C. R. Biologies 336 (2013) 148–151

Contents lists available at SciVerse ScienceDirect

Comptes Rendus Biologies

www.sciencedirect.com

Medical sciences/Sciences médicales

Hematopoietic stem cell transplantation in SCD

Jean-Hugues Dalle [a,*,b]

[a] Service d'hémato-immunologie pédiatrique, hôpital Robert-Debré, AP–HP, 48, boulevard Sérurier, 75935 Paris cedex 19, France
[b] Faculté de médecine, université Paris Diderot, 5, rue Thomas-Mann, 75205 Paris cedex 13, France

ARTICLE INFO

Article history:
Available online 12 October 2012

Keywords:
Sickle cell disease
Transplantation
Children
Myeloablative

ABSTRACT

Hematopoietic stem cell transplantation (HSCT) is the one and only curative therapy available for patient with severe sickle cell disease (SCD). Until today, several hundreds of patients have undergone geno-identical HSCT. More than 200 patients were transplanted in France. The first indication was cerebral vasculopathy. Among both malignant and non-malignant diseases treated with HSCT, the success rate obtained in SCD patients appears as the best one. From the year 2000, more than 95% of transplanted patients survived the HSCT procedure and more than 90% are completely cured and experience a very satisfying health condition post-transplantation. However, the current standard procedure includes a myeloablative conditioning regimen for warranting engraftment. Such regime is linked to severe long-term side effects such as hypofertility. Due to the excellent obtained results, we have to think about a possible widening of indications, a decrease of conditioning intensity and toxicity, and about HSCT from alternative stem cell sources, such as mismatch family donor, unrelated volunteer donor or unrelated cord blood.

1. Introduction

The first hematopoietic stem cell transplantation (HSCT) in the frame of sickle cell disease (SCD) was performed in United States in a child who presented with acute lymphoblastic leukaemia [1–3].

More than 25 years after this first transplantation, and despite the development and enhancement of different supportive care, including hydroxyurea and transfusion programs, allogeneic stem cell transplantation still remains the only curative therapy for severe sickle cell disease patients [4–8].

HSCT for SCD appeared as the success story of allogeneic stem cell transplantation from a sibling donor, since in wider and more recent series more than 95% of patients survive and 90% of patients are cured after transplantation [4,6,7,9,10].

The concept is relatively simple: to ensure the replacement of abnormal haematopoiesis by a normal one, but the equation for winning it is very complex! The transplantation procedure is divided into several steps: identify patient with HSCT indication, have satisfying HLA compatible donor, select a good stem cell source, define and prescribe the good conditioning regime i.e. a regime leading to engraftment with the least possible side effects. Each term of this equation has to be discussed.

2. Indications

In 2010, the French National Health Agency named Haute Autorité de santé (HAS) published a document related to the diagnostic and treatment for sickle cell disease patients [5]. This publication was written by expert panel. In this document, it could seem surprising that HSCT was reduced to a single and short chapter, whereas this approach is considered as the only curative therapy. However, experts differentiate worldwide recognized indications, and these have to be discussed. Standard indications were symptomatic or asymptomatic cerebral vasculopathy, recurrent acute chest syndrome or recurrent

* Service d'hémato-immunologie pédiatrique, hôpital Robert-Debré, AP–HP, 48, boulevard Sérurier, 75935 Paris cedex 19, France.
E-mail address: jean-hugues.dalle@rdb.aphp.fr.

1631-0691/$ – see front matter
http://dx.doi.org/10.1016/j.crvi.2012.09.004

vaso-occlusive crisis despite hydroxycarbamide therapy with good patient compliance. All other indications are considered as not consensual and have to be discussed by experts.

In 2011, the Paediatric Disease Working Party of European Group for Blood and Marrow Transplantation organized an expert meeting in order to publish European guidelines for HSCT in both SCD and Thalassaemia. Regarding SCD, the experts consider this disease as a severe chronic disease with important complications during adulthood that impaired quality of life and life expectancy [4,5,7,11–27]. Then they have made the following recommendation: "*young patients with symptomatic SCD who have a matched sibling donor should be transplanted as early as possible, preferably in pre-school age*" (manuscript in preparation).

It appears probably difficult or excessive to propose allogeneic transplantation for the very children presenting with SCD only because they have a sibling donor; however, to indicate HSCT once disease symptoms appear seems to be the best therapeutic option for the long-term quality of life. Then, recurrent vaso-occlusive crisis, recurrent acute chest syndrome, allo-immunisation, recurrent splenic sequestration, osteonecrosis may appear as reasonable indications for HSCT from a sibling donor. Regarding the age for transplantation, both donor and recipient age appeared as prognostic factors for the results of HSCT whatever the indication for which transplantations were performed. However, a recent publication from Kuentz et al. reported similar results for SCD patients transplanted beyond 16 years of age compared to younger patients [10].

From 2011, we – at the Robert-Debré hospital – organize three to four times a year a national web meeting with 10 to 15 participating centers for discussing difficult or so-called non-conventional indications for SCD patients. Up to today, more than 30 patient-cases have been debated and we always reached consensus.

3. Donors

Almost all transplantation performed to date for SCD used sibling HLA compatible donors and all widely published series include only such a donor [2,5–7,28–32]. In France, among more than 220 patients transplanted for SCD, about 10% received cryopreserved cord blood from sibling. The results obtained when using HLA 6/6 related cord blood were similar to those obtained when using bone marrow.

The use of HLA compatible volunteer unrelated donor appears as almost impossible, since the wide majority of SCD patients have HLA-haplotypes under-represented or not represented at all in bone marrow donor registries all around the World [29,33]. For example, in France, we simulated a donor search for SCD patients previously transplanted from sibling donor. Among 100 patients, only one has had a 9/10 compatible donor on BMDW (Bone Marrow Donors Worldwide) (personal data).

The results when using unrelated partially matched unrelated cord blood appeared as not sufficient for extending this approach outside academic investigational protocol. Ruggeri et al. published in 2011 the results of unrelated cord blood transplantation for both thalassaemia and SCD [34]. Regarding SCD, the event-free survival rate was about 50%. Such a result is not acceptable for a non-malignant disease with other available therapies even though these therapies are not curative. Some American colleagues currently conduct a prospective study evaluating unrelated transplantation after reduced intensity conditioning regimen for SCD patients. At the beginning they decided to use either unrelated HLA compatible volunteer donors or unrelated cord blood. Due to the very high rejection rate, they decided to stop the unrelated cord blood set and still continue only unrelated volunteer donors [35]. As this study is still on going, the results for patients who receive transplantation from unrelated donor are not yet known. Some other cooperative groups think about a prospective study using T-repleted haplo-identical HSCT from related donor followed by cyclophosphamide administered after transplantation as reported by Munchel et al. in 2011 [36,37]. This approach, developed in a hematological malignant disease setting, could appear as very interesting in the non-malignant disease setting, since no graft versus leukemia or tumor effect is required. In SCD, this approach may overcome the absence of HLA compatible volunteer donors since almost all patients have available partially matched-related donor. Of course, we need investigational prospective study to evaluate this procedure.

4. Stem cell source

As discussed above, more than 90% of transplantations performed and reported to date for SCD used bone marrow. The remaining 10% used related cord blood. Very few or virtually no HSCT were performed from peripheral blood stem cells (PBSC). Thus, we do not have strong results leading to strong conclusions. However, the results of HSCT performed with PBSC in the setting of malignant hematological diseases like acute lymphoblastic leukemia are known. Different cooperative study groups reported higher cumulative incidence of graft versus host disease when using PBSC comparing to bone marrow as stem cell source in pediatric setting [38]. These results will be very important for subsequent discussions related to the conditioning regimen intensity since intensity reduction may be counter-balanced by stem cell dose increase and then encourage the possible switch from bone marrow to PBSC.

5. Conditioning regime

The wide, French experient in SCD-HSCT, as the other international published experiments, was built on myeloablative conditioning regimen as part of transplantation procedure [3,6,8,9,31,39,40]. In France, our "standard" conditioning regime was cyclophosphamide 200 mg/m^2 total dose and busulfan 16 mg/kg total dose taken orally, and from 10 years by using intra-venous product (body weight adapted dosage equivalent to 1 mg/kg per single dose $\times$ 16) and the addition of rabbit anti-thymoglobulins (20 mg/kg total dose, Genzyme®, France) from 1992. Transplantation is followed by immunosuppressive

therapy with cyclosprin A and short-course of methotrexate. As described above, with this conditioning regime and this immunosuppressive therapy, the global results obtained were very satisfying, with more than 95% of overall survival and 92% of disease-free-survival. Despite these excellent results, we have huge concerns regarding the later effects due to such a conditioning regime and particularly hypofertility or even sterility [6,9,31,40–46]. These concerns are shared by every other groups who perform HSCT in pediatric populations. We have to develop and experiment a so-called reduced intensity conditioning regime in order to maintain the good results we have at this time and to avoid side effects as much as possible. In this line, the Austrian experiment reported by Mathhes-Martin et al. during the last PDWP-EBMT meeting in Prague (June 2012) appear very interesting [47]. This team has transplanted eight pediatric patients following a reduced intensity conditioning regime containing Fludarabine, Melphalan and Thiotepa with GvHD prophylaxis based on serotherapy associated to cyclosporine and a short-course of methotrexate. With this procedure, all patients experienced hematopoietic engraftment, none have had any acute or chronic GvHD, and finally the majority of patients experienced full donor chimerism either spontaneously or after donor lymphocyte infusion. Of course, as such conditioning procedure has to be evaluated in a larger patient cohort, but if the results obtained here are confirmed the expected side effects would lesser and lighter than those previously described. Other authors tried for using reduced intensity conditioning regimen [48–51]. Some authors reported unsatisfying results, such as Iannone et al. in 2003. They did not obtain any stable engraftment among six patients who received fludarabine and 2 Gy–TBI association as conditioning regime [48]. However, there are some with very interesting results, such as those obtained and published by Hsieh et al. in 2009 regarding nine adult patients transplanted after 3 Gy–TBI and alemtuzumab 1 mg/kg as conditioning regimen. At report-time, all patients were alive without SCD and without any GvHD related symptoms [51].

6. Conclusion

In conclusion, HSCT appears as the only curative therapy for sickle cell disease patients. Results are very satisfying when using either bone marrow or cord blood from sibling donor after myeloablative conditioning regimen associated to strong and prolonged immunosuppressive therapy. Due to long-term side effects, a reduced intensity and reduced toxicity conditioning regime have to be developed. Due to the virtual absence of HLA compatible unrelated donor for SCD patients, alternative transplantation from either unrelated partial mismatch cord blood or haplo-identical related donor has to be investigated. Non-conventional approaches have to be developed only in the frame of prospective studies.

Disclosure of interest

The author declares that he has no conflicts of interest concerning this article.

References

[1] F. Bernaudin, G. Souillet, J.P. Vannier, et al., Treatment of severe forms of sickle cell anemia with bone marrow allograft: French experience (15 cases). SFGM, Nouvelle Revue Française d'Hématologie 35 (3) (1993) 319–323.
[2] F.L. Johnson, W.C. Mentzer, K.A. Kalinyak, et al., Bone marrow transplantation for sickle cell disease. The United States experience, The American Journal of Pediatric Hematology/Oncology 16 (1) (1994) 22–26.
[3] M.C. Walters, M. Patience, W. Leisenring, et al., Bone marrow transplantation for sickle cell disease, The New England Journal of Medicine 335 (6) (1996) 369–376.
[4] C.T. Quinn, Z.R. Rogers, T.L. McCavit, et al., Improved survival of children and adolescents with sickle cell disease, Blood 115 (17) (2010) 3447–3452.
[5] Santé Had. Syndromes drépanocytaires majeurs de l'enfant et de l'adolescent 2010. Available from: http://www.has-sante.fr/portail/upload/docs/application/pdf/2010-04/ald_10_pnds_drepano_enfant_web.pdf.
[6] M.C. Walters, K.M. Sullivan, Stem cell transplantation for sickle cell disease, The New England Journal of Medicine 362 (10) (2010) 955–956 (author reply 6).
[7] P.L. Kavanagh, P.G. Sprinz, S.R. Vinci, et al., Management of children with sickle cell disease: a comprehensive review of the literature, Pediatrics 128 (6) (2011) e1552–e1574.
[8] C. Vermylen, G. Cornu, A. Ferster, et al., Haematopoietic stem cell transplantation for sickle cell anaemia: the first 50 patients transplanted in Belgium, Bone Marrow Transplantation 22 (1) (1998) 1–6.
[9] F. Bernaudin, Stem cell transplantation in sickle cell disease: results, perspectives, Archives de Pédiatrie : Organe Officiel de la Societé Française de Pédiatrie 15 (5) (2008) 633–635.
[10] M. Kuentz, M. Robin, N. Dhedin, et al., Is there still a place for myeloablative regimen to transplant young adults with sickle cell disease? Blood 118 (16) (2011) 4491–4492 (author reply 2–3).
[11] F. Bernaudin, S. Verlhac, L. Coic, et al., Long-term follow-up of pediatric sickle cell disease patients with abnormal high velocities on transcranial Doppler, Pediatric Radiology 35 (3) (2005) 242–248.
[12] D.K. McClish, L.T. Penberthy, V.E. Bovbjerg, et al., Health-related quality of life in sickle cell patients: the PiSCES project, Health and Quality of Life Outcomes 3 (2005) 50.
[13] J.A. Panepinto, K.M. O'Mahar, M.R. DeBaun, et al., Health-related quality of life in children with sickle cell disease: child and parent perception, British Journal of Haematology 130 (3) (2005) 437–444.
[14] E.S. Klings, D.F. Wyszynski, V.G. Nolan, et al., Abnormal pulmonary function in adults with sickle cell anemia, American Journal of Respiratory and Critical Care Medicine 173 (11) (2006) 1264–1269.
[15] M. Hysing, I. Elgen, C. Gillberg, et al., Emotional and behavioural problems in subgroups of children with chronic illness: results from a large-scale population study, Child: Care, Health and Development 35 (4) (2009) 527–533.
[16] M. Hysing, B. Sivertsen, K.M. Stormark, et al., Sleep in children with chronic illness, and the relation to emotional and behavioral problems: a population-based study, Journal of Pediatric Psychology 34 (6) (2009) 665–670.
[17] Y.J. Martinez, K. Ercikan, Chronic illnesses in Canadian children: what is the effect of illness on academic achievement, and anxiety and emotional disorders? Child: Care, Health and Development 35 (3) (2009) 391–401.
[18] D.D. Amendah, M. Mvundura, P.L. Kavanagh, et al., Sickle cell disease-related pediatric medical expenditures in the US, American Journal of Preventive Medicine 38 (4 Suppl) (2010) S550–S556.
[19] L.J. Becton, R.V. Kalpatthi, E. Rackoff, et al., Prevalence and clinical correlates of microalbuminuria in children with sickle cell disease, Pediatric Nephrology (Berlin, Germany) 25 (8) (2010) 1505–1511.
[20] F. Bernaudin, S. Verlhac, C. Arnaud, et al., Impact of early transcranial Doppler screening and intensive therapy on cerebral vasculopathy outcome in a newborn sickle cell anemia cohort, Blood 117 (4) (2011) 1130–1140 (quiz 436).
[21] M.R. Debaun, S.A. Sarnaik, M.J. Rodeghier, et al., Associated risk factors for silent cerebral infarcts in sickle cell anemia: low baseline hemoglobin, gender and relative high systolic blood pressure, Blood 119 (16) (2012) 3684–3690.
[22] E.M. van der Plas, X.W. van den Tweel, R.B. Geskus, et al., Mortality and causes of death in children with sickle cell disease in the Netherlands, before the introduction of neonatal screening, British Journal of Haematology 155 (1) (2011) 106–110.
[23] C.J. Wang, P.L. Kavanagh, A.A. Little, et al., Quality of care indicators for children with sickle cell disease, Pediatrics 128 (3) (2011) 484–493.
[24] W.C. Wang, Sickle cell disease and compromised cognition, Pediatric Blood & Cancer 56 (5) (2011) 705–706.

[25] V. Brousse, C. Elie, M. Benkerrou, et al., Acute splenic sequestration crisis in sickle cell disease: cohort study of 190 paediatric patients, British Journal of Haematology 156 (5) (2012) 643–648.
[26] M.R. Debaun, F.D. Armstrong, R.C. McKinstry, et al., Silent cerebral infarcts: a review on a prevalent and progressive cause of neurological injury in sickle cell anemia, Blood 119 (20) (2012) 4587–4596.
[27] M.J. Hollocks, T.B. Kok, F.J. Kirkham, et al., Nocturnal oxygen desaturation and disordered sleep as a potential factor in executive dysfunction in sickle cell anemia, Journal of the International Neuropsychological Society: JINS 18 (1) (2012) 168–173.
[28] W.C. Mentzer, S. Heller, P.R. Pearle, et al., Availability of related donors for bone marrow transplantation in sickle cell anemia, The American Journal of Pediatric Hematology/Oncology 16 (1) (1994) 27–29.
[29] M.C. Walters, M. Patience, W. Leisenring, et al., Barriers to bone marrow transplantation for sickle cell anemia, Biology of Blood and Marrow Transplantation: Journal of the American Society for Blood and Marrow Transplantation 2 (2) (1996) 100–104.
[30] F. Locatelli, V. Rocha, W. Reed, et al., Related umbilical cord blood transplantation in patients with thalassemia and sickle cell disease, Blood 101 (6) (2003) 2137–2143.
[31] F. Bernaudin, G. Socie, M. Kuentz, et al., Long-term results of related myeloablative stem cell transplantation to cure sickle cell disease, Blood 110 (7) (2007) 2749–2756.
[32] J.A. Panepinto, M.C. Walters, J. Carreras, et al., Matched-related donor transplantation for sickle cell disease: report from the Center for International Blood and Transplant Research, British Journal of Haematology 137 (5) (2007) 479–485.
[33] L. Krishnamurti, S. Abel, M. Maiers, et al., Availability of unrelated donors for hematopoietic stem cell transplantation for hemoglobinopathies, Bone Marrow Transplantation 31 (7) (2003) 547–550.
[34] A. Ruggeri, M. Eapen, A. Scaravadou, et al., Umbilical cord blood transplantation for children with thalassemia and sickle cell disease, Biology of Blood and Marrow Transplantation: Journal of the American Society for Blood and Marrow Transplantation 17 (9) (2011) 1375–1382.
[35] N.R. Kamani, M.C. Walters, S.<et-al> Carter, Unrelated donor cord blood transplantation for children with severe sickle cell disease: results of one cohort from the phase ii study from the blood and marrow transplant clinical trials network (BMT CTN), Biology of Blood and Marrow Transplantation: Journal of the American Society for Blood and Marrow Transplantation 18 (8) (2012) 1265–1272.
[36] A. Munchel, C. Kesserwan, H.J. Symons, et al., Non-myeloablative, HLA-haplo-identical bone marrow transplantation with high dose, post-transplantation cyclophosphamide, Pediatric Reports 3 (Suppl. 2) (2011) e15.
[37] A.T. Munchel, Y.L. Kasamon, E.J. Fuchs, Treatment of hematological malignancies with non-myeloablative, HLA-haplo-identical bone marrow transplantation and high dose, post-transplantation cyclophosphamide, Best Practice & Research Clinical Haematology 24 (3) (2011) 359–368.
[38] D. Gallardo, R. de la Camara, J.B. Nieto, et al., Is mobilized peripheral blood comparable with bone marrow as a source of hematopoietic stem cells for allogeneic transplantation from HLA-identical sibling donors? A case-control study, Haematologica 94 (9) (2009) 1282–1288.
[39] F. Bernaudin, G. Souillet, J.P. Vannier, et al., Bone marrow transplantation (BMT) in 14 children with severe sickle cell disease (SCD): the French experience. GEGMO, Bone Marrow Transplantation 12 (Suppl. 1) (1993) 118–121.
[40] M.C. Walters, R. Storb, M. Patience, et al., Impact of bone marrow transplantation for symptomatic sickle cell disease: an interim report. Multicenter investigation of bone marrow transplantation for sickle cell disease, Blood 95 (6) (2000) 1918–1924.
[41] M.C. Walters, K.M. Sullivan, F. Bernaudin, et al., Neurologic complications after allogeneic marrow transplantation for sickle cell anemia, Blood 85 (4) (1995) 879–884.
[42] F. Bernaudin, Hematopoietic stem cell graft: cure for sickle cell anemia? La Revue du Praticien 54 (14) (2004) 1565–1567.
[43] C. Brachet, C. Heinrichs, S. Tenoutasse, et al., Children with sickle cell disease: growth and gonadal function after hematopoietic stem cell transplantation, Journal of Pediatric Hematology/Oncology 29 (7) (2007) 445–450.
[44] B. Eggleston, M. Patience, S. Edwards, et al., Effect of myeloablative bone marrow transplantation on growth in children with sickle cell anaemia: results of the multicenter study of haematopoietic cell transplantation for sickle cell anaemia, British Journal of Haematology 136 (4) (2007) 673–676.
[45] M.C. Walters, K. Hardy, S. Edwards, et al., Pulmonary, gonadal, and central nervous system status after bone marrow transplantation for sickle cell disease, Biology of Blood and Marrow Transplantation: Journal of the American Society for Blood and Marrow Transplantation 16 (2) (2010) 263–272.
[46] P. Jadoul, J. Donnez, How does bone marrow transplantation affect ovarian function and fertility? Current Opinion in Obstetrics & Gynecology 24 (3) (2012) 164–171.
[47] S. Matthes, A. Lawitchka, G. Fritsch, et al. Stem cell transplantation for sickle cell disease with reduced intensity conditioning regimen, 8th meeting of the EBMT Paediatric Diseases Working Party and 3rd meeting of the EBMT; Prague, 2012.
[48] R. Iannone, J.F. Casella, E.J. Fuchs, et al., Results of minimally toxic non-myeloablative transplantation in patients with sickle cell anemia and beta-thalassemia, Biology of Blood and Marrow Transplantation: Journal of the American Society for Blood and Marrow Transplantation 9 (8) (2003) 519–528.
[49] M.E. Horwitz, I. Spasojevic, A. Morris, et al., Fludarabine-based non-myeloablative stem cell transplantation for sickle cell disease with and without renal failure: clinical outcome and pharmacokinetics, Biology of Blood and Marrow Transplantation: Journal of the American Society for Blood and Marrow Transplantation 13 (12) (2007) 1422–1426.
[50] L. Krishnamurti, S. Kharbanda, M.A. Biernacki, et al., Stable long-term donor engraftment following reduced intensity hematopoietic cell transplantation for sickle cell disease, Biology of Blood and Marrow Transplantation: Journal of the American Society for Blood and Marrow Transplantation 14 (11) (2008) 1270–1278.
[51] M.M. Hsieh, E.M. Kang, C.D. Fitzhugh, et al., Allogeneic hematopoietic stem cell transplantation for sickle cell disease, The New England Journal of Medicine 361 (24) (2009) 2309–2317.