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Multicenter Long-Term Follow-Up of Allogeneic Hematopoietic Cell Transplantation with Omidubicel: A Pooled Analysis of Five Prospective Clinical Trials

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Abstract

Omidubicel is a cord blood derived *ex vivo*-expanded cell therapy product that has demonstrated faster engraftment and fewer infections compared with unmanipulated umbilical cord blood (UCB) in allogeneic hematopoietic cell transplantation. While the early benefits of omidubicel have been established, long-term outcomes are still unknown. We report on a planned pooled analysis of five multi-center clinical trials, featuring 105 patients with hematologic malignancies or sickle cell hemoglobinopathy who underwent omidubicel transplantation at 26 academic transplant centers worldwide. With a median follow-up of 22 months (range, 0.3–122), the 3-year estimated overall survival and disease-free survival were 62.5% and 54.0%, respectively. With up to 10 years follow-up, omidubicel showed durable trilineage hematopoiesis. Serial quantitative assessments of $CD3^+$, $CD4^+$, $CD8^+$, $CD19^+$, $CD116^+CD56^+$, and $CD123^+$ immune subsets revealed median counts remaining within normal range through up to 8 years follow-up. Secondary graft failure occurred in 5 patients (5%) in the first year, with no late cases reported. One case of donor-derived myeloid neoplasm was reported at 40 months post-transplant. This was also observed in a control arm patient who received only unmanipulated UCB. In conclusion, omidubicel demonstrated stable trilineage hematopoiesis, immune competence, and graft durability in extended follow-up.

Introduction

Allogeneic hematopoietic cell transplantation (HCT) remains the only potentially curative treatment for most hematologic malignancies. Umbilical cord blood (UCB) provides an important alternative source of hematopoietic stem and progenitor cells (HSPCs) for allogeneic HCT, but its use is constrained by low cell dose. Early attempts at UCB

expansion were able to achieve robust ex vivo expansion of stem cells, but have mostly relied on a co-administered unmanipulated UCB unit for long-term engraftment.[1–3]

Omidubicel is a first-in-class, UCB-derived cellular therapy product expanded using nicotinamide.[4] It was the first ex vivo expanded stem cell graft to be transplanted as a standalone unit. A recent randomized multicenter phase III trial of allogeneic HCT with standalone omidubicel showed faster engraftment and fewer infectious complications compared to unmanipulated UCB transplantation.[5] While the early benefits of omidubicel have been demonstrated, long-term outcomes are unknown.[6] Given the theoretical concerns surrounding durability of expanded stem cell grafts, we set out to perform a long-term follow-up study to confirm the safety, immune function, and graft durability of omidubicel transplantation. Here we report on a pooled analysis of five multi-center clinical trials evaluating omidubicel transplantation in patients with hematologic malignancies and sickle cell hemoglobinopathy.

Methods:

In this planned secondary analysis (NCT02039557), long-term outcomes were pooled from five clinical trials evaluating omidubicel transplantation between January 2011 and April 2021. Four studies (HEME1: NCT01221857, HEME2: NCT01816230, HEME3: NCT02730299, SCD1: NCT01590628) have previously been reported, while the remaining (SCD2: NCT02504619) closed early due to sponsor decision.[5,7–9] Three trials assessed patients with hematologic malignancies, and two enrolled patients with sickle cell hemoglobinopathy (Table 1). Patients treated in the two phase I studies received omidubicel co-administered with an unmanipulated UCB graft. All patients received myeloablative conditioning regimens, and graft-versus-host disease (GVHD) prophylaxis comprised of a calcineurin inhibitor and mycophenolate mofetil. Additional protocol information may be found in the supplemental appendix. In order to examine omidubicel-specific outcomes, all patients who fully engrafted with an unmanipulated UCB were excluded from this long-term follow-up study. Written informed consent was provided by all patients, and the study was approved by each site's institutional review board. Survival was estimated using the Kaplan-Meier method. Cumulative incidences were calculated via competing risk analysis, with the competing risks being death, graft failure, and relapse. Statistical analyses were performed using R 4.1.2 (R Core Team, Austria) and Graphpad Prism (Graphpad Software, USA).

Results:

Among 116 patients across 26 academic transplant centers who received omidubicel, either alone ($N = 92$) or co-administered with an unmanipulated UCB graft ($N = 24$), 11 fully engrafted with an unmanipulated UCB and were excluded from this analysis (Supplemental Figure 1). The remaining 105 patients were comprised of 97 (92%) who fully engrafted with omidubicel, 2 (2%) with mixed chimerism with omidubicel and an unmanipulated UCB, 5 (5%) with primary graft failure, and 1 (1%) who died before engraftment could be assessed. Baseline characteristics are described in Table 1. The median age at transplantation was 42 years (range, 2–62) and 41 (39%) belonged to a racial minority group. The most

common indications for transplantation were acute myeloid leukemia (AML) (41%), acute lymphoblastic leukemia (ALL) (27%), myelodysplastic syndrome (MDS) (12%), and sickle cell hemoglobinopathy (8%). At data cutoff in October 2021, the median duration of follow-up was 22.0 months (range, 0.3–122.5) for all included patients and 35.7 months (range, 11.7–122.5) among survivors.

Omidubicel demonstrated durable long-term trilineage hematopoiesis with up to ten years follow-up (Figure 1A–1C). Similarly, lymphocyte subsets including median $CD3^+$, $CD4^+$, and $CD8^+$ T cell counts, as well as $CD19^+$ (B-cell), $CD116^+CD56^+$ (NK cell), and $CD123^+$ (plasmacytoid dendritic cell) counts, were within the expected range with up to 8 years follow-up (Figure 1D–1I). Secondary graft failure was observed in five patients (5%) at a median of 40 days post-transplant (range, 12–262) (Supplemental Table 1). Three of these patients underwent a second allogeneic HCT, one patient died without another transplant, and one patient with hemoglobinopathy received an autologous stem cell rescue infusion.

The estimated 3-year overall survival and disease-free survival were 62.7% (95% CI, 52.1–71.6) and 56.4% (95% CI, 45.9–65.6), respectively (Figure 2A, 2B). The most common primary causes of death were disease relapse ($N = 16$), infection ($N = 11$), and acute GVHD ($N = 6$). The 3-year cumulative incidence of chronic GVHD was 36.6% (95% CI, 26.9–46.2) (Figure 2C). The maximum grade of chronic GVHD was predominantly mild (55%), with 33% and 13% experiencing moderate and severe disease, respectively. No deaths were attributed to chronic GVHD. The estimated 3-year cumulative incidence of disease relapse in all patients was 22.2% (95% CI, 14.5–31.1) (Figure 2D).

Regarding secondary hematologic malignancies, two patients (2%) were diagnosed with post-transplant lymphoproliferative disorder at 17- and 20-months post-transplant. In addition, one patient with AML received omidubicel alone and later developed a donor-derived MDS at 40 months post-transplant, requiring a second allogeneic HCT (Supplemental Table 2). Of note, there was also a case of donor-derived AML in the control arm of the phase III trial. This patient with ALL received an unmanipulated UCB transplantation and therefore was not included in the study cohort, but is reported here for comparison.

Discussion:

Data on the long-term outcomes of ex vivo expanded stem cell grafts have been limited.[3,10,11] This planned secondary analysis of pooled multi-institutional data provides the longest follow-up thus far of patients who received omidubicel. In our cohort, patients with long-term engraftment of omidubicel showed durable trilineage hematopoiesis and immune reconstitution. These findings demonstrate the reliability of omidubicel over extended durations and support future studies in younger populations in need of alternative stem cell donors for allogeneic HCT.

Three of 98 patients with hematologic malignancies (3%) experienced secondary graft failure, which is comparable to the 1–3% reported after allogeneic HCT from mobilized peripheral blood and bone marrow.[12] The two remaining patients with secondary graft

failure had sickle cell hemoglobinopathy, which is associated with an increased risk of graft rejection.[13,14] Although there has been concern that *ex vivo* expansion technologies may detrimentally impact long-term repopulating HSPCs, the ability of the nicotinamide-expanded omidubicel to maintain durable engraftment and hematopoiesis without the need for a concurrent unmanipulated UCB graft suggests that repopulating activity has been preserved.[15–17]

Donor-derived myeloid neoplasms were an adverse event of special interest in this population due to the expansion of the HSPCs involved in omidubicel production. Genetic aberrations related to myeloid neoplasms are known to occur as early as in utero and can be detected at low levels in a small minority of cord blood units.[18,19] Retrospective case series have estimated the real-world incidence of secondary donor-derived myeloid neoplasms in UCB transplantation to be in the range of 0.6–2%.[20–23] We observed donor-derived MDS in a single patient (1%) who received omidubicel, which was mirrored by a similar case of donor-derived AML in a patient who did not receive an expanded graft, suggesting comparable rates between ex vivo expanded grafts and unmanipulated UCB. The overall incidence may have been higher in this cohort due to the increased vigilance during a clinical trial compared to real world practice in which donor cell origins are not routinely assessed. The utility of screening for pre-malignant clones in at-risk stem cell donors and cord blood units prior to allogeneic HCT is still unclear and requires further investigation.[24,25]

The results from this multi-center analysis support the long-term safety and durability of omidubicel, and may inform survivorship care in patients who undergo omidubicel transplantation. On August 1st, 2022, the U.S. Food & Drug Administration granted priority review to the biologics license application for omidubicel in allogeneic HCT.[26] Notably, 39% of this study's cohort were non-white, highlighting a key demographic with more limited donor availability.[27] If approved for commercial use, omidubicel will expand the potential donor pool for these underrepresented racial minority groups.[28] Future studies are still needed to compare outcomes of omidubicel with other stem cell sources.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Sharing Statement:

Individual participant data will not be shared. Queries about the data can be made to corresponding author or medicalinformation@gamidacell.com.

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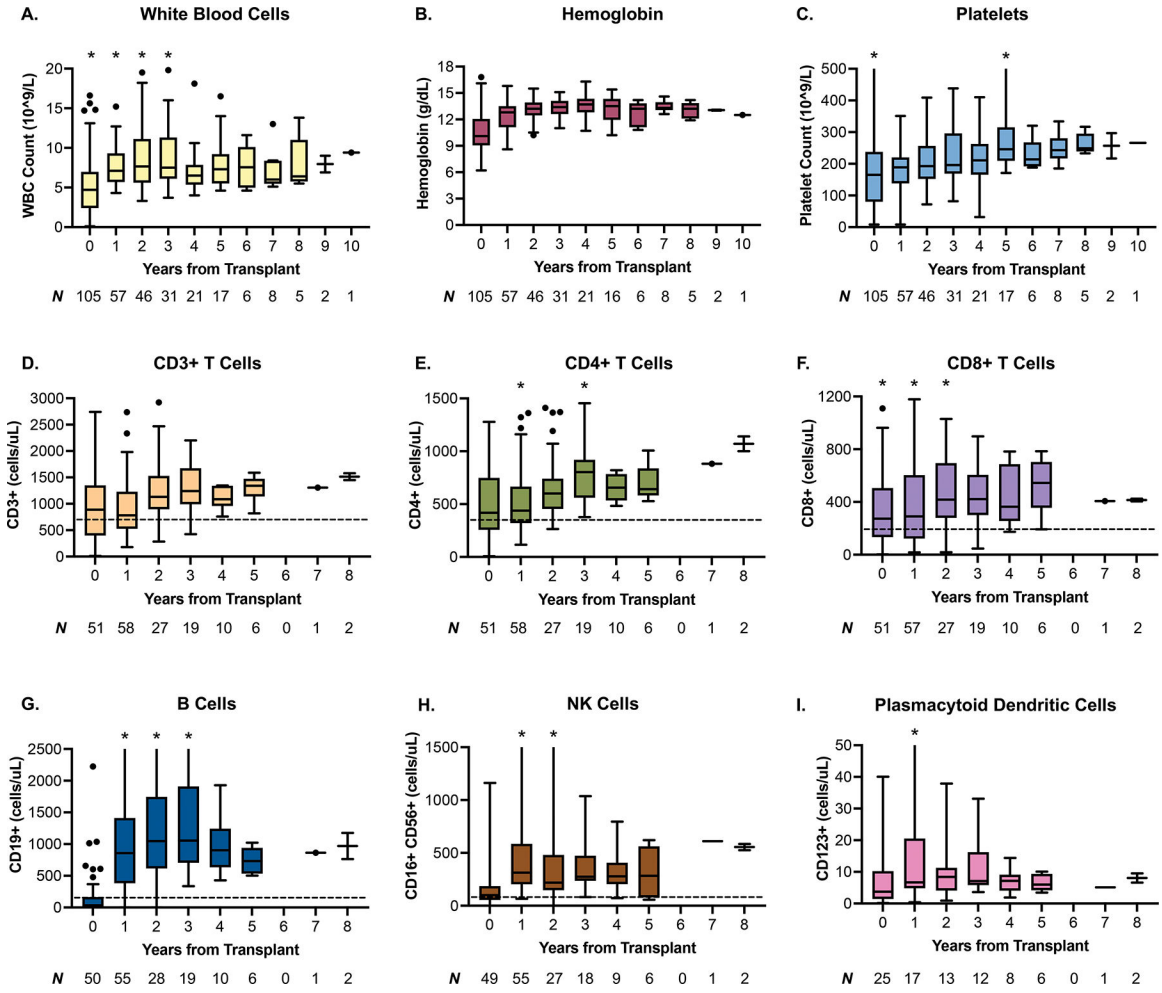

Figure 1.

Tukey box and whisker plots depicting trends of trilineage hematopoiesis and immune competence at up to 8–10 years post-transplant. **A-C.** Omidubicel demonstrates durable trilineage hematopoiesis over long-term follow-up. **D-I.** median counts of immune subsets fell within the normal range beginning at 1 year (early post-transplant immune reconstitution data not shown). Whiskers extend to the farthest points not considered outliers (1.5x the interquartile range from the median). Outliers are indicated by individual data points, while asterisk (*) indicate additional outlier points beyond the range of the figure. The lower limit of normal for various immune subsets are indicated by the dotted line, where available. WBC: white blood cells, NK cells: natural killer cells.

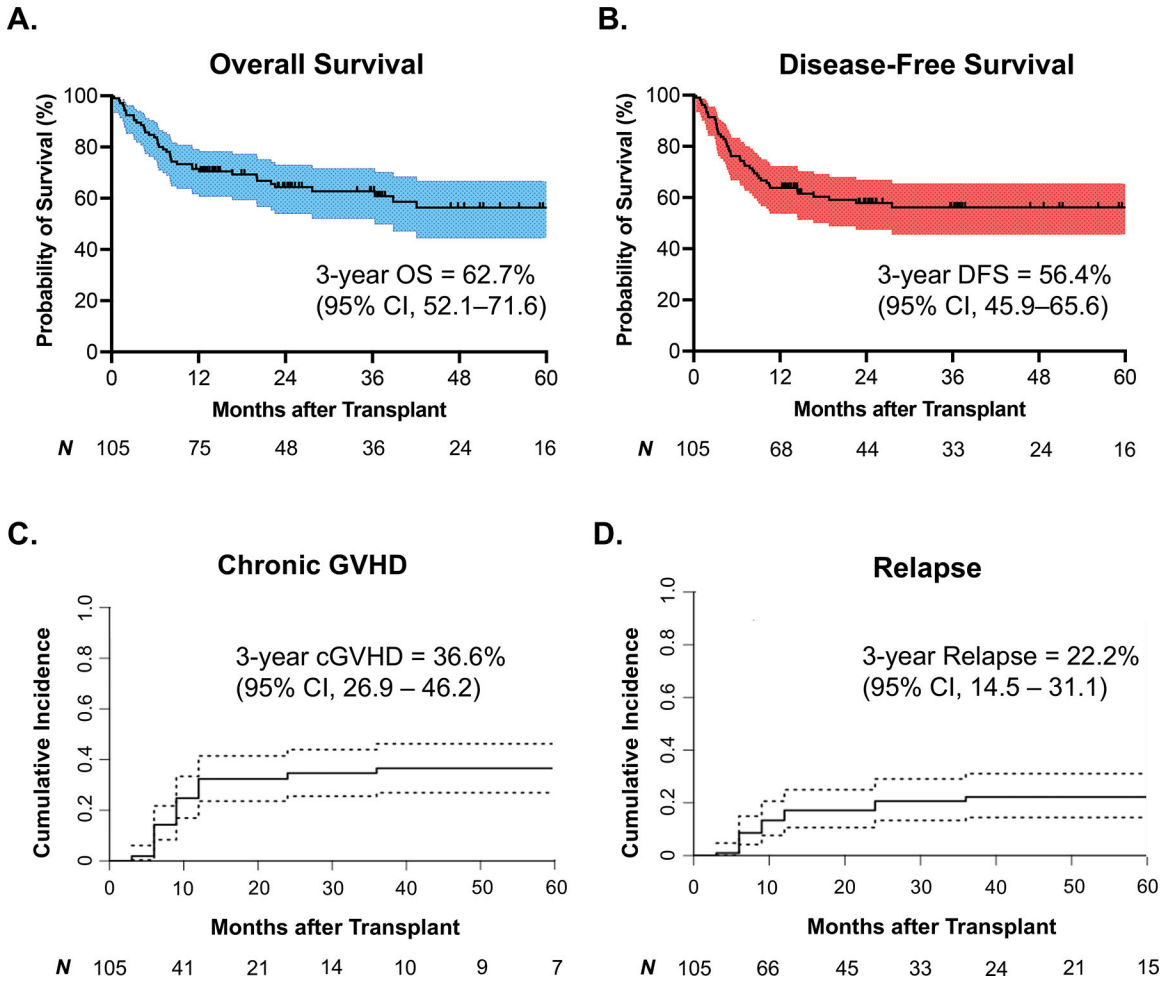

Figure 2.

Survival analyses and cumulative incidence estimates among all included patients (*N* = 105). **A, B.** Kaplan-Meier survival curves depicting overall survival and disease-free survival in all patients. **C, D.** Competing risk analyses estimating the cumulative incidences of chronic GVHD and disease relapse in all included patients. The competing risks for chronic GVHD were death from any cause, disease relapse, and graft failure. The competing risks for disease relapse were death from any cause and graft failure. cGVHD: chronic graft-versus-host disease, CI: confidence interval. OS: overall survival, DFS: disease-free survival, CI: confidence interval.

Table 1.

Baseline Characteristics by Clinical Trial

	NCT01221857 HEME1 (*N* = 9)	NCT01816230 HEME2 (*N* = 36)	NCT02730299 HEME3 (*N* = 52)	NCT01590628 SCD1 (*N* = 7)	NCT02504619 SCD2 (*N* = 1)	**Total (*N* = 105)**
Phase	I	I / II	III	I	I / II	
Trial Design	Single Arm	Single Arm	Two Arm RCT[≠]	Single Arm	Single Arm	
Disease Type, *N* (%)						
AML	4 (44%)	17 (47%)	22 (42%)	0	0	**43 (41%)**
ALL	1 (11%)	9 (25%)	18 (35%)	0	0	**28 (27%)**
MDS	2 (22%)	6 (17%)	5 (10%)	0	0	**13 (12%)**
Sickle Cell Hemoglobinopathy	0	0	0	7 (100%)	1 (100%)	**8 (8%)**
Other	2 (22%)	4 (11%)	7 (13%)	0	0	**13 (12%)**
Disease Risk Index, *N* (%)						
Low/Moderate	6 (67%)	22 (61%)	34 (65%)	0	0	**62 (59%)**
High/Very High	2 (22%)	12 (33%)	18 (35%)	0	0	**32 (30%)**
Unknown/Unevaluable	1 (11%)	2 (6%)	0	7 (100%)	1 (100%)	**11 (10%)**
Transplantation Strategy, *N* (%)						
Double Cord	9 (100%)	0	0	4 (57%)	0	**13 (12%)**
Single Cord	0	36 (100%)	52 (100%)	3 (43%)	1 (100%)	**92 (88%)**
Omidubicel Cell Dose, Median (range)						
TNC Dose (x 10^7 cells/kg)	3.9 (2.1–8.5)	4.9 (2.0–16.3)	4.7 (1.7–12.4)	7.7 (4.2–11.8)	28.8	**4.8 (1.7–28.8)**
CD34 Dose (x 10^6 cells/kg)	3.7 (0.9–18.3)	6.3 (1.4–14.9)	9.0 (2.1–47.6)	12.7 (6.6–19.0)	50.8	**7.3 (0.9–50.8)**
Omidubicel HLA Match, *N* (%)						
4 / 6	6 (67%)	26 (72%)	36 (69%)	7 (100%)	1 (100%)	**76 (72%)**
5 / 6	3 (33%)	8 (22%)	15 (29%)	0	0	**26 (25%)**
6 / 6	0	2 (6%)	1 (2%)	0	0	**3 (3%)**
Conditioning Regimen[*], *N* (%)						

	NCT01221857 HEME1 (*N* = 9)	NCT01816230 HEME2 (*N* = 36)	NCT02730299 HEME3 (*N* = 52)	NCT01590628 SCD1 (*N* = 7)	NCT02504619 SCD2 (*N* = 1)	**Total (*N* = 105)**
TBI/Flu/Cy	2 (22%)	8 (22%)	20 (38%)	0	0	**30 (29%)**
TBI/Flu/Thio	0	2 (6%)	7 (13%)	0	0	**9 (9%)**
TBI/Flu	7 (78%)	5 (14%)	0	0	0	**12 (11%)**
Bu/Flu/Clo	0	2 (6%)	0	0	0	**2 (2%)**
Bu/Flu/Thio	0	19 (53%)	25 (48%)	0	1 (100%)	**45 (43%)**
Bu/Flu/Cy	0	0	0	6 (86%)	0	**6 (6%)**
Bu/Flu/ATG	0	0	0	1 (14%)	0	**1 (1%)**
GVHD Prophylaxis, *N* (%)						
Tacrolimus + MMF	9 (100%)	15 (42%)	29 (56%)	0	0	**53 (50%)**
Cyclosporine + MMF	0	20 (56%)	23 (44%)	7 (100%)	1 (100%)	**51 (49%)**
MMF	0	1 (3%)	0	0	0	**1 (1%)**
Engraftment Outcome, *N* (%)						
Omidubicel	7 (78%)	33 (92%)	50 (96%)	6 (86%)	1 (100%)	**97 (92%)**
Mixed Chimerism	1 (11%)	0	0	1 (14%)	0	**2 (2%)**
Primary Graft Failure	1 (11%)	2 (6%)	2 (4%)	0	0	**5 (5%)**
Death Before Engraftment	0	1 (3%)	0	0	0	**1 (1%)**
Male Sex, *N*(%)	4 (44%)	20 (56%)	27 (52%)	3 (43%)	1 (100%)	**55 (52%)**
Non-White or Hispanic, *N*(%)	3 (33%)	7 (19%)	23 (44%)	7 (100%)	1 (100%)	**41 (39%)**
Age at Transplant, Median (range)	45 (21 – 61)	44 (13 – 62)	40 (13 – 62)	14 (8 – 16)	2	**42 (2 – 62)**
Karnofsky PS ≥ 80%, *N* (%)	9 (100%)	35 (97%)	51 (98%)	6 (86%)	1 (100%)	**102 (97%)**

Baseline characteristics of patients included in the long-term follow-up study by clinical trial. Patients received either single cord transplantation with omidubicel or double cord transplantation with omidubicel and an unmanipulated UCB unit. Patients who engrafted with UCB were excluded from this long-term follow up study.

[≠]Patients randomized to receive an unmanipulated UCB in the control arm of this phase III trial were not included in the study.

[*]All conditioning regimens were myeloablative.

RCT: randomized controlled trial, UCB: umbilical cord blood, AML: acute myeloid leukemia, MDS: myelodysplastic syndrome, ALL: acute lymphoblastic leukemia, TBI: total body irradiation, Bu: busulfan, Flu: fludarabine, Cy: cyclophosphamide, Thio: thiotepa, Clo: clofarabine, ATG: antithymocyte globulin, PS: performance status, HLA: human leukocyte antigen, MMF: mycophenolate mofetil, GVHD: graft versus host disease.