Haematopoietic cell transplantation in the treatment of sickle cell disease

Robert C Atkins & Mark C Walters†
Children's Hospital & Research Center at Oakland, Blood and Marrow Transplantation Program, 747 52nd Street, Oakland, CA 94609, USA

Allogeneic haematopoietic cell transplantation (HCT) is presently the only treatment which offers the possibility of a cure for patients with sickle cell disease (SCD). While ~ 84% of patients survive disease-free after human leukocyte antigen (HLA)-identical sibling donor HCT, this therapy has traditionally been reserved for patients who have suffered serious complications due to the risk of transplant-related morbidity and mortality. Typically, these sickle-related complications have included recurrent episodes of acute chest syndrome, recurrent vaso-occlusive episodes and stroke. The future of HCT for haemoglobinopathies undoubtedly will evolve as transplant-related complications are reduced and as the process of selecting patients for HCT is refined.

Keywords: bone marrow transplant, haemoglobinopathy, sickle cell disease, stem cell transplantation, thalassaemia


1. Introduction

The treatment of sickle cell disease (SCD) by haematopoietic cell transplantation (HCT) was initiated > 20 years ago, but its role in the treatment of SCD has shifted as perceptions about this and other treatment options evolve. Historically, the application of HCT for non-malignant disorders has been governed by considerations of when and for whom to administer a therapy that carries a risk of life-threatening complications [1]. While the Kaplan–Meier probability of survival after human leukocyte antigen (HLA)-identical sibling HCT for SCD is 93% (Figure 1), this is balanced by a median lifespan that exceeds 40 years among sickle cell anaemia patients who receive supportive care [2]. While it is possible that symptomatic patients such as those who are eligible for transplantation might experience increased mortality, the alternatives of supportive or other therapeutic interventions still warrant careful consideration. As the natural history of SCD shifts to longer survival in response to improved supportive care, the targeting of selected patients for whom risk/benefit considerations warrant intervention by HCT gains importance.

2. Transplantation for non-malignant disorders

The modern era of transplantation began in the late 1960s, when HLA typing made it possible to select histocompatible donors. As a result of this and other advances in the development of effective immunosuppressive agents, the potential to correct hereditary disorders by replacing defective host haematopoietic cells with those from healthy histocompatible donors became possible [3]. Thus, the development of HCT for SCD followed from the historical application of bone marrow transplantation for non-malignant disorders. The conventional approach was to
Haematopoietic cell transplantation in the treatment of sickle cell disease

Table 1. Worldwide experience of HCT for SCD.

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Belgium</th>
<th>Pesaro</th>
<th>France</th>
<th>Multi-centre</th>
<th>Other US/Europe</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>BU, CY/BU, CY, ATG</td>
<td>36</td>
<td>14</td>
<td>19</td>
<td>60</td>
<td>59</td>
<td>16*</td>
</tr>
<tr>
<td>BU, CY/BU, CY, ATG</td>
<td>8.6 (1.7 - 23)</td>
<td>7</td>
<td>8.8 (4 - 38)</td>
<td>9.9 (2.2 - 22)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BU, CY/BU, CY, ATG</td>
<td>34 (94)</td>
<td>14 (100)</td>
<td>54 (90)</td>
<td>55 (94)</td>
<td>13 (81)</td>
<td>182 (91)</td>
</tr>
<tr>
<td>Deaths</td>
<td>2</td>
<td>0</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>19</td>
</tr>
<tr>
<td>Graft rejection/recurrent SCD (%)</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>5</td>
<td>1</td>
</tr>
</tbody>
</table>

*3 French patients were reported in two series, 1 of whom died after HCT.
*1 patient was disease-free after a 2nd HCT.
*1 patient had Morquio's disease and 2 had acute leukaemia concomitantly.

Figure 1. Kaplan–Meier estimates of survival and event-free survival after bone marrow transplantation for sickle cell disease – multi-centre investigation outcome after transplantation for 59 children with advanced symptomatic sickle cell disease. Kaplan–Meier estimates for survival and event-free survival following marrow transplantation are shown. An event was defined as death, graft rejection or recurrence of sickle cell disease. A cumulative incidence curve for graft rejection and return of sickle cell disease is also depicted.

ATG: Antithymocyte globulin; BU: Busulfan; CY: Cyclophosphamide; HCT: Haematopoietic cell transplantation; SCD: Sickle cell disease; TLI: Total lymphoid irradiation; TBI: Total body irradiation.
eliminate the pre-existing dysfunctional marrow by cytodestruction. However, this requirement for myeloablation was circumvented when treating patients with immunodeficiencies and severe aplastic anaemia (SAA), because marrow ablation was not required for engraftment of donor cells in these disorders. Instead, either no pregrafting immunosuppression was administered before HLA-identical sibling HCT, as in patients with severe combined immune deficiency syndrome, or, in patients with SAA, immunosuppression by cyclophosphamide (CY) alone was used to suppress host immunity and thereby promote engraftment [4].

The approach for other non-malignant disorders, in which hosts were partially or fully immunocompetent, required the use of myeloablative conditioning prior to transplant to ensure engraftment. Successful transplantation was performed in children with Wiskott–Aldrich syndrome after administration of myeloablative doses of total body irradiation (TBI) either alone or in combination with antithymocyte globulin (ATG) [5,6]. Due to concerns about the long-term effects of radiation in children, this regimen was eventually replaced by a combination of busulfan (BU) and CY [7,8]. Together, these early studies showed that myeloablative preparative regimens were effective for non-malignant diseases in children and had an acceptable safety profile [6]. This regimen was extended to thalassaemia major when, in 1982, a 16-month old Italian boy with Cooley’s anaemia received a successful HLA-identical sibling allograft [9]. This first experience suggested that the combination of BU and CY was sufficiently immunosuppressive and myeloablative to overcome the hypercellular marrow of haemoglobinopathies and to satisfy the requirement of immunosuppression to facilitate engraftment. Since this pioneering Seattle case, a team of investigators from Pesaro, Italy has performed > 800 transplantation cases for thalassaemia major and defined optimal risk-based regimens for transplant recipients [10,11].

The development of HCT for SCD followed a somewhat different course. The first case report of HCT for SCD in 1984 involved a patient with acute myelogenous leukaemia who was cured of both disorders [12]. Since 1988, several groups in the US, Belgium, France and Italy have studied HCT as a primary means of treating symptomatic SCD. Patients with SCD who had recurrent acute chest syndrome (ACS), recurrent vaso-occlusive painful crises or stroke received myeloablative doses of BU and CY, with or without ATG, before HCT, and cyclosporine (CSP) alone or in combination with methotrexate and in other combinations for postgrafting immunosuppression. Other preparative regimen variations included the use of total lymphoid irradiation (TLI) in European centres before the widespread use of ATG [13,14]. Over the ensuing 12 years, ∼ 201 patients received an allogeneic sibling-donor HCT, with an overall disease free survival of 83% (Table 1) [15]. Together, this experience suggested that, as in thalassaemia major and other hereditary haematological disorders, HCT was an effective therapy for SCD.

3. Current options for treatment of sickle cell disease

Data from the Cooperative Study of Sickle Cell Disease (CSSCD) demonstrated a reduction in sickle cell-related morbidity and mortality since 1978 [16]. In comparison with previous reports of a median lifespan of 14.3 years in 1973, the CSSCD reported in 1994 that men and women with sickle cell anaemia had a median lifespan of 42 and 48 years, respectively. Clinical factors associated an increased risk of early death with low levels of fetal and total haemoglobin and leukocytosis at baseline [17]. These data documented significant improvement that correlated with improved availability of supportive care and patient education, but also demonstrated a 30-year decrement in lifespan compared with African-Americans who lack SCD. The urgency for implementing new interventions that extend survival becomes immediately apparent.

The growth in therapeutic options for SCD has accelerated over the past 2 decades. The clinical and investigative experiences with interventions such as hydroxyurea (HU) and chronic transfusions, and with supportive care measures, have altered perceptions about the timing and indications for HCT. By simply instituting appropriate newborn screening and follow-up of affected infants, mortality from SCD has been significantly decreased [18]. Prophylaxis with oral penicillin has dramatically decreased the incidence of pneumococcal sepsis, and the newer 7-valent conjugate pneumococcal vaccine may provide additional protection [19]. These and other interventions have profoundly improved the outlook of children who inherit SCD.

Transfusion, when applied judiciously and appropriately, is an essential therapeutic modality in SCD for the prevention and management of complications such as cerebrovascular accidents (CVA). Infarctive stroke occurs most frequently in children with haemoglobin SS disease (Hb SS) who are < 20 years of age (0.44 episodes per 100 patient years), but adults who are ≥ 30 years of age are also at risk [20,21]. The overall prevalence of stroke among patients with Hb SS is ∼ 5%. Chronic transfusions to reduce the haemoglobin S level to < 30% have reduced the probability of a subsequent CVA from 90 to 10% in patients observed for > 1 year after the first event [21,22]. Patients maintained at these low levels of haemoglobin S also benefit from a reduced incidence of severe pain crisis and acute chest crisis [23]. In contrast, haemorrhagic stroke, which is more common in the third decade of life, may not be prevented by chronic transfusion. To screen for high-risk patients, transcranial Doppler ultrasoundography (TCD) has become an important tool. In a randomised clinical trial of transfusions to prevent stroke in high-risk children who were 2 – 16 years of age, 16% of children who had an abnormal TCD, treated by observation alone, had a CVA, compared with 2% in the group treated by chronic transfusions [22]. Transfusions are also essential in the management of severe ACS and are routinely used to
Haematopoietic cell transplantation in the treatment of sickle cell disease

prevent complications such as ACS that are associated with general anaesthesia and surgery [24].

Red blood cell (RBC) transfusions are not without adverse effects, some of which are particularly germane to patients with SCD. Alloimmunisation is a phenomenon which follows in part from under-representation of volunteer African–American blood donors [25]. This problem has been observed in up to 36% of patients with SCD. Among all transfusion recipients from the CSSCD, 18.6% were sensitised to minor RBC antigens, primarily those in the Rhesus and Kell systems [26,27]. Iron overload caused by chronic transfusion exposures is associated with multi-organ injury, and its prevention and treatment requires regular chelation therapy by desferoxamine, although alternative oral chelating alternatives are under development [28]. Additional transfusion risks include the potential for exposure to blood-borne infections and transfusion reactions. Together, these risks and complications limit the universal application of RBC transfusions for SCD. In addition, its place in the therapeutic hierarchy for SCD may shift as less-toxic therapeutic alternatives are identified.

For many years, it has been observed that fetal haemoglobin (HbF) inhibits the formation of haemoglobin S polymers. This property has been linked to a clinical benefit, as those who have naturally elevated levels experience amelioration of the SCD severity [29]. These observations have provided the basis for trials of chemotherapeutic agents that increase HbF levels. The best studied agent to date is HU. HU appears to act by increasing HbF in red blood cells and by reducing neutrophil and monocyte levels in the blood, thereby impacting the milieu of inflammation that exists in SCD. In a double-blind, placebo-controlled, prospective trial of HU in adults with symptomatic SCD, there was a 44% reduction in the annual rate of pain crisis [30]. There were also fewer hospitalisations, fewer episodes of chest syndrome and fewer transfusions in patients who received HU compared with controls. The long-term effects of chronic HU use remain incompletely defined, but a 40% reduction in mortality was recently observed by the Multicenter Study of Hydroxyurea in Sickle Cell Anaemia [31]. Other benefits associated with HU may include a better quality of life, but there may also be a risk of secondary malignancy [32].

The role of HCT for SCD is affected by the safety and efficiency of alternative therapies. These alternatives, however, do not in every case adequately reduce the severity of SCD, and thus it may be reasonable to reserve HCT for those who fail to respond to front-line therapies. In reality, however, for those who have an HLA-identical sibling donor, the options of chronic RBC transfusions, HU and HCT typically are considered side-by-side. This follows from observations that transplantation outcomes are optimised by proceeding to HCT early rather than late in the course of this and other disorders, and that there is a higher rate of acute and chronic graft-versus-host disease (GVHD) among older recipients [33]. In addition, the alternative supportive therapies may impact on transplant outcomes. For example, there is a potential for exposure to minor histocompatibility antigens in the course of receiving chronic RBC transfusions that may increase the risk of graft rejection after HCT. Ideally, a prospective clinical trial comparing these three treatment options should be conducted to better define the appropriate indications for and timing of the individual therapies. In the absence of comparative outcome data, the decision-making process remains a difficult one.

4. Experience of HCT for haemoglobinopathies

4.1 β-thalassaemia major

To date, > 1500 patients have received HCT worldwide, with the Pesaro group accounting for more than half of these [33]. In 1990, initial results among 222 patients who were < 16 years of age demonstrated Kaplan–Meier probabilities of survival and event-free survival that were 82 and 75%, respectively [34]. The factors associated with poor outcome were poor quality of chelation, the presence of hepatomegaly and the presence of portal fibrosis by liver biopsy. These observations formed the basis for assigning risk categories to patients before transplantation. Class I patients had neither hepatomegaly or portal fibrosis and had a 94% event-free survival [34]. Class II and III patients had one or two risk factors, respectively, and had a probability of event-free survival that was 77 and 53%, respectively. These data confirmed the notion that outcomes were optimised when patients were transplanted early in the course of the disease. Specifically, high-risk patients with poor outcome had transfusional iron overload. It is very likely that iron overload was the primary cause of portal fibrosis and hepatomegaly, particularly in those who were not receiving regular chelation therapy. As a result, the Pesaro investigators concluded that patients with suitable donors should be transplanted as soon as possible.

4.2 Sickle cell disease

On average, patients with SCD and thalassaemia experience significant morbidity and mortality that diminish the quality if not quantity of life. In addition, the underlying genetic defect results in an anaemia that is treated by RBC transfusions and is accompanied by a hyperproliferative state in the marrow. Not surprisingly, the approach to transplantation for these disorders has been similar, as have been outcomes. However, HCT for thalassaemia was investigated first, due in part to a predictable phenotype based on a thalassaemia genotype. In contrast, SCD has broad phenotypic variability, which impairs the ability to predict who is destined for severe disease and, thus, might have the most to benefit from a successful HCT. As a result, prospective clinical investigations of HCT for SCD lagged behind thalassaemia trials by nearly a decade. Ultimately, the largest trials were conducted by groups in France, Italy and Belgium, and a multi-centre collaborative group which included North and South American and European centres [35]. Inclusion criteria typically included patients with recurrent ACS, recurrent pain crisis or a history of
stroke. Many SCD patients had received regular RBC transfusions and had multi-organ dysfunction before HCT. The majority of patients were prepared for HCT with BU, cyclophosphamide and ATG, and GVHD prophylaxis consisted of methotrexate and CSP for most patients. Of 200 patients treated worldwide, the overall survival was 91% and the disease-free survival was 83% (Table 1). Twenty patients (10%) died after HCT and most died of complications related to GVHD. A complication unique to SCD was the observation of neurological complications in nearly 25% of patients after HCT, which included intracranial haemorrhage in several patients. It is also of interest that a subset of 14 patients in the Belgian study, who had received fewer than three transfusions and had not suffered from any serious SCD-related complications, experienced a superior outcome. The survival and disease-free survival in this smaller subset were 100 and 93%, respectively [1,13,36,37].

To date, these very good results in children have not been observed in older patients with SCD. Ancodotal reports of transplantation for adults with sickle cell anaemia suggest a poor outcome [15]. Results from a multi-centre national trial included two patients who were 16 and 28 years of age (MC Walters, unpublished data). Unfortunately, both patients experienced substantial transplant-related adverse events and died of multi-organ failure as a result of sepsis and GVHD. Newer conditioning regimens that reduce the toxicity of HCT, and more effective prevention and treatment of GVHD will be necessary to expand the role of transplantation for adults with SCD.

While disease-free survival was defined as freedom from anaemia and other clinical complications of SCD, there was evidence to suggest that there was not only cessation of sickle-related events, but also recovery from sickle-related organ dysfunction after HCT [15]. Splenic recovery and remodelling of bony abnormalities were observed after HCT, and the transmural diameter of stenotic cerebral arteries increased after HCT [38-41]. In addition, other measures of pre-existing neurological disease and pulmonary function remained stable after HCT. Linear growth improved in patients enrolled in the multi-centre trial [1].

Figure 2. Serial determinations of donor chimaerism and Hb S fractions after transplantation. The fraction of donor cells in the blood (closed circles) and Hb S fraction (open triangles) are depicted at regular intervals after transplantation with a period of follow-up extending to >5 years after transplantation. The relationship between donor chimaerism and the Hb S fraction is shown. Patients 13, 18 and 49 who had Hb AA donors are shown.

BMT: Bone marrow transplantation; Hb: Haemoglobin.
underlying disease, even when as few as 11% of donor cells are in the marrow (Figure 2). Thus, it may be appropriate to pursue clinical investigations of less-intensive regimens that promote the mixed chimaerism state and thus reduce the risk of transplant-related complications [1]. These clinical observations might also predict that similar levels of chimaerism after replacement gene therapy will generate a significant clinical effect, and recent breakthroughs in vector design and in vivo selection of virally transduced donor marrow may soon permit initiation of a clinical trial [44,45].

In addition to graft rejection, acute and chronic GVHD, gonadal dysfunction and neurological complications were significant complications associated with HCT for SCD. Acute and chronic GVHD occurred in 25 and 12% of patients, respectively. Chronic GVHD was associated with 8 deaths among 201 patients treated worldwide. Gonadal dysfunction has been noted in males and females after HCT. Of the patients in the multi-centre trial who were older than 13 years at time of evaluation, five of seven females and none of four males had abnormally elevated follicle stimulating hormone and luteinising hormone levels [1]. One male who was 16 years of age had an abnormally elevated follicle stimulating hormone and luteinising hormone levels [1]. One male who was 16 years of age had a testosterone level that was prepubertal. As noted earlier, neurological complications occurred frequently and with equal frequency in those with and without a history of stroke before HCT. Most events were seizures which had no apparent long-term deleterious effects. In addition, two patients had intracranial haemorrhages, which prompted the implementation of measures to prevent these complications. During the administration of CSP, patients receive prophylactic anticonvulsants, hypertension is controlled aggressively and transfusions are administered to maintain the haemoglobin concentration in the range 9 – 11 g/dl and the platelet count > 50,000/mm [3]. There were no further incidents of haemorrhage after these measures were instituted, but the frequency of seizures was not altered significantly [1]. Secondary malignancy was not observed in the multi-centre study, but there is a theoretical risk after HCT.

4.2.1 Future directions for HCT in sickle cell disease

There are several pathways currently under investigation to expand the accessibility of HCT for SCD. These efforts aim to improve the short- and long-term quality of life by reducing transplant-related complications, and to increase the number of patients who might benefit from HCT. A difficult consideration that remains is who should be offered HCT. As discussed, HCT is more likely to be successful in younger patients who have not yet had significant complications of SCD. However, until HCT is safer, it might be difficult to convince presymptomatic patients and their families that the risks associated with conventional HCT are acceptable. These difficulties might be mitigated by having the ability to predict disease severity reliably, and efforts to discover epistatic and epigenetic factors associated with severe disease are ongoing. As reliable predictors of poor outcome are identified, it may become possible to intervene by HCT before sickle-related adverse events occur and, in so doing, reduce the risk of transplant-related complications. In an effort to identify clinical features of adverse outcomes in SCD, an analysis of data from the CSSCD was conducted in children < 10 years of age. The analysis showed that those who had combinations of dactylitis, severe anaemia and leukocytosis in the first 2 years of life had an increased risk of an adverse outcome, defined as death, stroke, frequent pain episodes and recurrent episodes of acute chest syndrome [46]. However, the practical utility of these clinical predictors of adverse outcome remains uncertain.

Because the clinical suppression of the underlying haemoglobinopathy in stable mixed chimaerism is indistinguishable

Table 2. Results of non-myeloablative HLA-identical sibling HCT for sickle cell anaemia [47-51].

<table>
<thead>
<tr>
<th>Conditioning regimen</th>
<th>Minimal-toxicity conditioning regimen</th>
<th>Reduced-intensity conditioning regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>11†</td>
<td>9‡</td>
</tr>
<tr>
<td>Patient age (median, yrs)</td>
<td>10 (range, 3 – 28)</td>
<td>22 (range, 2 – 56)</td>
</tr>
<tr>
<td>Conditioning regimen (dose)</td>
<td>Flu (90-150)/TBI (200) [5]; Flu (125-150)/ATG/TBI (200) [6]</td>
<td>Flu (175)/BU (8)/ATG/TLI (500) [4]; Flu (120)/Mel (140)/ATG [2]; Flu (120)/Mel (140)/Campath-1H (100) [2]; Flu (120)/CY (120) [1]</td>
</tr>
<tr>
<td>Source of stem cells (no. of patients)</td>
<td>Marrow (9); PBHC (2)</td>
<td>Marrow (3); PBSC (3); UCB (1)</td>
</tr>
<tr>
<td>No. with graft rejection/ disease recurrence</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>No. with GVHD</td>
<td>Acute, 1 (Gr I); chronic, none</td>
<td>Acute, 4 (Gr II – IV); chronic, 3 (2 fatal)</td>
</tr>
<tr>
<td>No. of deaths</td>
<td>None</td>
<td>2</td>
</tr>
<tr>
<td>No. with event-free survival</td>
<td>1</td>
<td>5</td>
</tr>
</tbody>
</table>

†Includes 2 patients with thalassaemia major.
‡Includes 1 patient with thalassaemia major.

ATG: Antithymocyte globulin; BU: Busulfan; CY: Cyclophosphamide; Flu: Fludarabine; Gr: Grade; GVHD: Graft-versus-host disease; HCT: Haematopoietic cell transplantation; HLA: Human leukocyte antigen; Mel: Melphalan; No.: Number; PBSC: Peripheral blood stem cells; TBI: Total body irradiation; TLI: Total lymphoid irradiation; UCB: Umbilical cord blood.
from full donor chimaerism, modulated conditioning regimens are being evaluated for their ability to induce stable chimaerism after less-intensive preparation. Fludarabine has been used in combination with TBI, BU or melphalan [47]. ATG and TLI have also been utilised to suppress host-versus-graft reactions [48]. The preliminary attempts to accomplish stable mixed chimaerism after non-myeloablative HCT for sickle cell anaemia are summarised in Table 2 [49-51]. The preparative regimens are divided into two groups. In the reduced intensity group, an older group of patients received moderately intensive therapy associated with hospitalisation. Five of nine survive free of disease, but GVHD was problematic and contributed to mortality in two. In addition, two patients had graft rejection. The minimal toxicity regimen, modelled after the preclinical and clinical experiences of R Storb and his colleagues from Seattle enrolled younger patients and used therapy that was largely administered in an out-patient setting. In this group, GVHD was uncommon, as was other transplant toxicity. Unfortunately, when post-transplantation immunosuppression was withdrawn, in all but one case, there was graft rejection accompanied by autologous recovery. However, none of these patients died after HCT. It is likely that an optimal regimen will utilise a level of pre- and post-transplantation immunosuppression intensity that resides somewhere between the two treatment groups summarised here.

Another potential problem after non-myeloablative transplantation to establish stable mixed chimaerism is that the level of donor chimaerism in some patients might not be sufficient to correct the underlying anaemia and half clinical vaso-occlusive events. In this setting, it might be possible to convert patients to full chimaeras by administering a donor lymphocyte infusion (DLI) [52,53]. Owing to the risk of GVHD and marrow aplasia that follows DLI, this therapeutic option is unlikely to be considered in most patients.

In the multi-centre study of bone marrow transplantation for SCD, 315 (6.5%) of 4848 patients who were <16 years of age were designated as eligible for enrolment. Of these, only 128 (41%) had HLA typing performed, and 44 (14%) of eligible patients had an HLA-identical sibling. Seven patients who had an HLA-identical sibling donor did not proceed to HCT owing to parental refusal [54]. This experience illustrates the most common barriers that limit HCT for SCD, and suggests strategies that might be pursued to expand its availability. If lacking a suitable donor is the chief barrier, then the use of cord blood haematopoietic cells (CBHC) might make it possible to consider HLA-mismatched or unrelated donors, because of a reduced risk of GVHD after HCT [55]. CBHC is already an established source of haematopoietic stem cells and has been utilised from matched siblings in the treatment of SCD with success. Locatelli et al. recently published results demonstrating a 2-year event-free survival of 90% following sibling CBHC transplantation in patients with SCD [56]. These patients also benefited from a low incidence of acute and chronic GVHD, while the incidence of graft rejection was similar to that observed after bone marrow transplantation. If this early success of cord blood transplantation for SCD can be extended in a prospective multi-centre trial, it may be reasonable to study the efficacy of unrelated donor cord blood transplantation for haemoglobinopathies.

The results of HLA-matched unrelated donor HCT were recently reported in a group of 32 patients with β-thalassaemia major, who had a probability of disease-free survival of 66% after pretransplant preparation with BU and CY, alone (n = 4) or in combination with thiopeta (n = 28) [57]. By identifying allelic differences between unrelated donors and their recipients, and by selecting donors to minimise the risks of GVHD and rejection, it may be possible to improve results of unrelated HCT for haemoglobinopathies [58,59]. This was illustrated by HLA haplotype matching between unrelated donor-host pairs among 22 recipients with thalassaemia major. Of those who were HLA identical for at least one extended haplotype, 19 patients survived; 17 free of thalassaemia major [57]. Of course, by increasing the resolution for optimal HLA-matching between donor–recipient pairs, a greater stringency of donor selection is very likely to restrict even further the donor availability for ethnic groups such as African–Americans.

Another obvious potential alternative source of stem cells might be manipulated bone marrow from haploidentical donors. While its availability would dramatically expand HCT for non-malignant disorders, the concurrent problems of infection associated with T cell depletion and delayed immune reconstitution, and problems of graft rejection, must be overcome by current techniques. However, novel T cell depletion techniques may transform the future of haploidentical transplantation, as might our understanding of regulatory T cell and natural killer populations that facilitate engraftment [60]. One approach that is currently under development in the sickle mouse model involves the use of photochemical crosslinking by psoralen compounds to inactivate donor T cells. These donor T cells, treated ex vivo, appear to promote engraftment, but not cause GVHD following their addition and infusion with T cell-depleted, major histocompatibility complex-mismatched donor murine marrow [61]. Phase I trials in patients with haematological malignancies have been initiated. In addition to careful review of the scientific basis for translating advances in transplantation biology to SCD, the ethics of these trials was discussed during consensus conferences about the status of sibling and alternate donor HCT for SCD [62,63].

5. Conclusion

In contrast to HU and chronic RBC transfusions, HCT remains the sole treatment for SCD that has curative potential. Ongoing studies may elucidate novel transplantation regimens that permit stable engraftment of donor haematopoietic cells without hospitalisation and significant transplant-related morbidity. At present, the most acute challenges have to do
Haematopoietic cell transplantation in the treatment of sickle cell disease

with patient selection and the paucity of suitable donors. A 1991 study by ethicists and medical researchers found that only 54% of parents with children who suffer from sickle cell anaemia were willing to accept any risk of short-term mortality in order to undergo an HCT [64]. It is difficult to imagine a significant change in these attitudes about standard and alternate donor transplantation until substantial improvement in the ability to determine disease severity prospectively and in transplantation outcomes have been achieved.

6. Expert opinion

HLA-identical sibling HCT for SCD is curative in 84% of recipients. The impact of this important result has been softened in part by a perception that this cure is secured at the cost of unacceptable toxicity and by its limited application due to constraints in donor availability. A facile transition to non-myeloablative transplantation has been hindered by a high rate of graft rejection and it is, therefore, unlikely that an alternative to conventional HCT will emerge soon. Thus, today, very few patients are offered HCT by their physicians and even fewer accept its associated risks.

However, the key features of SCD are shifting from events characterised by a series of life-threatening acute episodes in childhood, each having the potential for early mortality, to ongoing complex management issues of a chronic illness of adulthood, characterised by an inexorable accrual of significant health problems that adversely affect the quality of life. Thus, as follow-up studies after transplantation confirm the sustained benefit of donor erythropoiesis, which significantly improves the quality of life of those who survive with stable engraftment of donor cells, the importance of HCT as a preemptive therapy is very likely to increase. To support this, current investigations of transplantation for SCD are focused on methods that might reduce its toxicity and identify suitable alternate donors. Expanding the number of patients eligible for HCT will require a broad movement to organise and expand the recruitment of donors. It was estimated by Beatty et al. that an African–American volunteer donor is > 4 times more likely than a Caucasian volunteer to act as a HLA-matched donor for an African–American recipient [65]. The rapid application of new transplantation technology that includes selection of an optimal stem cell source, conditioning regimen and treatment to prevent and treat GVHD for SCD, will also promote the availability of HCT.

Acknowledgements

MCW is supported by NIH grants HL 68177 and HL 68091.

Bibliography

Papers of special note have been highlighted as either of interest (*) or of considerable interest (**) to readers.

17. PLATT OS, BRAMBILLA DJ, ROSSE WF et al.: Mortality in sickle cell disease. Life...
exponentially and risk factors for death. 


41. HORAN J, LIESVELD J, ROCHON P et al.: Hematopoietic stem cell transplantation for sickle cell disease and thalassemia after low dose TBI. *Fludarabine
Haematopoietic cell transplantation in the treatment of sickle cell disease


Affiliation
Robert C Atkins & Mark C Walters†
†Author for correspondence
Children’s Hospital & Research Center at Oakland, Blood and Marrow Transplantation Program, 747 52nd Street, Oakland, CA 94609, USA
Tel: +1 510 428 3574; Fax: +1 510 601 3916; E-mail: mwalters@mail.cho.org