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REVIEW

Advances in umbilical cord blood transplant: a summary of the 11th International Cord Blood Symposium, San Francisco, 6–8 June 2013

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Abstract

The 11th International Cord Blood Symposium was devoted to advances in umbilical cord blood (UCB) research and transplant. Results of cord blood transplant (UCB SCT) for congenital storage disease and hemoglobinopathies are encouraging, but UCB SCT may also be useful for older adults with hematologic malignancies, and UCB cells have potential in regenerative medicine, particularly for neurological disorders, and may serve as excellent targets for gene therapy. UCB donor selection should consider high resolution human leukocyte antigen (HLA) typing, maternal HLA typing and detection of donor specific HLA antibodies. The issue of delayed hematopoietic reconstitution has hamstrung UCB SCT, but is addressed to a large extent by co-infusion of third-party progenitor cells. A number of cell expansion technologies also have great potential. Novel data show more limited benefits of double versus single umbilical cord blood transplant. Advances in quality control (QC) of UCB products and other improvements in cord blood banking technology will further improve the quality of stored UCB products.

Keywords: Basic biology, clinical results, adoptive cellular therapies, cord blood

Introduction

From 6 to 8 June 2013 the annual International Cord Blood Symposium was held in San Francisco. The meeting was devoted to advances in umbilical cord blood (UCB) research, with a major focus on translational and clinical results in cord blood transplant and in regenerative medicine. Over 3 days, a comprehensive summary of the state of the art was provided, including the presentation of many novel data. Herein are summarized the most important data, organized around four main themes.

Indications for umbilical cord blood transplant

Cord blood transplant for hematological malignancies: a role in older adults?

Treatment of children and young adults with hematologic malignancies represents the most common indication for UCB transplant. The often delayed engraftment after UCB transplant (see below) has limited its use in older adults.

Dr. Milano from Fred Hutchinson's Cancer Center in Seattle compared the outcomes of related, unrelated and UCB stem cell transplant (SCT) in Seattle. In univariate analysis the outcome of UCB SCT was superior, but this difference was not maintained in multivariate analysis. Strikingly, the relapse rate after UCB SCT was much reduced compared with that after sibling and unrelated donor transplant. These data are consistent with several previous studies demonstrating low recurrence rates after UCB transplant. Cord blood transplant is also associated with a remarkably low incidence of chronic graft-versus-host disease (GVHD). Both Dr. Weisdorf from the University of Minnesota and Dr. van Besien from Weill Cornell in New York City noted that the combination of low GVHD risk and low risk of disease recurrence is of particular interest for older patients, who frequently have unfavorable karyotype leukemia with a high risk for disease recurrence and who are extremely vulnerable to the sequelae of chronic GVHD. A preliminary analysis from the University of Chicago suggests that in patients older than 50, the outcomes of haplocord transplant are at least equivalent to those of related and matched unrelated donor transplant.

Congenital diseases: Hurler's syndrome and sickle cell disease

A number of presentations focused on the use of cord blood transplant for children with congenital disorders. Dr. Boelens from Utrecht, The Netherlands, presented the outcomes of a series of international studies on UCB transplant for

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Hurler's syndrome, a metabolic storage disease. It has long been established that children with Hurler's who have a matched sibling can benefit from SCT. For those without matched siblings, UCB transplant has been used. Thanks to multicenter collaboration, the results have steadily improved. In the most recent study, conditioning includes busulfan with pharmacokinetic monitoring of the area under the curve (AUC). T-cell depletion is avoided. In this study, the outcomes of transplant using UCB stem cells mirror those obtained with matched sibling or unrelated donor transplant.

Dr. Shenoy from Washington University presented data of a multicenter trial on cord blood transplant in children with sickle cell disease. The initial trial using fludarabine, melphalan and alemtuzumab resulted in a high rate of graft rejection. Hydroxyurea and thiotepa were then added to the regimen. Thirteen patients have been transplanted. There was one graft failure and one death due to GVHD. All others are doing well.

Regenerative medicine

An entire day of the conference was devoted to regenerative medicine. UCB cells have unique properties that may be somewhat similar to those of embryonic stem cells, but they are much more readily available and their use is not ethically controversial. The potential use of UCB cells for regenerative medicine is being explored in animal models, but also in early clinical studies. Dr. Tan from the University of Chicago showed data on intracerebral injection of UCB cells in mice that demonstrate their neuroregenerative potential. Others are interested in mesenchymal stem cells (MSCs) which are abundant in UCB and may have important regenerative potential. Some cord blood banks, in addition to collecting UCB hematopoietic stem cells, are now routinely collecting the umbilical cord stroma for generation of MSCs. Dr. Kraus from Perkin-Elmer/Viacord discussed how umbilical cord-derived MSCs are currently being considered/tested for several complications of prematurity, such as bronchopulmonary dysplasia, intraventricular hemorrhage and necrotizing enterocolitis. In animal models it has already been shown that these cells can differentiate into alveolar cells. It was speculated that because of their genetic identity, MSCs from newborns could one day become useful for regenerative treatments of parents or grandparents. Dr. Allickson from Wake Forest University discussed the isolation and potential utility of MSCs from amniotic fluid. These cells have stem cell-like properties and extensive regenerative capacity, and may ultimately become useful in regeneration of islet cells or cardiomyocytes.

Dr. Kurtzberg from Duke University presented preliminary results on intravenous injection of autologous UCB cells immediately after birth in babies with hypoxic ischemic encephalopathy. Preliminary results are encouraging, and a randomized trial is ongoing. A similar trial of intravenous injection of autologous cord blood cells is ongoing in children with cerebral palsy.

Dr. Wise Young from Rutgers University has led several trials of injection of partially matched UCB cells in patients with traumatic spinal cord injury. The phase I and phase II studies have shown spectacular radiological and clinical improvements in some subjects. A randomized trial is necessary to definitively demonstrate the utility of intraspinal UCB injection. Such a trial is ongoing in mainland China.

Technical mprovements in cord blood transplant

The appeal of cord blood transplant consists of its ready availability, the relatively low rate of acute and particularly chronic GVHD and the reduced rates of recurrence. However, UCB transplant can be complicated by severe acute GVHD. It also has several other limitations, including erratic and often delayed hematopoietic recovery and delayed immune reconstitution. Considerable discussion focused on methods to improve outcomes through better donor selection, through graft manipulation or through co-infusion of additional cell populations.

High-resolution human leukocyte antigen (HLA) typing and non-inherited maternal antigen (NIMA) and inherited paternal antigen (IPA) HLA antibodies in UCB donor selection

Traditionally cord blood units, in contrast to adult donors, have been selected based on low-resolution HLA typing for class I loci and without taking into account matching for HLA-C. High-resolution HLA typing may, however, be important in UCB SCT as well. Dr. Mary Eapen from the Medical College of Wisconsin presented data from a Center for International Blood and Marrow Transplant Research (CIBMTR)–Eurocord analysis using high-resolution typing at HLA-B, -C and -DR. Increasing mismatches at any of these loci (with the possible exception of mismatches at HLA-B) were associated with increased transplant related mortality (TRM). However, only severe mismatching (matching at fewer than five of the eight loci tested) was associated with worsening survival. Dr. Eapen recommended using high-resolution matching when selecting cord blood donors. Donors matching at fewer than five of eight loci should be avoided.

Nevertheless, Dr. Verneris from the University of Minnesota, using data from his own center, found no detectable impact of HLA mismatching on TRM. On the contrary, relapse, particularly in patients with acute myeloid leukemia (AML), was reduced when using mismatched transplant. He attributed the conflicting results with the CIBMTR–Eurocord analysis to the use of the double cord transplant methodology in Minnesota.

Dr. Scaradavou from the New York Cord Blood Center summarized the data on NIMA matching and IPA targeting. Any newborn has been exposed *in utero* to a mismatched HLA haplotype from its mother (NIMA) and is tolerant to it. When UCB cells are transplanted into donors who carry the NIMA from the donor's mother, such "NIMA matched" cord blood grafts have excellent outcomes. Taking into account maternal HLA type in the selection of cords may result in the selection of more appropriate cords. A limitation of this approach is the fact that many cord blood banks do not have data on maternal HLA typing and can therefore not

determine the NIMA of a particular cord. In a somewhat similar analysis, Dr. Scaradavou also showed the importance of the presence of the IPA in the recipient for maximal graft-versus-leukemia (GVL) effect of the graft.

Several, but not all, groups have previously shown that the presence of HLA antibodies in a transplant recipient which are directed against the donor (donor specific antibodies, DSAs) is associated with increased graft rejection and worse transplant outcomes. Dr. Ruggeri from the European Group for Blood and Marrow Transplantation (EBMT) showed data which further cement a role of donor specific HLA antibodies in graft rejection. A DSA level with median fluorescence intensity (MFI) >3000 was associated with a high risk of rejection. This presentation was followed by a discussion during which most experts felt that DSA analysis should now be incorporated in donor selection.

UCB cell dose

Many analyses indicate that the minimum cell dose for UCB SCT is $2.5–3\times10^7$ nucleated cells per kilogram recipient weight. Lower cell doses routinely lead to slower engraftment and worse outcomes. In an interesting observation, Dr. Barker from Sloan-Kettering pointed out that delayed engraftment not only is associated with early TRM but also leads after engraftment to continued problems related to GVHD. By contrast, Dr. van Besien from Weill Cornell Medical College and Dr. Kwon from the Hospital General in Madrid utilized third-party donor cells in combination with UCB grafts (see below). They observed accelerated recovery and durable engraftment of the UCB unit even at very low UCB doses.

One way to increase the cord blood cell dose consists of infusing two UCB units, a procedure that has gained considerable use, but the impact of which continues to be debated. Dr. Kurtzberg from Duke summarized the randomized Clinical Trials Network (CTN) trial of single versus double UCB transplant. Hematopoietic recovery, survival, disease-free survival, TRM and relapse rates were nearly identical between the two arms. Double UCB transplant was associated with somewhat delayed platelet recovery and more acute GVHD. She concluded that in children, double cord blood transplant should only be used when no sufficiently large single cord is available.

In adults the situation is more complex. Recently, Dr. Scaradavou *et al*. for CIBMTR published data showing similar outcomes after transplant of an appropriate volume single unit compared to double UCB transplant. Dr. Vanderson Rocha from Oxford presented new data from an analysis by Eurocord. They distinguished myeloablative and reduced intensity conditioning (RIC) groups. In the myeloablative group, no advantage was found to double UCB transplant, particularly if the "Spanish" busulfan–thiotepa–fludarabine conditioning regimen was utilized. In RIC transplant, rates of recurrence after RIC were high, but slightly less so with double UCB transplant.

Reducing the duration of pancytopenia

Erratic and delayed hematologic reconstitution constitutes the major limitation of UCB SCT. It leads to increased early TRM, prolonged hospitalizations and excessive costs. Many groups are working on methods to accelerate hematologic recovery, and five presentations addressed this issue.

Dr Shoemaker from Fate Therapeutics presented data on dimethyl-prostaglandin E2 (dmPGE2), a prostaglandin that induces expression of genes which increase the homing capacity of stem cells. In murine models, pretreatment of cord blood cells with dmPGE2 results in improvement in engraftment and in survival. A pilot study in humans also yielded encouraging results, with rapid hematopoietic recovery in most patients. Further trials are ongoing. Dr. Kurzberg from Duke summarized preliminary data of an ongoing study with the Nicor expansion system. Dr. Delaney from Seattle uses a Notch ligand to *in vitro* expand stem cell populations. Initial efforts were focused on expanding cord blood stem cells. Current efforts are focused on developing an off-the-shelf (not HLA matched) product that could be used to transiently enhance hematopoietic recovery. Preliminary results from an ongoing trial show partial correction of neutropenia.

Dr. Broxmeyer from Indiana University presented an update on the role of dipeptidyl peptidase 4 (DPP4) in hematopoiesis. DPP4 is a proteolytic enzyme that cleaves many cytokines at the penultimate proline or alanine and thus inactivates them. In return, inhibition of DPP4 with sitagliptin (Januvia®) should potentiate activity of these cytokines. Initial efforts focused on stromal cell derived factor 4 (SDF4), a major determinant of homing of stem cells. SDF4 is inhibited by DPP4 mediated cleavage. It was hypothesized that treatment with oral sitagliptin should improve stem cell homing and enhance recovery after UCB SCT. An initial trial of oral administration of sitagliptin did not improve hematopoietic recovery after UCB SCT, but this may have been related to insufficient drug levels and insufficient suppression of DPP4. A new trial with twice-a-day dosing is planned. DPP4 also interacts with numerous other cytokines, and likely has a larger role in the regulation of hematopoiesis. DPP4 levels rise upon exposure to radiation or chemotherapy. Teleologically its role may be to dampen chemotherapy induced cytokine storm.

Both Dr. Kwon from Madrid and Dr. van Besien for the groups at the University of Chicago/Weill Cornell Medical College presented data on a combination transplant, where UCB cells are co-infused with CD34 selected haploidentical cells. Early hematopoietic recovery derives from the adult cells, which over time are replaced by durable engraftment of UCB cells. Close to 300 patients have now been treated, and times to neutrophil recovery and platelet recovery mirror those of adult allogeneic transplant. Dr. van Besien for Chicago/Weill Cornell presented data on 92 patients with hematologic malignancies. He emphasized the steady improvements in outcome, and reduction in TRM, thanks to better UCB selection (avoidance of DSAs) and aggressive treatment for Epstein–Barr virus (EBV) viremia. UCB cell dose does not appear to matter for long-term UCB engraftment, and emphasis is given to more accurate HLA matching rather than higher cell doses. Dr. Kwon from Spain compared outcomes of haplo-cord with those of unrelated donor transplant, and found comparable long-term survival with less chronic GVHD.

Gene therapy and cord blood transplant

Several investigators are utilizing UCB cells as targets for gene therapy. Dr. Laurence Cooper from M. D. Anderson presented an update on the generation of chimeric antigen receptor (CAR) cells targeting CD19 using a "sleeping-beauty" methodology. Phase I studies are ongoing. Dr. Ann Leen from Baylor presented exciting data from a recently published study on engineered T-cells with specificity for three viruses, cytomegalovirus (CMV), adenovirus and EBV. The cells are generated as an "off-the-shelf" product consisting of 32 cell lines with different HLA types. To be eligible, patients had to share at least one HLA allele with one of the cell lines. Eighty-four patients were screened and suitable cell lines were identified for 72. Fifty were treated and 45 were evaluable. The cells were used for patients with refractory EBV, adenovirus or CMV after allogeneic transplant. Fourteen of 19 with CMV, 14 of 17 with adenovirus and six of nine with EBV had either partial or complete responses to the cellular therapy. Most responses were durable, although the T-cells themselves rarely persisted beyond 4 weeks. Side effects were minimal. This treatment strategy, under development for many years, is now reaching maturity. Efforts are ongoing to scale up the production process.

Cord blood banking issues

Cost and resource utilization were discussed by Michael Boo, JD, from the National Marrow Donor Program (NMDP) and by Dr. Querol from Barcelona. The UCB inventory keeps growing, and fewer units are utilized than collected. There is also increasing demand for larger units, based on the disappointing results of transplant with smaller units. Growing inventories create considerable financial pressures on non-profit cord blood banks. In order to be more economically feasible, a number of initiatives were considered, including: (1) greater efficiencies in the collection and storage process; (2) improved international collaboration, particularly as it relates to identifying grafts for patients of minority descent; and (3) restriction of storage to units that are considered high quality, discarding those that are unlikely to be used. Each of these solutions has its own hurdles, including: (1) increased regulatory burden, which creates additional expenses for local centers and which may make it difficult for international centers to meet US standards; and (2) uncertainty over what constitutes a high-quality unit. Most speakers emphasized cell number as the major determinant of high quality, but Dr. van Besien from Weill Cornell said that high-resolution HLA typing is equally important, and may be much more important than the UCB cell dose after haplo-cord transplant. Well-matched minority units are likely to be rather small in terms of cell dose.

In a further effort to better define what constitutes a high-quality unit, Dr. Scaradavou presented a detailed quality analysis from the New York Cord Blood Center. A number of assays of cord blood viability are routinely performed at cord blood banks prior to cryopreservation of the unit. However, there is limited information on how well these assays relate to cord blood quality upon thawing and infusion. Dr. Scaradavou showed how the two most commonly used assays at cryopreservation, namely the viable CD34 content and the colony forming unit (CFU) content of the stem cell collection, closely correlate. She also compared the viable CD34 and CFU content as measured at the cord bank with that obtained post-thawing at the customer site (in this case Memorial Sloan-Kettering Cancer Center) and found an excellent correlation between CD34s, but not between the CFU assays. She concluded that determination of the viable CD34 content at the time of processing represents currently the most reliable and reproducible measure of quality.

In an intriguing presentation, Dr. Louis from Montreal found that prolonged (72 h) exposure of thawed UCB cells to room temperature affects their long-term engraftment capability in SCID (severe combined immune deficiency) mice, although viability assays and CFUs are barely affected. This observation, if confirmed, may have important implications for cord blood processing and for quality control (QC) assays.

Potential conflict of interest: Disclosure forms provided by the authors are available with the full text of this article at www.informahealthcare.com/lal.