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Salvage of primary graft failure with allogeneic hematopoietic stem cell transplantation from a deceased organ donor: report of a novel graft source

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Primary graft failure (PGF) following allogeneic hematopoietic stem cell transplantation (HSCT) can lead to life-threatening complications from prolonged cytopenias.[1] The standard approach to PGF is salvage HSCT using a new donor graft,[2] however limited donor availability significantly increases morbidity and mortality. Alternatives to donor options beyond the historically desired fully human leukocyte antigen (HLA)-matched (8/8) donor include haploidentical (half-matched, 4/8), mismatched ($\leq 7/8$) and cord blood sources – all of which are collected from living donors.[3] Deceased organ donors (deceased-donors) represent a novel stem cell source using grafts isolated directly from bone marrow and cryopreserved. The whole bone marrow is harvested from the spine within ischemia time limit established criteria and is not manipulated.[4] *In vivo* data demonstrates this cryopreserved graft source retains excellent viability and function for more than 5 years. [5] The deceased-donor graft biobank, currently developed by Ossium Health (Indianapolis, IN, USA), is available through two ongoing clinical programs including a phase 1 prospective clinical trial (PRESERVE 1, NCT05589896) and an expanded access program (HPC Offered for PRESERVE Expansion, HOPE; NCT07145411) for patients age 12-80 years with indication for allogeneic HSCT and without any other available donor and who are otherwise ineligible for the PRESERVE trial or transplanted in centers that are not participating in this trial. The first clinical experience using these deceased-donor grafts was recently reported for three high-risk acute myeloid leukemia patients on HOPE who received bone marrow (BM) grafts matched at at-least 4/8 HLA loci and with robust CD34 cell doses of $4.5\text{--}5.3 \times 10^6$ CD34 cells/kg.[6] Patients were conditioned with reduced intensity conditioning in 2 and myeloablative in 1, and received post-transplant cyclophosphamide (PT-Cy)-based graft-versus host disease (GVHD) prophylaxis. All patients engrafted between D15-20, achieved full donor chimerism and grade ≥ 3 acute GVHD occurred in one patient, treated to resolution, with no cases of chronic GVHD. Two patients are still alive without relapse 300 days post-transplant, with one patient expiring due to respiratory failure on D+282 post-transplant.[6] These early findings, while awaiting more data from PRESERVE 1 trial, demonstrate promising safety and efficacy of this approach for patients without other standard donor options.

An important potential advantage of these deceased-donor grafts is that a BM sourced graft involves a significantly decreased risk of chronic GVHD compared to peripheral blood (PB),[7] though due to logistical limitations PB mobilization remains the main method of stem cell collection from live donors, currently representing 91% of grafts used in the U.S.[8] Further, deceased-donor grafts are available off-the-shelf with turn-around times as low as 72 hours from time of graft request.

We present here the first known report of successful engraftment after use of an HLA-mismatched, cryopreserved, off-the-shelf deceased-donor graft for allogeneic HSCT after primary graft failure.

A 42-year-old African American male with history of high-risk myelodysplastic syndrome (MDS) with monosomy 7 and mutations in *DNMT3A* and *SETB1* received 3 cycles of azacitidine therapy and was scheduled for peripheral blood allogeneic HSCT with curative intent. After initiation of myeloablative conditioning with Fludarabine and busulfan his unrelated donor developed an undisclosed medical emergency that precluded donation of stem cells. There were no available back up HLA-identical sibling nor fully HLA (8/8 allele) matched unrelated donors from the registry, and the patient proceeded to receive a haploidentical stem cell graft from his sister. After stem cell infusion he received post-transplant cyclophosphamide PT-Cy-based GVHD prophylaxis with tacrolimus and mycophenolate, with daily G-CSF per institutional protocol. The patient exhibited no clinical signs of engraftment at D+28 and a bone marrow biopsy was hypocellular (5%) with lack of hematopoietic elements and revealing post-therapy stromal changes. Concurrent BM chimerism showed absent donor T cell chimerism and mixed chimerism when unseparated (Table 2A). In the absence of hematopoiesis with continued pancytopenia, and after extensive infectious and metabolic workup was unrevealing to any other potential causes, he was diagnosed with primary graft failure.[9] Donor-specific antibodies were assessed prior to transplant and were notably negative and repeated at time of PGF diagnosis prior to selecting next donor option. The hospital course was complicated by development of hemorrhagic cystitis from Human polyomavirus 1 (BK) for which he required increased platelet transfusions, which developed prior to diagnosis of PGF.

Only highly mismatched-donor options were available through the national marrow registry and required a 4–6-week wait. After understanding that no feasible living donor option was available for the patient, an initial inquiry was submitted five days after confirmation of GF through an Institutional Review Board (IRB)-approved expanded access program (HOPE), which identified several potential deceased-donor graft options in the deceased organ donor bank on the same day of donor request. Weighing the significant risks of ongoing pancytopenia and infection, the patient consented to proceed with a mismatched (6/10, mismatched at one loci for HLA-A and -DQ and two loci for HLA-DR) deceased-donor bone marrow graft for his second salvage HSCT (**Table 1**). Non-myeloablative conditioning was started after receipt of the donor graft, and included fludarabine, cyclophosphamide and total body irradiation (TBI; 2Gy), with PT-Cy-based GVHD prophylaxis including PT-Cy (50 mg/kg/day for two days on D+3 and D+4), and tacrolimus 0.03 mg/kg/day and mycophenolate 15 mg/kg three times daily both starting on D+5. The patient received a dose of 5.9×10^6 CD34 cells/kg with his stem cell infusion, which occurred approximately 2.5 weeks after confirmation of GF. He exhibited neutrophil engraftment on D+22 after his second HSCT (**Figure 1**). D+30 chimerism showed full donor chimerism (**Table 2A**). Three months after transplant, the patient exhibits good immune reconstitution, including lymphocyte recovery and immunoglobulin levels (**Table 2B**), and no signs of GVHD or relapse.

This case details the use of a novel, safe and readily available salvage stem cell graft option from a deceased organ donor, while highlighting the challenges of donor access for patients of diverse backgrounds. PGF often leaves patients at risk of life-threatening complications resulting from prolonged cytopenia during the process of trying to identify a second donor. Here, a readily available deceased- donor graft significantly shortened that duration.

Deceased-donor bone marrow grafts has the potential to serve as a new donor source for those with limited living donor availability and urgent medical need for HSCT. The rapid turnaround time for donor selection and subsequent infusion of graft accelerates time to transplant while reducing barriers to access for individuals of racially/ethnically diverse ancestry. Swiftly proceeding to transplant offers benefits from prevention of disease relapse and reducing the risk for infectious complications. Further, the potential benefit of lowering chronic GVHD rates with use of BM graft is intriguing, especially given the practical challenges of collecting BM grafts from living donors and the current culture of prioritizing of PB grafts from the perspective of health systems utilization/costs and personal donor preference.[8] Data on chronic GVHD and the long-term safety and efficacy of this graft option from the ongoing prospective phase 1 trial (PRESERVE I, NCT05589896) and planned upcoming larger PRESERVE II trial will hopefully confirm the promise of this novel graft source. The early findings suggest that deceased-donor bone marrow grafts serve as a new frontier, providing an off-the-shelf graft option that increases donor pool availability, decreases time-to-transplant and offers the potential for improved clinical outcomes for our HSCT patients.

This transplant was conducted in accordance with the Declaration of Helsinki and through an expanded access program approved by our institutional IRB for which written informed consent from the patient was obtained.

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Table 1. Donor graft characteristics

	Donor for HSCT #1	Donor for HSCT #2
Live/Dead	Living donor	Deceased donor
Stem Cell Source	Peripheral Blood	Whole Bone Marrow
Age (years)	46	44
Sex	Female	Male
HLA-match	5/10	6/10
Relation	Related	Unrelated
ABO Rh	O positive	O positive
Fresh vs cryo	Fresh	Cryopreserved
Cell dose	4.9 x 10 ⁶ CD34/kg 2.8 x10 ⁸ CD3/kg	5.9 x 10 ⁶ CD34/kg 0.2 x10 ⁸ CD3/kg

Table 2. Post-transplant immune studies. Post-transplant (A) chimerism and (B) immune reconstitution studies.

(A)

Chimerism subset	HSCT #1 D+30	HSCT #2 D+30	HSCT #2 D+60	HSCT #2 D+90
Sample	BM	WB	WB	WB
Unseparated % Donor	71.6	99.7	100.0	>99.5
B Lymphocytes % Donor	66.2	99.0	100.0	99.3
T Lymphocytes % Donor	2.2	99.5	98.8	>99.5
Myeloid % Donor	100	99.6	99.4	>99.5

*WB, whole blood; BM, bone marrow

(B)

Peripheral blood test	Ref. Range (units)	HSCT#2 D+100	HSCT#2 D+180
CD19 (Abs. count, cells/mcL)	110-660 (cells/mcL)	24	18
CD3 (Abs. count, cells/mcL)	840-3060 (cells/mcL)	178	364
CD4+ (Abs. count, cells/mcL)	490-1740 (cells/mcL)	164	331
CD8+ (Abs. count, cells/mcL)	180-1170 (cells/mcL)	15	45
CD56 (Abs. count, cells/mcL)	100-400 (cells/mcL)	125	220
IgG (mg/dL)	610.3-1616 (mg/dL)	421.81	711.16

*Abs., absolute; IgG, immunoglobulin G

Figure 1. Absolute neutrophil count throughout sequential transplantations demonstrating initial graft failure and subsequent engraftment after 2nd salvage HSCT. Approximately 2.5 weeks elapsed between confirmation of graft failure to HSCT #2 infusion.

