The 3rd Annual International Umbilical Cord Blood Transplantation Symposium took place in Los Angeles, California, on June 3–4, 2005. The Symposium was presented by the California Blood Bank Society, and was supported by unrestricted educational grants from International Cord Blood Bank StemCyte, the National Marrow Donor Program (NMDP), and the Health Resources Services Administration and was sponsored by several local and international companies.


There were 31 speakers from Canada, France, Japan, Spain, Taiwan, and the USA.

The Program objectives were:

- To describe patient selection and outcomes for pediatric and adult patients undergoing unrelated cord blood (CB) transplantation versus transplantation from other stem cell sources.
- To identify factors that affect transplant outcomes, including CB unit selection and HLA matching criteria, conditioning regimens, infectious complications, supportive care strategies, and the quality of CB stem cell products.
- To discuss the potential roles of CB stem cells and cord transplantation based on new research developments.
- To discuss current critical issues in CB banking.

The first of three sessions of the opening day of the Symposium was focused on umbilical CB transplantation in adults and reviewed current results and the future direction of that procedure.

Dr. Eliane Gluckman of the Hospital St. Louis (Paris, France) the center which performed the very first CB transplantation for the 5-year-old Fanconi patient in 1988, spoke on behalf of Eurocord. She presented the outcome of CB transplantation in 171 adult patients with malignancies who lacked an HLA-identical bone marrow (BM) donor. The median age of the group of patients who received CB was 29 years (range: 15–55 years) and the median follow-up time was 18 months. Most patients suffered from acute or chronic leukemia (n=142, 83%, and n=91, 53%) were transplanted in advanced phase, and 32 (19%) had previously failed an autologous transplant. Most patients (87%) received an HLA-incompatible CB unit with 1–2 HLA mismatches. The median number of total nucleated cell (TNC) infused was $2.1 \times 10^7$/kg and the median number of CD34$^+$ cells infused was $1 \times 10^5$/kg. The median day of hematological recovery ($\text{ANC} > 500$) was 28 days (range: 11–57 days). A higher TNC and the use of hematopoietic growth factors were independently associated with faster neutrophil recovery. The comparison of unrelated CB transplantation with unrelated, unmanipulated BM transplantation in adults with acute leukemia showed that CB recipients had delayed neutrophil recovery compared with BM recipients. The incidence of acute graft-versus-host disease (GVHD) > grade II was higher in the group transplanted with BM. At two years post-transplantation the incidence of chronic GVHD, transplant-related mortality (TRM), relapse, survival, and leukemia-free survival were not different between the two groups. When the CB transplant patients were compared with a similar group of patients receiving haplo-identical m-PBSC, the results were not different as far as TRM, the rate of relapse, engraftment, GVHD, and disease-free survival. However, there was a higher incidence of
GVHD in the CB recipients. LFS was higher in the CB group. Dr. Gluckman concluded that, despite increased HLA disparity, umbilical CB from unrelated donors is an acceptable source of stem cells for adult donors. She postulated that the donor search process for BM and CB from unrelated donors should be started simultaneously in adults, especially in patients with acute leukemia, where time is a very important factor. The selection of CB units with higher TNC count and earlier transplantation are likely to provide better results.

Cord blood has been successfully utilized as an alternative source of stem cells in the treatment of malignant and non-malignant diseases. One of the long-recognized limitations of CB transplantation in adults is the inadequate number of nucleated cells present in CB units. The recipients of a nucleated cell dose <2.5×10^7/kg have slow hematopoietic recovery and significantly lower incidence of engraftment. There exist several approaches to overcome this limitation. Dr. John Wagner from University of Minnesota (Minneapolis, USA) presented data on the effectiveness of one of the approaches, a double CB transplant. The hypothesis behind the infusion of two partially HLA-matched CB units is to augment the cell dose and thereby enhance engraftment and the rate of hematopoietic recovery. Dr Wagner presented 31 adult and adolescent patients with a median age of 24 years (range: 13–53), median weight of 73 kg (range: 48–120), and with high-risk hematological malignancy, who were transplanted with two partially matched CB units after myeloablative conditioning. Patients had AML (n=15), ALL (n=12), CML (n=3), or NHL (n=1). The median dose of TNC was 3.7×10^7/kg and 4.9×10^5 CD34+ cells/kg. All the patients engrafted at a median of 23 days (range: 14–41) with one unit predominating. No factor (TNC dose, CD34+ cell dose, HLA match, ABO, gender, order of infusion) predicted which unit would predominate. Incidence of platelet recovery (>50,000/µl) was 73% at day 180. Incidence of grade II–IV and III–IV acute GVHD was 65 and 17% at day 100. Disease-free survival was 72% at 1 year for patients transplanted in CR, with no relapse in this cohort. This outcome exceeded the historical data from transplants with a single CB unit. This study concluded that double unit infusion extends the application of CB transplantation to nearly all adults and adolescents by removing the cell number limitation of single unit transplantation.

Another approach to overcome the limited number of TNCs in CB is ex vivo expansion. This topic, which received more attention in the previous years, was greeted with more skepticism due to the fact that as yet no one has shown the feasibility of stem cell expansion. Many believe that the increase in cell numbers in vitro might represent the differentiation process rather than the renewal of the true stem cell. Additional hurdle is that not many transplant centers are equipped with laboratories accredited for cell expansion. Despite of this criticism there are still centers working on the ex vivo expansion approach. Dr. Elizabeth Shpall from the MD Anderson Bone Marrow Transplant Department in Houston (Texas, USA), presented several changes that their laboratory introduced to the expansion techniques. In one of the current trials, patients with hematological malignancies are now being randomized to receive either two unmanipulated CB units or one unmanipulated unit and one unit of ex vivo expanded cells. For the patients randomized to the expansion, on day –14 one of their CB units is CD133-selected using the Clinimax device. The CD133+ fraction containing T cells is frozen and the CD133+ fraction is cultured ex vivo for 14 days in media containing SCF, G-CSF, and thrombopoietin. Following administration of the preparative regimen, the un-manipulated CB unit is infused on day 0, followed by the thawed CD133+ fraction, and finally the 14-day cultured cells. This trial is in progress. Another expansion trial involves the use of the copper chelating agent TEPA, which has been shown to expand a more primitive population of CD34+ cells when combined with growth factors. An alternative approach to ex vivo expansion is the co-culture of CB cells with BM mesenchymal stem cells, which provide a microenvironment for self-renewal as well as the regulation of the differentiation and maturation of hematopoietic progeny. Pre-clinical trials are pending.

Another strategy to augment the effectiveness of CB transplantation was presented by Dr. Bruce R. Blazar from University of Minnesota Cancer Center (Minneapolis, USA). The subpopulation of naive CD4+ T cells that co-express CD25, the IL-2Rα chain, has been shown to have a potent suppressor activity. Ex vivo expanded CD4+CD25+ cells, called T regulatory cells (Tregs), co-transplanted with hematopoietic stem cells in experimental settings were able to rescue the recipients from GVHD. Of clinical significance, Treg cells did not inhibit the graft-versus-leukemia effect. Dr. Blazar presented unpublished data of more than 100 CB cell lines generated in order to set the stage for clinical trials of CD4+CD25+ cells for GVHD inhibition and therapy as well as engraftment promotion.

To avoid regimen-related toxicity, some centers are administering CB transplantation in non-myeloablative settings. Dr. Wagner presented such a study in 51
adults with advanced hematological malignancies. The conditioning included cyclophosphamide 50 mg/kg, fludarabine 200 mg/m², and 200 cGy TBI. The probability of overall survival at 1 year was 44%. Notably, only poor fitness, not advanced age, was associated with poor outcome. This approach extends access to transplant to many adults who would otherwise be ineligible based on the lack of a donor and/or an inability to tolerate high-dose conditioning. This study needs longer follow-up.

Several speakers brought up the issue of the minimal TNC dose from CB units and acceptable HLA mismatch between donor and recipient. Generally, low cell dose \(<2.5\times10^7/\text{kg}\) correlates with slow hematological recovery and significantly lower incidence of engraftment, and low overall survival. Dr Gluckman’s group suggested that a higher cell dose in the infusion could partially overcome the negative impact of HLA disparity. According to others, a CB unit with a 2-antigen mismatch and a higher TNC dose is a worse choice than one antigen mismatch with a lower cell dose. Dr. Satoshi Takahashi from the University of Tokyo (Japan) had a similar observation. He reported outcomes in 92 adult patients with hematological malignancies who received CB and 71 patients who received BM transplants after myeloablative conditioning. The overall survival and GVHD was the same in both groups; however grade III–IV GVHD was lower in the CB group. He observed that hematological recovery was faster in the CB recipients when the CD34+ cell dose was \(>0.9\times10^5/\text{kg}\). The 2-year probability of disease-free survival in the CB group was 95% in the standard-risk patients (n=39) and 60% in the high-risk patients (n=53). This highly positive outcome in the Japanese center could be attributed to the long, over 4-month post-transplant hospitalization of the adult patients.

Dr. Pablo Rubinstein from the New York Blood Center discussed current and new paradigms in deciding which unrelated progenitor cell source to use for transplantation in patients lacking related donors. Analysis of the 1750 New York Bank CB transplantations (with 396 patients older than 16) revealed that an unrelated CB unit should be considered before unrelated BM, followed by a 5/6 matched (with no rejection direction mismatch) CB unit. It is not yet clear if class I antigen mismatch overrides the class II mismatch.

Another interesting topic from the field of transplantation is the post-thaw characterization of progenitor cell viability and immunophenotype in CB products. In our own experience of thawing over forty CB products for transplantation in pediatric patients at Children’s Hospital Los Angeles (California, USA), recovery of CD34+ cells is very low, despite the high recovery of TNC, reflecting the loss of polymorphonuclear cells present in the graft. The CD34+ cell viability measured by the 7-AAD three color Flow Cytometry method is also very low compared with Trypan Blue (TB) viability. The explanation could be that the contact with DMSO changes the antigen expression on the cell surface, which does not necessarily indicate a loss of stem cell potential. Dr. Rafael Borstein from Madrid Cord Blood Bank (Madrid, Spain) and Dr. Michael Creer from St. Louis Cord Blood Bank (St. Louis, Missouri, USA) addressed those issues. Dr. Creer showed that none of the parameters measured in the post-thaw sample (TNC, TB viability, CD34 enumeration) correlated with patient survival. The only post-thawing test which correlated with outcome was a CFU functional test. In view of those results it seems reasonable to report pre-cryopreservation values of TNC, viability, and CD34+ cell dose, as they correlate better with engraftment and survival after transplantation. The cutoff point should be set on the units providing a nucleated cell dose of \(\geq2.5\times10^7/\text{kg}\) and a CD34+ cell dose \(\geq2\times10^5/\text{kg}\) (pre-thawing). All transplant centers should establish their standards for thawing a CB unit, since the presented data indicated that the CB transplant outcome was worse in centers with less experience. Dr. Creer also compared post-thawing data of the CB progenitor cells cryopreserved with Propanediol, used for freezing embryos, versus commonly used DMSO. Post-thawing data were as follows: TNC recovery 91% vs. 76%, CD34+ recovery 91% vs. 53%, TB viability 96% vs. 79%, and CD34+ 7-AAD 95% vs. 42%. Propanediol seems to be less toxic to the progenitor cells, and may be considered in cryopreservation of products.

Dr. Jo-Anne van Burik from University of Minnesota (Minneapolis, USA), and Dr. Mary Laughlin from Case Western Reserve University (Cleveland, Ohio, USA) discussed the problem of infectious complications following unrelated CB transplantation. Dr. Nelson Chao from Duke University (North Carolina, USA) presented the principles of immune reconstitution post CB transplantation, explaining the delay in hematological recovery and several donor and recipient factors contributing to those post-transplant infections.

The second day of the Symposium covered several aspects of CB transplantation in children with Crabbe and Hurler syndrome, Thalessemia, as well as acute leukemia.

Dr. Catherine Verfaillie from University of Minnesota (Minneapolis, USA) presented the population
of primitive cells called Multipotent Adult Progenitor Cell, or MAPC. Dr. David Prockop from Tulane University (New Orleans, Louisiana, USA) discussed the biology of mesenchymal cells and their application in hematopoietic cell transplantation. Dr. Curtis Cetrulo from Tufts University School of Medicine (Boston, Massachusetts, USA) suggested that Wharton’s Jelly stem cells could be potentially used as accessory supporting cells for CB transplantation. Wharton’s Jelly is a layer which protects the cord and placental vessels. The cells found in this tissue express matrix receptors: CD44, CD51, integrin markers CD29, CD51 but not CD34, CD45, and they also express mesenchymal stem cell markers SH2, SH3. They have high telomerase activity, self-renewal capacity, and are able to differentiate into bone, cartilage, muscle cells (cardiac), and nerve cells.

The Symposium ended with several talks addressing quality issues in CB banking, as well as presenting accreditation agencies and their standards. The main highlights were the cooperative efforts of several agencies (ISCT, NMDP, FACT, ASBMT) to join forces in creating a standardization of collection, laboratory processing, banking, and data collection on the outcome of CB transplantation. The Foundation for the Accreditation of Cellular Therapy (FACT) was co-founded in 1996 by the American Society for Blood and Marrow Transplant and the International Society for Cellular Therapy. The purpose was to establish standards for quality medical and laboratory practice and implement voluntary inspection and accreditation program. FACT, together with NET-CORD, a large group of international CB banks with an inventory of 93,000 CB units (3400 transplanted), are working together to produce international standards. Ideally, the long-term goal is to create one common database of the CB units collected all over the world, so that the search for a CB unit would be one-stop shopping.

Overall, this Symposium brought some structure and clarity to the rapidly growing but still chaotic field of allogeneic umbilical CB transplantation.

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