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.

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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
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 BMDB (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 experiment 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/m² 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 × 16) and the addition of rabbit anti-thymoglobulins (20 mg/kg total dose, Genzyme®, France) from 1992. Transplantation is followed by immunosuppressive
therapy with cyclosporin 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 MathesMartin 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 Thiopeta with GvHD prophylaxis based on serotherapy associated to cyclosporine and a short-course of methotrexate. With this procedure, all patients experienced hematopoietic engraftment, none 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


