% (CI 38-70%). These data show that when donor selection is based on stringent compatibility criteria, the results of unrelated transplantation in thalassemia patients are comparable to those obtained when the donor is a compatible sibling.

[Comment: The authors suggest that the use of stringent compatibility criteria were the basis for their excellent results. Improved results can be expected in transplantation outcomes when using adult stem cell donors when high resolution HLA typing is used to match donor and recipient. However, this may not be the case in cord blood transplantation. Indeed, Kogler et al have reported that high-resolution typing hardly improves long-term clinical outcome in cord blood transplantation. (See [IX. HLA Matching, Citation #5](#)) Thus, cord blood transplants using unrelated donors and a high cell dose (easily obtainable in young patients) even without stringent compatibility criteria may be a feasible option in transplantation of patients with thalassemia.]

4. **Allogeneic stem cell transplantation from unrelated donor for class 3 beta-thalassemia major using reduced-intensity conditioning regimen.** Zhu KE, Gu J, Zhang T. *Bone Marrow Transplant.* 2006;37:111-2.

The authors point out that patients classified as class 3 in the Pesaro classification who had evidence of organ damage from iron-overload had poor outcomes after hematopoietic cell transplantation, and were more likely to experience transplant-related mortality or disease recurrence. One approach to reduce transplant-related mortality is to use reduced-intensity stem cell transplantation (RIST). **The authors describe successful transplantation from 6/6 matched unrelated donors using reduced-intensity conditioning for two children with class 3 thalassemia major who had evidence of organ damage.**

The conditioning regimen was composed of cyclophosphamide, busulfan, fludarabine and rabbit ATG. As GVHD prophylaxis patients received cyclosporine and methotrexate. Mycophenolate mofetil was administered from day -1 to day +30.

One year after transplant, the first patient had 100% donor cells and had no clinical features of thalassemia, although his cardiac and pulmonary functions were still slightly decreased, and his Karnofsky score was 90. At two years posttransplant, the second patient also had 100% donor cells, had no clinical features of thalassemia, her cardiac and pulmonary functions were normal, and the Karnofsky score was 100.

The authors point out that, owing to its immunosuppressive potency and additional myeloablation, **fludarabine** has been included into the nonmyeloablative regimen. As far as the authors were aware, there has been no previous experience with **reduced-intensity conditioning** in children with thalassemia major undergoing **unrelated donor transplantation**. This regimen appears to be well tolerated, leading to durable engraftment.

5. **Complete substitution of cyclophosphamide by fludarabine and ATG in a busulfan-based preparative regimen for children and adolescents with beta-thalassemia.** Sauer M, Bettoni C, Lauten M, Ghosh A, Rehe K, Grigull L, Beilken A, Welte K, Sykora KW. *Bone Marrow Transplant.* 2005;36:383-7. [Abstract](#)

The authors reiterate the known fact that allogeneic HCT represents the only rational therapeutic modality to cure β -thalassemia. HCT from a genotypically identical family donor has dramatically improved the prognosis of patients with homozygous β -thalassemia. Young patients transplanted at an early stage of the disease were reported to have a disease-free survival of 91% and a mortality risk of 8%.

The authors cite evidence that there is a strong correlation between blood levels of various cyclophosphamide metabolites and VOD. They postulated that the formation of these metabolites depletes the liver of glutathione (GSH) resulting in significant toxicity. Fludarabine, however, is not known to deplete the GSH content and this might be of increasing importance in patients entering HCT with pre-existing liver damage. In addition, nucleoside analogs such as fludarabine are reported to exert synergistic effects with alkylating agents such as busulfan. Therefore, the authors replaced cyclophosphamide completely by fludarabine in a busulfan-based conditioning regimen for children and adolescents with thalassemia. The goal of this pilot

study was to determine whether a combination of 180 mg/m² fludarabine, ATG, and 14 mg/kg busulfan can provide donor-derived engraftment after allogeneic **BMT from matched related family donors** without an increased incidence and severity of transplant-related complications.

Five patients with β -thalassemia who were Lucarelli class 2 or 3 were transplanted. Three patients received conditioning with fludarabine (30 mg/m²/day x 6), oral busulfan (3.5 mg/kg/day x 4), and ATG rabbit Fresenius (10 mg/kg/day x 4). Two children received intravenous busulfan instead of oral busulfan at a dose of 2 x 1.4 mg/kg/day x 4 days. All children were transplanted with a fresh bone marrow graft from an HLA-identical sibling.

Overall, 5/5 patients achieved donor engraftment and are alive and well. No GVHD exceeding grade I was observed, and 2/5 children maintained donor chimerism at 100%. Three of the 5 children developed mixed hematopoietic chimerism within the first 50 days after transplantation. Therefore, CSA was started to be tapered before day +60 in those children. In all these three children donor-derived hematopoiesis increased from 75, 95, and 62 to 100, 97, and 89%, respectively. Follow-up times of these patients with early development of mixed hematopoietic chimerism are 2, 3, and 20 months. One patient maintains mixed hematopoietic donor chimerism being between 94 and 97% nearly 5 years after transplant.

6. Bone mineral density in children with thalassaemia major: determining factors and effects of bone marrow transplantation. Leung TF, Hung EC, Lam CW, Li CK, Chu Y, Chik KW, Shing MM, Lee V, Yuen PM. Bone Marrow Transplant. 2005;36:331-6.

Abstract

The authors point out that osteoporosis and osteopenia are major long-term complications of thalassemia major and affect up to half of such patients. They hypothesized that the diminished bone mineral density (BMD) seen in thalassemia major patients may improve when their disease is cured by BMT. They investigated the effects of acquired factors and BMT on BMD in these patients. In all, 53 patients on regular transfusion (BT group) and 33 patients at 5.7±1.9 years post transplant (BMT group) were recruited. BMD was measured by dual energy X-ray absorptiometry.

Severe BMD deficit of the spine and hip were noted in 62% and 35% of BT group, respectively. Severe BMD deficit was less common among BMT than BT patients (6 vs 35%; *P*=0.036). The authors concluded that BMD deficit is common in Chinese patients with thalassemia major and transplantation may reverse BMD deficit in these patients.

7. Growth and endocrine function following bone marrow transplantation for thalassemia major. Li CK, Chik KW, Wong GW, Cheng PS, Lee V, Shing MM. Pediatr Hematol Oncol. 2004;21:411-9. **Abstract**

Growth failure and endocrine dysfunction are common in thalassemia major (TM) patients when they are treated by conventional treatment. The endocrine dysfunction is usually due to iron overload after repeated blood transfusion. Desferrioxamine is an effective iron-chelating agent but it also causes growth retardation and skeletal abnormalities.

Thirty-two TM patients who had survived more than 2 years after bone marrow transplantation (BMT) were recruited for growth and endocrine study. The patients all received busulfan, cyclophosphamide and ATG in the conditioning regimen. None of the patients received irradiation and none developed chronic GVHD.

Patients were followed up annually for growth, and the height was expressed as height standard deviation score (HtSDS). The HtSDS at baseline was -1.51 and was more reduced in patients older than 7 years (-1.99) as compared with those younger patients (-0.79) (*p* = .027). The HtSDS gradually improved after BMT and increased by 0.59 (CI 0.16-1.01) at 5 years after BMT. Forty percent of patients were below 2 SD at time of BMT but this decreased to 15% at the latest assessment.

With a median follow-up of 67 months, ovarian failure was universal among the 10 girls evaluable for puberty and all required hormonal replacement for either induction of puberty or secondary ovarian failure. Eight of 10 boys had spontaneous puberty but 3 of them had gonadal impairment. The cause of the gonadal impairment in males was more likely due to iron-induced damage on endocrine organs before BMT. One patient developed diabetes mellitus and one had growth hormone deficiency after BMT.

In conclusion, improvement of growth after BMT in TM was common, probably related to stopping of further administration of desferrioxamine. However, busulfan-induced ovarian failure was universal in girls, and boys were spared from gonadal failure if transplant was performed early.

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8. **Unrelated bone marrow transplantation in high-risk adult thalassaemia patients.** La Nasa G, Gacocci G, Argioli F, et al. Bone Marrow Transplant 2005;35(suppl 2):289 (abstract).

The authors conducted a clinical trial using high-resolution Class I and II HLA typing to select unrelated bone marrow donors for 15 male and 12 female (median age 22 years) high-risk (Class III, Pesaro classification) thalassemia patients. No donor had more than a single allele-level mismatch with the patient.

Conditioning regimens used were busulfan 14 mg/kg, thiotepa 10 mg/kg and cyclophosphamide 120 or 160 mg/kg in 16 cases, and busulfan 14 mg/kg and cyclophosphamide 120 or 160 mg/kg in the remaining 11 cases. GVHD prophylaxis consisted of short-course methotrexate and cyclosporine.

At a median follow-up of 42 months, 20 of 27 (74%) of patients are alive and transfusion independent. Three of 25 (12%) evaluable patients developed grades III-IV GVHD and 8 of 22 (36%) evaluable patients experienced chronic GVHD (2 patients developed extensive chronic GVHD).

The authors indicated that, despite the advances made in the last two decades in transfusion and chelation therapy, complications from iron overload remain a serious problem for thalassemia patients. In addition, continual transfusions and daily chelation therapy are difficult to maintain with advancing age. Therefore, a thalassemia patient without an HLA-identical sibling donor should consider hematopoietic cell transplantation sooner rather than later, before the patient develops irreversible severe complications of iron overload.

(Comment: The 26% mortality in this series is much higher that would occur were transplants carried out at an early age before complications arise, as recommended by the authors of this report and as practiced by Jaing et al who transplanted young patients without complications of the disease (see ii. Thalassemia C. Umbilical Cord Blood Transplantation, citation #2). In the report of Jaing et al, all 5 patients survived and were cured of thalassemia. However, it should be noted that Dr. Jaing reported at the 3rd Annual International Cord Blood Transplantation Symposium in Los Angeles on June 4, 2005 that he had now performed a total of 9 unrelated cord blood transplants and one patient died (mortality 11%). With modern supportive therapy but without transplantation, 32% of patients can be expected to die by the age of 35, as indicated by Cao et al (see ii. Thalassemia A. Clinical Aspects citation #1) Thus, the recommendation to transplant at a early age before complications arise as suggested by Jaing et al and La Nasa et al appears sound.)

9. **Gonadal function of young patients with beta-thalassemia following bone marrow transplantation.** Vlachopapadopoulou E, Kitra V, Peristeri J, Goussetis E, Karachaliou F, Petropoulos D, Fotinou A, Michalacos S, Graphakos S. J Pediatr Endocrinol Metab. 2005;18:477-83. [Abstract](#)

Homozygous β -thalassemia is one of the most common single gene disorders. The traditional therapeutic approach consists of blood transfusions. Patients develop a number of complications including growth failure, hypogonadotropic hypogonadism, diabetes mellitus, cardiac toxicity, liver toxicity and osteoporosis, mainly due to iron toxicity.

Hematopoietic cell transplantation can induce short-and long-term impairment of gonadal function. Patients with β -thalassemia represent a special group, as the pathophysiology of thalassemia and its treatment with blood transfusion can both induce gonadal dysfunction. In this study, the authors report on the gonadal function outcome in 25 patients with β -thalassemia who underwent allogeneic BMT during childhood and adolescence. There were 12 males with a mean age of 13.9 ± 2.8 years, and 13 females with a mean age of 13.4 ± 3.7 years. The conditioning regimen included busulfan and cyclophosphamide and did not include TBI.

The impact of BMT appears to be different in the two sexes. Males seem to be more resistant to gonadal damage. All male patients who were pubertal at the time of transplantation had normal testosterone levels and all but one had normal gonadotropin levels. Only one patient had elevated FSH levels. Furthermore, almost two-thirds of the patients who were prepubertal when they underwent BMT proceeded to normal pubertal development. However, germ cell damage was evident by increased FSH serum levels in 25% of them and small testicular volumes.

Post-menarcheal females seem to be an extremely sensitive group to the deleterious effect of chemotherapy. All post-menarcheal females exhibited amenorrhea and elevated gonadotropin levels. However, the authors have previously reported reversal of ovarian failure in patients treated for Hodgkin's disease up to 9 years post-treatment so that longer follow-up is necessary.

A girl who was transplanted at a younger age (11.1 years) had elevated gonadotropins at the initial post-BMT evaluation, but subsequently she was found with normal gonadotropin levels and she menstruated spontaneously. Other reports have indicated that girls who underwent TBI in preparation for BMT at a younger age have higher possibilities for recovery of ovarian function.

In the group of females who had not entered puberty prior to transplantation due to hypogonadotropic hypogonadism, it is not

easy to assess ovarian toxicity.

10. **The cure of thalassemia by bone marrow transplantation.** Lucarelli G, Andreani M, Angelucci E. Blood Rev 2002; 16:81-85.

The authors summarized their extensive experience with this report of 886 bone marrow transplants from HLA identical family members in *thalassemic patients* aged from 1 to 35 years at the time of transplant. Overall thalassemia-free survival was 73%. However, in 124 class 1 patients, thalassemia-free survival was 91% and in 297 class 2 patients it was 84%. For class 3 patients aged less than 17 years, survival was 79% and thalassemia-free survival was 58%. However, preliminary results obtained in 23 class 3 patients younger than 17 years who were transplanted with a new regimen were consistent with >90% thalassemia-free survival.

In a shorter review of the same data, the authors concluded their article by stating that all thalassemic patients, together with their parents and siblings, should be HLA typed and when an HLA-matched donor is available, *bone marrow transplantation is mandatory* in those thalassemic patients in class 1 and class 2 and in those of class 3 aged less than 17 years. (**The cure of thalassemia by bone marrow transplantation.** Lucarelli G, Andreani M, Angelucci E. Blood Rev 2002; 16:81-85.

(NOTE: The authors do not comment on the role of *cord blood transplants* or other sources of matched unrelated donors for those patients who do not have an HLA-matched family member. As with all persons needing a transplant, only a minority will have an HLA-matched family member. The excellent results with HLA-matched family members suggests that attempts should be made to extend this therapy to a wider group of patients in need.)

11. **New insights into haematopoietic stem cell transplantation for patients with haemoglobinopathies.** Locatelli F, Stefano PD. Br J Haematol. 2004;125:3-11

This is a detailed review by experienced investigators of available information on hematopoietic stem cell transplantation (HSCT) for patients with sickle cell disease and thalassemia with a view to the future management of these disorders. The authors point out that HSCT is the only curative treatment for these patients although it is associated with a risk of complications that can dramatically shorten the life duration of some patients. For this reason HSCT using unrelated donors did not meet consensus until recently. However, recent reports demonstrating that more precise HLA matching using high-resolution molecular typing for both classes I and II loci can reduce transplantation risk have provided the rationale for considering HSCT from unrelated donors. However, it is well known that only 25-30% of patients potentially curable with HSCT have an HLA-compatible family member. The authors indicate that the use of cord blood hematopoietic stem cells can open new scenarios that can make the procedure safer and more readily available. In contrast, they suggest that infusion of a high number of CD34+ cells from an HLA-partially matched relative results in a prolonged state of immune incompetence and causes a remarkable risk of serious, often fatal, infectious complications. They point out that data regarding non-myeloablative strategies indicate that stable donor engraftment is more difficult to achieve in patients with hemoglobinopathies than in adults with malignancy and they do not encourage the use of this approach at present.

12. **Bone marrow transplantation for beta-thalassaemia major: the UK experience in two paediatric centres.** Lawson SE, Roberts IA, Amrolia P, Dokal I, Szydlo R, Darbyshire PJ. Br J Haematol 2003; 120:289-295. [Abstract](#)

The authors indicate that β -thalassaemia major is an important cause of morbidity and premature death in young adults worldwide. There are now more than 800 patients in the UK with β -thalassaemia major or other transfusion-dependent thalassaemias. Although there are reports of improvements in medical management, recent data from the UK Thalassaemia Registry indicate that, despite the availability of good medical treatment, approximately 50% of affected patients in the UK die before the age of 35 years. The authors point out that the only curative treatment available for patients with β -thalassaemia major is BMT, or stem cell transplantation using cord or peripheral blood haematopoietic stem cells. The first successful BMT for thalassaemia major was performed in 1982, and now over 1500 transplants have been performed worldwide. This report describes results of allogeneic BMT in 55 children with β -thalassaemia major (median age was 6.4 years) who received a hematopoietic cell transplant from an HLA-matched family member. Although the majority of patients were classified as Pesaro class 2 or 3, transplant-related mortality was low (5.4%). The principal complication was graft rejection accompanied by autologous reconstitution that occurred in 13.2% of transplants. Following modification of the conditioning regimen, the rejection rate fell to 4.6% and remained low. aGVHD of grade II-IV occurred in 31% and cGVHD in 14.5%. They concluded that allogeneic BMT is an important treatment option for children with β -thalassaemia major.

13. **Outcome of transplantation with unrelated donor bone marrow in children with severe thalassaemia.** Hongeng S, Pakakasama S, Chaisiripoomkere W, Chuansumrit A, Sirachainan N, Ungkanont A, Jootar S. Bone Marrow Transplant. 2004;33:377-9. [Abstract](#)

The authors conducted a study of unrelated donor bone marrow transplantation (BMT) in 11 children with severe thalassaemia. The conditioning regimen consisted of busulphan, cyclophosphamide and antilymphocyte globulin. All received T-cell nondepleted bone marrow. The median marrow-nucleated cell dose was 4.9×10^8 /kg (range; $3.5-8.0 \times 10^8$ /kg). Median time of granulocyte recovery was 16 days (range; 13-21 days), and of platelet recovery was 39 days (range; 14-196). Grade 2-4 acute graft-versus-host disease (GVHD) developed in six patients (54%), and grade 3-4 in one patient (9%). Three (27%) of 11 evaluable patients had chronic GVHD (limited stage). **All 11 patients are alive without thalassaemia after a median follow-up time of 397 days (range; 171-814 days).** This study lends support to consideration of unrelated donor BMT as an acceptable therapy to cure severe thalassaemia especially in patients who are young and do not yet show irreversible severe complications of iron overload.

14. **A new approach for bone marrow transplantation in class 3 thalassemic patients aged less than 17 years.** Sodani P, Gaziev D, Polchi P, Erer B, Giardini C, Angelucci E, Baronciani D, Andreani M, Manna M, Nesci S, Lucarelli B, Clift RA, Lucarelli G. Blood 2004;104:1201-3. [Abstract](#)

When prepared for transplantation with busulfan (BU) 14 mg/kg and cyclophosphamide (CY) 120 - 160 mg/kg, thalassemic patients in risk class 3, aged younger than 17 years, transplanted from HLA identical donors, had a 30% incidence of transplant rejection with recurrence of thalassemia. This, relatively poor, outcome was ascribed to insufficient immune suppression or to inadequate eradication of the thalassemic marrow, or both. In an attempt to enhance both immune suppression and eradication of the thalassemic clones, hydroxyurea, azathioprine and fludarabine were added to the BU and CY. This regimen, called Protocol 26, was applied to 33 consecutive class 3 thalassemic patients aged less than 17 years and was well tolerated with 93% survival. The incidence of recurrent thalassemia after the transplant decreased from 30 to 8 percent. The authors concluded that the protocol presented in this report appears to be a well-tolerated and effective association of drugs for eradication of the hemopoietic system of thalassemic patients.

15. **Homozygous alpha-thalassaemia treated with intrauterine transfusions and postnatal hematopoietic stem cell**

transplantation. Thornley I, Lehmann L, Ferguson WS, Davis I, Forman EN, Guinan EC. Bone Marrow Transplant 2003; 32:341-342.

In malaria-endemic Southeast Asia, deletions in the globin gene cluster on chromosome 16 are common, with carrier rates for the most prevalent deletion ranging from 3.5 to 14%. In this report, homozygous thalassemia was confirmed in utero, and the fetus was treated with intra-uterine transfusions. After birth, the patient was supported with RBC transfusions, and at age 23 months was transplanted using bone marrow from his 4-year-old HLA-matched sister. Three years after transplantation, he has attained all appropriate developmental milestones, and is growing with normal velocity. He has no evidence of chronic GVHD. The authors also cite two previous reports of hematopoietic cell transplant for homozygous thalassemia (one of which used *cord blood* obtained from a sibling mismatched at one MHC locus). Both transplants resulted in a functional hematologic "cure" despite the presence of mixed hematopoietic chimerism in one patient.

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