Leukemia patients and patients with other hematological diseases require transplantation of hematopoietic stem cells available in bone marrow or mobilized peripheral blood. As with all transplantations, patient and donor have to be matched carefully on human leukocyte antigen (HLA) residues. Since the first successful transplantation of umbilical cord blood (UCB) into a young Fanconi Anemia patient in the eighties, cord blood has been increasingly used as a therapy for hematologic patients lacking a suitable HLA-matched donor. Since then, cord blood is collected at birth in several centers around the world and cryopreserved for later use in transplantation. For reasons not yet fully understood, cord blood transplantation results in less severe graft versus host disease (GvHD) complications post-transplant despite HLA mismatching, thus expanding the potential recipient pool significantly. However, to date, large scale application has been compromised by limiting cell doses single unit cord blood transplants causing problems, particularly in larger children and adults. While in the bone marrow transplant setting the donor can be solicited to donate again if engraftment is compromised, in the case of cord blood transplantation this is not possible, as collection is a one-time event.

The UCB total nucleated cell (TNC) threshold cell dose for adult patients has been delineated to be a minimum of $2.5 \times 10^7$/kg recipient weight, resulting in favorable outcomes similar to that observed in patients receiving standard bone marrow or mobilized peripheral blood stem cell grafts from adult donors. For larger adults however, such cell doses are difficult to attain with cells contained within one single cord blood collection (unit). More recently, two-unit UCB graft infusions has been explored in an attempt to overcome these graft cell dose limitations for adult patients in myeloablative and non-myeloablative setting. Important challenges to the analyses of clinical trials published...
to date include a variance in patient selection, a lack of uniformity in patient characteristics in those receiving one vs. two-units with a large proportion of single unit recipients being pediatric patients, as well as changes over time in conditioning and GvHD prophylaxis, including anti-thymocyte globulin (ATG) administration. Two large single institution series (published to date) report retrospective experience with patients transplanted with one or two UCB units after non-myeloablative conditioning. However, changes in the preparatory regimens used, patient selection differences including marked age variation, and modifications in supportive care including graft vs. host disease (GvHD) prophylaxis and ATG administration during the course of these studies, have rendered interpretation of potential benefit of two unit transplantation difficult. Importantly, however, two additional large retrospective series showed lower relapse rates particularly in early stage patients who received two UCB units, suggesting a benefit in transplanting two units.

Interestingly, after a transient chimerism where cells of both cord blood units can be observed, one cord blood unit emerges quickly as dominant, from which long-term hematopoiesis is then derived. Potential UCB immunologic and stem cell homing mechanisms underlying the engraftment of the dominant unit are still unclear.

A recent prospective phase I/II study compared the safety and efficacy of one vs. two UCB units infused into adult patients. Importantly, the patients were treated uniformly with the same reduced intensity conditioning (RIC), GvHD prophylaxis, and supportive care regimen, to determine whether rates and kinetics of engraftment, acute GvHD incidence, relapse rates, and survival may differ after infusion of one unit compared to two units. This study also examines the influence, if any, of UCB graft infused TNC, CD34+ hematopoietic progenitors, natural killer (NK), and T-cell doses on procedure outcomes including: overall survival, allogeneic engraftment, and event free survival. The study design specified one UCB unit if the cryopreserved total nucleated cell dose was $\geq 2.5 \times 10^7$/kg recipient weight, otherwise 2-units matched at minimum 4/6 HLA loci to the patient and 3/6 to each other were infused. Twenty-seven patients received 1 unit, 23 patients received two units. The median time to absolute neutrophil recovery was 24 days, with no significant difference between 1 unit recipients and 2 unit recipients. Three-year event free survival (EFS) was also similar in both patient groups.

Interestingly however, infusion of two units was associated with significantly lower relapse risk, with only 30% of the two unit patients relapsing, compared to 59% of the 1 unit patients relapsing. Infused cell doses (TNC, CD3+, CD34+, CD56-CD34+) did not impact engraftment, overall survival, or EFS. Conclusions drawn from this study suggest that single unit UCB transplantation with a threshold cell dose $\geq 2.5 \times 10^7$/kg recipient weight after RIC is a viable option for adults, and that infusion of two units confers a lower relapse incidence to these patients.

This study was the first prospective investigation directly comparing a single UCB unit versus a two-unit approach in adult hematologic malignancy patients treated with uniform RIC and supportive care including acute GvHD prophylaxis. The patients enrolled were reflective of an adult hematology practice including the predominance of myeloid leukemia over lymphoid malignancy, and were comparable to other reports in terms of age and weight range. Of note, most patients included in previous reports on RIC outcomes with bone marrow and UCB grafts, had either none or had received prior autologous hematopoietic cell transplantation. In this study however, patient population were extremely high-risk for disease and were heavily pretreated, including over half of patients receiving prior autologous or allogeneic transplantation, implicating a possible higher risk of relapse- and non-relapse mortality. Despite this high risk, these data compare favorably to previous single institution trials and larger retrospective series, and recent data published by the National Marrow Donor Program summarizing transplant outcomes in adults treated with RIC and conventional adult-derived graft sources.

A major concern for UCB transplant safety and efficacy for adult patients is the limited TNC and CD34+ progenitor cell content in the graft, generally a log lower than adult-derived grafts. Several studies have shown neutrophil engraftment after UCB transplantation correlating with graft TNC dose, CD34+ cell dose, CD3+ cell dose and CD8+ cell dose. However, the influence of these graft cell populations is not seen consistently across all trials.

In the two-unit setting, infusion of two UCB units did significantly impact the relapse risk in high risk patients, with 1-unit recipients having a relapse risk significantly higher than two-unit recipients, suggesting a strong graft-vs. malignancy effect of two-unit UCB infusion as reported in prior retrospective studies. Sixteen (59.3%) patients in the one-unit group in this study notably relapsed, compared to only 7 (30.4%) patients in the two-unit group (p=0.045). The benefit of stronger graft vs. lymphoma effect has also been reported by the Eurocord-Netcord and lymphoma working party of the European group for Blood and Marrow Transplantation in 104 adult patients treated with one- or two-unit UCB after RIC with lower risk of relapse observed in recipients of double-unit UCB (p=0.03).

Consistently, one UCB unit predominates in transplant recipients receiving two or more UCB units usually by 4-6 weeks after transplant. Infusion of the non-engrafting unit may augment UCB engraftment via immune activation and/or inhibition of recipient-mediated immune rejection. Since RIC transplantation depends on “allogeneic effect” to eliminate malignancy, each UCB unit represents an intact immune system with potential donor-recipient and donor-donor interactions that may render additional benefits of two-unit infusion, including enhanced graft vs. malignancy effects. Despite of ongoing immune interactions between the two infused cord blood units and the patient, surprisingly there is no increase in acute or chronic GvHD frequency nor severity when infusing two cord blood units.

While single unit UCB transplantation at threshold nucleated cell dose exceeding $2.5 \times 10^7$/kg recipient weight remains a valid treatment option, it remains to be seen whether two unit transplants will become an option for adult patients where such a
cell dose cannot be attained. The observed lower relapse risk after the infusion of two umbilical cord blood units, with similar survival outcomes seems promising, but current data available is insufficient, given the heterogeneity of patient populations and the small number of patients studied in settings where patient characteristics and treatment were comparable. Further studies are needed in larger multi-institutional prospective trials: 1) to firmly establish the minimum safe threshold dose for single unit UCB in adult patients treated with RIC, and 2) to identify key parameters for graft selection in the two UCB unit setting that may contribute to enhance graft vs. malignancy effects confirmed in this prospective single institution study.

References

About the Author
Mary J. Laughlin is a tenured Professor of Medicine at the University of Virginia and holds their Cancer Center Endowed Chair. Dr. Laughlin is a scientist of exceptional creativity who initiated her groundbreaking work in umbilical cord blood allogeneic stem cell transplantation while holding a post as Assistant Professor at Duke University initially in 1994 and has carried this work forward over the past 17 years. She has made important contributions to the field of hematology and stem cell transplantation, bringing forth this new stem cell source as an effective treatment modality for adult patients with life-threatening hematologic disorders, and providing new insights in neonatal hematopoietic stem cell and T lymphocyte biology.