Transplant Outcomes in Bone Marrow Failure Syndromes and Hemoglobinopathies

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Allogeneic hematopoietic stem cell transplantation (HSCT) is the only potential cure for most bone marrow (BM) failure syndromes and hemoglobinopathies. Over the past decade, umbilical cord blood (UCB) has been used more frequently as a stem cell source in patients who lack a suitable BM donor. Although graft failure remains a significant problem, UCB transplantation (UCBT) using the optimal conditioning regimen can be a salvage treatment for patients without a suitable BM donor and warrants evaluation in further prospective studies.
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Despite the heterogeneity of bone marrow (BM) failure syndromes and hemoglobin disorders, many of the challenges to successful hematopoietic stem cell transplantation (HSCT) are similar. These include the identification of a suitable donor, optimization of preparative therapy to reduce transplant-related mortality (TRM) and still ensure engraftment, the elimination of graft-versus-host disease (GVHD), and the reduction of late effects. In addition, each disease has unique obstacles to successful HSCT. This chapter will give a brief overview of these unique challenges and focus on umbilical cord blood transplantation (UCBT) outcomes.

BONE MARROW FAILURE SYNDROMES

BM failure syndromes are a heterogeneous group of rare diseases often grouped in categories of acquired and congenital disorders. Unrelated donor allogeneic HSCT is a treatment option for patients with acquired BM failure syndromes who fail immunosuppressive treatment.[1] Congenital disorders account for approximately one third of BM failure syndromes in childhood and include many different genetic diseases: Fanconi anemia (FA), dyskeratosis congenita, Blackfan Diamond disease, Kostmann syndrome, and others. Although little is known about the pathogenesis of the BM failure in each of these disorders, allogeneic HSCT is the only curative effective treatment for most patients.[2–4] Umbilical cord blood (UCB) offers an alternative hematopoietic stem cell source for patients lacking a suitable sibling or matched unrelated BM donor.

ACQUIRED SEVERE APLASTIC ANEMIA

Graft failure, GVHD, and regimen-related toxicities have been the major obstacles to successful HSCT for patients with acquired severe aplastic anemia (SAA), particularly after unrelated donor HSCT. Historically, BM was chosen as the stem cell source because of the high risk of graft failure. However, more recently UCB has been used with improving success.

Related UCBT for SAA

The Eurocord database recorded the outcomes of 19 patients who received related donor UCBT for acquired BM failure syndromes between 1991 and 2006 (Eurocord, unpublished data). Eighteen patients were transplanted for SAA and one had pure red cell aplasia. Seventeen patients received a single UCB unit, and two patients a single UCB unit with BM from the same donor. Thirteen patients received reduced-intensity conditioning (RIC). Two patients failed to engraft, both of whom had received a low cell dose. For the remaining 17 patients, the median time to neutrophil recovery was 27 days. Of seven patients who had chimerism analysis performed, six were full donor and one had mixed chimerism. Six patients developed grade I–II acute GVHD. One patient developed extensive chronic GVHD. With a median follow-up of 4 years, 16 of 19 patients are alive and well. These results demonstrate that the outcome after human leukocyte antigen (HLA)-

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identical sibling UCBT is very similar to HLA-matched sibling BM transplantation (BMT) for SAA.

Unrelated UCBT for SAA

Seventy-one patients who received UCBT between 1996 and 2009 as an initial allograft for acquired SAA (n = 62) or paroxysmal nocturnal hemoglobinuria (PNH) (n = 9) were reported to Eurocord (unpublished data). Fifty-five patients with SAA had received at least one cycle of immunosuppressive treatment prior to transplant. Among the 57 single UCB unit recipients, donors were matched at 6/6 HLA loci (n = 5), or mismatched at 1 locus (n = 17), 2 loci (n = 26), or 3 loci (n = 3). Among 14 recipients of 2 UCB units, the greatest cord–recipient level of HLA disparity was 1 HLA locus (n=3), 2 loci (n=7) or 3 loci (n=1) (2 patients had missing HLA data). The median total nucleated cell and $CD34^+$ cell doses infused were 3.2×10^7/kg and 1.8×10^5/kg, respectively, for single UCB recipients and 6.2×10^7/kg and 2.8×10^5/kg, respectively, for double UCB recipients. Forty-six patients (69%) were prepared with a RIC regimen. The probability of neutrophil recovery was 56% at a median of 25 days. The median time to platelet recovery was 57 days. No late graft failure was reported. Of the 37 patients who achieved neutrophil recovery, 27 had full donor chimerism and five had mixed chimerism (data are missing for five patients). The probability of grade II–IV acute GVHD was 22%. Eleven of 34 patients at risk developed chronic GVHD. The probability of 2-year survival was 40% ± 6%.

Results Reported in the Literature

Yoshimi et al reported the outcome after UCBT for SAA in a group of 31 patients (median age, 28 years; range, 0.9–72 years).[5] The cumulative incidences of neutrophil and platelet recovery were 55% and 72%, respectively. The cumulative incidences of acute and chronic GVHD were 17% and 20%, respectively. The probability of overall survival at 2 years was 41%. Interestingly, the overall survival was 80% among patients who received a conditioning regimen of low-dose total body irradiation (TBI) (2–5 Gy), fludarabine (FLU), and cyclophosphamide (CY). In 2008, Chan et al reported the HSCT outcomes in nine children with refractory SAA.[6] Six patients engrafted after the first UCBT, and two of three patients with primary graft failure engrafted after a second UCBT. At a median follow-up of 34 months, seven patients were alive and transfusion-independent. Most patients had received a conditioning with FLU, CY, anti-thymocyte globulin (ATG), and low-dose TBI. It appears that additional immunosuppression before transplantation is important for ensuring donor engraftment after unrelated UCBT for SAA.

Recommendation for Donor Choice for UCBT in SAA

Current results of UCBT for patients with SAA show that the most important complication is graft rejection. However, with modifications to the eligibility of patients, selection of the UCB unit, and choice of the conditioning regimen, engraftment rates have improved and resulted in superior survival. For patients with SAA who lack an HLA-matched sibling donor, the question as to when to bring them to transplant has been a matter of much debate. Many centers prefer to repeat several courses of immunosuppressive treatment before proceeding to an unrelated donor HSCT. Usually an unrelated donor search is performed and UCB search undertaken only if a suitable marrow donor is unavailable. As factors such as number of transfusions and active severe infections decrease the likelihood of a successful outcome, our current recommendation is to search for an unrelated donor if immunosuppressive treatment has failed at 3 months. Suitable donors include a 9/10 or 10/10 HLA-matched BM or 0, 1, or 2 HLA locus–mismatched UCB units.

Our previous study has shown that donor selection criteria vary according to diagnosis.[7] Compared to malignant diseases, we found that a higher cell dose and stricter HLA matching should be pursued for UCBT in nonmalignant diseases. For this reason, our current recommendation for nonmalignant diseases is to use UCB units that contain $>5 \times 10^7$ nucleated cells/kg and $>2 \times 10^5$ $CD34^+$ cells/kg at collection, with the best possible HLA match (antigen level for HLA class I and allele level for HLA class II). If an acceptable number of cells cannot be located in a single UCB unit, consideration should be made to use 2 UCB units to achieve an adequate total number of cells. UCB units with a cell dose of <3.5 nucleated cells/kg with 2 or 3 HLA loci mismatches should not be used.

With respect to conditioning therapy and GVHD prophylaxis, a FLU-based regimen with cyclosporine A (CsA) and mycophenolate mofetil appears to yield the best HSCT outcomes. Considering the rarity of SAA, it is also important to consider a common protocol with standardized data collection in international cooperative efforts.

FANCONI ANEMIA

FA is a genetically and phenotypically heterogeneous disorder characterized by congenital malformations, progressive marrow failure, and marked predisposition to malignancy.[8] As of 2010, allogeneic HSCT remains the only treatment modality with the potential for correcting the hematological manifestations of FA.[9] Early experiences with HSCT were mostly unsuccessful, secondary to high risks of TRM and acute GVHD.[10,11] Over the last two decades, sequen-

tial changes to the approach to HSCT have resulted in reduced regimen-related toxicity, superior engraftment, less GVHD, and therefore improved survival. The two pivotal changes that most influenced these improvements were the addition of FLU to the preparative regimen to augment engraftment, and the use of T-cell depletion to reduce GVHD. The reduction of GVHD is particularly important as it is associated with the development of head and neck malignancies in FA patients after HSCT.[12] With these improved HSCT outcomes, indications for HSCT are consistent regardless of donor source.

HSCT for FA patients from HLA-identical sibling donors is generally associated with an excellent outcome if performed prior to development of myelodysplasia (MDS) or leukemia, and within the first decade of life. In experienced centers, hematopoietic recovery occurred in more than 85% patients and survival rates are greater than 75% using the standard Gluckman approach of low-dose CY and limited-field irradiation.[13–17] The International Bone Marrow Transplant Registry (IBMTR) reported the outcomes of 209 FA patients transplanted with HLA-identical sibling donor HSC from 1994 to 1999.[18] The 3-year survival was 81% in patients less than 10 years of age (n = 109) and 69% in older patients (n = 100). Over the past decade, there has been a growing interest in the use of non-irradiation conditioning regimens, often with FLU for patients undergoing HLA-identical sibling HSCT with good success.[19–21] Long-term follow-up, however, is required before determining whether such an approach will reduce late effects, particularly the risks of malignancy, sterility, and endocrinopathies.

The majority of FA patients do not have an HLA-identical unaffected sibling donor and require an alternative (ie, an HLA-mismatched related or unrelated) donor. Historically, HSCT for FA using alternative donors has been less successful than HLA-identical sibling HSCT due to high rates of graft failure, TRM, GVHD, and opportunistic infections.[13]

In 1995, Gluckman et al reported the outcomes of alternative donor HSCT in 48 FA patients from multiple institutions, using the database of the IBMTR.[13] Graft failure occurred in 24% patients, and overall survival at 2 years was 29%. Similar rates of graft failure after alternative donor HSCT were observed by other investigators, indicating that the RIC regimen was insufficient to achieve sustainable engraftment. In 2000, MacMillan et al observed a higher rate of graft failure in FA patients with T-cell mosaicism, suggesting that the presence of diepoxybutane (DEB)-resistant T cells increased the risk of graft rejection and the standard regimen of CY/TBI/ATG was insufficient for their complete eradication.[22] Based on these observations, most centers in the last decade have included FLU in the conditioning regimens, with improved engraftment rates and overall survival.[23–25]

Similar finding were observed by Wagner et al[26] in 2007 in a report of the outcomes after alternative donor HSCT in 98 FA patients on behalf of the CIBMTR. Of 83 patients surviving at least 21 days, the overall incidence of neutrophil recovery was 78% at a median of 11 days after HSCT. In multivariate analysis, the use of FLU-containing regimens was associated with a higher probability of neutrophil engraftment. In addition, 3-year adjusted overall survival rates were significantly higher in FLU-containing regimens than non–FLU-containing regimens: 52% versus 13% ($P < .001$). Other factors associated with higher survival were younger recipient age (<10 years), cytomegalovirus (CMV) seronegativity in the recipient, and a history of fewer than 20 blood product transfusions.

Because of the high historical rate of graft failure in FA patients, the preference was to use BM as subsequent cells might be required in the event of graft failure. Over time, the use of UCB evolved. The first successful UCBT in the world was performed by Gluckman et al[27] in a patient with FA. With the development of in vitro fertilization and pre-implantation genetic diagnosis, sibling donor UCB is being used more often.[28]

In 2007, Gluckman et al[29] reported the outcomes of unrelated donor UCBT in 93 patients with FA on behalf of Eurocord and the European Group for Blood and Marrow Transplantation, restricting the analysis to recipients of an HLA-matched (6/6, n = 12) or partially matched (5/6, n = 35; 3–4/6, n = 45) unrelated UCB unit. The incidence of neutrophil recovery was 60%, with a higher likelihood of recovery in recipients of FLU and a unit containing $\geq 4.9 \times 10^7$ nucleated cells/kg recipient body weight. The incidences of acute grade II–IV GVHD and chronic GVHD were 32% and 16%, respectively. The overall survival was 40%, with higher survival rates in CMV-seronegative patients, in recipients of FLU-containing regimens, and with units containing $\geq 4.9 \times 10^7$ nucleated cells/kg. Survival by HLA match was 74% (6/6 match, n = 12), 48% (5/6 match, n = 35), and 25% (3–4/6 match, n = 45). Thus, with proper selection of the UCB unit, the results after unrelated donor BMT and UCBT from unrelated donors are quite similar. However, these results suggest 3–4/6 HLA-matched UCB units are not suitable grafts.

With improved HSCT outcomes after alternative donor HSCT, indications for HSCT are consistent regardless of donor source. In order to avoid transfusions, standard-risk patients (<18 years of age, good organ function, absence of advanced MDS or leukemia) should undergo HSCT when persistent and moderately severe cytopenia develops (hemoglobin <8 g/dL; absolute neutrophil count <500/μL; and/or platelets <20,000/μL). Patients with evidence of advanced MDS or leukemia should also be considered for HSCT. Patients with specific mutations deemed to be particularly high risk for rapid progression to MDS or leukemia

and poor survival (as with the presence of biallelic breast cancer [*BRCA*] gene mutations)[30] may benefit from earlier transplantation.

OTHER CONGENITAL BM FAILURE SYNDROMES

Allogeneic HSCT has been performed in other congenital BM failure syndromes with varied results[4,31]; these diseases include congenital dyserythropoietic anemia,[32-35] dyskeratosis congenita,[36,37] reticular dysgenesis,[38] cartilage hair hypoplasia,[39] and amegakaryocytic thrombocytopenia.[40-42] Regardless of the specific etiology, obstacles to successful HSCT for all patients with congenital marrow failure include finding a suitable hematopoietic stem cell donor, elimination of early and late toxicities, achieving durable engraftment, and decreasing the risk of GVHD.

Sixty-four patients who received a related (n = 20) or unrelated donor UCBT (n = 44) were registered with Eurocord and the European Bone Marrow Transplant Group (EBMT) database (Eurocord, unpublished data). The related donor group was composed of 13 patients with Diamond Blackfan anemia (DBA), three with amegakaryocytic thrombocytopenia, two with dyskeratosis congenita, one with Shwachman Diamond syndrome, and one with Kostmann disease. The conditioning regimen varied according to the centers, and 20% of patients received a RIC regimen and 85% received CY before UCBT. GVHD prophylaxis was CsA-based in all patients. The median infused total nucleated cell dose was 5×10^7/kg and CD34, 1.7×10^5/kg. The cumulative incidence of neutrophil recovery was 95% by day 60 and platelet recovery was 89% by day 180. The cumulative incidence of grade II–IV acute GVHD was 5% and two of 18 patients had chronic extensive GVHD. The 3-year overall survival was 95%.

The unrelated donor UCB group diagnoses were eight DBA, 13 amegakaryocytic thrombocytopenia, six dyskeratosis congenital, one Shwachman Diamond syndrome, 13 Kostmann disease, two congenita agranulocytosis, and one unclassified aplastic anemia. Eighty-three percent of patients were transplanted with UCB mismatched at 1 or 2 HLA loci and three patients received a double UCBT. The conditioning regimen varied in different centers, with 36% patients receiving a RIC regimen and 74% receiving a high-dose CY regimen. GVHD prophylaxis was CsA-based in 91% of patients. The median infused total nucleated cell dose was 5.7×10^7/kg and the median $CD34^+$ cell dose was 1.9×10^5/kg. The median follow-up was 32 months. The cumulative incidence of neutrophil recovery was 63% by day 60 and platelet recovery was 67% by day 180. The cumulative incidence of grade II–IV acute GVHD was 24% and 12 of 22 patients had chronic GVHD, which was extensive in eight. The probability of 2-year overall survival was 61%.

Ruggeri et al recently reported the outcomes of a Eurocord phase II trial that assessed the feasibility and the safety of double UCBT in 14 patients with BM failure syndromes (nine inherited, five acquired), of whom six previously rejected an initial allograft.[43] Neutrophil recovery with full donor chimerism from a single UCB unit was observed in eight patients and acute GVHD in 10 patients. With a median follow-up of 13 months, six patients died, one with acquired and five with inherited BM failure syndromes. The estimated overall survival rates were 80% ± 17% and 44% ± 16% for acquired and hereditary BM failure syndromes, respectively. Transplantation of 2 partially HLA-matched UCB units is thus feasible and facilitates salvage treatment in these high-risk patients with BM failure syndromes.

SICKLE CELL DISEASE

Even though allogeneic HSCT is the only curative treatment for sickle cell disease (SCD), its use has been limited so far by reports of TRM risks. The first transplants for SCD began in 1984.[44] Worldwide experience with pretransplant RIC showed similar results with an overall TRM risk of 7% for the United States (n = 50), Belgian (n = 50), and French (n = 87) groups and an event-free survival of 82% to 86%.[45-49] As the worldwide experience with transplantation for SCD has expanded, the use of HSCT has transitioned from an experimental intervention reserved for the most severely affected patients to a treatment that is offered to increasingly younger children with early signs of SCD-related morbidity.

Review of results of BM transplantation with HLA identical sibling donors shows that expected long-term disease-free survival ranges between 80% and 90%. Considering these excellent results, indications have changed, the goal being to transplant patients early, before irreversible morbidity involving mostly the brain appears. Therefore, most widely accepted criteria are young patients with HLA identical donors with at least one of the following complications: stroke without severe cognitive disabilities; stenosis or occlusions on cerebral magnetic resonance angiography; ischemic lesions demonstrated by cerebral magnetic resonance imaging; recurrent vaso-occlusive crisis and/or acute chest syndrome and/or priapism despite hydroxyurea; osteonecrosis in multiple joints; or red blood cell immunization with two or more antibodies; or with one or more severe risk factors (abnormal high velocities on transcranial Doppler, severe chronic anemia [hemoglobin <7g/dL], or tricuspid jet regurgitation >2.5 m/s on cardiac Doppler).

Related UCBT for SCD

Most centers have the experience of RIC increasing the risk of non-engraftment.[50] Bernaudin et al for the

French group[45] showed that a conditioning with busulfan (Bu) 16 mg/kg, CY 200mg/kg, and rabbit ATG 20mg/kg resulted in no rejection, while the same regimen without ATG had a probability of 25% rejection. In a series of 60 patients who received an HLA-identical sibling BMT or UCBT, event-free survival was 82% without any difference between stem cell sources. The incidence of acute GVHD was 27% after BMT and 0% after UCBT. With this conditioning regimen, no death occurred and all patients were full chimera with the same hemoglobin profile as the donor, without any vaso-occlusive episode, no requirement for transfusion, and seven cases of limited chronic GVHD. No patients experienced a stroke and, of interest, several patients had an improvement of cerebral occlusions.

Locatelli et al[51] analyzed for Eurocord a series of 44 patients, including 11 with SCD, who received an HLA-identical sibling UCBT; most received the conditioning with Bu/CY/rabbit ATG. Median time to neutrophil recovery was 25 days and for platelet recovery, 39 days. The incidence of acute GVHD was 11% and chronic GVHD, 6%. For SCD, overall survival was 100% and event free survival was 90%. In order to decrease toxicity, several authors attempted to use a RIC.[50,52] This approach resulted in an increased rate of failure with autologous reconstitution. New conditioning regimens using thiotepa (TT) and FLU are under investigation and might produce even better results.

Kabara et al compared, for Eurocord, outcomes of UCBT and BMT from HLA-identical siblings (manuscript in preparation). In this series, there were 130 patients with SCD who received BMT and 26 UCBT. Neutrophil engraftment was 93% in the BMT group and 90% in the UCBT group; GVHD was 10% after UCBT and 20% after BMT. There was no difference in overall survival between BMT and UCBT recipients. Event-free survival was 92% in SCD. From this study, we conclude that HLA-identical sibling HSCT for SCD gives excellent outcome. Results were not statistically different according to the source of stem cell. UCBT is associated with less acute GVHD but delayed neutrophil engraftment. Sibling cord blood banks for hemoglobinopathies should be encouraged to avoid the discomfort and risk of BM harvest.

Unrelated UCBT for SCD

The use of unrelated UCB for SCD patients without related donors would be a logical approach. However, a review of US studies where unrelated 4/6 HLA-matched UCB was employed reports rather disappointing results in terms of GVHD and rejection rates.[53–55] Eurocord and CIBMTR (manuscript in preparation) have collected data on 25 patients who received an unrelated UCBT; 16 had thalassemia and nine had SCD. Among the SCD patients, five engrafted at day 28, three had full chimerism, two had a second transplant, and none had acute or chronic GVHD. Three patients survived with a functioning graft, including three of the seven who received a myeloablative conditioning and neither of the two patients who received RIC. These results indicate that new strategies for conditioning and facilitating engraftment must be investigated.

Cord Blood Banking for Related UCBT

Since allogeneic HSCT is a curative therapy for patients with SCD, why do only a small fraction of patients receive this treatment, especially considering that the TRM risk is no greater than the risk of SCD-related mortality? Walters et al[56] reported that only 6.5% of SCD patients met criteria for HSCT and that 14% of those meeting entry criteria for HSCT had an HLA-identical sibling, but a wide variation was observed among the institutions (0.9%–36%). These findings suggest that other barriers such as parental and/or physician refusal, and lack of financial or psychosocial support are operating. In order to increase the probability of locating HLA-identical donors, sibling UCB cryopreservation should be systematically offered to families and pre-implantation genetic diagnosis, coupled with HLA selection discussion with the parents. In France, where cord blood cryopreservation has been systematically proposed to families with a SCD patient since 1998, the probability of having an indication for HSCT before the age of 18 years and an HLA-identical sibling was 35%. Considering this experience from one center and that 250 babies are born with SCD each year in France, about 80 genoidentical HSCTs for this disease could be performed per year in one country alone.

THALASSEMIA MAJOR

The only definitive cure for thalassemia is to correct the genetic defect by allogeneic HSCT.[57] As in other nonmalignant indications for transplantation, the potential for delayed or failed engraftment after UCBT for thalassemia major is balanced by the benefit of a lowered risk of GVHD, a complication that offers no apparent benefit in nonmalignant disorders.[58–60] Thus, the initial reports of UCBT for thalassemia focused on the tempo and durability of engraftment, and on rates of acute and chronic GVHD. In one retrospective survey of sibling–donor UCBT, seven of 33 children with thalassemia developed graft rejection after transplantation with an event-free survival of 79%.[51] However, the rates of acute and chronic GVHD were quite low, and only four of 38 evaluable children with SCD or thalassemia developed acute GVHD after UCBT; two of the four had an HLA-disparate donor. The Kaplan-Meier probability of chronic GVHD was 6%. Thus, as predicted, the higher incidence of graft rejection after UCBT was balanced by a lower incidence of GVHD, when compared to rates historically observed after

BMT from an HLA-identical sibling donor. Moreover, the low rate of GVHD was associated with excellent survival probability, and none of the 33 patients with thalassemia died after UCBT.

These impressions were confirmed in a more recent retrospective analysis comparing outcomes after sibling donor BMT and UCBT.[61] This cohort included recipients with SCD and thalassemia major, and compared outcomes in 389 BM (259 with thalassemia) and 70 UCB (44 with thalassemia) recipients who were treated between 1994 and 2005 in 13 different centers. There was no difference in overall survival between the two groups, but individuals who received UCB were less likely to develop GVHD (10% *v* 20%), but had a lower probability of neutrophil recovery (90% *v* 93%).

The problem of graft rejection after sibling donor CBT reported in these initial sibling series was mitigated by optimizing pre- and postgrafting immunosuppressive regimens, and by augmenting the donor cell dose. In a retrospective analysis, children who received a traditional combination of BU, CY, with or without ATG experienced a higher probability of graft rejection than those prepared with BU, CY, and TT, or BU, FLU and TT (62% *v* 94% event-free survival).[51] Similarly, the use of methotrexate after transplantation for GVHD prophylaxis was associated with an inferior event-free survival (55% *v* 90% event-free survival). Thus, in a contemporary cohort from Pavia, children with thalassemia were prepared for UCBT with a combination of BU, FLU, and TT and received CsA alone for postgrafting immunosuppression.[62] All 27 survive free of thalassemia, and none experienced acute or chronic GVHD. Of interest, the majority of these individuals had stable mixed donor–host chimerism that persisted after UCBT, and thus mixed chimerism early after UCBT was not a predictor of graft rejection.

The cell dose of the UCB unit is another important predictor of outcome after UCBT for hematologic malignancies, particularly in the setting of unrelated donor UCBT.[58,60] Another method to improve cell dose in sibling UCBT is to combine the UCB unit with BM from the same sibling donor and thereby enhance the stem cell content of the combined graft.[45] This approach was selected in a series of 13 patients with nonmalignant disorders, seven of whom had thalassemia major.[63] None of the recipients had graft rejection after UCBT and there was no GVHD. Thus, the modification of pretransplantation and postgrafting immunosuppressive regimens appears to have optimized outcomes after UCBT for thalassemia. In addition, in cases in which it is feasible to augment the UCB unit with BM from the same donor, this too appears to be a safe and effective means to promote engraftment.

Attempts to expand UCBT for thalassemia by using unrelated donors are ongoing, but, as in the sibling UCBT setting, modification of the transplantation strategy may be necessary after the initial experience. The first reports demonstrated the feasibility of unrelated donor UCBT, documented by case reports or small series of patients.[64,65] Thalassemia recipients typically received unrelated UCB units matched at 4/6 and 5/6 HLA antigens and were prepared with a conventional combination of BU/CY/ATG. The largest series published in 2004 and 2005 from Asian centers reported that 10 of 11 patients survived free of thalassemia after successful UCBT, and none of the survivors had chronic GVHD.

Another small series, recently published, showed the potential for a successful outcome after double UCBT, in which five children with thalassemia received UCB units matched at 2–4/6 HLA antigens after preparation with BU/CY/ATG.[66] One of the five died of complications related to GVHD and pulmonary hemorrhage, and another had a late graft rejection. All four survivors had limited chronic GVHD after the double UCBT. More recently, double UCBT was also successful in rescuing from an initial graft failure after unrelated donor UCBT in three children with thalassemia major.[67]

A larger series of 51 children with a median age of 4.3 years (range, 0.3–20 years) from 14 Asian centers was updated in 2008.[68] The times to having an absolute neutrophil count $>500/\mu L$ and platelet count $>20{,}000/\mu L$ independent of transfusion support were 17 and 40 days, respectively. TRM was 13.7%, and 75% patients survived after UCBT. Eleven (21.6%) patients had graft failure or autologous recovery after unrelated UCBT. Together, these retrospective data showed the possibility of a successful outcome after unrelated UCBT, but also underscored a need to identify a safer and more effective transplantation regimen, and to address the problem of graft rejection after unrelated UCBT.

The largest single series of unrelated UCBT was reported by a team in Taiwan that treated 30 consecutive patients.[69] The recipients had Pesaro class I (n = 21), class II (n = 8), or unknown risk class assigned before UCBT and all were prepared with BU/CY/ATG before UCBT. To increase the cell dose delivered, nine patients received double UCB units before transplantation. The units were matched at 6/6 (n = 4), 5/6 (n = 11), and 4/6 or fewer HLA antigens (n = 24). The median total nucleated cell and $CD34^+$ cell doses before thawing the UCB unit were 10.9×10^7/kg and 4.0×10^5/kg, respectively. The probabilities of neutrophil and platelet engraftment after CBT were 96% and 92%, respectively. The overall and event-free survival rates at 3 years were 82% and 78%, respectively, with a median follow-up of 16 months. TRM was 13%, and 61% had grade II–IV acute GVHD, although only 4% had chronic GVHD. This single-center experience suggests that increasing the cell dose by using double UCBT mitigated the risk of graft rejection, but at the expense of causing more frequent GVHD. Nonetheless, the results suggests that it is possible to improve the outcome after unre-

lated UCBT by modulating the graft content, as was observed in the sibling donor setting. However, additional studies will be needed to identify an optimal conditioning regimen.

CONCLUSIONS

Despite the heterogeneity of the disorders, patients with BM failure syndromes and hemoglobinopathies share many similar HSCT issues. Recent results have shown excellent outcomes after HLA-identical sibling UCBT, stressing the importance of collecting cord blood in families when a child is affected by a genetic hematologic or immune disorder. Additionally, results are also promising after unrelated donor UCBT, but the number of patients in each disease category is quite small, making it difficult to draw general conclusions. Multicenter collaborative trials using similar approaches will provide the optimal means to determine the best approach to HSCT, particularly with UCB, for these rare disorders.

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