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Brief Article

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

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A B S T R A C T

Omidubicel is an umbilical cord blood (UCB)-derived ex vivo-expanded cellular therapy product that has demonstrated faster engraftment and fewer infections compared with unmanipulated UCB in allogeneic hematopoietic cell transplantation. Although the early benefits of omidubicel have been established, long-term outcomes

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remain unknown. We report on a planned pooled analysis of 5 multicenter clinical trials including 105 patients with hematologic malignancies or sickle cell hemoglobinopathy who underwent omidubicel transplantation at 26 academic transplantation centers worldwide. With a median follow-up of 22 months (range, .3 to 122 months), the 3-year estimated overall survival and disease-free survival were 62.7% and 56.4%, respectively. With up to 10 years of 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 ranges through up to 8 years of 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-transplantation. This was also observed in a control arm patient who received only unmanipulated UCB. Overall, omidubicel demonstrated stable trilineage hematopoiesis, immune competence, and graft durability in extended follow-up.

INTRODUCTION

Allogeneic hematopoietic cell transplantation (HCT) remains the sole 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 doses. Early attempts at UCB expansion were able to achieve robust ex vivo expansion of stem cells but mostly relied on a coadministered 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 stand-alone unit. A recent randomized multicenter phase III trial of allogeneic HCT with stand-alone omidubicel showed faster engraftment and fewer infectious complications compared to unmanipulated UCB transplantation [5]. Although the early benefits of omidubicel have been demonstrated, long-term outcomes are unknown [6]. Given the theoretical concerns surrounding the 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 5 multicenter clinical trials evaluating omidubicel transplantation in patients with hematologic malignancies and sickle cell hemoglobinopathy.

METHODS

In this planned secondary analysis (ClinicalTrials.gov identifier NCT02039557), long-term outcomes were pooled from 5 clinical trials evaluating omidubicel transplantation between January 2011 and April 2021. Four of the trials — designated in our manuscript as HEME1 (NCT01221857), HEME2 (NCT01816230), HEME3 (NCT02730299), and SCD1 (NCT01590628)—have been reported previously. The fifth trial, SCD2 (NCT02504619), closed early due to sponsor decision [5,7-9]. Three trials assessed patients with hematologic malignancies, and 2 trials enrolled patients with sickle cell hemoglobinopathy (Table 1). Patients treated in the 2 phase I studies received omidubicel coadministered with an unmanipulated UCB graft. All patients received a myeloablative conditioning regimen and graft-versus-host disease (GVHD) prophylaxis composed of a calcineurin inhibitor and mycophenolate mofetil. Additional protocol information is provided in the Supplementary Data.

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 incidence was calculated via competing risk analysis, with the competing risks of death, graft failure, and relapse. Statistical analyses were performed using R 4.1.2 (R Core Team, Vienna Austria) and Prism (GraphPad Software, San Diego, CA).

RESULTS

Among 116 patients across 26 academic transplantation centers who received omidubicel, either alone (n = 92) or coadministered with an unmanipulated UCB graft (n = 24), 11 fully engrafted with an unmanipulated UCB and were excluded from this analysis (Supplementary Figure S1). The remaining 105 patients included 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 presented in Table 1. The median age at transplantation was 42 years (range, 2 to 62 years), and 41 patients (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 the time of data cutoff in October 2021, the median duration of follow-up was 22.0 months (range, .3 to 122.5 months) for all included patients and 35.7 months (range, 11.7 to 122.5 months) among survivors.

Omidubicel demonstrated durable long-term trilineage hematopoiesis with up to 10 years of follow-up (Figure 1A-C). Similarly, lymphocyte subsets including median $CD3^+$, $CD4^+$, and $CD8^+$ T cell counts, as well as $CD19^+$ (B cell), $CD116^+CD56^+$ (natural killer cell), and $CD123^+$ (plasmacytoid dendritic cell) counts, were within the expected ranges with up to 8 years of follow-up (Figure 1D-I). Secondary graft failure was observed in 5 patients (5%) at a median of 40 days post-transplantation (range, 12 to 262 days) (Supplementary Table S1). Three of these patients underwent a second allogeneic HCT, 1 patient died without another transplantation, and 1 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% to 71.6%) and 56.4% (95% CI, 45.9% to 65.6%), respectively (Figure 2A,B). 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% to 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% to 31.1%) (Figure 2D).

Table 1
Baseline Characteristics by Clinical Trial

Characteristic	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 ($\times 10^7$ 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 ($\times 10^6$ cells/kg)	3.7 (.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 (%)†						
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)
Nonwhite or Hispanic, n (%)	3 (33)	7 (19)	23 (44)	7 (100)	1 (100)	41 (39)
Age at transplantation, yr, median (range)	45 (21-61)	44 (13-62)	40 (13-62)	14 (8-16)	2	42 (2-62)
Karnofsky Performance Status ≥80, n (%)	9 (100)	35 (97)	51 (98)	6 (86)	1 (100)	102 (97)

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.
RCT indicates randomized controlled trial; TBI, total body irradiation; Bu, busulfan; Flu, fludarabine; Cy, cyclophosphamide; Thio, thiotepa; Clo, clofarabine; ATG, antithymocyte globulin; MMF, mycophenolate mofetil.
* Patients randomized to receive unmanipulated UCB in the control arm of this phase III trial were not included in the study.
† All conditioning regimens were myeloablative.

Regarding secondary hematologic malignancies, 2 patients (2%) were diagnosed with post-transplantation lymphoproliferative disorder, at 17 months and 20 months post-transplantation. In addition, 1 patient with AML received omidubicel alone and later developed donor-derived MDS at 40 months post-transplantation, necessitating a second allogeneic HCT (Supplementary Table S2). Of note, there was also a case of donor-derived AML in the control arm of the phase III trial. That patient with ALL received an unmanipulated UCB transplantation and thus 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

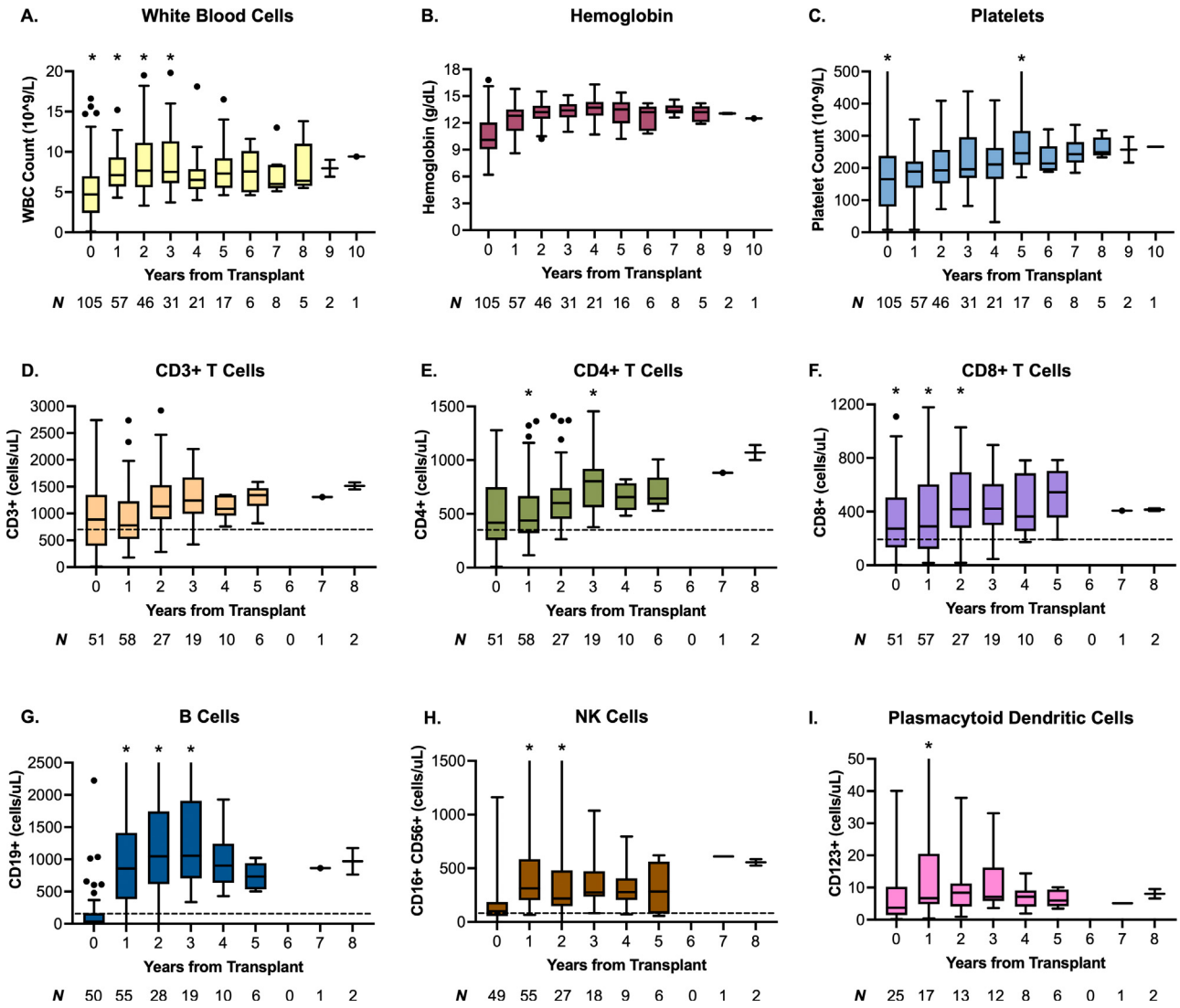

Figure 1. Tukey box-and-whisker plots depicting trends of trilineage hematopoiesis and immune competence at up to 8 to 10 years post-transplantation. (A-C) Omidubicel demonstrates durable trilineage hematopoiesis over long-term follow-up. (D-I) Median counts of immune subsets fell within the normal range beginning at 1 year (early post-transplantation immune reconstitution data not shown). Whiskers extend to the farthest points not considered outliers (1.5 times the interquartile range from the median). Outliers are indicated by individual data points, and asterisks 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. NK, natural killer.

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% to 3% reported after allogeneic HCT from mobilized peripheral blood and bone marrow [12]. The 2 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 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 owing 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 UCB 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 .6% to 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 grafts. The overall incidence may have been higher in this cohort owing 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

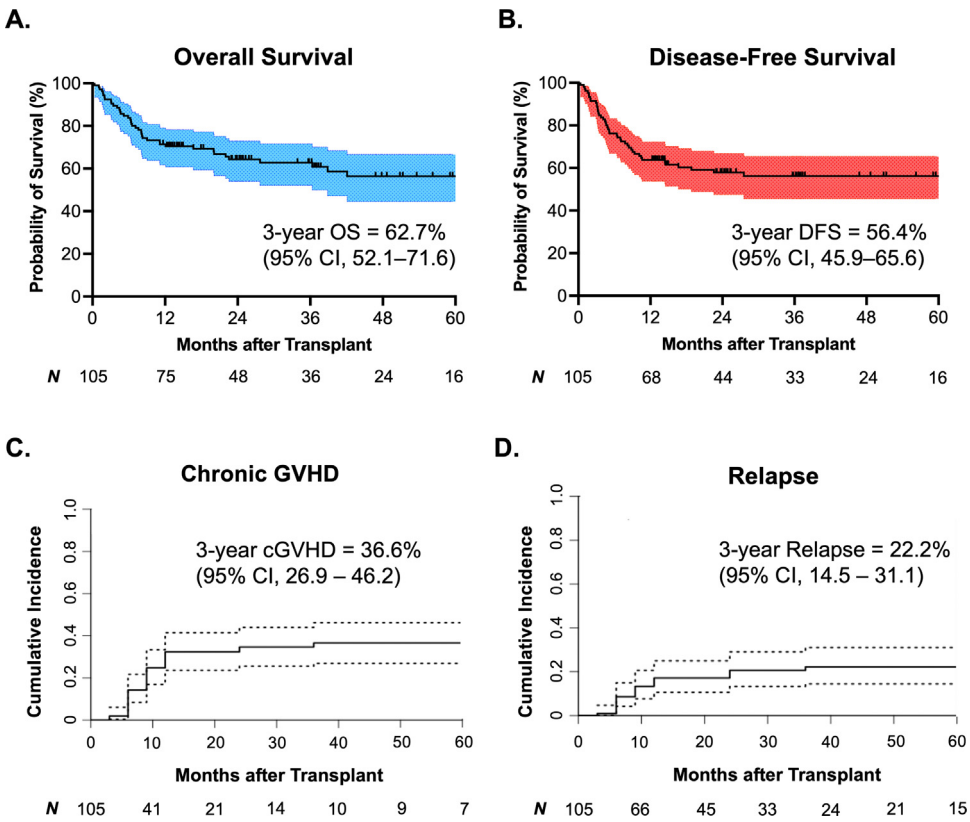

Figure 2. Survival analyses and cumulative incidence estimates among all included patients (N = 105). (A and B) Kaplan-Meier survival curves depicting overall survival (OS) and disease-free survival (DFS) in all patients. (C and D) Competing risk analyses estimating the cumulative incidences of chronic GVHD (cGVHD) and disease relapse in all included patients. The competing risks for cGVHD were death from any cause, disease relapse, and graft failure. The competing risks for disease relapse were death from any cause and graft failure.

premalignant clones in at-risk stem cell donors and UCB units prior to allogeneic HCT is still unclear and requires further investigation [24,25].

The results from this multicenter analysis support the long-term safety and durability of omidubicel and may inform survivorship care in patients who undergo omidubicel transplantation. On August 1, 2022, the US Food and Drug Administration granted priority review to the biologics license application for omidubicel in allogeneic HCT [26]. Notably, 39% of this study's cohort were nonwhite, 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 between omidubicel and other stem cell sources.

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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.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jtct.2023.01.031.

REFERENCES

1. Popat U, Mehta RS, Rezvani K, et al. Enforced fucosylation of cord blood hematopoietic cells accelerates neutrophil and platelet engraftment after transplantation. *Blood*. 2015;125:2885–2892.
2. Delaney C, Heimfeld S, Brashem-Stein C, Voorhies H, Manger RL, Bernstein ID. Notch-mediated expansion of human cord blood progenitor cells capable of rapid myeloid reconstitution. *Nat Med*. 2010;16:232–236.
3. Wagner Jr JE, Brunstein CG, Boitano AE, et al. Phase I/II trial of StemRegenin-1 expanded umbilical cord blood hematopoietic stem cells supports testing as a stand-alone graft. *Cell Stem Cell*. 2016;18:144–155.
4. Peled T, Shoham H, Aschengrau D, et al. Nicotinamide, a SIRT1 inhibitor, inhibits differentiation and facilitates expansion of hematopoietic progenitor cells with enhanced bone marrow homing and engraftment. *Exp Hematol*. 2012;40:342–355. e1.
5. Horwitz ME, Stiff PJ, Cutler C, et al. Omidubicel vs standard myeloablative umbilical cord blood transplantation: results of a phase 3 randomized study. *Blood*. 2021;138:1429–1440.

6. Lin C, Sajeev G, Stiff PJ, et al. Health-related quality of life following allogeneic hematopoietic cell transplantation with omidubicel versus umbilical cord blood. *Transplant Cell Ther*. 2023;29. 52.e1-52.e9.
7. Horwitz ME, Chao NJ, Rizzieri DA, et al. Umbilical cord blood expansion with nicotinamide provides long-term multilineage engraftment. *J Clin Invest*. 2014;124:3121–3128.
8. Horwitz ME, Wease S, Blackwell B, et al. Phase I/II study of stem-cell transplantation using a single cord blood unit expanded ex vivo with nicotinamide. *J Clin Oncol*. 2019;37:367–374.
9. Parikh S, Brochstein JA, Galamidi E, Schwarzbach A, Kurtzberg J. Allogeneic stem cell transplantation with omidubicel in sickle cell disease. *Blood Adv*. 2021;5:843–852.
10. Cohen S, Roy J, Lachance S, et al. Hematopoietic stem cell transplantation using single UM171-expanded cord blood: a single-arm, phase 1-2 safety and feasibility study. *Lancet Haematol*. 2020;7:e134–e145.
11. de Lima M, McNiece I, Robinson SN, et al. Cord-blood engraftment with ex vivo mesenchymal-cell coculture. *N Engl J Med*. 2012;367:2305–2315.
12. Anasetti C, Logan BR, Lee SJ, et al. Peripheral-blood stem cells versus bone marrow from unrelated donors. *N Engl J Med*. 2012;367:1487–1496.
13. Robinson TM, Fuchs EJ. Allogeneic stem cell transplantation for sickle cell disease. *Curr Opin Hematol*. 2016;23:524–529.
14. Bolaños-Meade J, Fuchs EJ, Luznik L, et al. HLA-haploidentical bone marrow transplantation with posttransplant cyclophosphamide expands the donor pool for patients with sickle cell disease. *Blood*. 2012;120:4285–4291.
15. Kelly SS, Sola CB, de Lima M, Shpall E. Ex vivo expansion of cord blood. *Bone Marrow Transplant*. 2009;44:673–681.
16. Sica RA, Terzioglu MK, Mahmud D, Mahmud N. Mechanistic basis of ex vivo umbilical cord blood stem progenitor cell expansion. *Stem Cell Rev Rep*. 2020;16:628–638.
17. Dahlberg A, Delaney C, Bernstein ID. Ex vivo expansion of human hematopoietic stem and progenitor cells. *Blood*. 2011;117:6083–6090.
18. Williams N, Lee J, Mitchell E, et al. Life histories of myeloproliferative neoplasms inferred from phylogenies. *Nature*. 2022;602:162–168.
19. Mori H, Colman SM, Xiao Z, et al. Chromosome translocations and covert leukemic clones are generated during normal fetal development. *Proc Natl Acad Sci U S A*. 2002;99:8242–8247.
20. Dietz AC, DeFor TE, Brunstein CG, Wagner Jr. JE. Donor-derived myelodysplastic syndrome and acute leukaemia after allogeneic haematopoietic stem cell transplantation: incidence, natural history and treatment response. *Br J Haematol*. 2014;166:209–212.
21. Ballen KK, Cutler C, Yeap BY, et al. Donor-derived second hematologic malignancies after cord blood transplantation. *Biol Blood Marrow Transplant*. 2010;16:1025–1031.
22. Wang E, Hutchinson CB, Huang Q, et al. Donor cell-derived leukemias/myelodysplastic neoplasms in allogeneic hematopoietic stem cell transplant recipients: a clinicopathologic study of 10 cases and a comprehensive review of the literature. *Am J Clin Pathol*. 2011;135:525–540.
23. Nagamura-Inoue T, Kodo H, Takahashi TA, Mugishima H, Tojo A, Asano S. Four cases of donor cell-derived AML following unrelated cord blood transplantation for adult patients: experiences of the Tokyo Cord Blood Bank. *Cytotherapy*. 2007;9:727–728.
24. DeZern AE, Gondek LP. Stem cell donors should be screened for CHIP. *Blood Adv*. 2020;4:784–788.
25. Gibson CJ, Lindsley RC. Stem cell donors should not be screened for clonal hematopoiesis. *Blood Adv*. 2020;4:789–792.
26. *Gamida Cell announces FDA acceptance of biologics license application for omidubicel with priority review [news release]*. Gamida Cell Ltd; 2022.. August 1.
27. Gragert L, Eapen M, Williams E, et al. HLA match likelihoods for hematopoietic stem-cell grafts in the U.S. registry. *N Engl J Med*. 2014;371:339–348.
28. Gergis U, Khera N, Edwards ML, et al. Abstract 6 Projected impact of omidubicel on racial and ethnic disparities in allogeneic hematopoietic cell transplant access and outcomes for patients with hematologic malignancies in the U.S. *Stem Cells Transl Med*. 2022;11(suppl 1):S8.