



# Annotated Bibliography

## III. Multi-Cord Transplants



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1. **Umbilical cord blood transplantation after nonmyeloablative conditioning: impact on transplant outcomes in 110 adults with hematological disease.** Brunstein CG, Barker JN, Weisdorf DJ, Defor TE, Miller JS, Blazar BR, McGlave PB, Wagner JE. Blood 2007;110:3064-3070. **Abstract**

This report establishes the safety profile of a nonmyeloablative treatment regimen consisting of fludarabine (FLU), cyclophosphamide (CY) and single fraction total body irradiation (TBI) in recipients of UCB in 110 consecutive adult patients with hematological disease. Ninety-three of the 110 patients received a double cord transplant.

**Inclusion Criteria.** Patients with advanced or high-risk hematologic disease were eligible for UCB transplantation if they had no related donor matched at 5-6/6 HLA loci (A, B, and DRB1). Patients were eligible for nonmyeloablative therapy if they met any of the following criteria: age >45 years, pre-existing high risk clinical features for TRM (serious organ dysfunction; invasive mold infection within 4 months prior to transplantation; Karnofsky Performance score 50-60 or history of extensive prior therapy [defined as: >12 months alkylator-based chemotherapy; >6 months alkylator-based chemotherapy plus extensive radiation; or history of autologous transplantation]).

**UCB unit selection algorithm.** UCB units were required to be matched at >4 of 6 HLA antigens based on antigen-level HLA-A and B typing and allele-level HLA-DRB1 typing. UCB units were required to have a minimum cryopreserved total nucleated cell (TNC) dose of  $2.0 \times 10^7$ /kg. However, the target cell dose was  $3.0 \times 10^7$  TNC/kg resulting in the selection of a second partially HLA matched UCB unit if available. In those for whom a second UCB unit could be identified, the second unit also had to be 4 of 6 antigen matched with the first unit.

**Treatment.** 110 patients received a single dose of CY 50 mg/kg on day -6, FLU 40 mg/m<sup>2</sup> daily on days -6 to -2, and a single fraction of TBI 200 cGy without shielding on day -1. ATG was given at 15 mg/kg every 12 hours on days -3 to -1 in a subpopulation of patients who had received less than two cycles of multiagent chemotherapy within the 3 months prior to enrollment (and no history of autologous transplantation.). All patients received CsA twice daily from day -3 for at least 3 months with target trough levels of 200-400 ng/ml and MMF at 1 g intravenously or orally twice daily from day -3 to +30.

**Results.** Most patients received two UCB units (n=93) to achieve the required cryopreserved cell dose. Neutrophil recovery was achieved in 92% at median of 12 days. Incidences of grades III-IV acute and chronic GVHD were 22% and 23%, respectively. Transplant-related mortality was 26% at 3 years. Survival and event-free survival at 3 years were 45% and 38%, respectively.

Favorable risk factors were absence of high risk clinical features and absence of severe GVHD (p=0.04) for survival, and absence of high risk clinical features (p<0.01) and use of two UCB units (p=0.07) for event-free survival.

**Discussion.** The study supports the use of UCB transplantation after a non-myeloablative therapy in adults with hematologic disease. **It is clear that the use of the double UCB platform in the setting of a nonmyeloablative therapy extends the availability of transplantation to those who cannot find a suitably HLA matched adult volunteer marrow or peripheral blood donor and who are at increased risk of regimen-related toxicity and transplant related mortality, such as older or heavily treated patients.**

2. **Double umbilical cord blood transplantation.** Majhail NS, Brunstein CG, Wagner JE. Curr Opin Immunol. 2006; 18: 1-5.

### **Abstract**

Unrelated umbilical cord blood (UCB) is an alternative donor source for allogeneic hematopoietic cell transplantation and, compared with unrelated donor bone marrow, has the advantages of rapid availability, greater tolerance of HLA disparity and lower incidence of severe GVHD. However, the presence of a limited number of hematopoietic progenitor cells in a single unit, lack of access to donor lymphocytes for donor lymphocyte infusion if needed, and the brief clinical experience to date are some of the limitations of UCBT. **The aim of this review is to address one potential strategy for overcoming the cell dose limitation, namely the use of multiple units.**

The total nucleated cell (TNC) and CD34<sup>+</sup> cell dose has been shown to be a crucial determinant of hematopoietic recovery and overall outcome following UCBT, and the limited cell dose of single UCB units is clearly the most important barrier to its more widespread use, especially in adults.

**Pre-clinical** studies in nonobese diabetic/severe combine immunodeficient (NOD/SCID) mice have shown enhanced engraftment by the addition of a second UCB unit.

**Double UCBT: clinical studies.** (Published data are presented in a table. ) **Patients who receive UCBT using two UCB units, because of the unavailability of a single unit that has a satisfactory TNC dose, do as well as patients transplanted with a single adequately sized UCB unit.** Importantly, no increase in the incidence of severe aGVHD has been noted. Comparable outcomes have been obtained with myeloablative and non-myeloablative conditioning regimens.

Sustained hematopoiesis after double UCBT is usually derived from a single donor. It is not clear how to predict which of the two units will predominate.

**Transplantation of two cord blood units can potentially augment the graft-versus-leukemia (GVL) effect.** A recent report

indicates a reduced risk of relapse in patients with acute leukemia who received double unit UCBT.

**Unit selection.** The current protocols at the University of Minnesota select UCB units on the basis of cryopreserved TNC dose and HLA-A, -B and -DRB1 match using intermediate resolution antigen level typing for A and B, and allele level typing for DRB1. Single unit UCBT is performed if a 5 of 6 HLA-matched UCB unit is available that has a TNC of  $>3.0 \times 10^7$  cells/kg, otherwise patients are considered for double UCBT.

There are currently no available data that specifically address the optimal criteria for double UCBT unit selection. The protocol used at the U. of Minnesota is to preferentially select a 5 of 6 HLA-matched unit, regardless of the TNC dose as long as it exceeds  $2.5 \times 10^7$  cells/kg. Also, because immunological rejection is hypothesized to account for loss of one unit over time, the practice has required partial HLA matching between the two units. This requirement often results in the selection of units that are not necessarily the two units that have the greatest cell dose. HLA disparity between each unit and the recipient and between the two units does not necessarily have to be at the same loci. Each unit is required to have a cryopreserved TNC dose of at least  $1.5 \times 10^7$  cells/kg, such that the total graft dose is  $>3.0 \times 10^7$  cells/kg. If two units of equal HLA match having a TNC dose within  $0.3 \times 10^7$  cells/kg of each other are available, the one with the higher CD34+ dose is selected.

**Conclusions.** Double UCBT is a feasible, safe and effective transplantation strategy for patients that have life-threatening hematological disorders who need a hematopoietic stem cell transplant but lack a HLA-matched related or unrelated donor. It is an attractive option, especially for adults who are typically not eligible for single UCBT because of limitations of cell dose. Besides being rapidly available, an acceptable double unit graft can be identified for the majority of patients. The rates of engraftment, transplant-related mortality, GVHD, and survival are similar to those seen with single UCBT and unrelated donor BMT.

### 3. Transplantation of two partially HLA-matched umbilical cord blood units to enhance engraftment in adults with hematologic malignancy. Juliet N Barker, Daniel J Weisdorf, Todd E DeFor, Bruce R Blazar, Philip B McGlave, Jeffery S Miller, Catherine M Verfaillie, and John E Wagner. Blood 2005;105:1343-1347. (Also see Commentary by Dr. Mary Laughlin, [below](#).) [Abstract](#)

The investigators studied the safety and efficacy of umbilical cord blood transplantation (UCBT) using cord blood units from 2 partially HLA-matched donors as a method of augmenting cell dose in high-risk adults and adolescents with hematological malignancies.

Twenty-three patients (median age 24 years (range 13-53)) were enrolled in the study. All patients but one were considered high-risk for relapse. Patients were eligible if they had no 5-6/6 HLA-A,B,DRB1 matched related donor and no suitable volunteer donor available. Umbilical cord blood (UCB) was given priority over volunteer donors for patients requiring transplant within 3 months of referral. Patients were eligible for double unit UCBT if no single 4-6/6 HLA-A,B,DRB1 matched UCB unit of adequate cell dose was available (at least  $2.5 \times 10^7$  NC/kg in the earlier part of the study, and at least  $3.5 \times 10^7$  NC/kg in the latter part of the study). The largest available UCB unit that was 4-6/6 HLA-A,B,DRB1 matched was selected as UCB#1 and UCB#2 had to be both 4-6/6 HLA-A,B,DRB1 matched to the recipient and to UCB #1. The minimum allowed cryopreserved graft cell dose was  $1.5 \times 10^7$  NC/kg (UCB#1  $1.0 \times 10^7$  NC/kg; UCB #2  $0.5 \times 10^7$  NC/kg). The median infused cell dose was  $3.5 \times 10^7$  NC/kg (range 1.1-6.3). During the study period, the authors were able to find two appropriate cord blood units for 23 of 26 eligible patients; three patients (12%) received a single unit graft due to inability to identify a suitable second unit.

All patients received myeloablative conditioning using cyclophosphamide 120 mg/kg (60 mg/kg/day at 10:00 AM on days -7 and -6 for 2 doses), and total body irradiation (1320 cGy in 8 fractions) and immunosuppression with cyclosporine-A from day -3 for at least 6 months. In addition some patients received anti-thymocyte globulin and methylprednisone, or low dose fludarabine (25 mg/m<sup>2</sup>/day at 9:00 AM on days -8 to -6 for 3 doses) and mycophenolate mofetil 1 gm twice daily from days -3 to +30.

All evaluable patients (n=21) engrafted at a median of 23 days (range 15-41). At day 21, engraftment was derived from both donors in 24% and a single donor in 76%, with one unit predominating in all patients by day 100. While neither nucleated or CD34+ cell dose, nor HLA-A,B,DRB1 match, predicted which unit would predominate, the predominating unit had a significantly higher CD3+ dose ( $p < 0.01$ ). Incidences of grade II-IV and III-IV acute GVHD were 65% (95%CI: 42-88%) and 13% (95%CI: 0-26%), respectively.

**Disease-free survival was 57% (95%CI: 35-79) at one year, with 72% (95%CI: 49-95) of patients alive if transplanted in remission.**

The authors concluded that transplantation of 2 partially HLA-matched UCB units is safe, and may overcome the cell dose barrier that limits the use of UCB in many adults and adolescents. They indicate that double unit UCBT extends access to transplant to many patients who were previously disqualified on the basis of available cell dose in a single unit.

(*Comment:* Umbilical cord blood cannot satisfy society's need for stem cell donors for all patients in need of a transplant unless they can regularly be used for adults. This is true because a large majority of patients who have an indication for a hematopoietic cell transplant are adults. This publication is an important contribution to solving the problem of inadequate cell dose. The authors state that only 30% of adults at the University of Minnesota were able to find an adequately dosed UCB graft prior to the institution of double unit UCB transplantation. In contrast, because of the availability of double unit UCB transplantation, 23 of 26 (88%) eligible patients in this study received a transplant with an adequate cell dose (the median total infused graft cell dose was  $3.5 \times 10^7$  NC/kg). Three patients (12%) received a single unit graft due to inability to identify a suitable second unit.

Note that, if the patients required a transplant within 3 months of referral, cord bloods were given priority over alternative sources of stem cells, i.e., bone marrow or peripheral blood. For more information about the importance of obtaining a stem cell product properly see [Annotated Bibliography VI. Availability and time required to obtain cord blood versus bone marrow.](#))

### 4. Double unrelated reduced-intensity umbilical cord blood transplantation in adults. Ballen KK, Spitzer TR, Yeap BY, McAfee S, Dey BR, Attar E, Haspel R, Kao G, Liney D, Alyea E, Lee S, Cutler C, Ho V, Soiffer R, Antin JH. Biol Blood Marrow Transplant. 2007;13:82-89. [Abstract](#)

In an effort to increase the cell dose and decrease transplantation-related toxicity, the authors treated 21 adult patients (24-63 years) with a reduced-intensity conditioning regimen followed by sequential infusion of 2 partially matched umbilical cord blood (UCB) units. Two patients had aplastic anemia, one had myelodysplastic syndrome and the others had hematologic malignancies, the most common diagnosis being acute myeloid leukemia.

The reduced-intensity conditioning regimen consisted of fludarabine, melphalan, and antithymocyte globulin. The UCB units were a 4/6 HLA match or better with each other and with the patient and achieved a minimum precryopreservation cell dose of  $3.7 \times 10^7$  nucleated cells/kg.

The median time to an absolute neutrophil count  $> 0.5 \times 10^9/L$  was 20 days, and the median time to an unsupported platelet count  $> 20 \times 10^9/L$  was 41 days. Two patients experienced primary graft failure and underwent a second UCB transplantation. One patient had a late graft failure. Acute graft-versus-host disease (GVHD) grade II-IV occurred in 40% of patients. The 100-day TRM was 14%, and the 1-year disease-free survival was 67%. Mixed chimerism was associated with a higher risk of chronic GVHD.

The authors concluded that their findings indicate that adult patients can tolerate double UCB transplantation well and achieve sustained antitumor responses using this reduced-intensity conditioning regimen.

5. **Transplantation of 2 UCB units in adults.** Laughlin MJ Blood 2005;105915-916. [Full Text](#)

In this [commentary](#), Dr. Laughlin emphasizes key points in the article by Barker et al. Transplant outcomes were reported in 23 adults and adolescents with high-risk hematologic malignancies, treated with fully ablative conditioning prior to infusion of 2 partially HLA-matched unrelated cord blood units. Median age was 24 years (range, 13-53 years). Each patient received 2 HLA-mismatched umbilical cord blood (UCB) units thawed and infused without prior ex vivo expansion. Median combined infused nucleated cell dose was  $3.5 \times 10^7$  kg (range,  $1.1 \times 10^7/kg$  to  $6.3 \times 10^7/kg$ ). **All evaluable patients (n=21) engrafted** neutrophils at a median of 23 days (range, 15-41 days).

At the time of myeloid engraftment, chimerism revealed the presence of both UCB donors in some patients, with emergence of one UCB unit predominating in all patients by day 100. There does not appear to be crossed immunologic rejection. Neither nucleated or CD34<sup>+</sup> graft cell dose nor HLA match was predictive, but the predominating UCB unit had a significantly higher CD3<sup>+</sup> graft lymphocyte cell dose.

This report parallels other reports which indicate that the **use of unrelated cord blood is associated with a low incidence of aGVHD and that event-free survival approximates that observed in the unrelated setting after infusion with adult donor marrow and peripheral blood stem cell grafts.**

6. **Adult transplant outcomes, single versus pooled cord blood transplants.** Wofford JD, Regan DM, Creer MH. Biol Blood and Marrow Transplant 2005;11(Suppl 1):2.

The authors compared single cord blood transplants with double cord blood transplants in adults to determine whether augmenting the cell dose increases the safety of the transplants. They evaluated outcomes following 106 cord blood unit transplants performed at 27 transplant centers for adult patients ( $>18$  years of age). Population characteristics included an even distribution in gender in the two groups; diagnoses were primarily malignant diseases (95.1%); the median age was 43.8 years (range, 18.6-64.8); and median weight was 72 kg (range, 41.0-120.4). For single cord blood transplants, the median post-processing dose was  $2.6 \times 10^7/kg$  (range, 1.1-8.5), but post-thaw data indicates that only a median cell dose of  $2.0 \times 10^7$  cells/kg were infused (range, 0.62-6.9). In the dual cord protocol, 2 units were chosen to supply a median post-processing dose of  $4.7 \times 10^7$  cells/kg (range, 2.8-6.7), yielding a median infused dose of  $3.6 \times 10^7$  cells/kg (range, 2.3-5.7) after thawing. TNC recoveries after cryopreservation averaged 80%, but the impact was more profound in the single transplant setting, where cell dose was diminished to  $<2.0 \times 10^7$  cells/kg in 51.8% of all cases. When combining 2 units, a cell dose of  $>2.0 \times 10^7$  cells/kg was maintained in all cases.

The median time to ANC  $>500/mm^3$  was similar in single and double cord blood transplants (pooled, 18 days, n = 21; single, 21 days, n = 73), but the difference in overall survival between the 2 groups approached statistical significance (p = 0.0555). Overall patient survival was 13.26 months in the pooled group (n = 23) and 3.32 months in the single cord setting (n = 83).

Because TNC recovery is unaffected by product size, selection of a single umbilical cord blood unit for transplant in adults based on the post-processing cell dose may result in a less than adequate dose. Preliminary data indicate that pooling 2 units uniformly allows the maintenance of a cell dose of  $>2 \times 10^7$  cells/kg, resulting in improved patient outcome.

*(Comment: The authors emphasize that cell loss during thawing can have a significant effect on the cell dose actually infused. Evaluation of cell counts after thawing provides a more precise and realistic indication of cell dose.*

*Although the difference in survival did not reach clinical significance, the fact that double cord blood transplants can provide an adequate cell dose for patients weighing up to 120.4 kg emphasizes once again that the use of double cord blood transplants extends access to transplant to many patients who were previously disqualified on the basis of available cell dose in a single unit.)*

7. **Multiple unit unrelated donor umbilical cord blood transplantation in high risk adults with hematologic malignancies: Impact on engraftment and chimerism.** Barker JN, Weisdorf DJ, DeFor TE, et al. Blood 2002;100: 41a

Cell dose is a critical determinant of hematopoietic recovery and survival after unrelated donor umbilical cord blood transplantation. The authors hypothesized that the combined transplantation of two partially matched umbilical cord blood units would improve engraftment without crossed immunological rejection. *Twenty-three high-risk adults were transplanted using two umbilical cord blood units, and the results indicated that there was a high incidence of donor engraftment without an increase in severe acute GVHD.* The data further suggested that the second unit may facilitate engraftment by immunological mechanisms.

8. **Early engraftment kinetics of two units cord blood transplantation.** Kang HJ, Kho SH, Jang MK, Lee SH, Shin HY, Ahn HS. Bone Marrow Transplant. 2006; 38:197-201. [Abstract](#)

**The authors analyzed the early engraftment kinetics of 8 patients given two unit umbilical cord blood transplants in an attempt to clarify the early engraftment kinetics** of this complex form of transplantation with multiple donors.

The patients ranged in age from 6 to 17 years and in weight from 23 to 62.9 kg. Their diagnoses were AML, SAA, ALL and ALL Ph+. The patients received various conditioning regimens and GVHD prophylaxis according to disease status.

**The data revealed a dominance of one of two administered units in each patient from the day of engraftment (ANC  $>0.5 \times 10^9/l$ ).** The median values of the percentage of the dominant unit, the non-dominant unit and recipient by chimerism analysis on the days of engraftment were 89.5% (60-100%), 0% (0-16%) and 5% (0-40%), respectively. All patients achieved complete donor chimerism ( $>90%$ ) at day 28. The median values of the percentage of the dominant unit, non-dominant unit and recipient at day 28 were 94.5% (80-100%), 0% (0-12%) and 2.5% (0-8%), respectively.

Units with a higher number of TNC and CD34<sup>+</sup> cells predominated in two and four of eight patients, respectively, and units with higher numbers of CD3<sup>+</sup> cells predominated in three of seven patients. The better HLA-matched unit predominated in five of 8

patients. In another two with the same HLA mismatch of six serotype and low-resolution genotype, units better matching high-resolution genotypes HLA-A, -B, -C, -DRB1 and -DQB1 predominated.

**The most significant result of the present study was that dominance was found to occur early after transplantation.** However, the exact time for determining dominance has not been defined, and it may even occur just after the infusion of the two units.

**The authors concluded that multiple factors associated with outcomes of CBT could influence the determination of dominance,** such as those factors that affect the recipient environment, the characteristics of each UCB unit and HLA disparity.

9. **Enhanced engraftment of umbilical cord blood-derived stem cells in NOD/SCID mice by cotransplantation of a second unrelated cord blood unit.** Nauta AJ, Kruijselbrink AB, Lurvink E, Mulder A, Claas FH, Noort WA, Willemze R, Fibbe WE. *Exp Hematol.* 2005;33:1249-56. [Abstract](#)

Umbilical cord blood (UCB) is considered as an attractive alternative source of hematopoietic stem cells for allogeneic stem cell transplantations in patients who lack human leukocyte antigen (HLA)-matched donors. However, the low cell dose adversely affects hematopoietic recovery and therefore limits application of UCB transplantation in adults. **Transplantation of multiple UCB units could be a strategy to overcome cell dose limitations.**

The authors investigated the effect of double cord transplantation in nonobese diabetic/severe combined immunodeficient mice that were transplanted with human hematopoietic progenitor cells (CD34<sup>+</sup>) derived from two UCB units with HLA disparity. Human cell engraftment and donor origin were determined by flow cytometry.

**Results indicated that double CB transplantation resulted in increased engraftment levels in the bone marrow and peripheral blood in comparison with recipients of a single unit.** The authors considered the effect of cell dose by comparing double CB transplantation with single units containing equal cell numbers ( $2 \cdot 10^5$ ). In some cases, engraftment levels in recipients of single units containing  $2 \cdot 10^5$  cells were significantly higher than after transplantation of  $1 \cdot 10^5$  cells. These engraftment levels were similar to those observed after double CB transplantation. Chimerism analysis indicated that increased engraftment in recipients of two units was predominantly derived from one unit, whereas in other cases the contribution of the two units was similar.

**The authors concluded that their results indicate that engraftment of a single CB unit may be enhanced by addition of a second unrelated CB. The effect might be attributed to a cell dose effect or due to a graft-facilitating effect. This study provides proof-of-principle that combining multiple cords is a viable way of obtaining sufficient stem cells to perform a transplant when limited a number of stem cells are available.**

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