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CONCISE REVIEW

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STEM CELLS TRANSLATIONAL MEDICINE

Umbilical cord blood: The promise and the uncertainty

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Abstract

Unfortunately, many patients referred for hematopoietic cell transplant will not have a fully matched related donor, and finding matched unrelated donors through the registry may be difficult, especially if the recipient is not of Northern European descent [N Engl J Med 2014;371:339-348]. Umbilical cord blood (UCB) has been an available graft source for hematopoietic cell transplant for more than 30 years, since the first UCB transplant was performed in the late 1980s [N Engl J Med 1989;321:1174-1178]. UCB is readily available, has low immunogenicity, and does not require as strict of human leukocyte antigen (HLA) matching compared to other graft sources [N Engl J Med 2004;351:2265-2275]. According to data from the Center for International Blood and Marrow Transplant Research (CIBMTR), an estimated 500 patients in the US will have received a UCB transplant in 2018. Since 2014, haploidentical transplants have surpassed UCB transplants performed in the United States (CIBMTR Summary Slides, 2018, available at https://www.cibmtr.org). Increased use of haploidentical transplants has brought to light concerns about UCB transplants, including delayed engraftment and graft failure, increased nonrelapse mortality, increased infection risk, and UCB acquisition costs [Lancet Oncol 2010;11:653-660; Biol Blood Marrow Transplant 2019;1456-1464]. These concerns will need to be addressed for UCB to remain a viable option as a graft source for hematopoietic cell transplant. Other promising therapeutic benefits for UCB, in addition to hematopoietic cell transplant, is its use in regenerative medicine and immune modulation, which is currently being evaluated in ongoing clinical trials.

KEYWORDS

hematologic malignancies, hematopoietic cell transplant, umbilical cord blood

1 | INTRODUCTION

Approximately 8600 transplants were performed in 2017, according to the Center for International Blood and Marrow Transplant Research (CIBMTR).[1] Many patients referred for hematopoietic cell transplant will not have a matched related donor, so an unrelated donor search is often performed. The likelihood of finding a matched unrelated donor through the Be the Match registry ranges between 16% and 75% depending on the ethnicity and race of the recipient.[2] Alternative donors, including haploidentical donors and umbilical cord blood (UCB), remain viable options for transplant if a patient does not have a matched related or unrelated donor.[1] UCB grafts have the advantages of low immunogenicity and lower incidence of graft vs host disease (GVHD).[3,4] In 2018, an estimated 500 patients in the United States will have received a UCB transplant as reported by

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CIBMTR. Since 2014, haploidentical transplants have surpassed UCB transplants in numbers of alternative donor transplants performed.[1] Increased use of haploidentical transplants has brought to light concerns about UCB, including delayed engraftment and graft failure, increased nonrelapse mortality, and increased infection risk.[4] These concerns will need to be addressed for UCB to remain a viable option as a graft source for hematopoietic cell transplant into the future.

Significance statement

For the past 30 years, umbilical cord blood (UCB) has been a viable graft source option for hematopoietic cell transplant for both pediatric and adult patients with hematologic disorders. UCB may be particularly important for patients of diverse race/ethnicity. Future research needs to address the limitations of UCB transplant as well as to better understand the regenerative medicine and immune modulation potential of UCB.

1.1 | ADVANTAGES OF UCB TRANSPLANT

1.2 | Single vs double unit UCB transplant

UCB has been an available graft source for hematopoietic cell transplant for more than three decades, since the first UCB transplant was performed in a child with Fanconi's anemia in 1988.[5] Over the decades since the first transplant, UCB transplant has been expanded to adult recipients, in part by using two units of UCB per transplant with similar survival seen in patients with hematologic malignancies (Table 1).[3] In a study by Baron et al, single unit UCB transplants can be safely performed in adult recipients as long as there is an adequate total nucleated cell dose $\geq 2.5 \times 10^7$/kg. Neutrophil engraftment, relapse rate, nonrelapse mortality, GVHD survival, and overall survival were comparable to double unit UCB transplant. Recipients who had received a double unit UCB transplant had a trend toward increased grade II to IV acute GVHD by univariate analysis.[6] Cell dose per kilogram body weight should determine whether or not an adult recipient should receive one UCB unit or two for UCB transplant as there is no difference in engraftment, relapse, nonrelapse mortality, or overall survival.[3,6]

1.3 | Rapid availability

According to the World Marrow Donor Association, UCB banks are located around the world with more than 779 000 UCB units stored, allowing for rapid selection and transport of UCB units to the recipient's transplant program. Since these UCB units are collected and stored in advance, the units can be shipped to a recipient's transplant program with minimal notice.[7] The current severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has created problems in procurement of unrelated adult donor grafts due to disruptions in availability of donors, concerns regarding infection risk for the donor in their community, risk of transmission of SARS-CoV-2 from the donor to the recipient, and transportation interruptions. UCB remains an important graft source option when access to adult unrelated donors may be impacted through global events.

TABLE 1 Advantages and disadvantages for the use of UCB for hematopoietic cell transplant

Umbilical cord blood	
Advantages	**Disadvantages**
Single or double unit based on weight	Delayed engraftment
Rapid availability	Risk of graft failure
Expands donor pool	Increased transplant-related mortality
Low immunogenicity	Relapse (if high-dose ATG given)
Decreased chronic GVHD	Increased infection
Reduced relapse in minimal residual disease	Cost of graft acquisition

Abbreviations: ATG, antithymocyte globulin; GVHD, graft vs host disease.

1.4 | Low immunogenicity

UCB units have low immunogenicity allowing for less strict human leukocyte antigen (HLA) matching than adult donors allowing expansion of donor possibilities in patients who might not otherwise have a donor.[8] UCB availability is especially important for the African-American community since only 19% will have a fully matched 8/8 unrelated donor.[2] However, more recently the degree of allelic mismatch at HLA-A, HLA-C, or HLA-DR has been associated with a higher risk of transplant-related mortality (TRM).[9] In a retrospective study of single unit UCB transplant by Eapen et al, grades II to IV acute GVHD were associated with allelic mismatch. Relapse and overall mortality were similar unless mismatched at 4 and 5 alleles, respectively.[10] Choosing UCB units with fewer allelic mismatches for transplant may decrease TRM and acute GVHD.[9,10]

1.5 | Graft vs host disease

A retrospective review performed using CIBMTR registry data evaluated the incidence of acute and chronic GVHD in recipients of single and double unit UCB transplants for acute leukemia. Grade II to IV acute GVHD incidence was 45% and 39% in double and single unit UCB transplants, respectively. The 1-year chronic GVHD incidence was similar between the two groups.[11] Worse HLA match was associated with higher incidence of acute GVHD in both single[10] and double

UCB transplants,[9] whereas prior acute GVHD was associated with increased risk of chronic GVHD in both single and double unit UCB transplants.[12] In a study by Brunstein et al, 536 patients with hematologic malignancies undergoing matched related donor, matched unrelated donor, mismatched unrelated donor, and double unit UCB were compared for clinical outcomes. When compared to matched unrelated donor and mismatched unrelated donor transplants, UCB had a lower cumulative incidence of grade II to IV acute GVHD. Although matched related donors had the lowest incidence of grade III to IV acute GVHD, chronic GVHD was the lowest in the recipients of double unit UCB transplants.[3] When UCB transplant was compared to matched unrelated donor peripheral blood hematopoietic cell transplant, the incidence of moderate to severe chronic GVHD was 8% in the UCB transplant group and 44% following the matched unrelated donor group.[13] Decreased acute and chronic GVHD rates seen with UCB grafts could potentially reduce the morbidity and mortality of transplant.[3,9-13]

1.6 | Relapsed disease

UCB transplant has been associated with reduced risk of relapse in some studies.[14,15] Milano et al studied 582 patients with acute leukemia or myelodysplastic syndrome with minimal residual disease who received myeloablative conditioning followed by matched unrelated donor, mismatched unrelated donor, or UCB transplant. Relapse after UCB transplant was decreased compared to matched and mismatched unrelated donor transplants.[14] When relapse was evaluated according to disease status in patients over the age of 50 with leukemia or myelodysplastic syndrome, the relapse rate was similar between UCB, and matched and mismatched unrelated bone marrow transplant. Acute myeloid leukemia (AML) and acute lymphoblastic leukemia had similar relapse rates whether they received a UCB transplant or a matched unrelated bone marrow transplant.[15] Relapse risk after UCB transplant is potentially decreased compared to matched and mismatched unrelated donor transplants.[14,15]

2 | DISADVANTAGES OF UCB TRANSPLANT

2.1 | Delayed engraftment

Delayed hematopoietic recovery and increased rates of graft rejection are risks of UCB transplant (Table 1). Total nucleated cell dose is a limiting factor for the use of UCB, and using two partially matched UCB units extends the availability of UCB transplant to more adults.[3] Neutrophil recovery, relapse, and TRM were similar after single compared to double unit UCB transplant.[16] Using two units of UCB for transplant in adult recipients has decreased the risk of graft failure.[17,18] Use of two units of UCB per transplant expands the availability of this transplant to more adult patients and can decrease the risk of graft failure.[3,16-18]

2.2 | Transplant-related mortality

TRM has been shown to be increased with UCB transplant in some studies, and efforts are being made to try to reduce the risk of infection and other complications.[9,19] In a study by Oran et al, 133 patients who received a double unit UCB transplant for hematologic malignancies were evaluated for the effect of allele matching on TRM. TRM rapidly increased with a decrease in level of match of the dominant UCB unit. High resolution typing at HLA-A, -B, -C, and -DRB may reduce TRM in recipients undergoing double unit UCB transplants,[9] and should be the standard of care in 2020. A study of more than 600 patients with AML showed an increase in TRM compared to 8/8 unrelated donor transplants.[19] Future research studies need to find ways to reduce TRM through better HLA matching, faster engraftment (such as via expansion), and improved infection management.

2.3 | Relapsed disease

Antithymocyte globulin (ATG) is often given to UCB transplant recipients, especially in Europe. The in vivo T-cell depletion may decrease the risk of GVHD and graft failure.[20] In a study by Admiraal et al, patients with early CD4+ T-cell immune reconstitution had lower rates of relapse, graft failure, and death after UCB transplant. Lower exposure or no exposure to ATG was associated with better CD4+ immune reconstitution. Those patients who had achieved higher serum levels of ATG from their preparative regimen had worse event-free survival and infection.[21] The use of ATG in UCB preparative regimens remains controversial.

2.4 | Infection

UCB is associated with increased risk of infectious complications especially in the first 100 days after transplant.[22-24] After UCB transplant, there is a delayed recovery of naïve and memory T cells, thus increasing the risk of opportunistic infections and viral reactivations.[22] Karantanos et al evaluated the development of BK viremia and the immune recovery after UCB transplant. BK viremia developed most often in the first 8 weeks after transplant but persisted in some patients at 6 and 12 months after transplant. BK was associated with a lower number of CD8+ cells at 6 months and a lower number of CD4 cells at 12 months. Incidence of BK viremia may be associated with an increase in Treg cells immediately post-transplant.[23] In a retrospective study of 57 patients who underwent UCB transplant by Linder and associates, infectious complications were evaluated from 6 months prior to transplant to 2 years after transplant. Fifty-five patients had 179 episodes of infection, with 41% happening within 30 days of transplant. Viruses caused many of the infections with cytomegalovirus being the most common between day 30 and day 100. The most common virus seen between transplant and day 30 was human herpes virus 6. Bacterial infections accounted for 46% of infections and the most common were *Staphylococcus*,

Enterococcus, and *Enterobacteriaceae*. Aspergillosis fungal infections were also seen. Delayed immune recovery associated with UCB transplant was believed to the cause of the increased risk of infection.[24]

2.5 | Cost

Graft source acquisition costs and costs of the transplant are unique to the use of UCB units in contrast to other graft sources.[25,26] In a study at Medical College of Wisconsin and West Virginia University, acquisition charges for two units of UCB were $88 000 vs $35 000 for a haploidentical donor. Median 100-day charges, including inpatient, outpatient, and graft acquisition, was $605 000 for UCB transplant (range $318 000-$1 407 000) compared to $562 000 for haploidentical transplant (range $285 000-$1 479 000). In this study, overall survival, progression-free survival, and TRM were worse with UCB transplant.[25] In a study of hospital length of stay in the first 100 days after transplant in adult recipients, UCB was associated with fewer days alive and out of the hospital compared to matched unrelated donors and mismatched unrelated donors.[26] In these studies, only the immediate transplant costs were studied,[25,26] the long-term cost savings of reduced GVHD and relapse associated with UCB would be challenging to evaluate prospectively in the United States.

3 | IMPROVING UCB AS A GRAFT SOURCE

Delayed engraftment is a major concern regarding the use of UCB as a graft source for hematopoietic transplant for adults. Studies are ongoing evaluating different ways to improve the time to engraftment in UCB transplant recipients (Table 2). Mesenchymal stromal cell coculture,[27,28] notch-mediated expansion,[29] nicotinamide-associated expansion,[30-32] aryl hydrocarbon inhibition,[33,46] stem cell renewal agonist,[34] CD3/CD28 costimulation,[35] copper chelation,[36] and an automated continuous perfusion device[37] have been evaluated for safety, toxicity, and whether or not faster engraftment was seen with the ex vivo manipulation of the UCB unit. Homing strategies (dipeptidyl peptidase-IV [DPP-4],[43] complement fragment 3a,[42] fucosylation,[41] prostaglandin E2,[40] hyperbaric oxygen[39,47]) or direct intramarrow administration of UCB[44] are additional ways being studied to possibly improve time to engraftment.

TABLE 2 Mechanisms evaluated to improve UCB engraftment

Improving UCB engraftment	No. of patients	Neutrophil engraftment	Reference
Ex vivo expansion			
Mesenchymal stem cells	31	15 d	de Lima et al [27]
	27	12 d	Mehta et al [28]
Notch ligand	10	16 d	Delaney et al [29]
Nicotinamide	11	13 d	Horwitz et al[30]
	36	11.5 d	Horwitz et al[31]
	18	12.5 d	Anand et al [32]
Aryl hydrocarbon receptor inhibitor	17	15 d	Wagner et al[33]
Self-renewal agonist	27	18 d	Cohen et al [34]
CD3/CD28 costimulation	5	12, 17, 20 d	Hexner et al[35]
Copper chelation	10	30 d	de Lima et al[36]
Automated continuous perfusion device	28	22 d	Jaroscak et al[37]
Non-human leukocyte antigen (HLA) matched ex vivo expanded	29	N/A	Delaney et al[38]
Homing			
Hyperbaric oxygen-erythropoietin modulation	15	14 d	Aljitawi et al[39]
Prostaglandin E2	9	24 d	Cutler et al[40]
	12	17.5 d	
Fucosylation	22	17 d	Popat et al[41]
Complement fragment 3a priming	29	7 d	Brunstein et al[42]
DPP-4 inhibition	24	21 d	Farag et al[43]
Intrabone injection	87	23 d	Rocha et al[44]
Combined grafts			
UCB + haploidentical	97	90% by day 30	van Besien et al[45]

Abbreviations: DPP-4, dipeptidyl peptidase-IV; UCB, umbilical cord blood.

3.1 | Ex vivo expansion

In a study by de Lima et al, expansion of CD34 cells can increase by a factor of 30 when UCB is cocultured with mesenchymal stromal cells. When the expanded cells are infused with an unmanipulated UCB unit in a myeloablative transplant, the total nucleated cell and CD34 cells doses were higher in the cocultured group than using two unmanipulated UCB units. Neutrophil engraftment was faster by 9 days in the cocultured group.[27] A second study from MD Anderson Cancer Center evaluated UCB cocultured with mesenchymal precursor cells and outcomes compared to unmanipulated UCB units in reduced intensity hematopoietic cell transplant. Similar results were seen in neutrophil engraftment occurring at day 12 in the cocultured UCB transplant recipients and 16 days in the unmanipulated UCB transplant group.[28] Delaney et al developed a notch-mediated ex vivo UCB expansion process to increase the number of CD34 cells by 100-fold. When these cells were transplanted with an unmanipulated UCB unit in a phase I trial, rapid engraftment was achieved at a median of 16 days compared to 26 days.[29]

In the phase I nicotinamide expansion study of 11 patients, UCB products were expanded for 21 days with nicotinamide and a T-cell fraction to determine if this process can improve engraftment and shorten count recovery. Recipients of the expanded UCB units had shorter time to neutrophil engraftment compared to historical controls, 13 days vs 25 days. The nicotinamide expanded UCB units were

not associated with any adverse events in the phase I trial.[30] Nicotinamide expanded single unit UCB transplant was evaluated in a phase I/II clinical trial in 36 patients with hematologic malignancies.[31] Neutrophil recovery was a median 11.5 days in the expanded UCB group compared to 21 days. Fewer bacterial infections and shorter hospital length of stay were seen in the first 100 days after the expanded UCB product was infused compared to standard UCB transplant.[32] These promising results have led to an ongoing phase III international trial to further evaluate these outcomes.[30-32]

In a phase I/II safety and feasibility study performed by Wagner et al, StemRegenin-R (SR-1), an aryl hydrocarbon receptor inhibitor, blocked differentiation promoting expansion of CD34 progenitors; however, the cells maintained multilineage potential. UCB units expanded using SR-1 had a 330-fold increase in CD34 cells and all 17 patients engrafted with a median neutrophil engraftment of 15 days.[33] A new phase II clinical trial (Magenta Therapeutics) is evaluating MGTA-456, an aryl hydrocarbon receptor antagonist, in the expansion of UCB for patients with inborn errors of metabolism to determine whether or not ex vivo expansion decreases the time to engraftment after transplant.[46] UM171 is a stem cell self-renewal agonist that was studied in a phase I-II study by the University of Montreal in adult patients with hematologic malignancies. A total of 27 patients were enrolled, four patients received two UCB units in part 1 of the study, and 22 patients on the trial received a single UM171 expanded UCB transplant. A minimum of 0.52×10^5 CD34 cells were needed to have engraftment. Median time to ANC 500 was 18 days, and no graft failure was seen. Use of the UM171 expanded cords were determined to be feasible and safe.[34]

When T cells from a single UCB unit were activated by costimulation with CD3/CD28 and expanded with the goal of improving engraftment of a single UCB unit, neutrophil engraftment occurred between 12 and 20 days; however, acute GVHD was a complication.[35] Tetraethylenepentamine, a copper chelator, has been shown to preferentially expand early hematopoietic progenitors. Nine of 10 patients had neutrophil engraftment at a median time of 30 days.[36] An automated continuous perfusion device was evaluated for ex vivo expansion of UCB and durable engraftment was seen with neutrophil recovery at a median 22 days.[37] Additionally, investigators at the Fred Hutchinson Cancer Research Center evaluated the infusion of a non-HLA matched expanded cord blood after conditioning with clofarabine, cytarabine, and granulocyte-colony stimulating factor priming to decrease the time to hematopoietic recovery. Infusion of the expanded UCB was safe with only one infusion reaction likely related to the dimethyl sulfoxide. Common side effects seen with the expanded UCB was fever and infection. The expanded UCB cells were not seen after 14 days.[38] Cord blood expansion has been shown to improve time to engraftment in several small studies, but there is no published large-scale study to indicate improvement in survival.[27-37,46]

3.2 | Homing

Farag et al hypothesized that inhibition of DPP-4 would improve UCB stem cell homing and time to engraftment. Sitagliptin, an oral hypoglycemic agent, inhibits DPP-4 which regulates stromal derived factor 1α. Twenty-four patients received a single UCB transplant and oral sitagliptin for 4 days. Median time to neutrophil engraftment was 21 days and median chimerism was 100%.[43] Manipulation of SDF-1-CXCR4 through complement fragment 3a priming was believed to improve homing of UCB cells to the recipient's bone marrow by Brunstein et al. C3a activates CXCR4 which increases stromal derived factor 1α and improves homing of stem cells. Patients received a non-myeloablative double unit UCB transplant; one unit was unmanipulated and the second, smaller unit was primed with complement fragment 3a for 15 minutes. Neutrophil engraftment, overall survival, and mortality were similar between historical controls and the group that received the complement fragment 3a priming.[42] Popat et al evaluated whether the inability of UCB cells to home to bone marrow was a result of low level fucosylation of cell surface molecules required for binding selectins in the bone marrow microenvironment. Patients received a double unit UCB transplant; one unit was treated for 30 minutes ex vivo with fucosyltransferase-VI and guanosine diphosphate fucose. The 30-minute treatment was to increase the binding of the UCB stem cells with the microenvironment. Neutrophil engraftment occurred at a median 17 days vs 26 days in the controls.[41] A phase I study evaluated the role of the safety and efficacy of prostaglandin E2 on ex vivo modulation to improve hematopoietic engraftment after double unit UCB transplant. Neutrophil recovery was seen at 17.5 days in the 12 patients in cohort 2 vs 21 days for historical controls. Long-term engraftment of the prostaglandin treated UCB was seen in 10 of 12 recipients.[40]

Fifteen patients were enrolled on a clinical trial evaluating hyperbaric oxygen and its effects on erythropoietin levels. Reducing erythropoietin in the UCB recipient potentially enhances homing of UCB to the bone marrow environment. Median time to neutrophil recovery was 14 days and all patients had platelet recovery.[39] In long-term follow-up, overall survival at 6 months was better in patients treated with hyperbaric oxygen; however, there was no difference in overall survival between the treated patients and historical controls at 1 year. Hyperbaric oxygen-treated patients had lower relapse, less chronic GVHD, and decreased TRM.[47] Direct intramarrow injection of the UCB had a statistically significant median time to engraftment of 23 days compared to 28 days with the intravenous administration of two units UCB. Intramarrow injection of UCB was associated with reduced acute GVHD, faster neutrophil, and platelet recovery. A trend toward better disease control and disease-free survival was seen.[44] In general, homing strategies may be less complex and expensive than expansion strategies, but have not been shown to have a significant impact on survival.[39-44,47]

3.3 | Combined grafts

Reduced intensity conditioning haploidentical donor and UCB (haplo-cord) transplant was compared to a reduced intensity double unit UCB transplant in 97 and 193 recipients, respectively. The haplo-cord transplant had statistically significant faster neutrophil and platelet

engraftment, decreased relapse, and lower risk of acute GVHD. Overall survival was similar between the two groups. In general, the haploidentical graft provides short-term engraftment and then is rejected in favor of the UCB graft. Use of combined grafts for transplant, haploidentical grafts and UCB, may improve time to engraftment, thus reducing morbidity and mortality.[45]

4 | COMPARISON OF UCB TO OTHER ALTERNATIVE GRAFT SOURCES

When a potential hematopoietic cell transplant candidate does not have a matched related or unrelated donor available, three alternative donor options are available: UCB, mismatched unrelated donor, or haploidentical donor (Table 3). In a retrospective study performed by the European Society of Blood and Marrow Transplantation (EBMT)-Eurocord group, haploidentical transplant was compared to single unit UCB transplant using the myeloablative regimen thiotepa, busulfan, and fludarabine in patients with AML. Non-T cell depleted haploidentical cohort had 186 patients compared to 147 patients in the single unit UCB transplant arm. No difference was seen in relapse, 17% vs 12% for haploidentical transplant and single unit UCB transplant, respectively. Acute and chronic GVHD were similar between the two transplant types by multivariate analysis. Increased nonrelapse mortality, delayed engraftment, reduced overall survival, and decreased leukemia-free survival were seen in the single unit UCB arm.[48]

TABLE 3 Comparison of UCB to other alternative graft sources for hematopoietic cell transplant

Comparison of UCB to other alternative graft sources			
Ref.	**Disease**	**Conditioning**	**Donor (n)**
Milano et al [14]	AML, ALL, MDS	RIC, MAC	UCB (140) MUD (344) MMUD (98)
Tanaka et al [15]	AML, ALL, MDS	RIC, MAC	UCB (566) MUD (516) MMUD (295)
Gianotti et al [48]	AML	MAC	UCB (147) Haplo (186)
Brunstein et al [49]	AML, ALL, Lymphoma	RIC	UCB (50) Haplo (50)
Baron et al [50]	AML	NMA	UCB (291) MSD (701) MUD (611) Haplo (112)
Keating et al [51]	AML	MAC	UCB (183) MSD (61) MUD (73)

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; Haplo, haploidentical donor; MAC, myeloablative conditioning; MDS, myelodysplastic syndrome; MMUD, mismatched unrelated donor; MSD, matched sibling donor; MUD, matched unrelated donor; NMA, non-myeloablative conditioning; RIC, reduced intensity conditioning; UCB, umbilical cord blood.

Two parallel phase two trials comparing reduced intensity haploidentical transplant and double unit UCB transplant were performed through the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) in the United States. Overall and progression-free survivals at 1 year were 54% and 46% for UCB compared to 62% and 48% for haploidentical transplant. Grade II to IV acute GVHD was 40% after UCB transplant and 32% after haploidentical transplant. Relapse in the two trials was 31% and 45% for UCB transplant and haploidentical transplant, respectively. Nonrelapse mortality was higher in the UCB transplant trial.[49] These results were the basis for the development of the national randomized phase III clinical trial BMT CTN 1101. This clinical trial has been completed and results are pending. Additionally, a companion study was performed in conjunction with the randomized phase III trial evaluating the cost effectiveness of the two graft sources. Data collected include information on health insurance, out-of-pocket costs, and caregiver costs to better evaluate the economic impact of these two alternative donor sources. Final financial data analysis is pending completion of the BMT CTN 1101 trial.[52]

In a multicenter retrospective study from the EBMT evaluating reduced intensity conditioning with low dose total body irradiation in patients with AML, UCB grafts were compared to matched sibling donor, matched unrelated donor, and haploidentical grafts. Chronic GVHD occurred less often in the UCB transplant group and relapse rate was similar between the groups. GVHD-free relapse-free survival was lower in patients who had received UCB transplant after day 100.[50] When UCB transplant was compared to mismatched unrelated donor transplants in patients with acute lymphoid leukemia, AML, and myelodysplastic syndrome with minimal residual disease using myeloablative conditioning, the incidence of grade III to IV acute GVHD was lower in patients with UCB transplant compared to patients with mismatched unrelated donor transplants. The relapse rate was better for UCB transplant with decreased TRM and improved overall survival.[14] In a study by Tanaka et al, evaluating mismatched unrelated donor transplant and UCB transplant outcomes in patients older than 50 years of age, acute and chronic GVHD was less with UCB; however, both types of transplants had comparable rates of relapse and TRM.[15] In pediatric patients with AML, matched sibling donor, matched unrelated donor, single UCB, and double unit UCB transplants were associated with similar relapse, nonrelapse mortality, and leukemia-free survival. Only double unit UCB transplant recipients had worse survival compared to matched sibling donor transplants. Chronic GVHD incidence was lower in the UCB transplant groups compared to matched unrelated donor transplant.[51] These studies were retrospective and the use of post-transplant cyclophosphamide for GVHD prophylaxis was not routinely used at the time of the mismatched unrelated donor transplants.[14,15] In a parallel phase II evaluating post-transplant cyclophosphamide in haploidentical transplant and 1-antigen mismatched unrelated donor transplant, post-transplant cyclophosphamide GVHD prophylaxis was effective for both haploidentical transplant and 1-antigen mismatched unrelated donor transplant.[53] To date, UCB transplant outcomes have not been compared prospectively with 1-antigen mismatched unrelated donor transplant with post-transplant cyclophosphamide.

5 | UCB FOR IMMUNE MODULATION AND HEMATOPOIETIC REGENERATION

5.1 | Immune effector cells

Cytokine induced killer (CIK) cells have cytotoxic activity and potentially be used for antitumor therapy (Table 4). When Zhang et al compared UCB CIK cells to CIK cells derived from peripheral blood, UCB derived CIK had higher proliferation rates and a higher number of CD3+CD56+ cells. In a mouse model, the UCB CIK cells had more tumor growth inhibition.[54] UCB CIK cells have activity against B-cell acute lymphoblastic leukemia cell lines and their activity was increased by interferon-α in a mouse model.[55] UCB CIK cells were given to five patients with relapsed leukemia after UCB transplant, the CIK cells were well tolerated, and one patient had a partial response.[56] When UCB CIK cells were combined with second line chemotherapy in solid malignancies in a clinical trial, those patients who had received the UCB CIK cells had longer progression-free survival and overall survival compared to chemotherapy only.[57] UCB derived CIK cells may have cytotoxic activity for both hematologic malignancies and solid tumors alone and in combination with chemotherapy.[56,57]

Chimeric antigen receptor (CAR) T cells are an exciting new therapy for the treatment of acute lymphoblastic leukemia and diffuse large b-cell lymphoma. The use of CAR T-cells is limited by significant toxicities including cytokine release syndrome and immune effector cell associated neurotoxicity. Using natural killer (NK) cells for CAR therapy may reduce these side effects while preserving the cytotoxic efficacy toward tumor cells.[58,59] CAR-NK cells from UCB have been found to be easier to stimulate with higher expansion rates than adult NK cells.[60]

Interestingly, the group from McMaster University in Hamilton, Ontario evaluated the ability to isolate and ex vivo expand NK cells from cryopreserved UCB. NK cells were expanded from fresh UCB, cryopreserved units <1 year old, and longer-term cryopreserved units from 1 to 10 years. In their research, it was possible to obtain and expand UCB-NK cells from even the long-term cryopreserved units. The expanded NK cells had surface expression of activating markers, had a potent antitumor function, and produced high levels of pro-inflammatory interferon-γ and tumor necrosis factor-α. The expanded NK cells had cytotoxic activity toward breast cancer cells.[59] Liu et al have evaluated UCB NK cells, transduced with a retroviral vector to target specific markers, including CD19, IL-15, and caspase-9 based suicide gene, in targeting non-Hodgkin's lymphoma and chronic lymphocytic leukemia in 11 patients. NK cells were cytotoxic, killing tumor cells without the side effect of GVHD, cytokine release syndrome, or neurotoxicity seen with allogeneic T cells. CAR-NK cells were easily producible, had prolonged survival, and were efficacious toward selected targets.[58] UCB may be a source for allogeneic CAR-NK cells for tumor cytotoxicity without the side effects see with CAR T-cell therapy.[58–60]

TABLE 4 Use of UCB in immune modulation and hematopoietic regeneration

UCB for immune modulation and hematopoietic regeneration	
Immune effector cells	Cytokine-induced killer cells
	Chimeric antigen receptor natural killer cells
Red blood cell manufacturing	Red blood cell transfusions

Abbreviation: UCB, umbilical cord blood.

5.2 | Red blood cell manufacturing

In vitro generation of red blood cells may allow production and distribution of red blood cells to augment the national blood supply especially in times of shortages and provide red blood cells for patients with rare blood groups or alloimmunization.[61] Using supplements added to cell culture, in order to avoid animal components, UCB mononuclear cells were able to be differentiated into the erythroid cell lineage.[62] UCB cells stimulated with cytokines and cocultured with UCB mesenchymal stem cells generated clinical quality red blood cells.[63] While generation of red blood cells from UCB cord precursors is exciting, processes are limited by efficiency issues, inability to produce large quantities, and maturing cells to the adult phenotype.[64] These process issues will need to be overcome before UCB red blood cell manufacturing will be able to produce the quantities of red blood cells needed to augment the blood supply.[62-64]

6 | UCB FOR REGENERATIVE MEDICINE

Many clinical trials are evaluating the cellular regenerative properties of UCB and its role in immune modulation in nonhematologic diseases. Clinical trials using autologous or allogeneic UCB units are ongoing for type I diabetes, cerebral palsy, hypoplastic left heart, ischemic stroke, spinal cord injuries, and hypoxic brain injuries (Table 5). UCB usage in regenerative medicine is considered investigational at this time and has its challenges as well. Regenerative medicine trials may use either autologous or allogeneic units. Unfortunately, unproven stem cell therapies, based on minimal if any research, have been offered by stem cell clinics praying on the desperation of patients and families to treat or cure their diagnoses often at extraordinary costs to patients. The regenerative medicine discussed in the following sections is based on early phase clinical research published in peer-reviewed journals and ongoing clinical trials listed at https://ClinicalTrials.gov.

6.1 | Neurology

Most of the ongoing clinical research trials in UCB regenerative medicine have been in neurologic conditions (Table 4). Some early phase studies evaluating the safety and feasibility of UCB regenerative medicine have recently been published.[65-68] In a study of 36 children, ages ranging from 6 months to 20 years old with cerebral palsy, allogeneic

TABLE 5 Clinical trials using UCB for regenerative medicine

Summary of UCB trials for regenerative medicine in United States (www.ClinicalTrials.gov)					
Disease	**Specialty**	**Clinical trial number**	**Auto/allo**	**Status**	**Principal investigator**
Type I diabetes	Endocrinology	NCT04011020	Allo	Not yet recruiting	Yong Zhao, MD, PhD
Hypoplastic left heart	Cardiology	NCT01856049	Auto	Recruiting	Susana Peral, MD, PhD
	Cardiology	NCT03779711	Auto	Recruiting	Timothy Nelson, MD, PhD
	Cardiology	NCT01883076	Auto	Recruiting	Timothy Nelson, MD, PhD
Acute ischemic stroke	Cardiovascular	NCT03004976	Allo	Recruiting	Joanne Kurtzberg, MD
	Cardiovascular	NCT03735277	Allo	Not yet recruiting	Brian Mehling, MD
Viral infections	Infectious diseases	NCT03594981	Allo	Recruiting	Fahmida Hoq, MBBS, MS
Cerebral palsy	Neurology	NCT01072370	Auto	Recruiting	James Carroll, MD
Hypoxic-ischemic encephalopathy	Neurology	NCT02434965	Auto	Not yet recruiting	Mitchell Cairo, MD
Hypoxic neurologic injury	Neurology	NCT03526588	Auto	Recruiting	Matthew Harting, MD, MS
Spinal cord injuries	Neurology	NCT03979742	Allo	Not yet recruiting	Wise Young, MD, PhD

Abbreviation: UCB, umbilical cord blood.

UCB was infused intravenously or intra-arterially and compared to children who had received a placebo. Those children who had received UCB had improved muscle strength and gross motor performance. The greater the number of UCB cells infused the better the clinical outcomes. Anti-inflammatory changes were seen in the brain as well as immune responses in the body were seen in response to the UCB infusion.[65] Autologous UCB was given to 23 newborns with hypoxic ischemic encephalopathy in a safety and feasibility study, and was well tolerated.[66] Adult patients may benefit from allogeneic UCB for ischemic stroke of the middle cerebral artery. In a phase I study of 10 patients, a single intravenous infusion of UCB occurred 3 to 9 days after the stroke. No serious adverse events were seen.[67] Twenty-eight patients with spinal cord injuries had UCB injected above and below the injury. Patients who had received the UCB injections had improvement in walking as well as bowel and bladder control.[68] These early phase clinical trials show the potential for UCB regenerative medicine in neurological conditions.[65-68]

6.2 | Cardiology

Mesenchymal stem cells derived from UCB were transfected with AKT and injected into rats, which had the left anterior descending artery ligated. Those rats, which received the AKT modified mesenchymal UCB exosomes, had improved cardiac function and had evidences of angiogenesis.[69] Additionally, induced pluripotent stem cells, adult stem cells with an inserted transcription factor, can potentially regenerate heart tissue in patients with myocardial infarcts, a leading cause of death in adults.[70] Research with UCB in regenerative medicine for cardiac diseases is still developing.

7 | CONCLUSIONS

UCB remains a viable donor option for hematopoietic cell transplant and is an emerging cellular source for regenerative medicine. Rapid availability,[7] expansion of the donor pool due to low immunogenicity,[3,4,8] reduced incidence of chronic GVHD[3] and the potential for reduced incidence of disease relapse in recipients with minimal residual disease[14] are just a few of the advantages of UCB transplant. Delayed engraftment and graft failure,[3,16-18] TRM,[9,19] infection risk,[22-24] and cost of UCB acquisition[25] remain important concerns regarding the use of UCB for transplant. Despite multiple efforts with homing,[39-43,47] ex vivo expansion,[27-37,46] and combined graft sources,[45] no survival benefit has been demonstrated. In addition, many of the current techniques are expensive and only available in specialized centers.

When unrelated adult donors are not available due to global procurement issues and/or transportation disruptions like those being experienced now because of the SARS-CoV-2 pandemic, UCB may regain favor as a transplant graft source. Additionally, UCB remains an important graft source option for patients who do not have an unrelated donor. Encouraging minority ethnic groups to bank cord blood in public banks is needed to provide graft sources for these underserved ethnic groups.[2] Costs of acquisition of UCB will need to decrease and/or improved reimbursement by payors needs to be addressed to make UCB transplant economically feasible.[25] In order to improve the sustainability of UCB transplant, continued research on UCB expansion to improve the cell dose of UCB units has to occur. Additional research is needed to evaluate different techniques to improve time to engraftment in UCB transplant. By improving time to engraftment for UCB transplant, subsequent reductions in TRM and infection risk may be seen. In addition, given decreased use of UCB for traditional transplant indications, there are legitimate concerns about the sustainability of UCB banking. Higher nucleated count target levels, contingency planning, and collaboration with private banking or industry have been explored in the Rand Report and are beyond the scope of this review.[71] These concerns regarding UCB will need to be addressed through philanthropy, public service, and future clinical trials for UCB to remain a viable option as a graft source for hematopoietic cell transplant. The destiny of UCB may be in the ongoing clinic trials evaluating the

regenerative and immune modulatory properties of UCB for non-hematologic diseases.

CONFLICT OF INTEREST

The authors declared no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

K.K.B. and T.L.K.-K. participated in the conception and design as well as writing of the manuscript.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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