Title
The case for HLA-identical sibling hematopoietic stem cell transplantation in children with symptomatic sickle cell anemia.

Authors
Fitzhugh, Courtney D
Walters, Mark C

POINT The case for HLA-identical sibling hematopoietic stem cell transplantation in children with symptomatic sickle cell anemia

Courtney D. Fitzhugh[1] and Mark C. Walters[2]

[1]Sickle Cell Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD; and [2]UCSF Benioff Children's Hospital Oakland, Oakland, CA

This article has a companion Counterpoint by DeBaun and Clayton.

Sickle cell disease (SCD) is a hereditary red blood cell disorder that is characterized by early mortality and severe morbidity, including debilitating painful crises, chronic kidney injury that can progress to renal failure and dialysis,[1,2] avascular necrosis frequently culminating in joint replacement at an early age,[3] stroke,[4] poor neuropsychologic performance,[5,6] and cardiopulmonary complications.[7] Furthermore, adults can experience a chronic pain syndrome that is typically managed with long-term opioid administration. Sickle cell–associated complications, particularly painful episodes, are associated with high health care utilization[8-11] and extraordinary financial burden. One study reported that total health care costs increase with age from $892 per month in the 0 to 9 age group to $2853 per month in the 30 to 39 age group.[12] For these reasons, it is not unreasonable or controversial to assume that a successful outcome after a curative therapy for SCD early in life would have a significant beneficial effect on lifespan and the quality of life and reduce life-long health care expenditures.

Hydroxyurea (HU) was the initial US Food and Drug Administration–approved drug for SCD and is widely available, although approved only in adults. Although HU has been shown to significantly improve acute complications such as vaso-occlusive crises and acute chest syndrome in children of all ages,[13-16] there are challenges with HU adherence over the long term,[17] and HU has not been shown to prevent the organ damage that is associated with early mortality in adults.[18,19] The full benefit of HU is achieved only after a decade or longer of uninterrupted adherence; thus not all individuals experience its optimized effect. The vagaries of assuring continuous health insurance coverage in this and other chronic illnesses with access to informed, high-quality providers also impact the long-term outlook. Another supportive care option is regular red blood cell (RBC) transfusions to alleviate symptoms, but which can be complicated by alloimmunization, transfusion reactions, and iron overload. Although the vast majority of children survive to adulthood,[20] adults continue to die prematurely,[21,22] many clustered near the age of transition to adulthood,[20] and there are no reliable risk factors in children that predict severe disease and early mortality in adults. Last, some patients, not unlike the example chosen for this point-counterpoint discussion, continue to have significant sickle cell–specific complications despite receiving the maximum tolerated dose of HU. Recurrent vaso-occlusive complications have a negative impact on the quality of life.[23-27]

In contrast to life-long supportive care measures, hematopoietic stem cell transplantation (HSCT) offers a curative option for selected patients with SCD. Children who have a HLA-matched sibling donor traditionally have been treated with myeloablative conditioning chemotherapy and bone marrow grafts to replace the recipients' bone marrow with that of their donors. The most common indications for transplant are stroke, recurrent vaso-occlusive crises, and acute chest syndrome.[28] A recent study described the results of 1000 children who underwent HLA-identical transplant after predominantly myeloablative conditioning with a 5-year overall survival (OS) of 95% and 93% disease-free survival (DFS) in those <16 years of age.[29] Interestingly, Dedeken et al reported an 8-year OS and DFS of 97.4% after HLA-identical sibling bone marrow transplant (BMT) after the administration of HU for at least 3 months pretransplant.[30] Similarly, an Italian group reported a 7-year OS of 100% with 96% DFS among 24 patients.[31] After successful transplant, an improved quality of life in children with SCD has been observed.[32] Table 1 summarizes the recent experience of BMT for SCD with overall and DFS rates in patients who received myeloablative HLA-matched sibling transplantation. Although the success rate is improving, the treatment can be limited by severe chronic graft-versus-host disease (cGVHD), which is also associated with a decreased quality of life.[33-35] However, as seen in Table 1, the incidence of severe cGVHD is expected to be ~5% or less when an HLA-identical sibling donor is used.

Table 1. Survival and extensive cGVHD incidence among children undergoing myeloablative HLA-matched sibling hematopoietic stem cell transplantation

Reference	Survival	N	2 y (%)	4 to 5 y (%)	6 to 8 y (%)	cGVHD (%)
31		24				4
	OS		100	100	100	
	DFS		96	96	96	
30		38				0
	OS		97.4	97.4	97.4	
	DFS		97.4	97.4	97.4	
54		40				5
	OS		91	91	NR	
	DFS		91	91	NR	
36		130				5*
	OS		NR	NR	95*	
	DFS		NR	NR	92	
55		25				0
	OS		96	96	NR	
	DFS		96	96	NR	
49		57				8
	OS		93	93	93	
	DFS		85	85	85	
56		10				10
	OS		90	90	NR	
	DFS		90	90	NR	
57		67				5
	OS		97	97	NR	
	DFS		85	85	NR	
51		44				2.4
	OS		NR	100	NR	
	DFS		NR	95.6	NR	
58		50				6
	OS		98	96	NR	
	DFS		88	86.1	NR	
Total		485				5
	OS†		95	96	95	
	DFS†		89	90	91	

*Incidence not differentiated between patients with sickle cell anemia and thalassemia.
†Percentages are calculated based on the total number of patients reported at that time period because some manuscripts did not report survival at every interval listed in the table.
NR, not reported.

The results after related donor umbilical cord transplantation in children have also been encouraging. The largest study to date included 96 patients (30 with SCD and 66 with thalassemia major) who underwent HLA-identical sibling umbilical cord blood (UCB) transplant.[36] With a median follow-up of 5.8 years, OS was 97% with a DFS of 90%, and there was no chronic extensive graft-versus-host disease (GVHD). Other smaller studies have reported similar results.[37-39] Although ~40% of patients received HLA-identical sibling UCB supplemented with bone marrow from the same donor, this was accompanied by a very low incidence of GVHD.

Less intensive conditioning has been evaluated as a means of decreasing toxicity while maintaining efficacy in children and adults with SCD who have a HLA-matched sibling donor, but less often in children. With a median follow-up ranging from 3 to 4 years, 3 studies, each of which enrolled 7 to 15 patients, reported OS of 100% and DFS 86% in 1 study, and 100% OS and DFS in the other 2 studies. None of the patients experienced severe cGVHD.[40-42] A larger study was reported more recently that included 43 patients with SCD and 9 with transfusion-dependent thalassemia.[43] The OS was 94.2% and DFS 92.3% in patients with SCD. Although 7 patients (13%) experienced chronic extensive GVHD, all patients with cGVHD were >14 years of age. Thus, there might to be an opportunity to modify the transplant intensity and thereby further reduce transplant-related toxicity while ensuring a successful outcome.

Because full donor chimerism is not necessary for a successful outcome in SCD and because mixed chimerism may lower the risk of GVHD,[44,45] investigators have pursued a nonmyeloablative regimen with the goal of tolerance induction and stable mixed chimerism. The approach has been successful in adults, with OS of 97% and DFS of 87% in 1 study involving 30 patients.[46] Importantly, none of the patients experienced GVHD despite using mobilized peripheral blood stem cells in lieu of marrow. Eight children were recently reported to have received identical conditioning.[47] With follow-up ranging from 1 to 52 months, OS and DFS are both 100%, with no GVHD.

Together, these studies show excellent results after HLA-ID sibling HSCT, regardless of the conditioning regimen used and the source of hematopoietic cells selected for transplant. However, there is a persistent risk of mortality that ranges from 3% to 7% across the patient series reported, and which almost certainly is higher than the mortality risk experienced by children with SCD through the first 2 decades of life. Thus, the position argued here is that the short-term risks of HLA-identical sibling HSCT are favorably balanced by the long-term certainties of early mortality, extensive morbidity, and poor quality of life, with limited and inadequate supportive care options for adults with SCD.

We also refer to long-term follow-up studies after HSCT that have shown that sickle-related organ damage in most cases is stabilized, and in rare cases, improved. For example, although the benefit of RBC transfusions to prevent stroke in children with silent cerebral infarction was an important finding of the SIT trial, it was also observed that regular RBC transfusions did not universally prevent the progression of silent cerebral infarcts (6 of 99 children had progressive neurologic disease that included stroke in 1 and new or enlarged silent cerebral infarction in 5).[48] In 2 transplant observational series, central nervous system lesions were stable to improved after HSCT in patients with a history of stroke and/or silent cerebral infarct.[46,49] Elevated tricuspid regurgitant velocities, which are associated with early mortality in adults,[18] decreased to the normal range,[46] and 1 adult had resolution of pulmonary hypertension after transplant.[50] Osteonecrosis[51] and abnormal transcranial Doppler velocities[52] have also been shown to improve after successful transplant. However, this is balanced by long-term complications related to myeloablative busulfan that include infertility, primary or secondary gonadal failure, and cardiopulmonary complications. Although the risk of a malignancy related to HSCT is low in this population, systematic follow-up to characterize the incidence has not been universal and is indicated.

The gold standard when comparing 2 therapies, such as HLA-identical sibling HSCT and supportive care for SCD, is a randomized design. Unfortunately, it is not feasible to conduct a randomized transplant trial because there are very few patients who have an HLA-identical sibling donor and because the treatments are quite disparate in their intensity, risk of toxicity, potential for cure, and cost. Together, these considerations make it very unlikely that a comparative trial could be completed in an acceptable period of time, or that equipoise could be sustained in a trial in which 1 intervention generates a cure in most study participants, whereas the other treatment offers none. The decision to undergo HSCT is a complex process, and once physicians and patients accept the idea of curative therapy despite its risks, they are often unwilling to accept noncurative treatment when a suitable donor is available. In addition, the case presented here involves a treatment decision that is limited by the young age of the child. In 2010, Iltis examined whether guidelines made by the United Nations Convention on the Rights of the Child were based on a suitable framework for pediatric bioethics.[53] The Convention stated that for children who are not able to articulate views about decision making, decisions should be made per the patient's best interest. The American Academy of Pediatrics confirmed that health care decisions should be made according to what is best for them, and what is best should be based on parental consent and obtained in collaboration with the child's health care providers, who can offer critical information and guidance.[53] The notion of not pursuing a therapy with curative potential, based upon an assessment only of survival through the first 20 years of life after HSCT and supportive care, and in the absence of a randomized study, seems restrictive with a potential to limit family-centered decision making.

In conclusion, the results of HLA-identical sibling HSCT for SCD, although very good, show that the short-term mortality of the procedure is fixed at 5% to 10% and significantly exceeds the mortality rate experienced by children through the first 2 decades of life who receive optimal medical therapy. The data also strongly show that children after successful transplantation no longer experience vaso-occlusive episodes nor progressive sickle-related organ damage and do not appear to be at risk for early mortality beyond 1 year posttransplant. The ethical question we raise here is the following: should early mortality risk alone be used to restrict treatment choices in a child with SCD? Should this decision making exclude HSCT as a therapeutic option considered only as an experimental treatment of children with SCD, as has been suggested by the counterargument? We disagree strongly about restricting the option of transplantation in children with symptomatic SCD. This is based in part on our reasoning that, all things considered, given the option of living with the disease vs not having the disease, that a reasonable person, parent, child, and physician might choose not to have the disease and that the same decision-making group might also be able to carefully consider the risks and benefits of the therapy.

Authorship

Contribution: C.D.F. and M.C.W. wrote this paper.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

ORCID profiles: C.D.F., 0000-0002-5306-7167.

Correspondence: Mark C. Walters, UCSF Benioff Children's Hospital Oakland, 747 52nd St, Oakland, CA 94609; e-mail: mwalters@mail.cho.org.

REFERENCES

1. Yeruva SL, Paul Y, Oneal P, Nouraie M. Renal failure in sickle cell disease: prevalence, predictors of disease, mortality and effect on length of hospital stay. *Hemoglobin*. 2016;40(5):295-299.

2. Ataga KI, Orringer EP. Renal abnormalities in sickle cell disease. *Am J Hematol*. 2000;63(4):205-211.

3. Kamath AF, Sheth NP, Hosalkar HH, Babatunde OM, Lee GC, Nelson CL. Modern total hip arthroplasty in patients younger than 21 years. *J Arthroplasty*. 2012;27(3):402-408.

4. Ohene-Frempong K. Stroke in sickle cell disease: demographic, clinical, and therapeutic considerations. *Semin Hematol*. 1991;28(3):213-219.

5. Wang W, Enos L, Gallagher D, et al; Cooperative Study of Sickle Cell Disease. Neuropsychologic performance in school-aged children with sickle cell disease: a report from the Cooperative Study of Sickle Cell Disease. *J Pediatr*. 2001;139(3):391-397.

6. Gold JI, Johnson CB, Treadwell MJ, Hans N, Vichinsky E. Detection and assessment of stroke in patients with sickle cell disease: neuropsychological functioning and magnetic resonance imaging. *Pediatr Hematol Oncol*. 2008;25(5):409-421.

7. Fitzhugh CD, Lauder N, Jonassaint JC, et al. Cardiopulmonary complications leading to premature deaths in adult patients with sickle cell disease. *Am J Hematol*. 2010;85(1):36-40.

8. Carroll CP, Haywood C Jr, Fagan P, Lanzkron S. The course and correlates of high hospital utilization in sickle cell disease: evidence from a large, urban Medicaid managed care organization. *Am J Hematol*. 2009;84(10):666-670.

9. Lanzkron S, Haywood C Jr, Segal JB, Dover GJ. Hospitalization rates and costs of care of patients with sickle-cell anemia in the state of Maryland in the era of hydroxyurea. *Am J Hematol*. 2006;81(12):927-932.

10. Brousseau DC, Owens PL, Mosso AL, Panepinto JA, Steiner CA. Acute care utilization and rehospitalizations for sickle cell disease. *JAMA*. 2010;303(13):1288-1294.

11. Panepinto JA, Owens PL, Mosso AL, Steiner CA, Brousseau DC. Concentration of hospital care for acute sickle cell disease-related visits. *Pediatr Blood Cancer*. 2012;59(4):685-689.

12. Kauf TL, Coates TD, Huazhi L, Mody-Patel N, Hartzema AG. The cost of health care for children and adults with sickle cell disease. *Am J Hematol*. 2009;84(6):323-327.

13. Thornburg CD, Files BA, Luo Z, et al; BABY HUG Investigators. Impact of hydroxyurea on clinical events in the BABY HUG trial. *Blood*. 2012;120(22):4304-4310, quiz 4448.

14. Wang WC, Ware RE, Miller ST, et al; BABY HUG investigators. Hydroxycarbamide in very young children with sickle-cell anaemia: a multicentre, randomised, controlled trial (BABY HUG). *Lancet*. 2011;377(9778):1663-1672.

15. Jayabose S, Tugal O, Sandoval C, et al. Clinical and hematologic effects of hydroxyurea in children with sickle cell anemia. *J Pediatr*. 1996;129(4):559-565.

16. Ferster A, Vermylen C, Cornu G, et al. Hydroxyurea for treatment of severe sickle cell anemia: a pediatric clinical trial. *Blood*. 1996;88(6):1960-1964.

17. Walsh KE, Cutrona SL, Kavanagh PL, et al. Medication adherence among pediatric patients with sickle cell disease: a systematic review. *Pediatrics*. 2014;134(6):1175-1183.

18. Gladwin MT, Sachdev V, Jison ML, et al. Pulmonary hypertension as a risk factor for death in patients with sickle cell disease. *N Engl J Med*. 2004;350(9):886-895.

19. Fitzhugh CD, Hsieh MM, Allen D, et al. Hydroxyurea-increased fetal hemoglobin is associated with less organ damage and longer survival in adults with sickle cell anemia. *PLoS One*. 2015;10(11):e0141706.

20. Quinn CT, Rogers ZR, McCavit TL, Buchanan GR. Improved survival of children and adolescents with sickle cell disease. *Blood*. 2010;115(17):3447-3452.

21. Hassell KL. Population estimates of sickle cell disease in the U.S. *Am J Prev Med*. 2010;38(4 Suppl):S512-S521.

22. Maitra P, Caughey M, Robinson L, et al. Risk factors for mortality in adult patients with sickle cell disease: a meta-analysis of studies in North America and Europe. *Haematologica*. 2017;102(4):626-636.

23. Beverung LM, Strouse JJ, Hulbert ML, et al; SIT trial investigators. Health-related quality of life in children with sickle cell anemia: impact of blood transfusion therapy. *Am J Hematol*. 2015;90(2):139-143.

24. Beverung LM, Varni JW, Panepinto JA. Clinically meaningful interpretation of pediatric health-related quality of life in sickle cell disease. *J Pediatr Hematol Oncol*. 2015;37(2):128-133.

25. Palermo TM, Riley CA, Mitchell BA. Daily functioning and quality of life in children with sickle cell disease pain: relationship with family and neighborhood socioeconomic distress. *J Pain*. 2008;9(9):833-840.

26. Patel AB, Pathan HG. Quality of life in children with sickle cell hemoglobinopathy. *Indian J Pediatr*. 2005;72(7):567-571.

27. Fuggle P, Shand PA, Gill LJ, Davies SC. Pain, quality of life, and coping in sickle cell disease. *Arch Dis Child*. 1996;75(3):199-203.

28. Walters MC, De Castro LM, Sullivan KM, et al. Indications and results of HLA-identical sibling hematopoietic cell transplantation for sickle cell disease. *Biol Blood Marrow Transplant*. 2016;22(2):207-211.

29. Gluckman E, Cappelli B, Bernaudin F, et al; Eurocord, the Pediatric Working Party of the European Society for Blood and Marrow Transplantation, and the Center for International Blood and Marrow Transplant Research. Sickle cell disease: an international survey of results of HLA-identical sibling hematopoietic stem cell transplantation. *Blood*. 2017;129(11):1548-1556.

30. Dedeken L, Lê PQ, Azzi N, et al. Haematopoietic stem cell transplantation for severe sickle cell disease in childhood: a single centre experience of 50 patients. *Br J Haematol*. 2014;165(3):402-408.

31. Strocchio L, Zecca M, Comoli P, et al. Treosulfan-based conditioning regimen for allogeneic haematopoietic stem cell transplantation in children with sickle cell disease. *Br J Haematol*. 2015;169(5):726-736.

32. Bhatia M, Kolva E, Cimini L, et al. Health-related quality of life after allogeneic hematopoietic stem cell transplantation for sickle cell disease. *Biol Blood Marrow Transplant*. 2015;21(4):666-672.

33. Lawitschka A, Güclü ED, Varni JW, et al. Health-related quality of life in pediatric patients after allogeneic SCT: development of the PedsQL Stem Cell Transplant module and results of a pilot study. *Bone Marrow Transplant*. 2014;49(8):1093-1097.

34. Oberg JA, Bender JG, Morris E, et al. Pediatric allo-SCT for malignant and non-malignant diseases: impact on health-related quality of life outcomes. *Bone Marrow Transplant*. 2013;48(6):787-793.

35. Caocci G, Efficace F, Ciotti F, et al. Prospective assessment of health-related quality of life in pediatric patients with beta-thalassemia following hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant*. 2011;17(6):861-866.

36. Locatelli F, Kabbara N, Ruggeri A, et al; Eurocord and European Blood and Marrow Transplantation (EBMT) group. Outcome of patients with hemoglobinopathies given either cord blood or bone marrow transplantation from an HLA-identical sibling. *Blood*. 2013;122(6):1072-1078.

37. Miniero R, Rocha V, Saracco P, et al. Cord blood transplantation (CBT) in hemoglobinopathies. Eurocord. *Bone Marrow Transplant*. 1998;22(Suppl 1):S78-S79.

38. Brichard B, Vermylen C, Ninane J, Cornu G. Persistence of fetal hemoglobin production after successful transplantation of cord blood stem cells in a patient with sickle cell anemia. *J Pediatr*. 1996;128(2):241-243.

39. Gore L, Lane PA, Quinones RR, Giller RH. Successful cord blood transplantation for sickle cell anemia from a sibling who is human leukocyte antigen-identical: implications for comprehensive care. *J Pediatr Hematol Oncol*. 2000;22(5):437-440.

40. Krishnamurti L, Kharbanda S, Biernacki MA, et al. Stable long-term donor engraftment following reduced-intensity hematopoietic cell transplantation for sickle cell disease. *Biol Blood Marrow Transplant*. 2008;14(11):1270-1278.

41. Matthes-Martin S, Lawitschka A, Fritsch G, et al. Stem cell transplantation after reduced-intensity conditioning for sickle cell disease. *Eur J Haematol*. 2013;90(4):308-312.

42. Bhatia M, Jin Z, Baker C, et al. Reduced toxicity, myeloablative conditioning with BU, fludarabine, alemtuzumab and SCT from sibling donors in children with sickle cell disease. *Bone Marrow Transplant*. 2014;49(7):913-920.

43. King AA, Kamani N, Bunin N, et al. Successful matched sibling donor marrow transplantation following reduced intensity conditioning in children with hemoglobinopathies. *Am J Hematol*. 2015;90(12):1093-1098.

44. Walters MC, Patience M, Leisenring W, et al; Multicenter Investigation of Bone Marrow Transplantation for Sickle Cell Disease. Stable mixed hematopoietic chimerism after bone marrow transplantation for sickle cell anemia. *Biol Blood Marrow Transplant*. 2001;7(12):665-673.

45. Lisini D, Zecca M, Giorgiani G, 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): 1859-1867.

46. Hsieh MM, Fitzhugh CD, Weitzel RP, et al. Nonmyeloablative HLA-matched sibling allogeneic hematopoietic stem cell transplantation for severe sickle cell phenotype. *JAMA*. 2014; 312(1):48-56.

47. Guilcher G, Monagel D, Leaker M, et al. Non-myeloablative alemtuzumab/low dose total body irradiation conditioning for children undergoing HLA-matched sibling donor haematopoietic cell transplantation for sickle cell diseaes. Presented at the 43rd Annual Meeting of the European Society for Blood and Marrow Transplantation. 28 March 2017. Marseille, France.

48. DeBaun MR, Casella JF. Transfusions for silent cerebral infarcts in sickle cell anemia. *N Engl J Med*. 2014;371(19): 1841-1842.

49. Walters MC, Hardy K, Edwards S, et al; Multicenter Study of Bone Marrow Transplantation for Sickle Cell Disease. Pulmonary, gonadal, and central nervous system status after bone marrow transplantation for sickle cell disease. *Biol Blood Marrow Transplant*. 2010;16(2):263-272.

50. Pittman C, Hsieh MM, Coles W, Tisdale JF, Weir NA, Fitzhugh CD. Reversal of pre-capillary pulmonary hypertension in a patient with sickle cell anemia who underwent haploidentical peripheral blood stem cell transplantation. *Bone Marrow Transplant*. 2017;52(4):641-642.

51. Bernaudin F, Socie G, Kuentz M, et al; SFGM-TC. Long-term results of related myeloablative stem-cell transplantation to cure sickle cell disease. *Blood*. 2007;110(7):2749-2756.

52. Bernaudin F, Verlhac S, Arnaud C, et al. Long-term treatment follow-up of children with sickle cell disease monitored with abnormal transcranial Doppler velocities. *Blood*. 2016; 127(14):1814-1822.

53. Iltis AS. Toward a coherent account of pediatric decision making. *J Med Philos*. 2010;35(5):526-552.

54. Lucarelli G, Isgrò A, Sodani P, et al. Hematopoietic SCT for the Black African and non-Black African variants of sickle cell anemia. *Bone Marrow Transplant*. 2014;49(11):1376-1381.

55. McPherson ME, Hutcherson D, Olson E, Haight AE, Horan J, Chiang KY. Safety and efficacy of targeted busulfan therapy in children undergoing myeloablative matched sibling donor BMT for sickle cell disease. *Bone Marrow Transplant*. 2011;46(1): 27-33.

56. Majumdar S, Robertson Z, Robinson A, Starnes S, Iyer R, Megason G. Outcome of hematopoietic cell transplantation in children with sickle cell disease, a single center's experience. *Bone Marrow Transplant*. 2010;45(5):895-900.

57. Panepinto JA, Walters MC, Carreras J, et al; Non-Malignant Marrow Disorders Working Committee, Center for International Blood and Marrow Transplant Research. Matched-related donor transplantation for sickle cell disease: report from the Center for International Blood and Transplant Research. *Br J Haematol*. 2007;137(5):479-485.

58. Vermylen C, Cornu G, Ferster A, et al. Haematopoietic stem cell transplantation for sickle cell anaemia: the first 50 patients transplanted in Belgium. *Bone Marrow Transplant*. 1998; 22(1):1-6.