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Review

A new beginning: can omidubicel emerge as the next, viable alternative donor source?

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***Abstract*:** Umbilical cord blood (UCB) transplantation (CBT) has been an important alternative donor option for patients lacking matched related donor (MRD) or unrelated donor (URD) grafts. Only 30% of patients with high-risk hematologic malignancies have a human leukocyte antigen (HLA)-identical sibling; subjects without a MRD option are referred for HLA-matched URD selection, or utilize alternative donor sources such as HLA-mismatched URD, UCB, or haploidentical donor grafts. While CBT demonstrates an excellent graft-*versus*-leukemia (GVL) effect, use of UCB as a graft source is limited due to a lower cell dose that can result in delayed engraftment and an immature immune system with increased infectious risk as a consequence. Together, increased transplant related mortality (TRM) has been associated with UCB allografts. Omidubicel is an *ex vivo* expanded single cord blood product that has demonstrated rapid engraftment, improved immune reconstitution, and reduced infectious complications in clinical trials. Omidubicel has now been granted U.S. Food & Drug Administration approval to enhance neutrophil recovery and decrease infectious risk. This review will focus on CBT, benefits and barriers to using this alternative donor source, and finally the potential advancements with incorporation of omidubicel in the transplant setting for malignant and non-malignant diseases.

Keywords: allogeneic hematopoietic cell transplantation, alternative donor grafts, healthcare utilization, Omidubicel, umbilical cord blood transplantation

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Introduction

The first umbilical cord blood (UCB) transplant (CBT) was performed in 1988 in a 5-year old boy with Fanconi anemia, using cryopreserved blood obtained from the umbilical cord and placenta of his human leukocyte antigen (HLA)-identical (but not Fanconi-affected) sibling.[1] This case demonstrated proof of principle, that UCB stem cells possess multipotent potential and can be used to achieve hematopoietic reconstitution.[2] The field of CBT has greatly expanded since this first report, with over 40,000 CBTs performed worldwide for benign and malignant disorders, using matched, mismatched, related, and unrelated UCB units, and UCB units have become a viable option for alternate donor grafts.[3–5]

At present, the choice and selection of alternative donor allograft depends on the transplant center's expertise, patient-specific characteristics, donor availability, and the unique qualities of the different graft options. UCB cells are immunologically naïve, with a reduced number of mature alloreactive T-cells; this important distinction allows for less stringent HLA-matching requirements. Importantly, this increases the availability of allogeneic donors for transplantation, and by providing greater frequency of rare haplotypes, improves the donor selection pool for non-Caucasian populations.[3] This decreased alloreactivity also leads to a lower incidence of graft-*versus*-host disease (GVHD) and GVHD severity after CBT, and particularly chronic GVHD, as well as an enhanced responsivity to GVHD treatment.[6–8] Another major benefit of UCB units is their rapid availability, as these units are available 'off-the-shelf' as previously collected and cryopreserved units, leading to a

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faster time to transplantation than seen with peripheral blood or marrow grafts.[9]

However, the unique cell composition and characteristics of UCB grafts can also contribute to clinical challenges associated with their utilization. The smaller number of hematopoietic stem and progenitor cells provided with an UCB unit can result in delayed neutrophil and platelet engraftment, time to transfusion independence, and immune reconstitution (IR) after transplant, thus increasing the risk of infectious complications including viral reactivation. The lower cell doses seen with CBT also contribute to an increased risk for primary and secondary graft failure and early transplant-related mortality (TRM).[10,11] These risks are greatest in the adult transplant setting, given the lower weight-based $CD34^+$ and $CD3^+$ cell doses/kg, known to be associated with post-transplant outcomes. Strategies to overcome the UCB cell dose limitations include the use of two UCB units [double CBT (dCBT)], combination of an UCB unit with mobilized haploidentical peripheral blood $CD34^+$ cells, and UCB *ex vivo* expansion.[12–16]

UCB graft manipulation to enhance physiologic functionality and infused cell numbers has been pursued over the last two decades and a variety of *ex vivo* UCB cell expansion techniques have been evaluated. Currently, omidubicel has proved to be most successful, and in contrast to other expansion methods, provides a long-term engrafting unit, leading to its current status where it is undergoing regulatory review for approval for commercial use. Omidubicel uses nicotinamide (NAM) in *ex vivo* culture conditions with additional cytokines including Flt3 ligand, stem cell factor (SCF), thrombopoietin (TPO), IL-6 added to the antibody-selected $CD133^+$ UCB cell fraction, to increase the number of hematopoietic stem and progenitor cell numbers, and importantly to also enhance the functionality and efficiency of cell homing and engraftment.[17–19] Here, we aim to review the utilization of omidubicel as an alternative donor graft source and compare to standard UCB, as well as other approaches of UCB *ex vivo* expansion and homing strategies.

UCB – Graft selection and disparities

UCB selection

UCB selection involves consideration of total nucleated cell (TNC) and $CD34^+$ cell dose, as well as the level of HLA-matching. Published guidelines in the United States recommend a minimum pre-cryopreservation TNC dose of $\geq 2.5 \times 10^7$/kg for single unit grafts, and $\geq 1.5 \times 10^7$/kg per unit for dCBT; a minimum $CD34^+$ cell dose of $\geq 1.5 \times 10^5$/kg for single unit grafts, and $\geq 1.0 \times 10^5$/kg per unit for dCBT is advised.[20] Consideration of both the TNC and CD34 doses is critical, as the two cell numbers do not always correlate, and the $CD34^+$ cell number is the most reliable marker for engraftment after transplant and to ensure timely hematopoietic recovery.[21–23] Double CBT should be considered for patients for whom suitable single UCB unit options are not available.

HLA-matching for CBT is performed using high resolution HLA typing at 8-HLA loci (HLA-A, -B, -C, DRB1 allele-level typing) and this degree of HLA typing is now a requirement in Europe, United Kingdom and United States. It is recommended to identify CBUs that are ≥4/8 HLA allele matched, as this predicts for superior engraftment and lower rates of acute GVHD and TRM.[20,24] Other factors to be considered in UCB unit selection are the use of accredited banks [Foundation for the Accreditation of Cellular Therapy (FACT) in the United States], cryopreservation volume and RBC depleted units (approximately 25 mL with dimethyl sulfoxide (DMSO) or 50 mL in two 25-mL bags), as well as the year of UCB unit collection in which recent years are preferred. Avoidance of UCB units with a known presence of donor-specific antibodies (DSAs) is preferred due to the risk of graft failure, particularly for non-malignant diseases.[25,26]

Disparities in donor graft sources

Disparities in donor availability exist for patients in need of an alternative donor option. At centers where the alternate donor search strategy starts with an unrelated donor (URD) that is 8/8 or 7/8 HLA-matched followed by CBT, the distribution pattern varies for White Europeans when compared to African Americans: White Europeans and African Americans will have 8/8- matched URD (75% *versus* 19%), 7/8- matched URD (22% *versus* 57%), 5/6 or 6/6 UCB (1.2% or 0.5% *versus* 10% or 3%, based on age <20 years or ≥20 years of age), and 4/6 UCB (1.5% or 1.8% *versus* 13% or 14%, based on age) respectively. Thus the number of African Americans with an optimal graft is far fewer than for White Europeans.[27] In

an observational study at Memorial-Sloan Kettering, racial disparities persisted despite the advancements in alternative donor allogeneic hematopoietic cell transplantation (HCT), using mismatched URD, haploidentical, and UCB grafts.[28] In this real-world report conducted during 2016–2021, access to 8/8 URD had increased over time for Europeans *versus* non-Europeans, up to 95% *versus* 61% ($p < 0.001$) respectively. Thus, UCB use has proven successful in patients with high-risk malignancies who lack matched or single antigen mismatched URD options. As of 2021 data, there are more than 266,000 UCB units available for use in the National Marrow Donor Program (NMDP) registry from different races and ethnicities, with White donors making up 46% of registry units, but only 23% from Hispanic/Latino donors, 10% Black/African American donors, 5% Asian donors, 13% mixed racial group donors, and 0% from American Indian or Alaska Native donors.[29]

Cost implications with dCBT

While dCBT has been utilized to try to overcome the cell dose limitations of a single UCB unit, performing a dCBT procedure doubles the cost of stem cell graft acquisition. In adults, dCBT costs can be $80,000 or higher, notwithstanding the additional costs of the transplant hospitalization and immediate post-transplant care. Furthermore, an evaluation of the US inventory of public CB banks showed that only about <5% of UCB units have an adequate cell dose (TNC $\geq 2.5 \times 10^7$/kg) for patients weighing 70 kg or greater.[21]

Comparison of alternative donor graft sources

Choosing the optimal graft in the absence of a matched donor requires a critical assessment of the pros and cons of each alternative donor graft source such as UCB, haploidentical, or mismatched donor grafts. Historically, institutional preference and experience influenced decision making. To address this important question on alternative donor grafts on a multicenter level, two parallel phase II Blood & Marrow Transplant Clinical Trials Network (BMT CTN) trials using reduced intensity conditioning (RIC) followed by allogeneic HCT with dCBT (BMT CTN 0604) or haploidentical bone marrow (haplo-BM) (BMT CTN 0603) grafts were conducted.[30] The study objectives and eligibility criteria were similar between trials, and showed similar outcomes including 1-year overall survival (OS), time to neutrophil engraftment, and the rates of GVHD. The 1-year probabilities of OS and progression-free survival (PFS) were 54% and 46% respectively for dCBT, and 62% and 48% respectively for haplo-BM transplantations. The 100-day cumulative incidence of grade II–IV acute GVHD was 40% *versus* 32%, the 1-year cumulative incidences of non-relapse mortality (NRM) was 24% *versus* 7% while the relapse rate was 31% *versus* 45% for dCBT and haplo-BM transplants, respectively.[30]

The lack of an obvious superior approach of the parallel studies led to the phase III randomized, BMT CTN 1101 trial, comparing dCBT and haplo-BM allografts using RIC, conducted during 2012–2018 ($n = 368$).[31] The RIC regimen was comprised of fludarabine, cyclophosphamide, and total body irradiation (TBI); GVHD prophylaxis was a combination of calcineurin inhibitor and mycophenolate mofetil (MMF) for dCBT, and post-transplant cyclophosphamide, tacrolimus and MMF for haplo-BM transplants. The 2-year PFS was 35% and 41% with dCBT and haplo-BM grafts ($p = 0.41$), respectively. Prespecified secondary endpoints included 2-year NRM of 18% *versus* 11%, and 2-year OS of 46% *versus* 57% for dCBT and haplo-BM grafts ($p = 0.04$), respectively. Acute GVHD at day +180 was 35% *versus* 28% ($p = 0.14$) for grade II–IV, and 9% *versus* 7% ($p = 0.60$) for grade III–IV acute GVHD, while chronic GVHD at 2-years was 22% *versus* 26% ($p = 0.36$) for dCBT and haplo-BM transplants. There were increased deaths due to infection and hemorrhagic events in the dCBT group. Therefore, although not statistically significant, there was trend toward lower PFS for patients who received dCBT when compared to haplo-BM grafts.

Subsequently, a real-world analysis was conducted using the Center for International Blood and Marrow Transplant Research (CIBMTR) data for patients who underwent dCBT, haplo-BM, and haploidentical peripheral blood (haplo-PB) allografts, which was compared with the BMT CTN 1101 cohorts receiving dCBT and haplo-BM, during 2012–2018.[32] This analysis demonstrated generalizability of the BMT CTN 1101 findings with extended follow-up. The 5-year PFS and OS were similar for both groups while the NRM was lower in haplo-BM when

compared to dCBT (HR 0.64; 95% CI 0.42–0.96, $p=0.033$). The haplo-PB transplants had lower NRM and relapse/progression, and improved PFS and OS, compared to dCBT (trial and non-trial) and haplo-BM transplants. In summary, this CIBMTR analysis helped clarify utilization of alternative grafts in the real-world setting, in which haplo-PB and haplo-BM were favored compared to dCBT for reduced intensity allogeneic HCT; moreover, haplo-PB provided OS benefit over haplo-BM. Finally, quality of life (QOL) assessments were conducted longitudinally using FACT-BMT total score, the 36-Item Short Form Survey (SF-36) Physical Component Summary (PCS) and Mental Component Summary (MCS), the EQ-5D and the Global QOL scale at pre-transplant, 12, and 24 months.[33] This analysis did not show significant differences in the treatment and control arms using any of the QOL scores at those time points. Pre-transplant QOL score was the only predictor of post-transplant 12 and 24-month scores, which, notably, were not associated with OS or PFS in either arm. Relapse and grade III–IV acute GVHD were the two post-transplant events associated with significant declines in FACT-BMT and SF-36 PCS scores. Chronic GVHD was associated with a decline in mean EQ-5D utility scores.

Regarding relapse, earlier reports lack clarity regarding the risk of relapse after CBT in patients with acute leukemias. A single center retrospective study of over 500 patients demonstrated that CBT provided a robust graft-*versus*-leukemia (GVL) effect when compared to matched and mismatched URD grafts after TBI *versus* non-TBI based myeloablative conditioning.[34] Patients who did not have matched URD were transplanted using mismatched URD or UCB. This decision on the choice of graft and its source [marrow *versus* peripheral blood stem cell (PBSC) or single *versus* double *versus* double with one expanded cord] was not a randomized decision but based on graft availability or active clinical trials at the time. Notably, approximately 30% of the dCBT recipients received a manipulated, *ex vivo* expanded UCB unit plus an unexpanded unit (see below). Recipients of UCB grafts had improved survival and reduced incidence of relapse when compared to matched or mismatched URD grafts, particularly in patients with measurable residual disease positive status as measured by 10-color multiparameter flow cytometry. While this is an excellent demonstration of robust GVL effect from UCB, two retrospective EBMT studies and the available prospective, randomized clinical trials have not confirmed that UCB grafts are superior to matched or mismatched URD grafts for relapse control.[35,36] It is also important to remember UCB allograft recipients will lack future options for donor lymphocyte infusions in the event of post-allogeneic HCT relapse.

Clinical strategies to overcome UCB cell dose limitations and CBT outcomes

Strategies for overcoming the limited cell numbers provided by UCB include dCBT utilizing two UCB units, combination of a single UCB with a haploidentical graft, and *ex vivo* UCB expansion algorithms. Specific to UCB expansion methods, there is also the potential to enhance both expansion and homing of UCB stem and progenitor cells. *Ex vivo* expansion strategies have included the use of cytokines in liquid culture (SCF, TPO, and Flt3 ligand), mesenchymal stromal cell co-cultures to recreate the bone marrow microenvironment, and the incorporation of chemical molecules and/or proteins that regulate signaling pathways of hematopoietic stem and progenitor cells [a copper chelator tetraethylenepentamine (TEPA); inhibition of sirtuin-1 with nicotinamide (NAM); an aryl hydrocarbon receptor antagonist StemRegenin-1 (SR-1), a pyrimidoindole derivative (UM171), and immobilized Notch ligand (Delta-1)].[37,38] Often the *ex vivo* manipulated product was administered in combination with an unmanipulated UCB; expansion of committed hematopoietic progenitor cells instead of the long-term repopulating stem cells results in rapid transient engraftment, without long-term engraftment. Additionally, the lack of T-cells in the graft engineered UCB unit in some of these initial trials resulted in a graft *versus* graft effect against the expanded cord. Thus, the unexpanded cord can immunologically reject the manipulated cord, and coupled with the lack of long-term repopulating cells in the expanded unit, results in sustained long-term engraftment of the unmanipulated unit. Finally, homing strategies to enhance UCB function include dipeptidyl peptidase 4 inhibition, complement fragment 3a priming, increase in CXCR4 *via* dimethylprostaglandin E2 pathway, and fucosylation of cell surface molecules required for P- and E-selectin binding.[16,39,40]

Successful use of *ex vivo* expanded UCB requires effective expansion of the hematopoietic progenitor cells as well as stem cells, while maintaining their capacity for homing as well as for short and long-term engraftment. Graft manipulation strategies with UCB focus on these main aspects of CBT and omidubicel has shown the most success with adequate data to support progression to the recent completion of a randomized phase 3 study. An important distinction is that omidubicel was not only designed to provide hematopoietic recovery, but facilitated by the infusion of the omidubicel UCB unit non-selected T-cell fraction, to also allow durable engraftment of a single CBT.

UCB *ex vivo* expansion

Gamida (omidubicel, previously NiCord)

Gamida's omidubicel is an *ex vivo*-expanded UCB allograft derived from UCB that uses a small molecule, NAM, as the active agent to inhibit differentiation and enhance the functionality of hematopoietic stem and progenitor cells. In the presence of NAM, a vitamin B3 derivative, and the cytokines Flt3 ligand, SCF, TPO, and IL-6, there is increase in frequency of phenotypically primitive $CD34^+$ $CD38^-$ cells and decreased frequency of lineage-committed progenitor cells. Furthermore, $CD34^+$ cells cultured with NAM have increased migration toward stromal cell-derived factor 1 (SCF-1) and increased homing to the bone marrow, resulting in effective and rapid engraftment. NAM inhibits SIRT1-deacetylase as a target accountable for NAM modulation of $CD34^+$ cells in co-cultures. These culture conditions do not support expansion of mature lymphoid cells.[41]

Logistically an identified cord blood unit (CBU) is transported from the selected cord blood bank to Gamida Cell's good manufacturing practice facility in Maryland, USA or Jerusalem, Israel. Graft engineering begins with a unit of identified UCB that undergoes cell selection using immunomagnetic beads for $CD133^+$ progenitor cells, and these selected cells are co-cultured with NAM and Flt3 ligand, SCF, TPO, and IL-6 for 21 days. During the selection process, the flow-through eluate of $CD133^-$ cells is cryopreserved and later infused as a source of T-cells to prevent graft failure. This expansion process results in a median of 72-fold (range 16–186) expansion of the $CD34^+$ cells, with a median $CD34^+$ cell dose of 3.5×10^6/kg (range, $0.9–18.3 \times 10^6$), and generally with about 70% thaw recovery and a $CD3^+$ cell dose of 1.3×10^6/kg (range, $0.49–5.81 \times 10^6$).[17,19]

In the original phase 1 trial, patients with high-risk hematologic malignancies received a NAM-expanded UCB (NiCord) graft and the $CD133^-$ cell fraction, along with an unmanipulated UCB unit, after myeloablative conditioning. With a median follow-up of 21 months, 8 of 11 patients achieved engraftment, and the time to neutrophil engraftment was shorter for the NiCord combination graft than historical controls (13 *versus* 25 days, $p < 0.001$).[17] Long-term engraftment was identified from either the unmanipulated or the cultured UCB product components, and stable NiCord-derived hematopoiesis was observed at >7 years of follow-up. This safety study led to a phase I/II multicenter study of a single *ex vivo* expanded UCB unit as a stand-alone graft after myeloablative conditioning for patients with high-risk hematologic malignancies.[42] The median time to engraftment was shorter for neutrophils (11.5 *versus* 21 days, $p = 0.001$) and platelets (34 *versus* 46 days, $p < 0.001$), compared to a contemporary matched CIBMTR cohort. There was one patient with primary graft failure, and two with secondary graft failure. The cumulative incidence of grade II–IV acute GVHD was 44%, grade III–IV acute GVHD was 11%, 2-year moderate to severe chronic GVHD was 10%, non-relapse mortality was 24%, and relapse of 33%.

Based on these promising results, a randomized multicenter phase 3 trial of omidubicel (previously NiCord) *versus* standard CBT after myeloablative conditioning was performed in patients aged 12–65 years with a history of high-risk hematologic malignancies.[43] Most patients had acute leukemias, disease risk index was moderate (34%) to high (42%), and majority of the cords were four of six HLA-matched (range 4–6 of six HLA-matched). Nearly 44% of the study population was non-White, and included 16% Black, 14% Asian, 3% multiracial, and 13% Hispanic/Latino. Patients in the study arm received transplant at a median of 41 days *versus* 26 days in the standard UCB transplant, allowing for the time for *ex vivo* culture. The allograft was enriched for $CD34^+$ cells in the omidubicel product, with a 130-fold

expansion of the $CD34^+$ cells and a median $CD34^+$ cell dose of 9.0×10^6/kg (range 2.1–47.6×10^6 cells/kg) *versus* 0.3×10^6/kg (range 0.1–1×10^6 cells/kg) for standard unmanipulated arm. The median $CD3^+$ cell dose from the CD133-negative fraction was 3×10^6 cells/kg (range 1.1–12.4×10^6 cells/kg) in omidubicel *versus* 4.6×10^6 cells/kg (range 0–14.8×10^6 cells/kg) contained in the control graft. GVHD prophylaxis consisted of calcineurin inhibitor (tacrolimus or cyclosporine) and MMF. The primary endpoint was the cumulative incidence of engraftment by day +42, and was 96% *versus* 89% for neutrophils at a median of 10 *versus* 20 days ($p < 0.001$) for omidubicel *versus* control. The cumulative incidence of platelet engraftment by day +42 was 55% *versus* 35% ($p = 0.028$) and day +100 was 83% *versus* 73%, at a median of 37 *versus* 50 days ($p = 0.023$) for omidubicel *versus* control graft.[43] Grade II–IV acute GVHD, and moderate to severe 1- and 2-year chronic GVHD, were similar in both arms. After randomization, the cumulative incidence of NRM at 210 days was 11% *versus* 24% in the omidubicel *versus* standard arm ($p = 0.09$), cumulative incidence of relapse at 15 months was 25% *versus* 17% ($p = 0.32$), and there was a trend toward improved OS for omidubicel *versus* standard graft, respectively. Patients with omidubicel had reduced incidence of BMT CTN-defined grade 3 infections in the first year (6% *versus* 25%), had reduced hospitalization and health care utilization. Overall, this strategy results in improved transplant outcomes with early clinical benefit.[41]

An optional IR sub-study was conducted starting day +7 through day +365, using flow cytometry assays to study lymphocyte subsets. A total of 37 patients from 15 sites consented to this sub-study, 17 patients receiving omidubicel and 20 patients receiving dCBT. The median $CD3^+$ content of omidubicel prior to cryopreservation was lower than that of control's post-thaw, 180×10^6 *versus* 516×10^6 cells. Beginning day +7, $CD4^+$ T-cells, B-cells, NK-cells as well as monocyte and dendritic cell subsets were found to be higher in omidubicel patients. Higher B-cells (cells/mL) persisted throughout the first year, 12×10^3 *versus* 1×10^3 ($p = 0.013$) at day +7, 863×10^3 *versus* 543×10^3 ($p = 0.03$) at 6 months and 1492×10^3 *versus* 763×10^3 ($p = 0.02$) at 1-year, for omidubicel *versus* control. In this small correlative study, improved reconstitution occurred with omidubicel graft despite lower number of cells infused when compared to unmanipulated dCBT unmanipulated grafts.[44,45]

Additionally, this trial was one of the few trials with advanced graft manipulation and expansion techniques that incorporated health-related QOL (HRQL) assessments. Data were available from 75 of the 108 randomized subjects, and collected at screening and at days +42, +100, +180, and +365. Over the first year post-transplantation, assessment of mean changes in physical, functional, and total FACT-BMT scores indicated significantly better HRQL with omidubicel ($p < 0.05$). Omidubicel recipients were likely to do better as early as day +42 with durability at 1-year when compared to standard unmanipulated grafts.[46] Across all patients, adverse clinical outcomes, such as grade 3 viral infections and lower rates of neutrophil engraftment, were associated with worse HRQL scores.

Omidubicel and emerging therapies: UM171 expanded UCB graft

UM171 expanded UCB data from its early phase studies appears promising and comparable to omidubicel (Table 1). UM171 is a small molecule that belongs to the pyrimidoindole derivatives and when co-cultured with human UCB cells, it has the capacity to result in robust *ex vivo* expansion by enhancing the long-term hematopoietic stem cell (HSC) self-renewal machinery independently of aryl hydrocarbon receptor suppression.[47] Similar to the Gamida studies, investigators started with infusion of two CBUs, one unit expanded with UM171 and one unmanipulated unit as a safety measure in case the expanded cord did not engraft. Once engraftment was achieved, a single arm phase I/II study with dose de-escalation design was conducted to determine the minimal pre-cryopreservation CBU cell dose to achieve effective engraftment as a single unit. Cohort 1 required minimum TNC of 2.0×10^7 cells/kg with $CD34^+$ cell dose of 1.0×10^5 cells/kg and cohort 2 required minimum TNC of 1.5×10^7 cells/kg with $CD34^+$ cell dose of 0.5×10^5 cells/kg. Using these parameters, cohort 2 was able to access 47% of stored UCBs, with 11 of 22 (50%) of patients ⩾6 of 8 allele level match. Median time to engraftment was 18 days for neutrophils and 40.5 days for platelets. At 1 year, the cumulative incidence of

Table 1. Characteristics of patients and grafts on studies with omidubicel and UM171 expanded UCB.

Variable	Omidubicel	UM171
Trial	Phase 3	Phase 1–2
Year of publication	Oct 2021	Feb 2022
FDA approval	April 2023	–
No. CBU	1 expanded UCB ($n=52$) *versus* Standard UCB ($n=56$, single or d UCB)	1 expanded UCB plus 1 unexpanded UCB ($n=5$) 1 expanded UCB ($n=22$)
HLA match	>4 of 6	>4 of 6
CBU requirement before expansion (median dose)		
TNC ($\times 10^7$/kg)	3.0 (1.6–7.3)	2.92 (1.45–5.91)
CD34 ($\times 10^8$/kg)	0.14 (0.09–0.4)	1.44 (0.66–5.91)
Expansion culture duration (days)	21 ±2	7
Post expansion (median dose)		
CD34 ($\times 10^6$/kg)	9.0 (2.1–47.6)	2.87 (1.91–3.96)
CD34 expansion, fold	130 (1.91–3.96)	28 (19–35)
Hematologic malignancies, high risk	MDS, int-2 to high AML, CR1/CR2 ALL, CR1/CR2/CR3 CLL & Lymphomas	MDS, MPN Acute Leukemia, CR1/CR2/not in CR, CLL & Lymphomas
Conditioning	Myeloablative	Myeloablative
Engraftment		
ANC (days, range)	10 (8–13)	18 (12.5–20)
Platelets (days, range)	37 (33–42)	42 (35–47)
Acute GVHD		
Grade 2–3	56% at D100	64% at 1 year
Grade 3–4	14% at D100	0% at 1 year
Chronic GVHD		
All grade	35% at 1 year	17% at 1 year
Moderate-severe	27% at 1 year	0% at 1 year
Median F/U (months)	10 (1–19)	18 (12–22)
TRM	11% *versus* 24% at 210 days	5% at 1 year
Relapse	25% *versus* 17% ($p=0.32$) At 15 months	21% (9–51) At 12 months
GRFS at 1 year	36% *versus* 45% ($p=0.56$)	64% (43–86)

ALL, acute lymphocytic leukemia; AML, acute myelogenous leukemia; ANC, absolute neutrophil count; CLL, chronic lymphocytic leukemia; F/U, follow-up; FDA, U.S. Food & Drug Administration; GVHD, graft-*versus*-host disease; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; TNC, total nucleated cell; TRM, transplant related mortality; UCB, umbilical cord blood.

grade 2–4 acute GVHD was 64%, grade 3 acute GVHD was 10%, chronic GVHD was 17% and no patients had moderate to severe chronic GVHD. At 1 year, the TRM was 5% with OS of 90%, PFS of 74%, GVHD-free relapse-free survival (GRFS) of 64% and chronic GVHD-free relapse-free survival (CRFS) of 74%. UCB expansion with UM171 is much shorter (7 days) when compared to omidubicel (21 days) and if manufacturing remains successful on a larger scale it can rapidly bridge patients to transplant. UM171 patients had minimal TRM and they did not have moderate to severe chronic GVHD making this a very appealing graft. UM171-driven UCB expansion is known to modify cellular composition of the expanded product, including $CD34^+$ dendritic and mast cells. Unique cellular composition and improved survival outcomes of this product warrants further investigation[48] and there are two ongoing phase 2 trials, one in the United States and one in Canada.

Omidubicel in non-malignant hematologic disease

Severe aplastic anemia

Severe aplastic anemia (SAA) is a bone marrow failure syndrome for which the standard of care treatment of young patients is early allogeneic HCT from a MRD. However, many patients with SAA lack matched related or URDs and alternative donor options are necessary if immune suppressive therapy fails.[49,50] In a phase 2 study of patients with transfusion-dependent SAA, patients received combination omidubicel and $CD34^+$ selected haploidentical cells in cohort 1 ($n=3$), followed by omidubicel alone in cohort 2. Eligible patients (aged 4–55 years) had failed immunosuppressive therapy (IST), did not have ⩾4 of 8 HLA-matched UCB unit with a minimum of 1.8×10^7/kg TNC and 8×10^6 $CD34^+$ cells, and lacked DSAs to mismatched alleles on the UCB unit. Approximately 63% of these patient ($n=5$) had HLA-alloantibodies and were generally considered high risk for graft failure with conventional CBT. Conditioning consisted of horse anti-thymocyte globulin, cyclophosphamide, fludarabine, and 2 Gy of TBI; GVHD prophylaxis was tacrolimus and MMF. In an early report of eight treated patients, three of three patients in cohort 1, and four of five patients in cohort 2 had achieved engraftment.[51] One patient who did not engraft was salvaged with haploidentical transplant. The median time to neutrophil and platelet engraftment was 10 days (range 6–14) and 31 days (15–40), respectively. Among the seven patients with sustained engraftment, six had ⩾95% UCB myeloid chimerism by day +14 and ⩾95% T-cell chimerism by day +26. By day +100, IR analysis showed a median absolute CD4 count of 186/μL (interquartile range 118–340) and a mean (±SD) IgG level of 522 (±161) mg/dl. These preliminary results support the use of omidubicel grafts for SAA patients without matched donors. Final results of this ongoing trial remain to be reported (NCT03173937).

Sickle cell disease (SCD)

In selected patients with severe SCD, allogeneic HCT with a matched sibling donor is an acceptable strategy for curative intent. However, in an analysis of 85 pediatric patients with SCD without matched sibling donors, reported potential match probabilities within the study period -(2009–2013) were 20% for 8/8 matched URD, 84% for 7/8 matched URD, and 97% for two 4–6/6 matched UCB units suitable for *ex vivo* expansion.[52] In a phase 1/2, open-label, single-arm study, SCD patients received myeloablative conditioning followed by omidubicel as a single CBT ($n=3$), or omidubicel plus an unmanipulated cord as a dCBT ($n=13$). Units were HLA-matched at 4 of 6 loci, and in the dCBT cohort each unit was 3/6-matched to each other. Double mismatch at any locus on A, B, or DRB1 was not permitted. UCB units were excluded if the patient had DSA against any allele, as was often observed in heavily transfused individuals. All patients engrafted, with median time to neutrophil engraftment of 7–9 days. One patient receiving single unit omidubicel CBT developed secondary graft failure after cytomegalovirus (CMV) reactivation, with subsequent autologous marrow infusion and recovery. In the dCBT cohort, all patients achieved evidence of engraftment with the omidubicel product. However, in 10 of 12 patients with long-term engraftment, the unmanipulated unit became the predominant. There was high incidence of grade II–IV acute GVHD (69%), grade III–IV acute GVHD (23%), and chronic GVHD at 6- and 12-months (15% and 46%), respectively.[53] Notably, new approaches other than allogeneic HCT for SCD are including CRISPR-Cas9 gene editing for the SCD and beta-Thalassemia

hemoglobinopathies that are highly promising.[54] While we have only short-term experience with gene therapy manipulated autografts at this time, future comparison of short- and long-term outcomes will be warranted comparing gene therapy with allogeneic HCT approaches such as omidubicel, particularly recognizing the costs of the autologous gene therapy [$2.8 million USD for betibeglogene autotemcel, Zynteglo® (Bluebird Bio, Inc)].

Healthcare utilization and cost of *ex vivo* UCB expansion

Traditionally, CBTs have been associated with delayed engraftment, prolonged hospitalization, and higher costs of transplant compared with other donor sources. Omidubicel is an advanced cell therapy preserving stem cell function to optimize homing, engraftment, and self-renewal, and is manufactured from a single HLA-matched UCB unit per patient. Analysis of hospital and resource utilization comparing omidubicel *versus* standard of care CBT has been performed, using data collected from the phase 3 clinical trial.[55] Through day +100 post-HCT, patients receiving omidubicel experienced shorter average total length of hospital stay than conventional CBT recipients (mean 41.2 *versus* 50.8 days; $p = 0.027$) and more days alive and out of the hospital (mean 55.8 *versus* 43.7 days; $p = 0.023$). A total of 12% of omidubicel patients died before day +100 *versus* 16% on standard CBT. During the primary hospitalization, fewer omidubicel recipients required intensive care unit (ICU) stays (9.6% *versus* 23.2%), and spent fewer days in the ICU (mean 0.4 *versus* 4.7 days, $p = 0.028$) and transplant unit (mean 25.3 *versus* 32.9 days, $p = 0.022$) compared to standard of care CBT. Additionally, omidubicel recipients required fewer outpatient consultant ($p = 0.015$) and non-consultant visits (e.g. X-rays, scans, biopsies, etc., $p = 0.025$) and required fewer platelet or other transfusions within 100 days of transplant ($p = 0.051$, and 0.005 respectively). Beyond day +100, the resource utilization was similar in both arms although fewer omidubicel patients required readmission for GVHD [9% ($n = 3$) *versus* 47% ($n = 4$), $p = 0.01$].

Increasing attention is given to the cost of care of the allogeneic HCT patient. The purchase of an UCB unit is significant and the cost of purchasing cell products for a dCBT can actually surpass the entire Centers for Medicare and Medicaid (CMS) reimbursement for an allogeneic HCT. Previously, there have been multiple studies focused at the short-term total cost of care within the 3-months or first year of transplant, although increasingly, long-term cost analyses are being performed. Analyses of commercial claims database banks have estimated the 5-year adjudicated claims paid by payer to an institution approximating $450,000 for adult lymphoma allogeneic HCT, and $650,000 for pediatric ALL allogeneic HCT.[56,57] These studies were performed before the advent of small molecules, and more recent assessments of the cost of care for allogeneic HCT that include estimates for utilization of small molecules [e.g. FlT3 ITD (fms-like tyrosine kinase 3 internal tandem duplication) inhibitors] to prevent disease relapse and to treat chronic GVHD (e.g. ibrutinib, ruxolitinib, belumosudil), suggest that the cost of an individual undergoing allogeneic HCT currently will approach $900,000–$1,200,000.[58] In the United States, where incident of care reimbursement is standard rather than addressing reimbursement for the burden of disease over lifetime, innovation designed to be utilized early in the treatment course to avoid long-term complications, can actually negatively impact utilization as the cost of innovation often far exceeds the negotiated case rate for the allogeneic HCT procedure. CD34-selection has been shown to be efficacious and is approved for elderly AML patients in CR1, based on the BMT CTN 0303 trial, but is generally not performed.[59] Many new graft engineered HSC products are emerging (NCT05316701, NCT02665065, NCT04849910) as well as omidubicel that is now U.S. Food & Drug Administration (FDA) approved. We recognize that utilization may be limited by the current reimbursement structures, rather than acknowledging that the total cost of care can be reduced by limiting the need for long-term treatment with small molecules for disease relapse or prophylaxis, or by significantly decreasing the risk of chronic GVHD.

Long-term outcomes after omidubicel transplantation

One concern of any manipulated hematopoietic stem cell product is durability over time and avoidance of late graft failure. A pooled secondary

analysis of long-term outcomes of omidubicel recipients has now been published, extracting data from five multicenter prospective studies between 2016 and 2020.[60] All patients underwent myeloablative conditioning with planned follow-up for 10 years post-transplant. Of a total of 97 patients who engrafted with omidubicel, 64 subjects were included in the landmark study with follow-up of at least 1-year. Similar to standard allogeneic HCT, the most commonly treated diseases included ALL, AML, and MDS. The authors report a median follow-up of 22 months among all patients, and 35.7 months among survivors; the 3-year OS and disease-free survival were 62.7% and 56.4%, respectively. Key observation included that durable trilineage hematopoiesis was observed with median hemoglobin, platelets, and white blood count numbers remaining within normal range up to 10-years after treatment. Similarly, immune subsets were also identified in normal ranges up to 8-years post-transplant. Secondary graft failure was only identified in five patients (5%), all within the first year and occurring at a median of 40-days after transplant (range 12–262 days). Key long-term endpoints included 3-year cumulative incidence of chronic GVHD and relapse of underlying disease, occurring at 36.6% and 22.2% respectively. These data support the premise that the manipulated, expanded UCB allograft product can achieve long-term engraftment.

FDA approval: Omidubicel

On 27 April 27 2023, the FDA provided a Biologics License Application (BLA) approval for omidubicel (Omisirge®, Gamida Cell Ltd manufacturer, Israel) for both adult and pediatric subjects (aged 12 and over) with hematologic malignancies who are planned for myeloablative conditioning followed by umbilical cord blood transplantation.[61] The indication was outlined that the product can reduce the time to neutrophil recovery and decrease infection incidence compared to standard cord blood procedures. The approval was based upon the phase 3 trial (NCT02730299) described within this review. Following the recommended protocol, the omidubicel-onlv dose is two sequential infusions consisting of the following: UCB cultured Fraction with a minimum of 8.0×10^8 total viable cells with a minimum of 8.7% $CD34^+$ cells and a minimum of 9.2×10^7 total $CD34^+$ cells, followed by the non-cultured fraction with requirements of a minimum of 4.0×10^8 total viable cells with a minimum of 2.4×10^7 $CD3^+$ cells. The target indication is the accelerated median time to neutrophil recovery and reduction of bacterial and fungal infections through day 100, based upon the trial results. Specific additional requests from the FDA is that the dating period for omidubicel-onlv shall be 12 weeks from the date of manufacture when stored at $\leqslant -150°C$ for the cultured fraction and 15 weeks from the date of manufacture when stored at $\leqslant -150°C$ for the non-cultured fraction. The date of manufacture shall be defined as the date on which the final formulated drug product is filled into its final container closure for cryopreservation. There was request for post-marketing commitments from the manufacturer to perform a residual impurities study on the drug product assessing whether any impurities could be retained in the process and whether or not elemental leachables could be detected. These requests appear to represent standard ongoing quality control of the manufacturing process.

Conclusion

Advancements in CBT using expansion strategies like omidubicel makes transplant safer and more successful. Data from the randomized phase 3 study against standard CBT demonstrate its role as a robust source of an alternative graft with *ex vivo* CD34 expansion, rapid engraftment, and robust IR, with reduced TRM and improved overall long-term outcomes and QOL measures. Given that omidubicel had superior outcomes compared to standard CBT, it draws in question whether there might be a potential benefit of omidubicel over haploidentical HCT. BMT CTN 1101 compared standard cord blood to haploidentical allografts, but in the RIC setting. In contrast, the experience of omidubicel has been developed in the myeloablative conditioning setting. There are no data comparing these alternative grafts but hopefully future studies will emerge to provide better clarity on this issue. Furthermore, this alternative stem cell product also assists overcoming the barrier of racial disparities in the donor selection process, since omidubicel grafts can be utilized for adults who lack available MRD or conventional URD grafts. The upfront cost of engineering the expanded cord product is expected to be high, but should incorporate the cost of purchase of the selected frozen, banked cord product.

However, long-term data and sophisticated cost analysis will likely determine whether this upfront investment will create a superior allogeneic HCT treatment option for patients who lack standard donor options, recognizing the enhanced engraftment and IR over standard CBT, which as a result contributes to reduced health care utilization and long-term costs due to the lower overall long-term rates of chronic GVHD and relapse.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Author contributions
Arpita P. Gandhi: Conceptualization; Writing – original draft; Writing – review & editing.

Laura F. Newell: Conceptualization; Writing – original draft; Writing – review & editing.

Richard T. Maziarz: Conceptualization; Investigation; Project administration; Resources; Supervision; Writing – original draft; Writing – review & editing.

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Competing interests
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