SYMPOSIUM SUMMARY

Seventh Annual International Umbilical Cord Blood Transplantation Symposium, Los Angeles, California, June 5-6, 2009

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The 34-member faculty for the symposium included leaders from major transplantation centers from around the world. Attendees were from Argentina, Australia, Austria, Belgium, Boliva, Brazil, Canada, Chile, People's Republic of China, Colombia, Cyprus, Denmark, Egypt, France, Germany, Greece, Guatemala, India, Israel, Italy, Japan, Korea, Kuwait, Malaysia, Mexico, The Netherlands, Saudi Arabia, Singapore, Slovenia, Spain, Switzerland, Taiwan, Thailand, United Arab Emirates, United Kingdom, United States, and Venezuela.

The program consisted of 6 plenary sessions and 4 simultaneous sessions. The plenary sessions covered (1) clinical results in umbilical cord blood transplantation (UCBT); (2) conditioning regimens in UCBT; (3) graft-versus-host disease (GVHD), infection, and relapse after UCBT; (4) nonhematopoietic uses of cord blood (CB); (5) new considerations in CB unit selection; and (6) selecting the optimal CB unit. The simultaneous sessions were (IA) CB processing and evaluation of potency, (IB) CB banking and federal support, (IIA) basic science/immunobiology, and (IIB) disease-specific outcomes and new approaches in UCBT. The comments presented herein emphasize significant aspects of selected presentations. Additional information is available on a DVD, which includes the audio and slides of consenting speakers and can be obtained by sending a request, including mailing address, to SymposiumDVD@cordbloodforum.org.

SESSION I. CLINICAL RESULTS IN UMBLICAL CORD BLOOD TRANSPLANTATION

John E. Wagner, MD, University of Minnesota, reviewed progress in UCBT. There has been a substantial decrease in treatment-related mortality (TRM) after UCBT, from 54% in 1994-1999, to 34% in 2000-2002 and 27% in 2003-2006. The reasons for this include a better understanding of requirements for cell dose, HLA matching, and their interaction, as well as improved conditioning regimens. In addition, there have been improvements in supportive care and in CB collection and quality. Another important factor is the move toward earlier referrals to minimize UCBT in patients with late-stage disease.

A significant body of data points to an interaction between HLA matching and cell dose, in that a high cell dose can overcome to some extent the negative effect of HLA mismatching. The minimum cell dose is now generally set at 2.5×10^7 total nucleated cells (TNCs)/kg. With increased HLA mismatching, a higher cell dose should be used. Suggested cell doses (in TNC/kg) are 2.5-3.0 for a 6/6 HLA match, 4.0 for a 5/6 HLA match, and 5.0 for a 4/6 HLA match. At the University of Minnesota, a double UCBT is performed if these cell doses cannot be achieved with a single CB unit.

Adults have greater difficulty finding adequate CB units for transplantation because of the limited number of cryopreserved units with a large cell dose in CB banks. Recent data comparing UCBT with the "gold standard" of allele-matched bone marrow transplantation (BMT) indicates that treatment failure (death or relapse) is now comparable (relative risk of treatment failure in BMT vs mismatched UCBT = 0.82 [$P = .13$]; in peripheral blood stem cell transplantation [PBSCT] vs mismatched

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UCBT = 0.85 [$P = .18$]). Nevertheless, there is much room for improvement regardless of the stem cell source.

The use of double UCBT is one way to extend the option of UCBT to adults who do not have a single CB unit with an adequate cell dose. Data from the University of Minnesota indicate that in 105 patients treated with myeloablative (MA) conditioning, the median time to engraftment was 23 days and the overall neutrophil engraftment rate was 89%. Using a nonmyeloablative (NMA) regimen in 188 patients, the median time to engraftment was 12 days and the neutrophil engraftment rate was 95%. In both instances, the overall survival (OS) and disease-free survival (DFS) were quite good. Also, relapse may be reduced with the use of double UCBT.

Vanderson Rocha, MD, PhD, Hôpital Saint-Louis, Paris, France, discussed Eurocord data. About 14,000 unrelated UCBTs were performed between 1997 and 2006 worldwide, and about 2000 to 3000 new UCBTs are performed annually. Eurocord has 3822 registered cases, including 3019 single UCBTs (81 second UCBTs), 572 double UCBTs (27 second UCBTs), 56 UCBTs using an expanded unit, 57 with CB + haplo, 51 with CB + BM, and 70 with intrabone UCBTs. In children with malignancies (n = 1099), OS was 46% in early-phase disease, 37% in intermediate-phase disease, and 30% in advanced disease.

There has been a learning curve in UCBT, as indicated by the trend in OS in adults with malignant disease over the years: 23% in 1994-1998, 31% in 1999-2000, 36% in 2001-2003, and 38% in 2004-2008. The major factors affecting outcomes are increasing cell dose (double UCBT), improved donor choice, decreasing HLA disparities (because of increasing inventory of CB banks), better indications, increased center experience, better infection management, and modifications of GVHD prophylaxis and conditioning regimens. Before 2000, 55% of patients who underwent transplantation had advanced disease, compared with only 38% between 2005 and 2008. In adults with malignancies (n = 769) receiving single-unit UCBT, DFS was 24% in those with advanced disease, 33% in those with intermediate disease, and 40% in those with early-phase disease.

Intrabone injection of single CB units resulted in an increased incidence of platelet recovery and decreased grade III-IV acute GVHD (aGVHD), but no statistically significant improvement in neutrophil recovery, relapse, nonrelapse mortality (NRM), or OS.

The use of double UCBT and reduced-intensity conditioning (RIC) is increasing steadily. Between 2003 and 2007 MA. Of the 74 patients, 51% had acute myelocytic leukemia (AML), 49% had acute lymphocytic leukemia. While most were in complete remission (CR, 34% CR1 and 50% CR2), 16% were in an advanced phase of the disease. The median time to neutrophil recovery was 26 days; aGVHD at day 100 was 45% (grade III, 7%; grade IV, 3%). OS at about 1 year was 47% for patients who underwent transplantation while in remission (n = 60) and 18% in those who underwent transplantation with advanced disease (n = 14).

Outcome data are available on 155 UCBTs using RIC (96 single UCBTs and 59 double UCBTs). The conditioning regimen utilized cyclophosphamide (Cy), fludarabine (Flu), and total body irradiation (TBI). Median follow-up was 18 months, median patient age was 46.7 years, and 35% of the patients had received a previous autologous transplant. Neutrophil engraftment was 94% with 0 or 1 HLA disparity and 73% with 2 or more HLA disparities. The relapse rate was 36% for single UCBTs and 24% for double UCBTs ($P = .13$). DFS was 56% for double UCBTs and 49% for single UCBTs ($P = .53$); DFS was 70% with 0 or 1 HLA disparity and 42% with 2 or more HLA disparities ($P = .002$).

In conclusion, outcomes after UCBT in children and especially in adults have improved over the last 4 years; cell dose is the major factor for outcome in children and adults after MAC or RIC; delayed engraftment and early increased mortality are associated with higher number of HLA disparities; there is a need to increase the donor pool; other modifiable factors, such as conditioning regimen and GVHD prophylaxis, can improve outcomes; and encouraging results have been obtained with double UCBT after RIC or MAC, but follow-up is still short.

Mary Eapen, MD, The Medical College of Wisconsin, discussed the effect of stem cell sources on leukemia-free survival (LFS) after allogeneic transplantation for ALL and AML in children. A total of 116 BMTs were compared with 503 UCBTs performed in the United States between 1995 and 2003. The median follow-up of survivors was 5 years for BMT and 4 years for UCBT. All of the BMTs were HLA-matched at the allele level, whereas for the UCBTs (antigen-level matching), 7% were HLA-matched, 40% had 1 antigen mismatch (MM), and 53% had 2 antigen MMs. Results indicated that relative to matched BMT, matched and 1-antigen MM high–cell dose UCBTs had a lower rate of GVHD and similar rates of TRM, relapse, and LFS. Two-antigen MM UCBTs had lower GVHD, higher rates of early TRM, lower rates of relapse and similar rates of LFS.

In conclusion, HLA-mismatched UCBT with an adequate cell dose is an acceptable alternative when an 8/8 unrelated adult donor is not available or when treatment is urgent, as is often the case in patients with acute leukemia. In addition, an analysis of matching at the HLA-C locus indicated that the data do not support considering such matching outside the context of a research protocol.