HEMATOPOIETIC STEM CELL TRANSPLANTATION (HCT) WITH OMIDUBICEL LEADS TO ROBUST RECOVERY AND DIVERSITY OF T CELLS

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BACKGROUND

- Omidubicel is an advanced cell therapy used as a graft source for allogeneic hematopoietic stem cell transplant (HCT)
- Omidubicel is derived from umbilical cord blood (UCB). The unit undergoes immunomagnetic bead selection for CD133-positive cells, which are cultured for 21 ± 2 days in the presence of nicotinamide and cytokines. The CD133-negative flow-through (negative) fraction (NF) containing lymphocytes is retained and re-cryopreserved
- A phase III randomized study (NCT02730299) compared HCT with omidubicel to UCB (N=125)[1]
  - Median CD34⁺ cell expansion was 130-fold (range, 32- to 233-fold)
  - Median T cell count of the omidubicel NF was 30–60% of UCB
- Patients transplanted with omidubicel had faster neutrophil and platelet engraftment, lower rates of bacterial, fungal, and viral infection, and shorter hospitalization time.[1] Exploratory analyses demonstrated more rapid reconstitution of CD3⁺ cells[2]
- The current study provides further characterization of T cell development in the phase III substudy

OBJECTIVE

- Characterization of T cell development reflected by T cell receptor excision circles (TREC) and T cell receptor (TCR) diversity in omidubicel and UCB-transplanted patients

METHODS

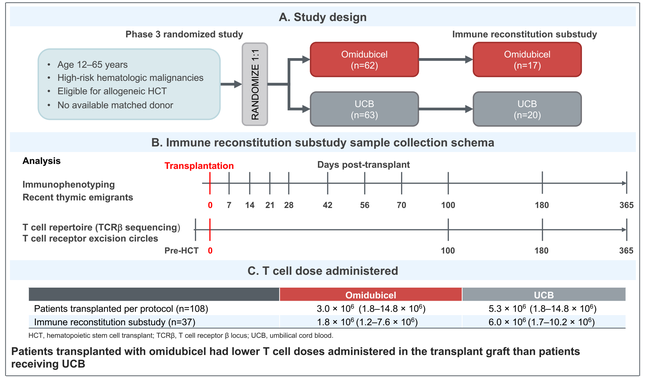
Study design

- 125 patients aged 12–65 years with hematologic malignancies were randomized to allogeneic transplantation following myeloablative conditioning **(Figure 1A)**
- 37 patients from 14 global sites were included in the optional immune reconstitution substudy: 17 transplanted with omidubicel and 20 with UCB
- Peripheral blood mononuclear cells were collected from patients, processed, and cryopreserved at various timepoints through 1 year post-transplant **(Figure 1B)**

Immune reconstitution

- Immunophenotyping assays using wide flow cytometric panels were used to track recent thymic emigrants (RTE), as defined by CD31⁺, CD45RA co-expression on CD4⁺ and CD8⁺ cellular subsets
- Genomic DNA was extracted from peripheral blood mononuclear cells. TREC was quantified by real-time quantitative PCR. TREC copies (T) were standardized to β actin transcripts (B) and T/B ratio was normalized per µg of DNA
- TCR diversity was measured using a total of 76 T cell receptor β locus (TCRβ) genes
- Human TCRβ repertoire was quantified using AmpliSeq for Illumina Immune Repertoire Plus SR assay. TCRβ metrics quantified the number of clones, Shannon's entropy, clonality, evenness, convergency, and Gini indexes
- Summary statistics by treatment and *p*-values based on Wilcoxon rank-sum test for treatment comparisons were analyzed without multiplicity adjustment

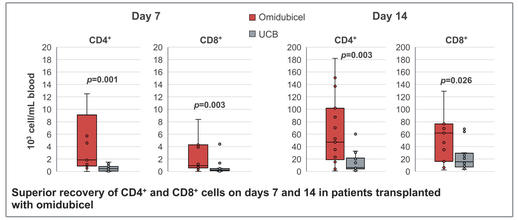
FIGURE 1. METHODS



Patients transplanted with omidubicel had lower T cell doses administered in the transplant graft than patients receiving UCB

RESULTS

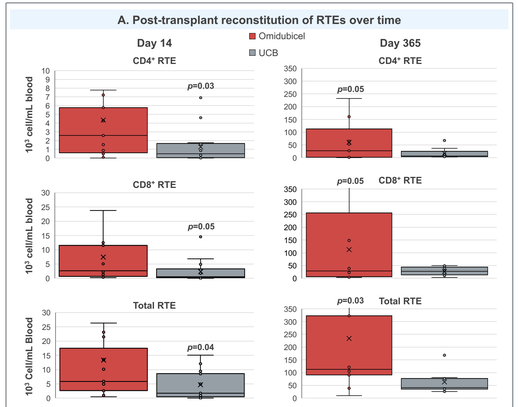
FIGURE 2. T CELL RECONSTITUTION



Superior recovery of CD4⁺ and CD8⁺ cells on days 7 and 14 in patients transplanted with omidubicel

UCB, umbilical cord blood.

FIGURE 3. THYMIC RECOVERY

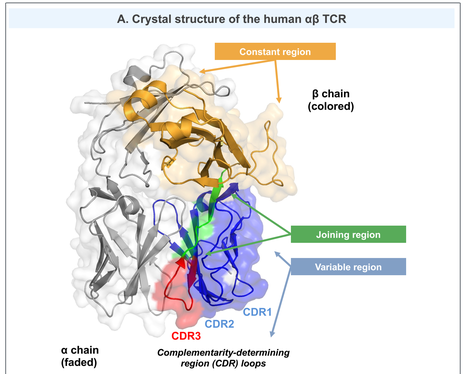


Superior RTE recovery for CD4⁺ and CD8⁺ on days 14 and 365, suggesting more rapid thymopoiesis, in patients transplanted with omidubicel

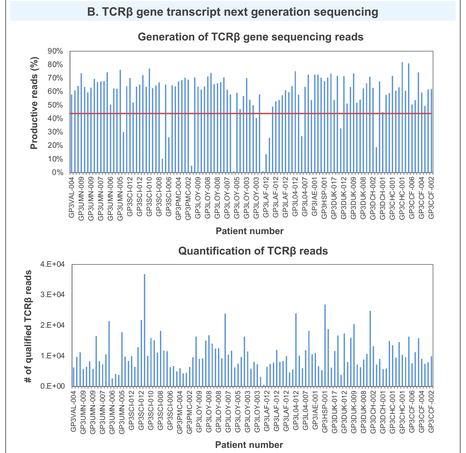
Comparable levels of TRECs between days 100 and 365 in patients transplanted with omidubicel and UCB

RTE, recent thymic emigrant; TREC, T cell receptor excision circle; UCB, umbilical cord blood.

FIGURE 4. T CELL RECEPTOR DIVERSITY



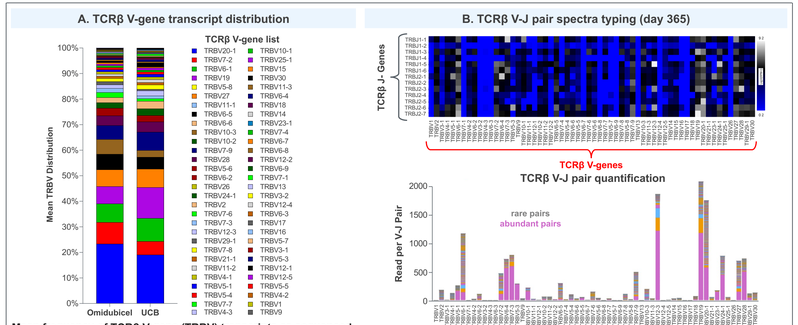
Quaternary structure of the human αβ TCR (PDB: 4GRL). Recombination of Joining (J) and Variable (V) regions genes defines TCR diversity



TCRβ gene transcript library was generated. Productive reads were qualified and enumerated for individual patients (x-axis). 101/112 samples considered quality control pass (>40% productive reads)

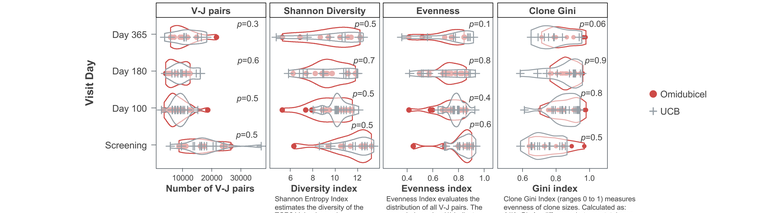
TCR, T cell receptor; TCRβ, T cell receptor β locus.

FIGURE 5. T CELL RECEPTOR DIVERSITY SPECTRA TYPING ANALYSIS



Mean frequency of TCRβ V-gene (TRBV) transcripts as sequenced from peripheral blood T cells from 9 patients transplanted with omidubicel compared with 9 patients transplanted with UCB. Each color represents a TRBV-related specific group of V-J pairs

Representative quantification of TCRβ metrics from 1 omidubicel-treated patient



Shannon Entropy Index estimates the diversity of the TCRβ V-J pairs pool, considering the total and unique number of pairs. Higher index indicates larger TCR diversity

Evenness Index evaluates the distribution of all V-J pairs. The upper index value (1) indicates more equally distributed V-J pairs. Lower index value (0) indicates skewed TCR distribution

Clone Gini Index (ranges 0 to 1) measures evenness of clone sizes. Calculated as: A/(A+B), A - difference between total area under line of equality and area under the Lorenz Curve (B). Higher value indicates dissimilar V-J pair sizes

Patients transplanted with omidubicel and UCB had comparable T cell receptor diversity as measured by Shannon Diversity, Evenness, and Gini Indices

TCR, T cell receptor; TCRβ, T cell receptor β locus; TRBV, TCRβ V-gene; UCB, umbilical cord blood.

CONCLUSIONS

- Patients transplanted with omidubicel had robust and diverse T cell reconstitution
- Significantly higher numbers of de novo recent thymic emigrant T cells (RTEs) in peripheral blood at 1 year suggest faster thymopoiesis in patients transplanted with omidubicel
- There was no marked difference in TCR repertoire diversity between omidubicel and UCB groups
- These data provide mechanistic rationale for the lower viral and overall infection rates in patients transplanted with omidubicel

REFERENCES

1. Horwitz ME, et al. *Blood.* 2021;138:1429–1440.
2. Szabolcs P, et al. *Trans Cell Ther.* 2022;28(Suppl):S4–S5.

DISCLOSURES

PS is a co-inventor/licensee for Forge Therapeutics; participates in clinical trials and is a consultant for Gamida Cell; and is a consultant for Prevail Therapeutics. DY and SL are employees of Gamida Cell. MH is a consultant for AbbVie, CareDx, Kadmon, and Magenta; and receives research support from Gamida Cell. XC is a consultant for Gamida Cell.

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