Paediatric Umbilical Cord Blood Transplantation

Abstract:

The majority of children under the age of 14 who require stem cell transplant will have such donors because the majority of red blood cell and isohemagglutinins were removed in the washing process. Donor/recipient ABO incompatibility was not a major concern because the majority of red blood cell and isohemagglutinins were removed in the washing process. Donor/recipient ABO incompatibility was not a major concern.

Introduction

Allogeneic transplantation using haematopoietic stem cells (HSC) from bone marrow or peripheral blood can be limited by the unavailability of HLA-matched related donors. Although 58% of Irish patients will have a matched related donor, only about 42% of children under the age of 14 who require stem cell transplant will have such donors. The remaining patients requiring transplant must receive transplant from an unrelated donor or a HLA-mismatched related donor. These patients are at a higher risk of developing acute and chronic graft-versus-host disease (GVHD) of the remaining patients requiring transplant must receive transplant from an unrelated donor or a HLA-mismatched related donor. These patients are at a higher risk of developing acute and chronic graft-versus-host disease (GVHD) and chronic GVHD was graded according to the established criteria.

For GVHD prophylaxis, patients either received ciclosporin A alone or in combination with prednisolone, mycophenolate, cyclophosphamide, fludarabine, and ATG. Patients with HS were given cyclophosphamide, busulphan, and alemtuzumab. Patients with FA were treated with total body irradiation (TBI), to each patient’s disease. JMML patients received cyclophosphamide, busulphan, melphalan, and anti-thymocyte globulin (ATG). ALL patients received cyclophosphamide, busulphan, and melphalan. AA patients were given cyclophosphamide, fludarabine, and alectinumab. ATG. Patients with HS were given cyclophosphamide, busulphan, and alemtinumab (Table 1).

For GVHD prophylaxis, patients either received ciclosporin A alone or in combination with prednisolone, mycophenolate, or methotrexate. Patients were evaluable daily for acute GVHD while inpatient, and at outpatient clinics during the first 100 days post transplant. Diagnosis was based on clinical signs and histopathological evidence. Acute and chronic GVHD workup criteria was graded according to the established criteria. The majority of patients were given prophylactic ursoodeoxycholic acid (for veno-occlusive disease prevention), co-trimoxazole, aciclovir, and then infused to the recipient through a central venous catheter. TNC, CD34+ cell count, and viability were measured.

Also, a threshold CD34+ cell count of at least 1.7 x 105 cells/kg correlates with a higher probability of survival. Recent studies were supported using not only HLA-matched cord blood, but also one or two antigen HLA-mismatched cord blood in children needing transplant.

This report describes the clinical characteristics and outcomes of 15 patients with haematologic and metabolic disorders who have undergone UCBT in Ireland between 1998 and 2009.

Methods

This study reviewed 15 patients who received UCBT from March 1998 to June 2009. Any patients who did not have fully HLA matched and CMV-matched bone marrow donors or peripheral blood stem cells (PBSC) donors were considered for UCBT. This success demonstrated that a single cord blood unit could contain enough HSC for haematopoietic reconstitution. Furthermore, it also showed that a cord blood unit could be collected at birth, cryopreserved, thawed at a later date, and then transplanted into a myeloablated host without causing the HSC to lose their regenerative potential.

The advantages of UCBT include ease of collection, rapid availability, a high degree of permissive disparity between donors and recipients, and lower incidence of GVHD. However, the major limitation of UCBT is that the limited number HSCs in a cord blood unit may result in delayed engraftment, thus precluding transplantation into larger recipients.

Many factors influence the likelihood of successful engraftment in UCBT, including total nucleated cell dose (TNC), nucleated cell viability, and colony-forming unit (CFU) activity. A minimum TNC of 3.0 x 107 cells/kg is associated with higher engraftment probability.

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Results

Three patients had JMML (UPN 1-3); one had relapsed infant ALL (UPN 4); two had AA (UPN 5, 6); one had FA (UPN 7); and eight had HS (UPN 8-15). The median age at transplant was 1.1 year (range, 0.3 – 10.0 years), and the median weight was 12.6 kg (range, 5.5-30.0 kg). One patient was seronegative for CMV and received a CMV positive donor cord blood unit from a CMV positive mother. Fourteen units were from unrelated donors, and one unit was from a sibling donor (UPN 2). Twenty percent of the donor/recipient pairs were ABO-matched. Eight units were fully matched (6/6) and seven units had one HLA antigen mismatch (5/6). The median TNC and CD34+ doses post-processing were 6.5 x 10^7 cells/kg (range, 2.5-15.9) and 1.8 x 10^7 cells/kg (range, 0.7-5.9), respectively. Ninety-three percent of patients received a TNC dose > 3.0 x 10^7 cells/kg.

The median time to neutrophil engraftment was 30 days (range, 23-44). Eighty-six percent of patients achieved neutrophil engraftment within 60 days post UCBT (Table 2). Two patients died before achieving neutrophil engraftment. Six percent of patients achieved neutrophil engraftment by day 60. One patient reached platelet engraftment at day 53, and another eventually achieved recovery at day 148. Patient UPN 7 had not reached platelet recovery at day 168 when this report was written. Patient UPN 8 had not reached platelet recovery at day 48 when this report was written. Molecular engraftment studies after neutrophil recovery showed donor engraftment ranging from eighty-seven to one hundred percent.

Full blood counts were performed daily checking for haematopoietic recovery. Neutrophil recovery was defined as the first of 3 consecutive days with an absolute neutrophil count of ≥ 0.5 x 10^9/L. Platelet engraftment time was estimated as the first of 7 consecutive days with a platelet count of ≥ 100 x 10^9/L without transfusion. After neutrophil recovery was achieved, engraftment status was determined by molecular chimerism assessment methods. The probability of 2-year-overall survival was estimated from the time of transplant using the Kaplan-Meier method.
evaluates patients, 6 (46%) had acute cutaneous GVHD grade II-III (Table 3). Only patients with grade II GVHD were treated with prednisolone, all successfully. No patients had grade III-IV GVHD or hepatic or intestinal GVHD. Two patients treated with JM with MM died at day 4 and 6 respectively. Two AA patients (UPN 5 and UPN 6) died of Gram negative sepsis at day 15 and day 22; one achieved only neutrophil engraftment at day 14, and the other had no evidence of support. One HS patient (UPN 12) died of adenovirus and veno-occlusive disease at day 33, also without haematopoietic recovery. Median follow-up time was 4.5 years. The overall survival was 62.6% at 2 years (Figure 1).

* Patient 6 and 12 did not reach neutrophil recovery and were not included

\( \uparrow \) Patient 5, 6, 7, 12 did not reach platelet recovery and were not included

\( \downarrow \) Patient 5, 6, 7, 12 did not reach platelet recovery and were not included

Figure 1: Overall survival after UCBT

Discussion

We describe the results of single cord UCBT in 15 consecutive patients in a single paediatric centre. This review was undertaken to examine the clinical characteristics and outcome of UCBT, and to show its potential usefulness as an alternative source of stem cells when suitable bone marrow or PBSC are not available. Even though our UCBT patient population was small, it encompassed a wide range of conditions both benign and malignant. Thus, we were able to confirm that UCBT can be used in many haematological disorders and metabolic disorders.

We report the median neutrophil and platelet recovery times of 30 days and 48 days, respectively. These results are comparable with previous studies.

Time to haematological engraftment after UCBT is known to be longer than that after bone marrow transplantation (BMT). Most of our patients achieved greater than ninety-five percent donor engraftment. Given the number of patients in our study, we did not observe a significant correlation between the TNC or the CD34+ doses and engraftment time. Other large studies have documented that higher TNC and CD34+ doses improve neutrophil and platelet engraftment times. This lack of correlation in our study could be attributed to the low number of patients in the cohort, or could suggest that the number of progenitor cells in the cord units exceed the threshold needed for engraftment in a paediatric patient. As such, 93% of our patients received a TNC dose of greater than 3.0 \( \times 10^6 \) cells/kg, which is the recommended level needed for a successful engraftment. In this patient population, the overall incidence of acute GVHD was 46%. These patients developed only grade II-IV cutaneous GVHD. Grade III-IV GVHD was not observed in the current study. Other studies that have demonstrated lower incidence of GVHD in umbilical cord blood recipients compared to bone marrow recipients have reported incidence of grade II-IV GVHD in 14%.

The overall survival in this cohort at 2 years was 62.6%. This is in keeping with previous studies. Seven patients out of 8 with HS survived and their long-term outcome is being monitored closely. Correlation of survival with HS shows that most deaths occurred within 250 days post UCBT. The causes of death were: relapse (13%), infection (13%) and veno-occlusive disease (7%).

In summary, we have demonstrated that cryopreserved umbilical cord blood is a safe alternative source of hematopoietic stem cells that can be used for transplantation in paediatric patients. The high rate and low incidence of GVHD and grade III-IV acute GVHD despite HLA disparity make UCBT a favourable option when HLA-matched bone marrow or PBSC is not available. However, the major disadvantage of cord blood is the limited number of TNC compared to that of bone marrow. This drawback limits the use of UCBT in patients with malignant disease or in larger paediatric patients. To overcome this limitation, double cord transplantation and ex vivo stem cell expansion are currently in development as potential strategies.

Conclusions

To allow an expanded role for UCBT in both paediatric and adult patients.

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References