

## Umbilical Cord Blood Transplantation in Europe

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**Introduction.** Umbilical cord blood (UCB) is an appealing alternative source of hematopoietic stem cells for children and adults undergoing transplantation for a wide variety of diseases. Shorter time to transplant, which is particularly relevant for patients requiring urgent transplantation, and tolerance of 1–2 human leukocyte antigen (HLA) mismatches, which increases the chance of finding a suitable donor, are evident advantages over bone marrow transplantation (BMT) from a matched unrelated donor (MUD). The speed of engraftment is slower after UCB transplantation (UCBT), but this is counterbalanced by a lower incidence of severe graft-versus-host disease (GVHD). Cell dose and degree of HLA match are major factors influencing engraftment. Unrelated-donor UCBT (UD-UCBT) is now considered an acceptable alternative to MUD-BMT for children, and recent data in adults point the same way. From October 1988 to July 2004 more than 1,700 UCB transplants have been reported to the Eurocord registry by 273 transplant centers worldwide. Fourteen percent were UCB transplants from a related donor (RD) (n = 248) and 86% from an UD (n = 1447). Most RD-UCB transplants were performed in children (97%), but one-third of the UD-UCB transplants were carried out in adult patients (34%).

**Objective.** The purpose of this review was to summarize the results of different studies on UCBT performed by the Eurocord registry.

**Results.**

**RD-UCBT.** In a survey on 158 transplants, the 2-year probability of overall survival (OS)

was 48% in patients with malignancies, 78% in patients with bone marrow failures, 100% in patients with hemoglobinopathies, and 80% in patients with inborn errors of metabolism. In a recent study focused in RD-UCBT for hemoglobinopathies the 2-year probability of event-free survival (EFS) was 90% for 11 patients with sickle cell anemia and 79% for 33 patients with thalassemia. In this study, the use of methotrexate as GVHD prophylaxis was associated with a poorer outcome. A joint study by the Eurocord and the International Bone Marrow Transplant Registry compared the outcomes of 113 children who received UCB from HLA-identical siblings with that of 2052 children who underwent HLA-identical sibling BMT. Recipients of UCB transplants had slower recovery of neutrophils and platelets, and lower risk of acute and chronic GVHD, but no clear differences in relapse-related deaths, mortality rate at 100 days, and OS (3-year probability 64% for UCBT and 66% for BMT) were evident. These findings suggest that in the HLA-identical sibling setting, UCBT is as useful as BMT in children.

**UD-UCBT in children.** In a series of 47 patients with severe primary immunodeficiencies the 2-year probability of OS was 79% for patients with severe combined immunodeficiency and 60% for those with Wiskott-Aldrich syndrome or other immunodeficiencies. For 39 patients undergoing UD-UCBT for congenital bone marrow failure syndromes EFS and OS was 25% and 34% respectively. In a recent series of 44 patients with Fanconi anemia the 2-year OS was 36%. Survival was clearly

higher in patients given a higher dose of nucleated cells (NCs) and in those receiving a fludarabine-containing conditioning. In a study of 195 children with ALL (median age: 7 yr; stage: CR1 18%, CR2 44%, CR3 23%, more advanced 15%) undergoing UD-UCBT (median number of NCs infused:  $3.8 \times 10^7/\text{kg}$ ; HLA match: 6/6 11%, 5/6 43%, 4/6 42%, 2-3/6 4%), the cumulative incidence of engraftment was directly related to the number of NCs infused, the risk of relapse was higher in patients receiving methotrexate and in those not developing acute GVHD, and the probability of disease-free survival (DFS) was higher for patients transplanted in CR (DFS at 3 yr: CR1 38%, CR2 36%, CR3 32%, more advanced 15%), and for those undergoing UCBT in centers performing more than 10 UCBT transplants (DFS at 3 yr: 40% versus 20%). We have recently analyzed 95 children with AML (median age 6 yr; stage: CR1 20, CR2 47, more advanced 28) receiving UD-UCBT (median number of NC infused:  $4.4 \times 10^7/\text{kg}$ ; HLA match: 6/6 9%, 5/6 47%, 4/6 33%, 2-3/6 11%). Cumulative incidence of neutrophil recovery was 78% (higher for patients in CR1 and CR2, and for those receiving G-CSF), acute GVHD was 35% and 100-day transplantation-related mortality (TRM) was 20% (lower for those with a collected NC dose higher than  $5.2 \times 10^7/\text{kg}$ ). The 2-year cumulative risk of relapse was 29% and was associated with disease status. The 2-year DFS probability was 42% (59% in CR1, 50% in CR2, and 21% for children not in CR). Children with poor prognosis cytogenetic features had similar DFS compared with other patients. The Eurocord group has retrospectively compared the outcomes of 541 children with acute leukemia who underwent UCBT (n = 99), unmanipulated MUD-BMT (n = 262), and T-cell-depleted MUD-BMT (n = 180). Comparisons were performed after adjustment for patient, disease, and transplant variables. The major differences between the three groups were the higher number of HLA mismatches (92% of UCBTs, 18% of BMTs, and 43% of T-cell-depleted BMTs) and the lower cell dose in the UCBT group. Cord blood recipients were also more likely to have adverse prognostic factors

than the other transplant groups, including early relapse before transplantation, short interval from diagnosis to transplantation, and previous transplantation. Non-adjusted estimates of 2-year OS and EFS rates in the three groups did not show statistically significant differences (49% and 43% in the unmanipulated BMT group, 41% and 37% in the T-cell-depleted BMT group, and 35% and 31% in the UCBT group, respectively). UCBT recipients had delayed hematopoietic recovery, increased 100-day transplant-related mortality, decreased acute and chronic GVHD, and a similar relapse risk when compared with recipients of unmanipulated BMT. T-cell-depleted BMT recipients had decreased acute GVHD, increased risk of relapse, and higher overall mortality. Thus, this study showed that results in the three groups of patients were similar, although the types of complications were different.

**UD-UCBT in adults.** Eurocord has recently analyzed a series of 171 adults with hematologic malignancies who were conditioned with a myeloablative regimen, were transplanted with a single, non ex vivo expanded cord blood unit, and had not received a previous allogeneic transplant. The median age was 29 years, diagnoses were ALL (n = 53), AML (n = 46), secondary AL (n = 11), MDS (n = 16), CML (n = 32), NHL (n = 12) and HD (n = 1), and 32 had failed a previous autologous transplant. The stage of the disease at the time of UD-UCBT was early in 35 patients, intermediate in 45, and advanced in 91. The median number of NCs at infusion was  $2.1 \times 10^7/\text{kg}$  and 95% had a HLA disparity (5/6 46%, 4/6 41%, 3/6 8%). The cumulative incidence of neutrophil recovery at day 60 was 72% and was better in patients receiving more than  $2.7 \times 10^7$  NC/kg and hematopoietic growth factors. Cumulative incidence of acute GVHD above grade II was 32% and 2-year cumulative incidence of chronic GVHD, TRM and relapse was 36%, 51% and 22%, respectively. Advanced status of the disease was an adverse factor for relapse incidence and DFS (2-year DFS: early phase 41%, intermediate 34%, advanced 18%). More importantly, in a joint study by Eurocord and the EBMT, we compared the outcome of 98

adults with acute leukemia given an UD-UCBT with that of 584 adults receiving UD-BMT (transplants performed between 1998 to 2002). Recipients of UCBT were younger (median age 24.5 versus 32 yr), and had more advanced disease at transplant (52% versus 33%). All UD-BMT were HLA-matched whereas 96% of UD-UCBT were HLA-incompatible. The median number of NCs infused was  $0.23 \times 10^8/\text{kg}$  for UCBT compared with  $2.9 \times 10^8/\text{kg}$  for BMT. Multivariate analysis demonstrated a lower risk of grade II-IV acute GVHD after UD-UCBT, however neutrophil recovery was significantly delayed. TRM, relapse incidence, chronic GVHD, DFS, and OS were not significantly different between UD-UCBT and UD-BMT recipients.

**Conclusions.** All these results from Eurocord suggest that the long-term results after UD-UCBT are similar to those after MUD-BMT. Thus, in patients with hematologic malignancies requiring transplantation and lacking a HLA-matched sibling donor the search for an unrelated bone marrow donor and an UCB unit should be carried out simultaneously. The final choice between UCB and bone marrow should take into account the urgency of the transplant and the characteristics of the available bone marrow donors and UCB units. In this sense, a recently published Eurocord study on 550 UD-UCB transplants could provide some indications for a better choice of UCB units according to cell content and degree of HLA match.